SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

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BY

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DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

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Dedicated To

My Beloved Husband

P. S. BALAKRISHNAN

CONTENTS

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NCL, Pune 411008 (KAMALAM M.)

Dated March 1985

Certified that the work incorporated in the thesis "SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS" by Kamalam M. (Mrs. K. Balakrishnan) was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(A.V. RAMA RAO)
Supervisor

CHAPTER-I

SYNTHESIS OF 2,3,5-TRIMETHYLHYDROQUINONE

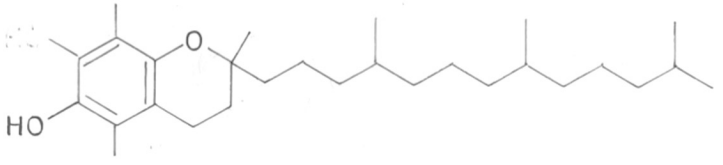
(AROMATIC PART OF VITAMIN-E)

Vitamins are described as a group of chemical substances present in the human nutrition and are indispensable for normal health and growth. Among them vitamin E is considered as an inevitable factor not only as a dietary constituent but also as a fertility drug. It is a controlling factor of various functions of the body. Vitamin E plays a major role in the transportation of oxygen and accelerates the turnover rate of nucleic acids[1] in the body. It functions as a co-factor in the electron transfer[2] system, controls the secretion of fertility-hormones, prevents the congenital anomalies and muscular distrophy. Recently it is discovered that vitamin E acts on the motility of sperms and keeps them virile and strong. Vitamin E, along with vitamin A and B_6, is routinely used in the treatment of various cardiovascular disorders. The antioxidant property of vitamin E protects the easily oxidisable substances (e.g. Vit. A) from destruction and counters the toxic effect of unsaturated fatty acids[3].

Vitamin E is widely distributed in our diets, the best dietary source being oils and fats, such as cottonseed oil, wheat germ oil, rice bran oil and linseed oil in minute quantities. It is also present in lettuce leaves and soya bean and many other vegetables.

Because of its diversified biochemical function coupled with the nutritional value, vitamin E has attracted the

attention of many scientists all over the world. The most active principle of vitamin E is ∝-tocopherol (1) [tocos:child birth, pheros: to bear], which is manufactured by synthesis.



1

Earlier methods for the synthesis of vitamin E

Most of the earlier workers have adopted more or less the same strategy for the total synthesis of vitamin E, which could be conveniently divided into three major parts:

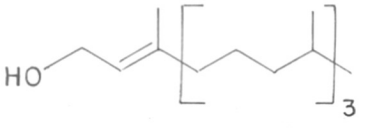
a) Synthesis of aliphatic moiety

b) Synthesis of aromatic moiety

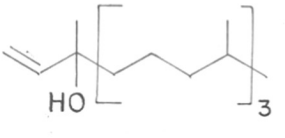
and c) the coupling reaction.

Synthesis of aliphatic moiety

The aliphatic part of vitamin E consists of phytol (2) or isophytol (3).



Phytol (2)

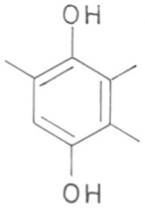


Isophytol (3)

Although phytol could be obtained from pseudoionone[4], citral[5], citranellol[6] the most convenient method is from the unsaturated ketone 4 as developed by Ister et al.[7]. This method gave phytol (2) and isophytol (3) in good yield (Scheme 1).

The commercial process[8] for phytol (2) is depicted in Scheme 2. The process involved ethynylation of the ketone (6) with sodium acetylide in liquid ammonia followed by partial hydrogenation of the ethynylcarbinol 7. The resulting vinyl carbinol 8 could be reacted with isopropenyl ethyl ether to give the next higher ketone (4) directly[9], whereas treatment of 8 with diketene leads to the allylic acetoacetate (9) which is then pyrolysed to the next higher ketone[10] 4. Finally the ketone (4n=3) is hydrogenated to phytone (5) which is converted to phytol (2) or isophytol as depicted in Scheme 1.

Synthesis of aromatic moiety 2,3,5-trimethylhydroquinone (10)



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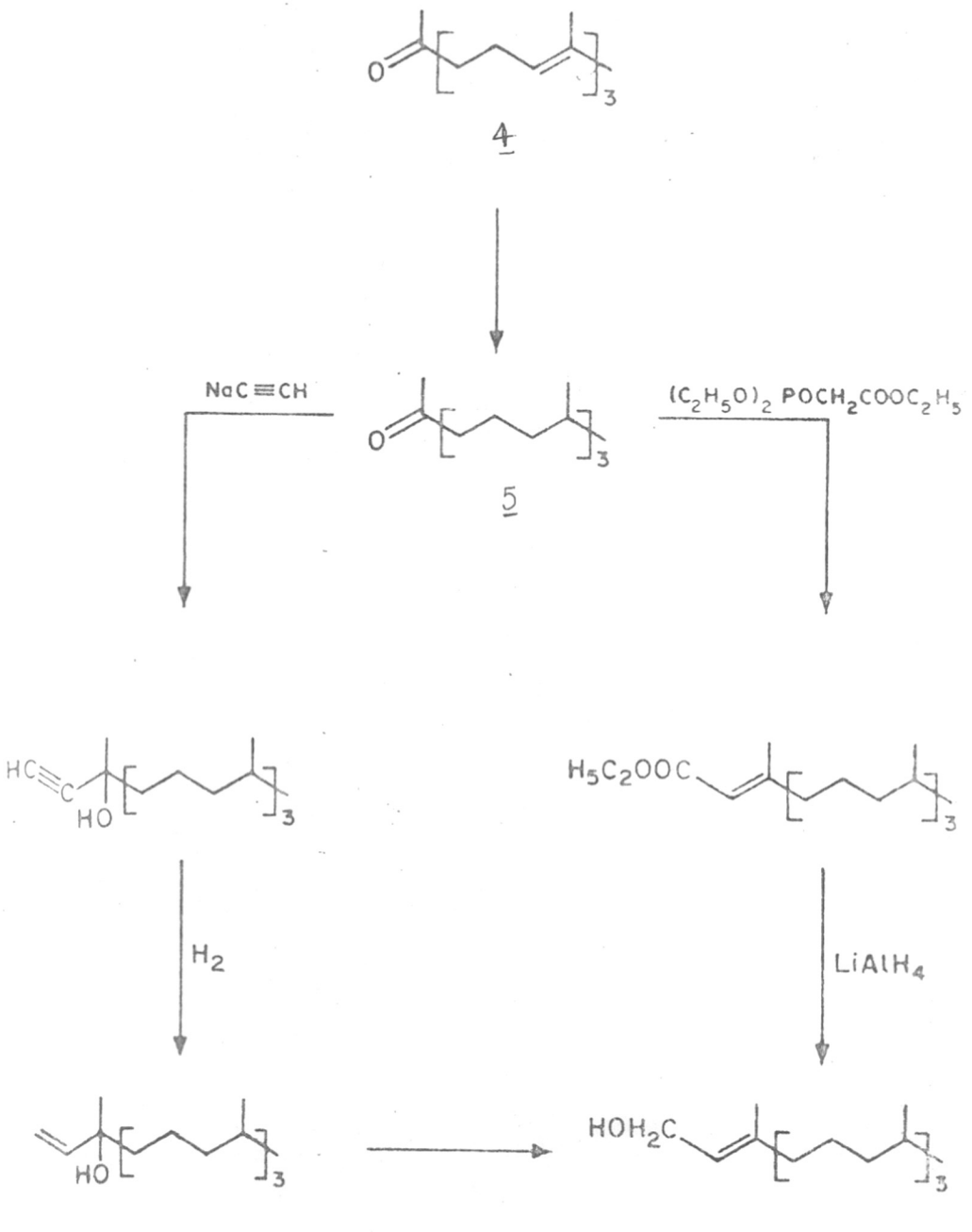
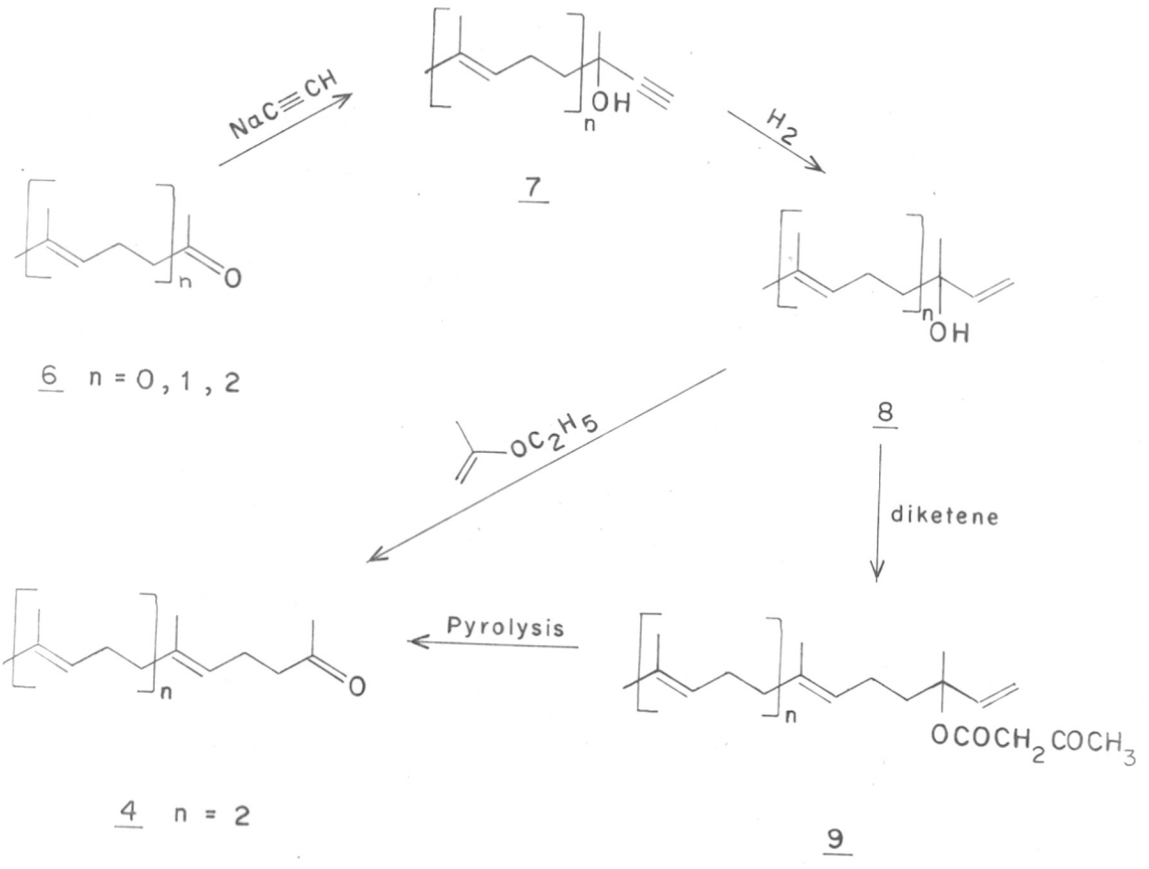
Trimethyl hydroquinone (10) has been synthesised by several groups of workers starting from p-xylene, m-xylenol,

SCHEME- 1


4
NaC≡CH
5
(C2H5O)2 POCH2COOC2H5
H2
LiAlH4
isophytol (3)
phytol (2)

SCHEME 2

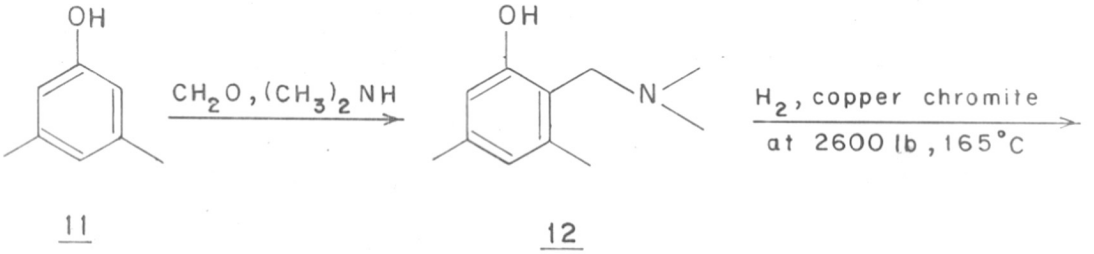

NaC≡CH
OH
n
7
H2
O
n
6 n = 0, 1, 2
OH
n
8
OC2H5
diketene
Pyrolysis
O
n
4 n = 2
n
OCOCH2COCH3
9

pseudocumene, pseudocumidine, hydroquinones and methylated hydroquines. To describe different methods in detail is beyond the scope of the thesis and therefore only those schemes which are related to the present work are included.

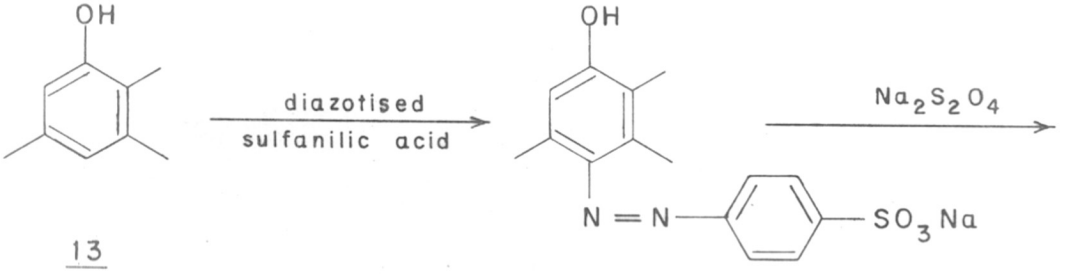
The method commercially utilised is discussed as follows (Scheme 3). 3,5-dimethyl phenol (11) was subjected to Mannich reaction[11] to afford the Mannich base which was hydrogenated to give 2,3,5-trimethylphenol (13). Conversion of the trimethyl phenol into trimethyl hydroquinone (10) was achieved by a standard set of reactions as shown in the scheme. Although the yields are moderate in each step of this route, the route suffered from a few drawbacks, such as high pressure and high temperature are required for the conversion of Mannich base to trimethyl phenol. Based on Mannich reaction, several groups of workers[12,13] have also synthesised 2,3,5-trimethylhydroquinone from, 2-methyl and 3,5-dimethyl hydroquinone and 4-benzyloxy phenol. In each case the reduction of Mannich bases were accomplished only at high pressure and high temperature.

Pongratz et al.[14] and Cheng Kuo Hui et al.[15] independently reported the preparation of 2,3,5-trimethylhydroquinone starting from pseudocumene (14) as shown in Scheme-4. It could be realised from the scheme that since protection and deprotection of the active site of the aromatic ring are

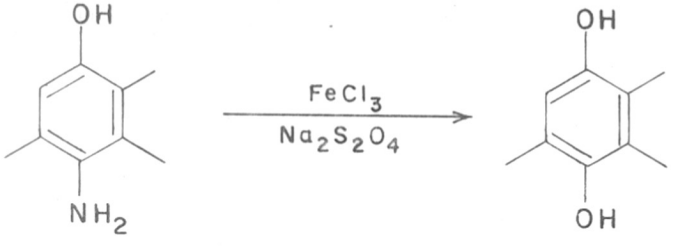
SCHEME 3



11 12



13



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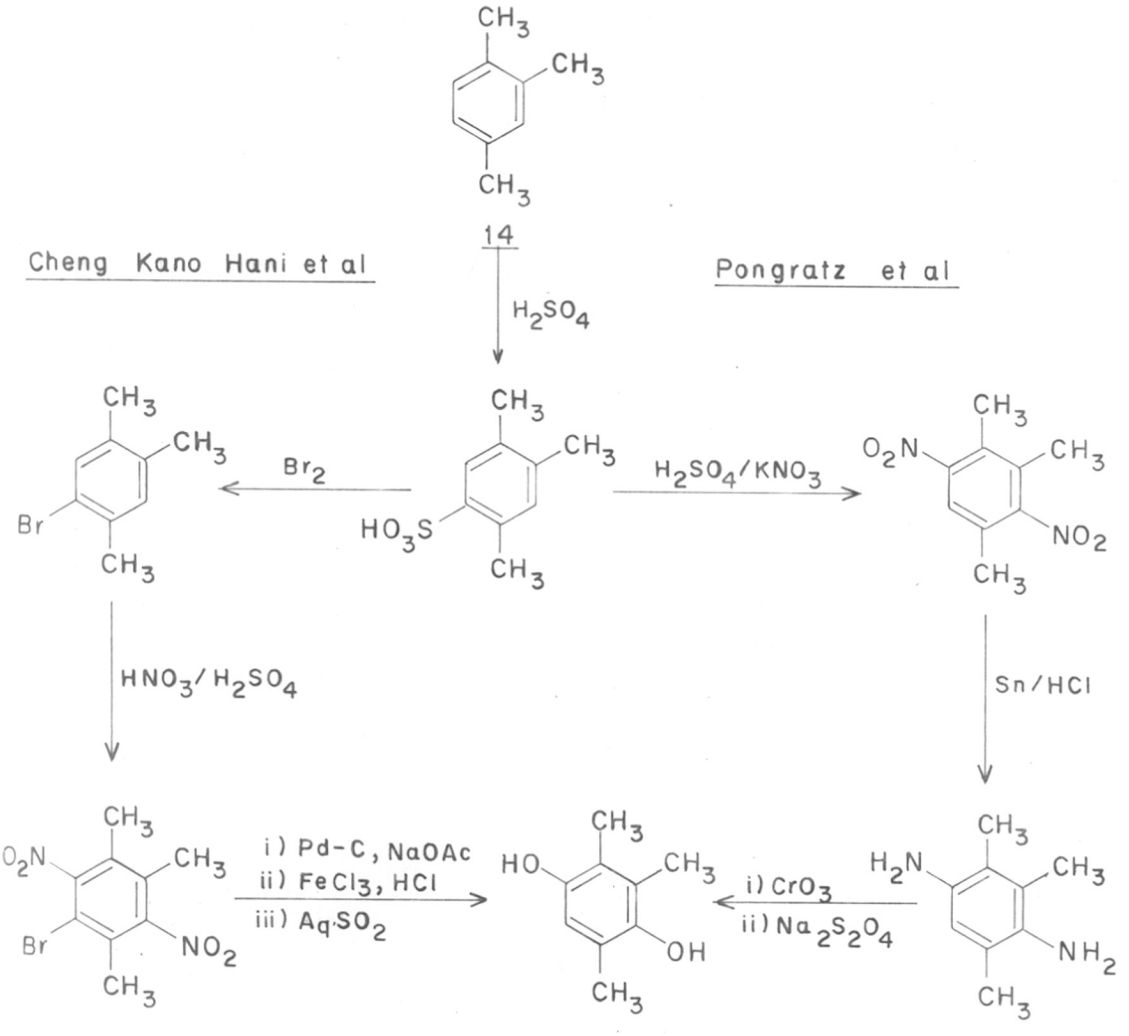
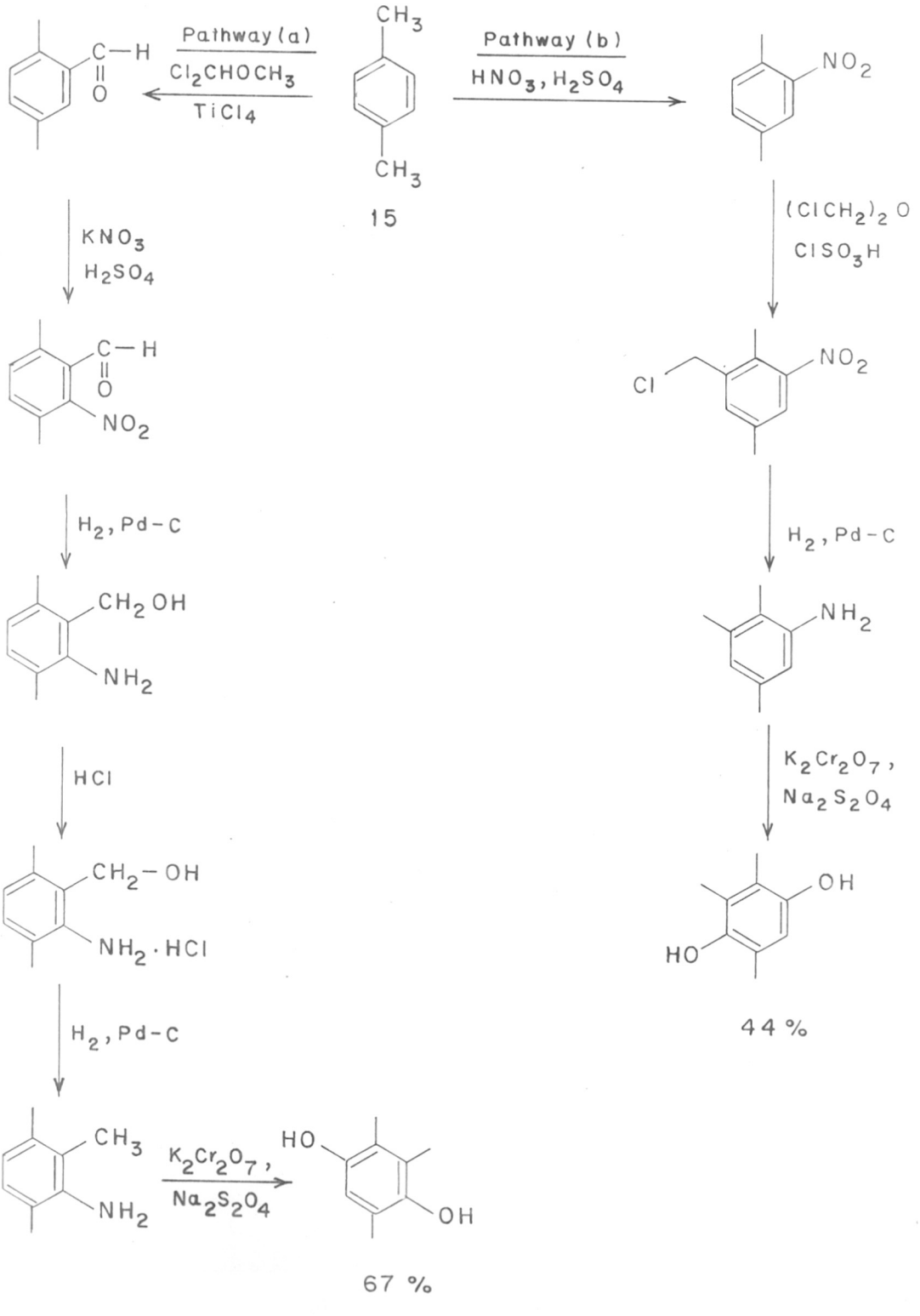
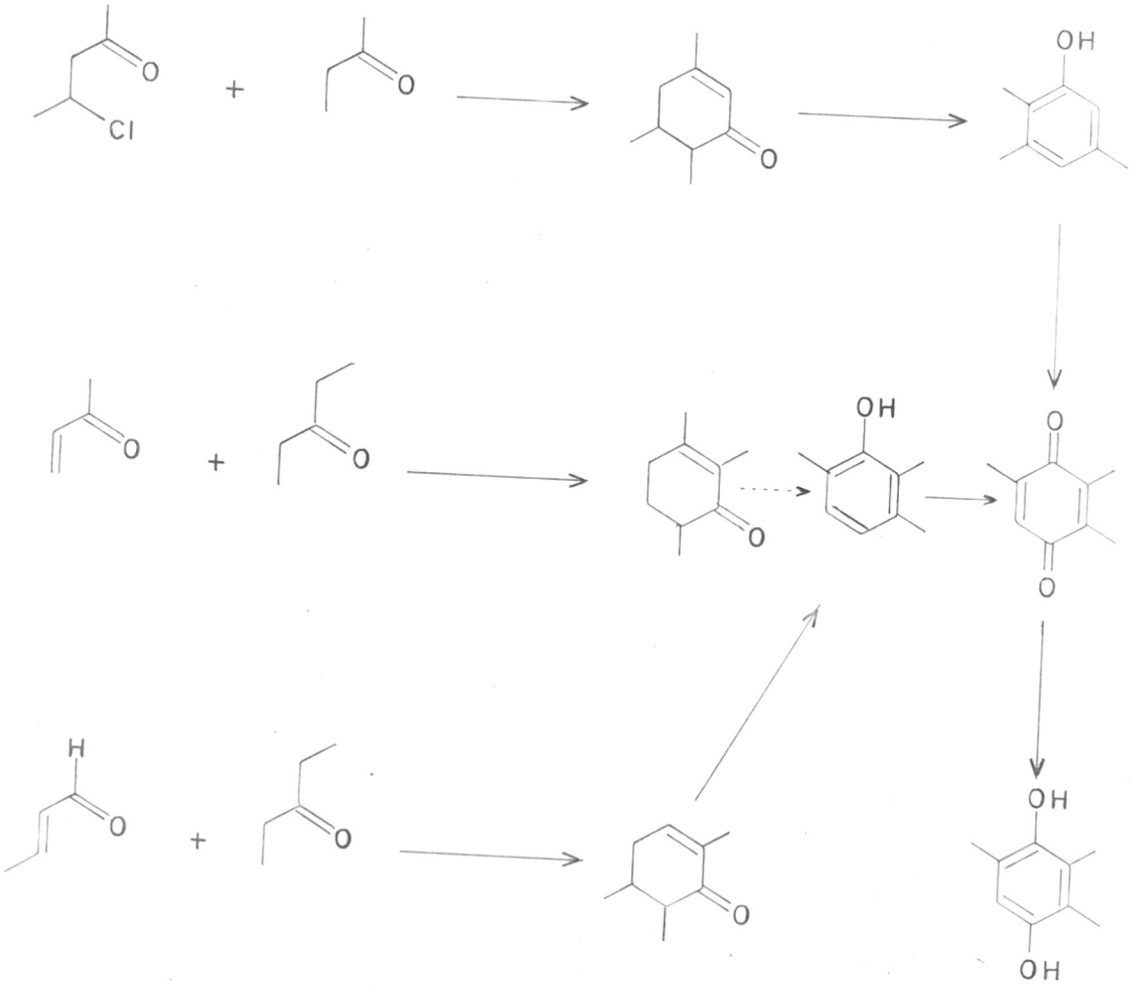
SCHEME 4


14
Cheng Kano Hani et al
Pongratz et al
H_2SO_4
Br_2
H_2SO_4/KNO_3
HNO_3/H_2SO_4
Sn/HCl
i) Pd-C, NaOAc
ii) $FeCl_3$, HCl
iii) Aq.SO_2
i) CrO_3
ii) $Na_2S_2O_4$
10

SCHEME 5


Pathway (a)
Cl_2CHOCH_3
$TiCl_4$
Pathway (b)
HNO_3, H_2SO_4
15
KNO_3
H_2SO_4
$(ClCH_2)_2O$
$ClSO_3H$
$H_2, Pd-C$
HCl
$K_2Cr_2O_7$,
$Na_2S_2O_4$
44 %
67 %

SCHEME 6



10

required prior to nitration step and number of steps are more which resulted in an overall low yield. Later Smith[16] by adopting similar strategy, prepared trimethylhydroquinone from pseudocumidine.

The approach developed by Sato and coworkers[12] using p-xylene (15) as the starting material (Scheme 5) was not commercially viable because of the low yield, costly reagents and the number of steps involved.

Synthesis of trimethylhydroquinone by a number of workers[17] (Scheme 6) from aliphatic precursors such as 4-chloro-2-pentanone with butanone, methyl vinyl ketone with 3-pentanone etc. also suffered several drawbacks which included nonavailability of starting materials, number of steps and overall low yields.

The coupling reaction

Although there are several different approaches for the synthesis of vitamin E, the most commonly used is the condensation of trimethylhydroquinone and the phytol derivatives in the presence of acidic reagents such as $ZnCl_2$, BF_3-etherate, P_2O_5, formic acid, acetic anhydride or toluene p-sulfonic acid as catalysts[18].

PRESENT WORK

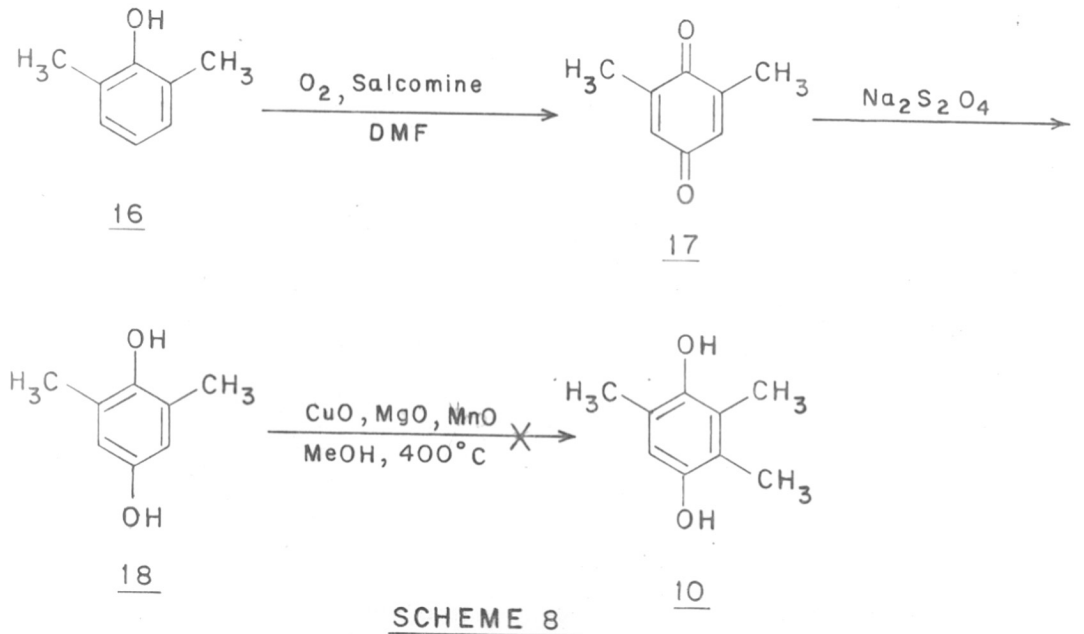
α-tocopherol which is commonly called Vitamin E is distributed throughout the tissues of animals and man. The rich source of vitamin E or 5,7,8-trimethyltocol is vegetable oils, green leaves, wheat germ oil etc. The biological functions which vitamin E performs and the diseases caused because of its deficiency are discussed in the preceding section.

The most logical approach towards the synthesis of vitamin E would be to construct the aliphatic and the aromatic moieties separately followed by a coupling reaction using a suitable catalyst.

This chapter describes studies related to the development of a suitable process for the synthesis of trimethylhydroquinone. The first strategy was to utilize the commercially available 2,6-dimethyl phenol (16). It was converted to the 2,6-dimethyl benzoquinone (17) by oxidation with oxygen using salcomine as catalyst[19-21] followed by sodium dithionite reduction to 2,6-dimethyl-hydroquinone (18) [Scheme 7]. The introduction of the methyl group to get 2,3,5-trimethylhydroquinone (10) was carried out by two methods.

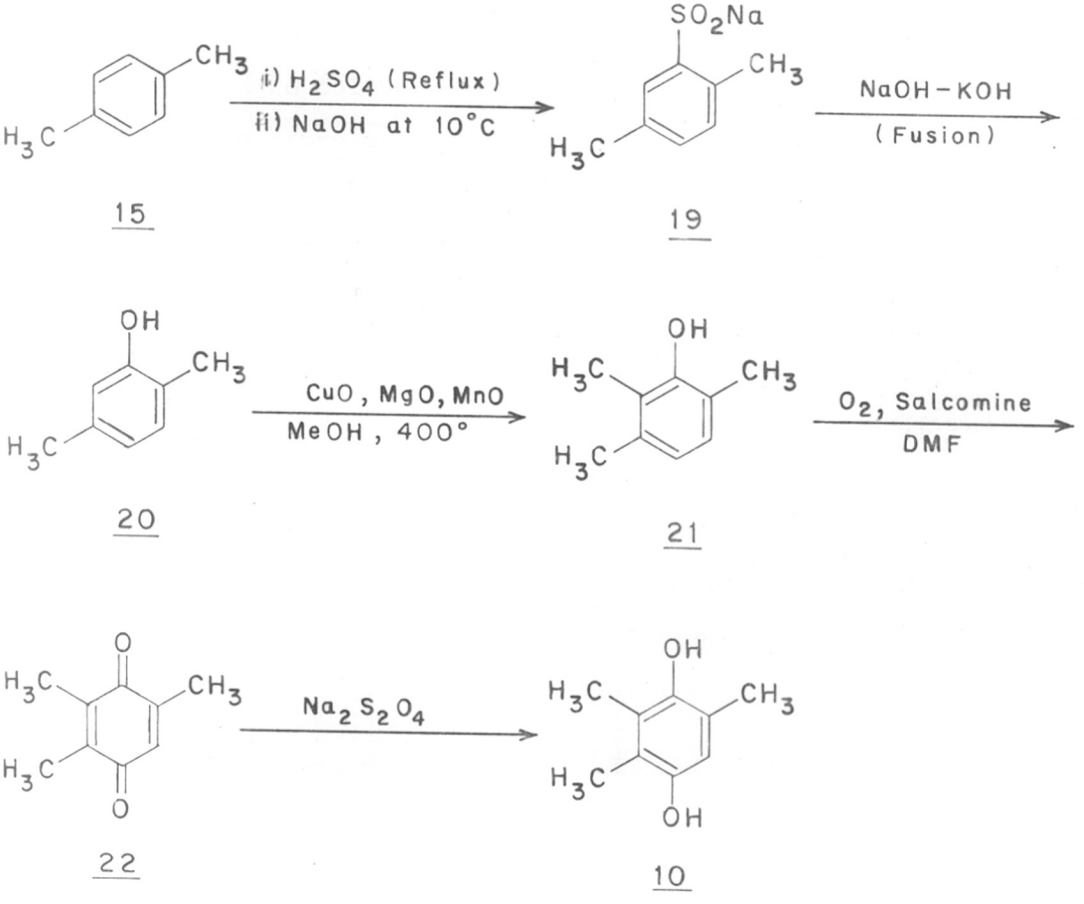
a) direct introduction of the methyl group by vapour phase methylation[22] using methanol and a suitable catalyst;

SCHEME 7



16 17 18 10

SCHEME 8



15 19 20 21 22 10

b) converting the hydroquinone (18) to 2,6-dimethyl-1,4-diacetyl benzene and then introducing a chloromethyl group to the C-3 position which could be subsequently reduced to a methyl group.

Ortho-alkylation of phenols to introduce methyl substituent ortho to hydroxyl group in vapour phase using methanol and a catalyst is a well known reaction[22] (discussed later). Similar reaction when applied to 2,6-dimethylhydroquinone, gave instead of the expected 2,3,5-trimethylhydroquinone (10), 2,6-dimethylbenzoquinone (17) as the sole product.

2,6-dimethyl-1,4-diacetylhydroquinone derived from 2,6-dimethylhydroquinone (18) by acetylation was then subjected to chloromethylation reaction, which afforded a complex mixture of products. In spite of the fact that by changing the conditions of temperature, solvent and reagents, a complex mixture always resulted, it was felt to abandon the route.

Having failed to introduce methyl group on hydroquinone (18), by orthoalkylation in vapour-phase, it was thought worthwhile to study ortho alkylation by vapour-phase on phenols using methanol and a suitable catalyst. In this connection the selection of starting material was of great importance. m-Cresol or 2,5-dimethylphenol (20) are the starting materials of choice. Since m-cresol on orthoalkylation

by vapour-phase would lead to a complex mixture of mono, di and trimethyl derivatives coupled with its high cost, 2,5-dimethylphenol was explored.

Accordingly, 2,5-dimethylphenol (20) was prepared from p-xylene as follows:

Treatment of p-xylene with sulfuric acid at reflux temperature and then with sodium hydroxide at 10°C gave p-xylene sulfonic acid sodium salt (19) in 90% yield. The sodium salt was then treated with sodium hydroxide-potassium hydroxide mixture at molten temperature giving rise to p-xylenol[23] (20) m.p. 74.5°C in 80% yield whose properties were identical with reported data.

It is well known that phenols or substituted phenols having a hydrogen ortho to the hydroxyl group can be selectively methylated in vapour phase using methanol and a suitable catalyst[22]. Several catalysts such as MgO, $MgO.UO_3$, $MgO.UO_3.B_2O_3$, $AlCl_3$, γ-Al_2O_3, $CuO.CrO_3$, CuO.MgO etc. are known in the literature[24-26]. In the present study, CuO.MgO-MnO was selected as the catalyst for the reasons that it could be prepared easily and moreover the life of the catalyst is long.

CuO.MgO.MnO was prepared from basic magnesium carbonate, manganese trioxide and copper nitrate as follows[27]. The aqueous suspensions of basic magnesium carbonate, copper oxide and manganese trioxide were mixed and the resulted thick

slurry was dried in the oven overnight at 100°C. The dry powder obtained was calcined in the furnace at 550°C under the atmosphere of nitrogen for 3 hr to give dark brown powder of CuO.MgO.MnO catalyst which was pelletised, crushed and sieved (mesh size 10-22).

The unit (Fig.1) for catalytic vapour phase methylation consisted of a preheater, reactor and a product collecting vessel. Nitrogen was used as a carrier gas. The preheater was packed uniformly with porcelain beads and wound with nichrome wire (outside) in order to ensure uniform heating. The preheater tube was continued with the reactor tube packed with the catalyst in the middle and porcelain beads (to fill the rest of the tube) and enclosed in the furnace. Both the preheater and the reactor was provided with the arrangement of the thermocouple and the temperature was maintained at 300° (preheater) and 400° (reactor). The reactor was in turn fitted downward with an efficiently cooled water condenser which was followed by a product collecting vessel (receiver) attached with one more cold water circulating condenser.

When the reaction mixture is injected to this unit by feed pump it vapourises in the preheater, passes through the reactor tube (catalyst), condenses in the condenser and finally collects in the receiver which is removed through the stopcock.

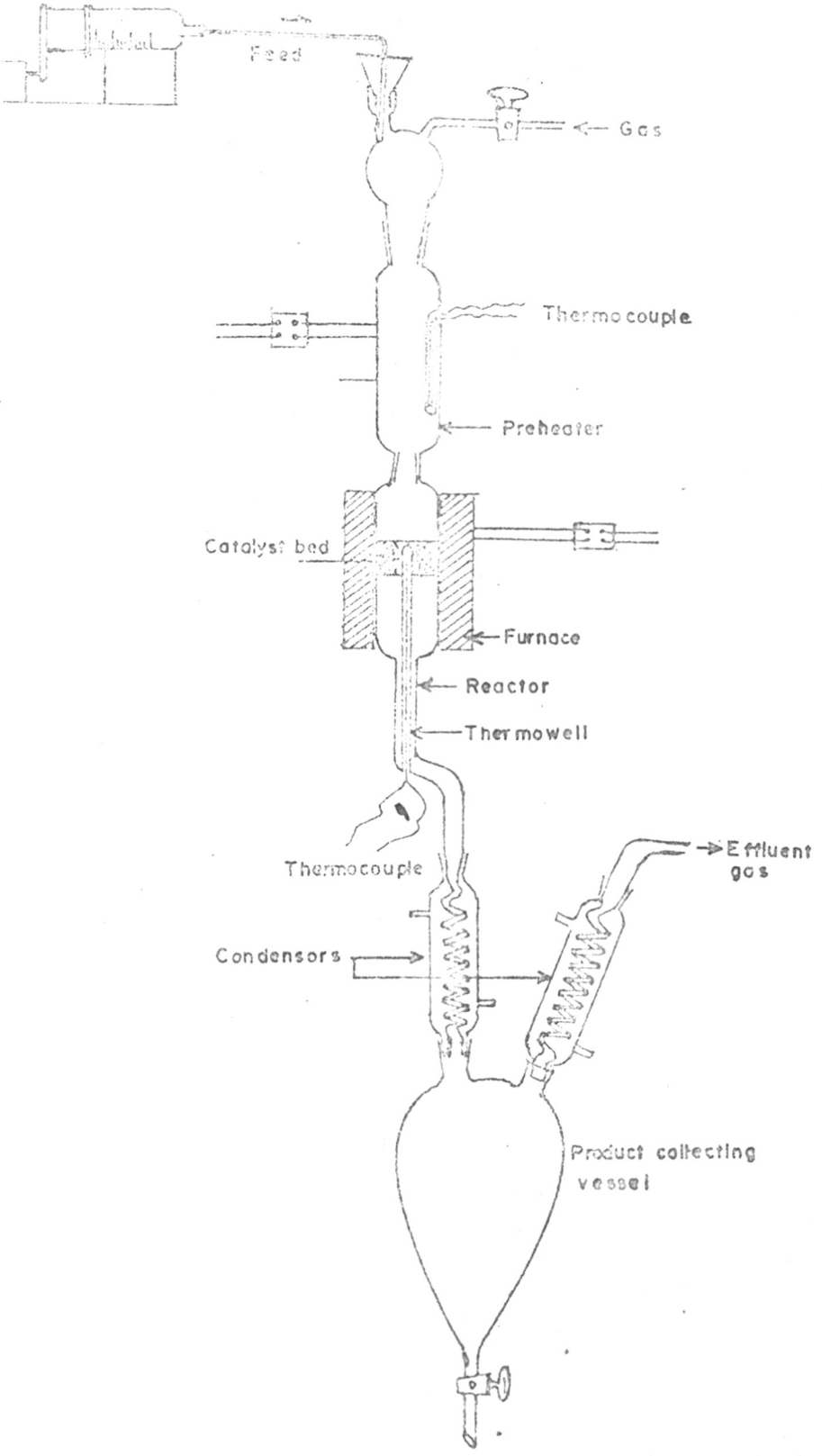


Fig.1 EXPERIMENTAL SET-UP FOR CATALYTIC VAPOUR PHASE REACTION

After setting up the unit at the desired temperature and catalyst, a mixture of methanol and 2,5-dimethyl phenol (20) in the ratio of 50:1, was injected into the preheater with a rate of 25 ml/hr. The product obtained was the required 2,3,6-trimethyl phenol (21) m.p. 63°C in 80% yield. The spectral and physical data were identical with the reported values[17] (vide Experimental).

Oxidation of 2,3,6-trimethyl phenol (21) was effected with oxygen using salcomine as catalyst in dimethylformamide to give the trimethylbenzoquinone (22) whose properties were similar to that of the reported compound[13].

The final conversion of the benzoquinone 22 to the required 2,3,5-trimethylhydroquinone (10) was conveniently effected with sodium dithionate as the reducing agent.

GENERAL REMARKS

Melting points are uncorrected. IR spectra (λ_{max} in cm^{-1}) were recorded in nujol or neat on a Perkin-Elmer Model 683 spectrophotometer with sodium chloride optics.

^{1}H-NMR spectra were obtained on Varian T-60 or Varian FT-80A in $CDCl_3$ or CCl_4 or DMSO-D_6 solutions containing TMS as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS.

Mass spectra were run on AEI MS 30 double beam mass spectrometer or CEC 21-110B spectrometer.

All solvents and reagents were purified and dried by standard techniques.

Solvents were removed on rotary evaporator at temperatures between 40-50°.

Progress of the reactions were checked by TLC on 0.2 mm layers of silica gel, using iodine chamber for visualisation.

EXPERIMENTAL

2,6-Dimethyl-1,4-benzoquinone (17)

A mixture of 2,6-dimethyl phenol 16 (12.2 g, 100 m.mol), salcomine (1.25 g, 0.38 m.mol) and dimethyl formamide (20 ml) was taken in a 50 ml, three-necked round bottomed flask. Oxygen was bubbled for 1 hr with stirring, after which it was poured into acidic ice-cold water. The separated orange yellow beautiful needles were filtered, dried and weighed to give 11 g (80.8%) of 2,6-dimethyl-1,4-benzoquinone (17) m.p. 71-72° (lit.[17] m.p. 72-73°C). ^{1}H-NMR (CCl_4): 2.00 (s, 6H, 2X $-CH_3$), 6.30 (s, 2H, olefinic). IR: 1600, 1630 cm^{-1} (quinone carbonyl). M^+ 136.

Analysis: Calculated for $C_8H_3O_2$: C, 70.81; H, 6.29; Found: C, 70.88; H, 5.38%.

2,6-Dimethyl-1,4-hydroquinone (18)

To a stirred solution of 17 (6.8 g, 50 m.mol) and methylene dichloride (100 ml) was added a saturated solution of sodium dithionite (11.5 g, 65.5 m.mol) at room temperature. After 30 min. silvery flakes started depositing on the sides of the flask. Stirring continued for another 30 min. The separated crystals were filtered, washed and dried to give 4 g of compound 18. The evaporation of the organic layer furnished 1.15 g after crystallisation from water, giving a total yield of 5.15 g (74%), m.p. 147-9° (lit.[29]

m.p. 149-51°). ^{1}H-NMR (DMSO-D_6): δ 2.07 (s, 1H, -OH, D_2O exchangeable), 8.36 (s, 1H, -OH, D_2O exchangeable). IR: 3240 cm^{-1} (-OH).

Analysis: Calculated for $C_8H_{10}O_2$: C, 69.90; H, 7.14; Found: C, 69.86; H, 7.24%.

Basic Magnesium carbonate

Commercial magnesium carbonate (100 g) was suspended in water (1000 ml), heated to 70-80°C for about 1.25 hr with mechanical stirring. This was cooled to room temperature filtered and dried in the oven at 100°C for 12 hr to give a dry, loose powder of basic magnesium carbonate.

Copper oxide - Magnesium oxide - Manganese oxide (CuO.MgO.MnO)

To a stirred suspension of basic magnesium carbonate (25 g), dimanganese trioxide (2 g) in water (50 ml) was added slowly (20-30 min) a solution of copper nitrite [$Cu(NO_3)_2$, 15 g] in water (30 ml). Lot of effervescence was noticed during the addition. Stirring continued for 30 min. after the addition. This thick slurry was poured into a trough and dried at room temperature. The resulted cake (33 g) was powdered and calcined in a furnace at 550°C under nitrogen gas for 3 hr and then cooled to room temperature. The dark brown, fine powder obtained was pelletised, crushed and sieved (10-22 mesh).

Attempted Preparation of 2,3,5-trimethyl-1,4-hydroquinone (10)

The unit for the vapour phase catalytic reaction was set up as described in the discussion, using copper oxide-magnesium oxide-manganese oxide (8 g) as the catalyst. A mixture of 2,6-dimethylhydroquinone (18) (2 g) and methanol (100 ml) was injected to the preheater at the rate of 25 ml/hr. The preheater and reactor was maintained at a temperature of 350°C and 450°C respectively. The product collected in the receiver was removed every 0.5 hr. After the addition of the reaction mixture, methanol (25 ml) was injected at a fast rate (10 min.) in order to wash the whole system. The reaction product collected from the receiver was concentrated, taken in chloroform, dried and evaporated the solvent to give orange yellow needles m.p. 69-70°. From the Rf value and other spectral data, it was confirmed that the product obtained was not the expected 2,3,5-trimethylhydroquinone, but 2,6-dimethyl benzoquinone (17)[28].

2,5-Dimethyl phenol (20)

A mixture of p-xylene (53 g, 500 m.mol), conc. sulfuric acid (50 g, 500 m.mol) and xylene (dry) was refluxed at 140°C azeotropically, with stirring for 4 hr till no water was separated. Solvent was removed by distillation and the reaction mixture was cooled to 10° and neutralised by aqueous sodium hydroxide. The separated

alkali salt was filtered and dried to give 100 g (96%) of p-xylene-sodium sulfonate (19).

Sodium hydroxide (40 g, 1 mol) and potassium hydroxide (56 g, 1 mol) were heated to 330-340°C in an iron pot to a uniform melt. The above alkali salt 19 was added to this sodium hydroxide-potassium hydroxide melt with agitation. It was mixed thoroughly and heated for 1 hr at that temperature, cooled to room temperature and then dissolved in water (500 ml). The aqueous layer was cooled to 0°C and acidified with conc.sulfuric acid (100 g). The separated solid was filtered, washed with brine and dried at low temperature to give 55 g (80%) of 2,5-dimethyl phenol (20) m.p. 72° (lit.[23] m.p. 71-73°). ^{1}H-NMR ($CDCl_3$): δ 2.23 (s, 3H, $-CH_3$), 2.32 (s, 3H, $-CH_3$), 4.57 (br.s, 1H, -OH, D_2O exchangeable), 6.59 (s, 1H, ArH), 6.53 - 6.71 (d, 1H, ArH), 6.68 - 7.07 (d, 1H, ArH). IR: 3600 cm^{-1} (-OH) M^+ 122,

Analysis: Calculated for $C_8H_{10}O$: C, 78.68; H, 8.19; Found: C, 78.65; H, 8.20%.

2,3,6-Trimethyl phenol (21)

The unit used for the vapour phase reaction was the same as described in the discussion (Fig.1). The catalyst used was CuO.MgO.MnO (8 g). A mixture of 2,5-dimethyl phenol (2 g), and methanol (100 ml) was injected to

the preheater at a rate of 25 ml/hr. The vapours were passed through the catalyst bed condensed in the condenser and was collected in the collecting vessel. The product collected was removed after 0.5 hr. and checked by TLC (benzene and traces of Et_3N). All the fractions were mixed, methanol was removed by slow distillation, taken the product in chloroform, dried over anhydrous sodium sulphate and removed the solvent again by distillation. The crude cream-coloured shining needles of 21 weighed 1.944 g (80%), m.p. 63°C (lit.[28] m.p. 63-64°) was pure enough to proceed with the next step. ^{1}H-NMR (CCl_4): δ 2.10 (s, 3H, $-CH_3$), 2.20 (s, 3H, $-CH_3$), 2.28 (s, 3H, $-CH_3$), 4.61 (s, 1H, -OH, D_2O exchangeable), 6.41 - 6.86 (q, 2H, -ArH). IR: 3420 cm^{-1} (OH) and M^+ 136.

Analysis: Calculated for $C_9H_{12}O$: C, 79.41; H, 8.82; Found: C, 79.49; H, 8.86%.

2,3,5-Trimethyl-1,4-benzoquinone (22)[13]

A mixture of 2,3,6-trimethyl phenol (21) (1.36 g, 0.10 m.mol) and salcomine (25 mg, 0.38 m.mol) were taken in dry dimethyl formamide (5 ml) in a round bottomed flask to which a balloon filled with oxygen was connected. The reaction was kept rocking for 1 hr, after 1 hr the reaction mixture mixture/was poured over acidic (dil.HCl) ice-cold water, extracted with hexane, washed with water, dried over sodium sulphate and the solvent was evaporated carefully to give

1.215 g (81%) of 22 as an orange volatile liquid. ^{1}H-NMR (CCl_4): δ 2.00 (s, 9H, 3X CH_3), 6.21 (s, 1H, olefinic). IR: 1650 and 1610 cm^{-1} (quinone carbonyl). M^+ 150.

2,3,5-Trimethyl-1,4-hydroquinone (10)

To a solution of 22 (750 mg, 5 m.mol) in methylene chloride (20 ml), a saturated solution (aqueous) of sodium dithionite (1.150 g, 5.125 m.mol) was added with constant stirring. After 30 min. silvery white flakes were deposited on the sides of the flask. This was filtered, washed with cold water, dried and weighed to give 500 mg of 10. The organic layer was separated, washed with water, dried over sodium sulphate (anhydrous), evaporated the solvent, and crystallised from water to give 185 mg, yielding a total weight of 685 mg (90.8%) of 10 m.p. 170-71°C (lit.[13] m.p. 170-71°C). ^{1}H-NMR (DMSO-D_6): δ 2.00 (s, 3H, -CH_3), 2.07 (s, 6H, 2X -CH_3), 6.34 (s, 1H, ArH), 7.28 (s, 1H, OH, D_2O exchangeable), 8.25 (s, 1H, OH, D_2O exchangeable). IR: 3280 cm^{-1} (OH). M^+ 152.

Analysis: Calculated for C, 71.05; H, 7.89; Found: C, 71.06; H, 7.90%.

REFERENCES

1 H.A. Harper
Review of Physiol. Chem., pp.64-68 (1961).

2 A. Nason and Lehman
J. Biol. Chem., 222, 511 (1956).

3 R.G. Gross
The Roche Courier, Vol.XVI, 6 (1965).

4 H. Mayer, P. Schudel, R. Ruegg and O. Isler
Helv. Chim. Acta, 46, 650 (1963).

5 L.I. Smith and J.A. Sprung
J. Am. Chem.Soc., 65, 1276 (1943).

6 P.Karrer, A. Geiger, H. Rentsohter, E. Zbinden and A. Kuglar
Helv. Chim. Acta, 26, 1741 (1944).

7 O. Isler and O.Wiss
Vitamins and Hormones, 17, 53 (1959).

8 D.B. McCormick, L.D.Wright, Eds.
Methods in Enzymology, Academic Press, New York, 1971, Vol.18, Part C, pp.492-95.

9 G. Saucy and R. Marbet
Helv. Chim. Acta 50, 2091 (1967).

10 W. Kimel, J.D. Surmatis, J. Weber, G.O. Chase, N.W. Sax and A. Ofner
J. Org. Chem. 22, 1611 (1957).

11 W.T. Coldwell and T.R. Thompson
J. Am. Chem. Soc. 61, 765 (1939).

12 K.Sato and S. Abe
J. Org. Chem. 28, 1928 (1963);
Jap. Patent Nos. 23558 and 23559 (1965);
C.A. 62, 10379e (1965).

13 W.J. Burke, J.A. Warburton, J.L. Bishop and J.L. Bills
J. Org. Chem. 26, 4669 (1961).

14 A. Pongratz and K.L. Zirm
Montash. Chem. 83, 13 (1952);
Austrian Patent No.176,837 (1953).

15 C.K. Kui, J. Vitaminol, Japan I, 8-12 (1954);
C.A. 50, 320e (1956).

16 L.I. Smith
J. Am. Chem. Soc., 56, 472 (1934).

17 P.A. Wehrli, R.I. Fryer, F. Pigott, G. Silverman
J. Org. Chem. 37, 2340 (1972).

18 W.H. Sebrell, Jr. and Roberts Harris, Eds.
"The Vitamins" Academic Press,New York, 1972,
Vol.V, pp. 204-209.

19 Diehl and C.C. Hack
Inorg. Syn. 3, 196 (1950).

20 C.R.H.I.Dejonge, H.J. Hajeman, G. Hoentjen and
W.J. Mijs
Org. Syn. Vol. 57, p.78 (1977).

21 H.M. VanDort and H.I. Geursen
RUCUEL, 86, 520-26 (1967).

22 K. Motoo, O. Kazushi, K. Akihide, K. Mokoto
(Mitsui Toatsu Chemicals, Inc.) Jpn. Kokai
Tokkyo Koho 7990, 129 (1979);
C.A. 91: 211075V (1979).

23 Chapman and Hall
Dictionary of Organic Compounds, Vol.2, p.2201 (1982).

24 Funakoshi, Wataru', Urasaki,Takamori',
Oka, Isao', Shima, Takeo;Japan Kokai 7407,235 (Cl.16C411.12)
22 Jan 1974; C.A. 80: 1205349 (1974).

25 Ruetgerswerke und Teerverwertung A.-G
(By Max Froitzheim, Karl F. Lang, Ludwig Rappen,
Erich Schweym and Johannes Turowski),
Ger. 1,254,155 (Cl.Co7C) Nov.16, 1967;
C.A. 68:104725.

26 Shell Internationale Research Maatschappij
N.V. Neth. Appl. 6713,253 (Cl CO7C) 01 Apr 1968;
Ger. Appl. 30 Sept. 1966, 10 PP; C.A. 69:96221W.

27 Raymond E. Kinle, D.F. Othemers
Encyclopodia of Chemical Technology Vol.8, p.596.

28 Chapman and Hall
Dictionary of Organic Compounds Vol.2, 2088.

29 Chapman and Hall
Dictionary of Organic Compounds, Vol.2, p.2079 (1982).

CHAPTER-II

SYNTHESIS OF 1-TRIACONTANOL

Extensive screening using much improved bioassay techniques has uncovered many naturally occurring plant constituents which possess plant growth regulating properties. Both these experimental studies and basic research have led to the use of synthetic growth substances in agriculture where they have assumed an importance equal to that of pesticides and fungicides. The growing consumption of plant growth regulators all over the world has been spurred by the benefit of higher crop yields of better quality combined with a reduction in labour costs.

A definition of plant growth substances is indeed a prerequisite to any study of their field. Plant regulators are defined[1] as organic compounds other than nutrients which in small quantities promote, inhibit, or otherwise modify any plant physiological process. Plant hormones are regulators produced by plants, which in low concentrations, regulate plant physiological processes. The term "hormone" correctly used is restricted to naturally occurring plant products. The term "regulator" however, is not necessarily restricted to synthetic compounds but can also include hormones. The word "regulator" may further be defined by adding to it the name of the process that it influences. For example, growth regulators are regulators that affect growth.

Naturally occurring plant growth substances can be broadly categorized into two types[2]. The first type includes the well known plant hormones. They are distributed widely and in fact are probably present in all higher plants. They have high activity, specific action and function in the regulation of growth and differentiation of plants. They include the auxins, gibberllins, cytokinins, abscisic acid and ethylene.

The second group of natural products, commonly referred to as secondary growth substances, include compounds such as phenols, aliphatic and aromatic carboxylic acids and their derivatives, steroids, terpenoids, amino acids and lipids. Some of these compounds are produced by plants in abundant quantity, but lack growth specificity. Others are present in minute quantities but show high specificity.

Research on modifying plant growth by the use of exogenous growth regulators is rapidly expanding, and consequently the number of commercial and practical uses[3] for these regulators is constantly increasing. Among many other uses other than herbicidal action plant growth regulators can -

promote rooting and propagation of the plant.

initiate or terminate the dormancy of seeds, buds and tubes.

promote or delay flowering.

induce or prevent leaf/or fruit drop (abscission).

control fruit set and further fruit development.

control plant or organ size.

prune the plant chemically.

increase plant resistance to pests.

enhance plant resistance to such environmental factors as temperature, water and air pollution.

prevent post-harvest spoilage.

regulate the chemical composition of plants and the colour of fruit.

influence mineral uptake from the soil.

change the timing of crop development.

It is definitely within the realm of possibility that at some time in the future all plant growth processes will be controlled by plant growth regulators.

Chemical companies have considerable interest in this field due to the potential role of plant growth regulators in positive crop development. Major efforts are being made in commercial and academic research centres to discover and develop simple and new growth regulators.

In 1977 Ries and coworkers[4] made an interesting observation that the application of alfalfa increased

the growth and yield of a number of crop plants. A crystalline substance isolated from the active fraction of alfalfa extract, caused phenomenal increase in crop yields even when sprayed in minute quantities, and was identified by mass spectrum to be n-triacontanol, a naturally occurring long chain alcohol. The response of several plant species to synthetic triacontanol was similar to that of natural triacontanol.

Both water uptake and dryweight enhanced with increasing amount of n-triacontanol applied in nutrient solution or to the foliage with optimum concentration between 0.01 and 0.1 μg/liter. The rapid increase in water uptake indicates that triacontanol affects transpiration but perhaps not directly. Because this alcohol increases the dryweight of test plants both in dark and light, it cannot have an effect on photosynthesis[5]. Ries had speculated that it might function by increasing the uptake of nutrients. Further experiments revealed that the increased growth caused by triacontanol is not simply by water uptake and cell enlargement but by an increase in cell number[6]. Chain length of C_{30} and the presence of terminal OH group appear to be specific for the growth promoting activity of n-triacontanol.

Ries laboratory experiments revealed that tiny amounts of 4 mgs per acre resulted in a 10% to 40% increase in the yields of tomatoes, cucumber, lettuce,

rice, corn and several other crop species.

Earlier methods for the synthesis of n-triacontanol:

Various synthetic methods for the preparation of n-triacontanol may be conveniently classified as those -

a) using β-ketoester intermediate;

b) employing organometallic compounds;

c) utilising enamine reaction and

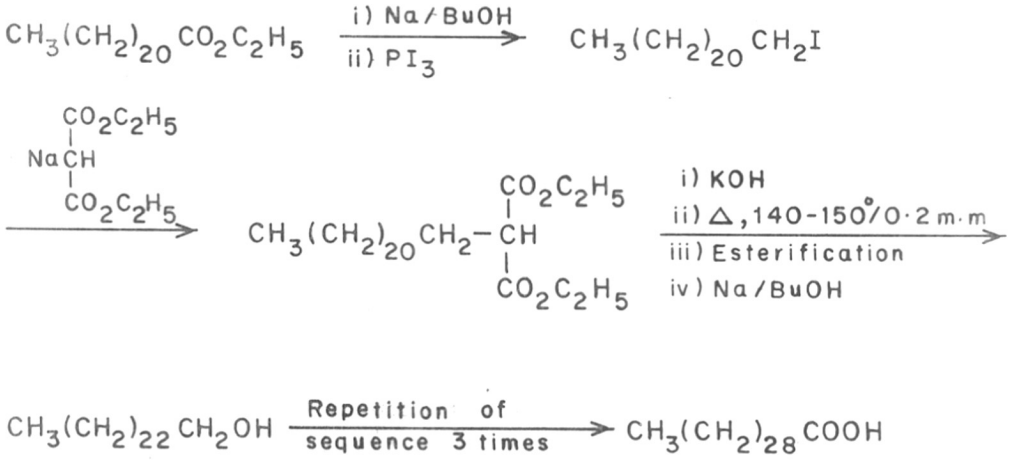
d) via metathesis of olefins.

a) β-keto ester intermediate:

Syntheses reported from the laboratories of Blyberg[7], Schuette[8], Robinson[9] and Watanabe[10] involved the use of β-ketoester as intermediate. For instance, Blyberg and Ulrich[7] synthesized n-triacontanoic acid starting from ethyl docosonate by repeating malonic ester synthesis sequence four times (Scheme-1). Schuette and his coworkers[8] adopted similar strategy as reported earlier[7] except a slight modification in the reduction reaction (Scheme-2), where H_2-copper-chromite was employed for the reduction. However both the syntheses suffered from poor yields. Robinson[9] synthesised triacontanol employing ethyl acetoacetate as the starting material, and carried out successive alkylation and acylation with ethyl-11-bromo undecanoate and octadecanoyl chloride respectively using sodium in alcohol as base (Scheme-3). Subsequent hydrolysis and

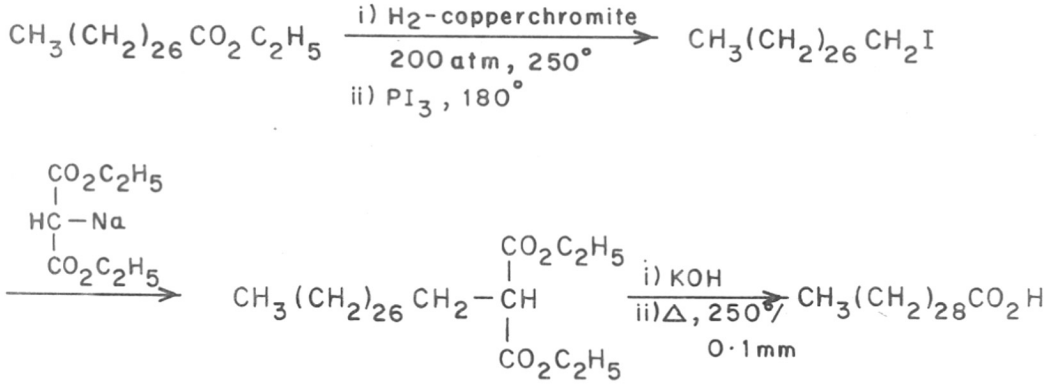
SCHEME - 1

Blyberg and Ulrich (1931)



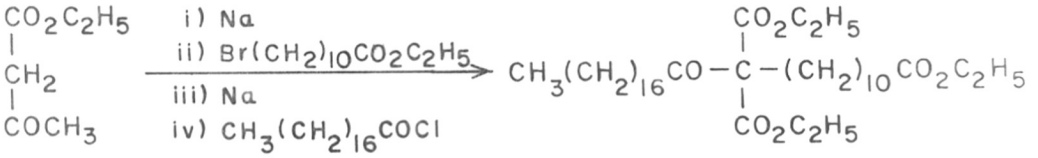
SCHEME - 2

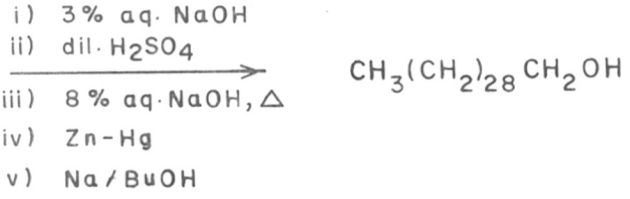
Schuette et al (1943)



SCHEME-3

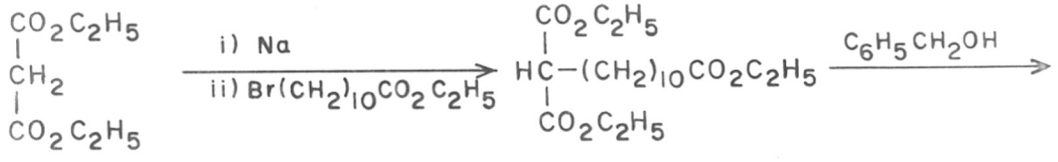
Robinson (1934)

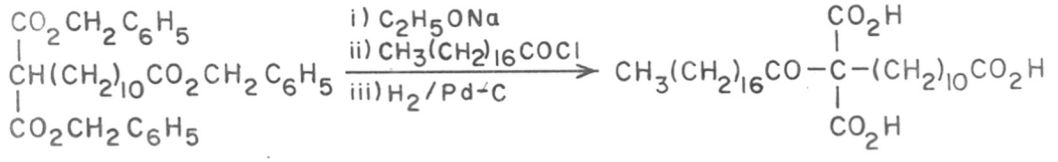


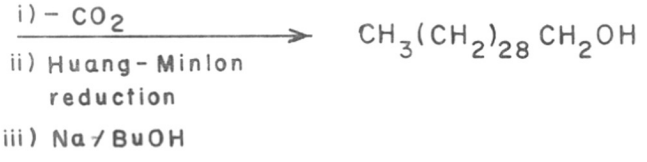


SCHEME-4

Watanabe et al. (1961)







reduction of the resulted product gave n-triacontanoic acid. Robinson's synthesis suffered from the disadvantage of low yields and the separation of the product was difficult. It may be caused by hydrolysis in two directions with partial elimination of the wrong 'acyl' group.

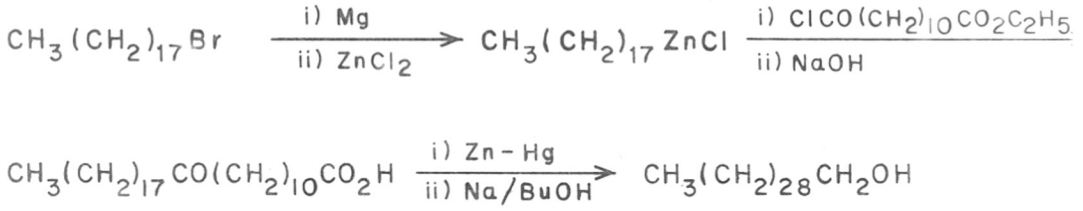
In order to circumvent the problems during ester hydrolysis as observed in the above synthesis Watanabe[10] substituted ethyl ester with benzyl ester (Scheme-4), before acylation step. This was then subjected to hydrogenolysis to give the triacid. Ketoacid thus obtained was reduced by employing Huang-Minlon method[11] and was further modified to triacontanol.

b) Organometallic intermediates

Methods for the preparation of n-triacontanol reported from the groups of Jones[12], Schildknecht[13] and Oura[14] are included in this subheading. Jones et al.[12] utilised a method involving organo zinc reagent where 12-oxotriacontanoic acid was prepared (Scheme-5) by employing octadecylzinc chloride and ω-carboethoxy-undecanoyl chloride. It was then transformed into triacontanol by reduction of carbonyl (Clemmensen) and carboxylic acid (Na-BuOH) functionalities. Later Schildknecht and coworkers[13] adopted the similar method reported by Jones, however, they differed in the final reduction where Huang-Minlon method[11] and lithium-aluminium hydride (Scheme-6) were employed.

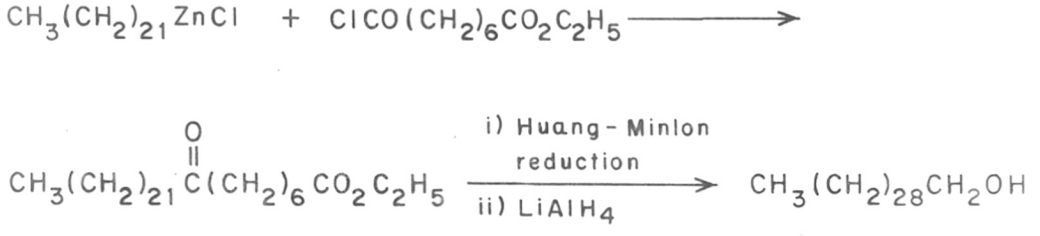
SCHEME-5

Jones et al. (1947)



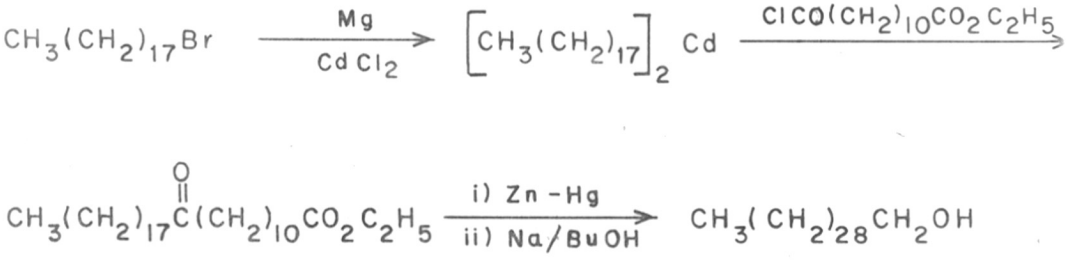
SCHEME-6

Schildknecht et al. (1964)



SCHEME-7

Oura et al. (1956)



By taking the advantage of the reactivity of cadmium reagent Oura et al.[14] reported a synthesis of (Scheme-7) n-triacontanol, where 12-oxotriacontanoic acid was prepared by the reaction of dioctadecylcadmium and ω-carboethoxyundecanoylchloride.

c) Enamine reaction

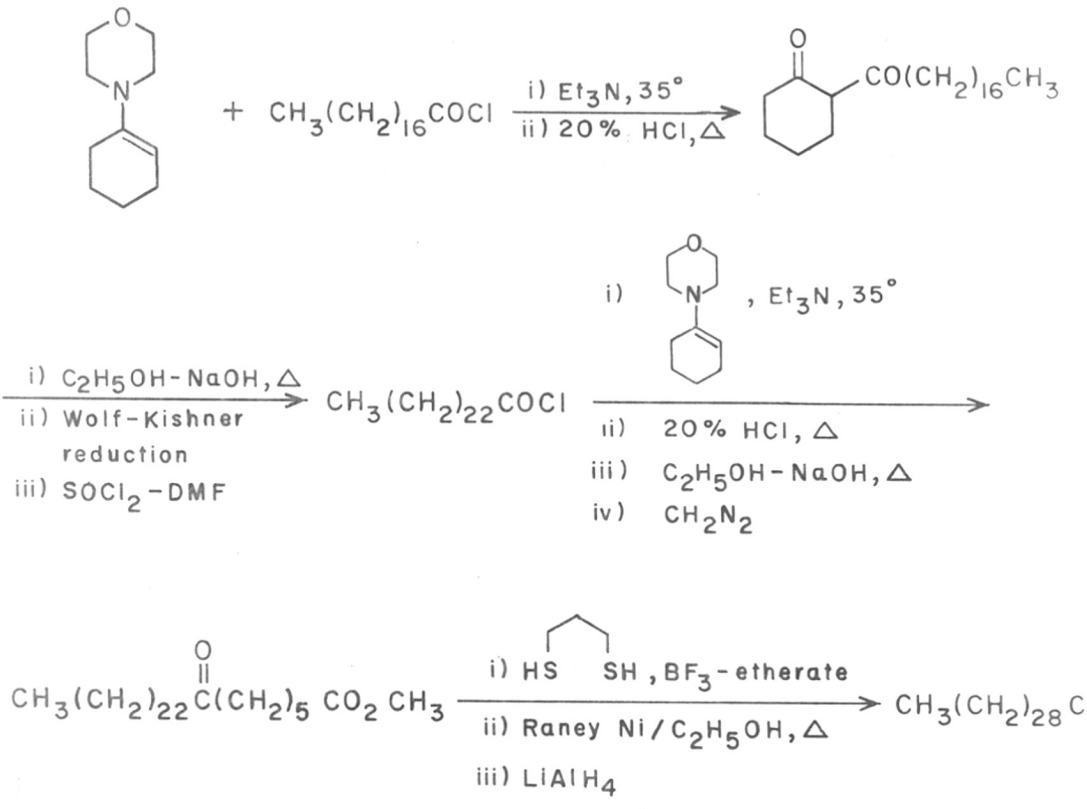
Rama Rao et al.[15] and Hunter et al.[16] made use of enamine intermediates for the synthesis of n-triacontanol. The main feature of Rama Rao et al.[15] synthesis (Scheme-8) was acylation of 1-morpholine cycohexene with octadecanoyl chloride and converting the resulted product into tetracosanyl chloride. It was then subjected to acylation reaction with a second molecule of 1-morpholinecyclohexene and further transformed into n-triacontanol. In Hunter et al.[16] synthesis (Scheme-9) 1-morpholinocyclododecene was acylated with octadecanoyl chloride and hydrolysed to afford 13-oxo triacontanoic acid, which was transformed into n-triacontanol by sequential reduction.

d) Via metathesis of olefins

An approach via metathesis of olefins utilised by Maruyama et al.[17] (Scheme-10) involved hexadecene to give a C_{30} olefin which was then subjected to successive hydroboration-isomerisation, and oxidation to give n-triacontanol. In this synthesis varying amounts of secondary alcohol was formed as a byproduct. This

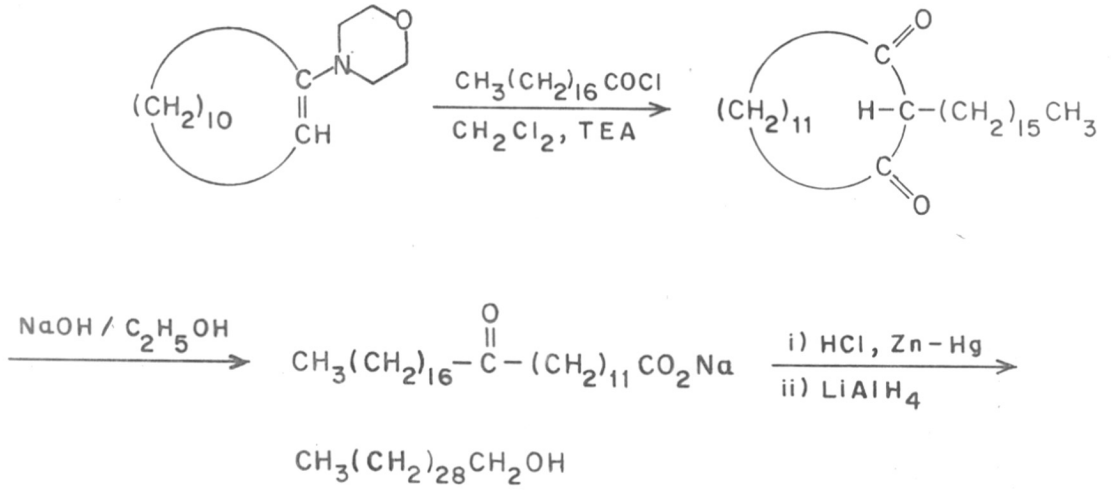
SCHEME-8

Rama Rao et al (1981)



SCHEME-9

Hunter et al (1981)



SCHEME-10

Maruyama et al. (1980)

$$CH_3(CH_2)_{13}CH = CH_2 \xrightarrow[80°,\ 5h]{\text{trichloroethylene}\ WCl_6, CH_3CN, Bu_4Sn} CH_3(CH_2)_{13}CH = CH(CH_2)_{13}CH_3$$

$$\xrightarrow[70°,\ 3h]{BH_3 - THF} CH_3(CH_2)_{27}CH_2\ CH_2\ BH_2 \xrightarrow{H_2O_2 - NaOH} CH_3(CH_2)_{28}CH_2OH$$

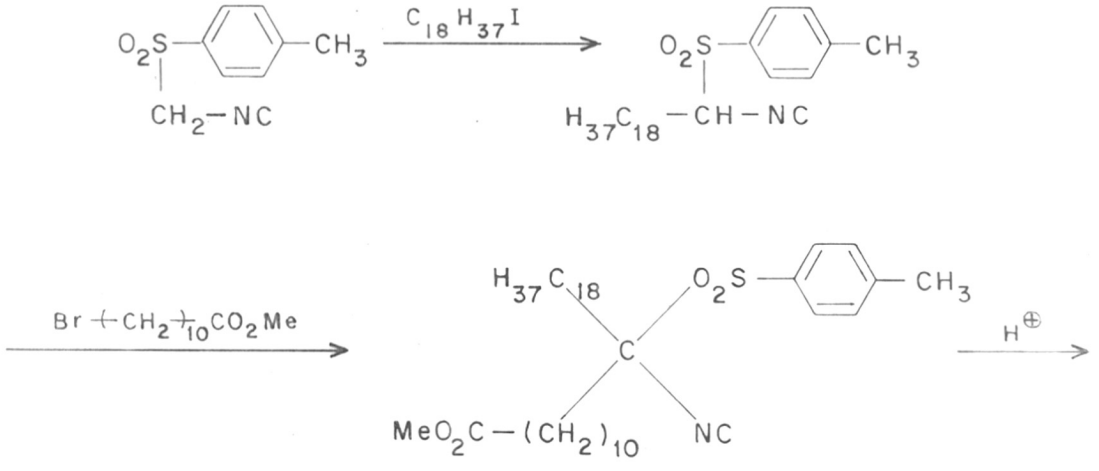
SCHEME-11

Gibson (1982)

$$C_{14}H_{29}CH = CH\ C_{14}H_{29} \xrightarrow[ii)\ t\text{-}BuOOH]{i)\ CP_2ZrHCl} CH_3(CH_2)_{28}\ CH_2OH$$

SCHEME 12

Rama Rao et al 1983



problem was overcome by Gibson[18] where C_{30}-olefin was treated with a zirconium reagent in preference to borane in hydrometallation step (Scheme-11).

Recently in this laboratory n-triacontanol has beenn synthesised by a different approach[19] (Scheme-12) based on the two successive alkylations of tosylmethylisocyanide [TosMIC]. TosMIC was monoalkylated with stearyl iodide and the second alkylation was performed using methyl-11-bromoundecanoate. Subsequent hydrolysis of the resulting product and reduction of the keto ester gave 1-triacontanol.

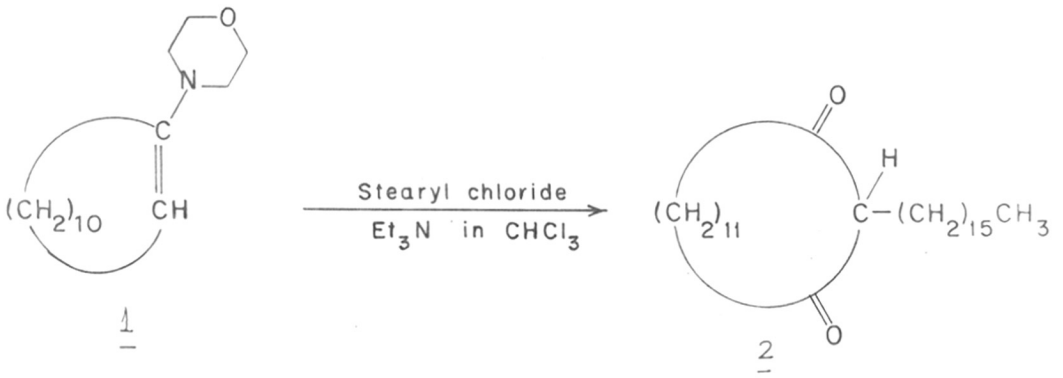
PRESENT WORK

Recently there has been considerable interest in the potential use of triacontanol as plant growth regulator. As a result many syntheses[15-19] have appeared in the literature and it is estimated that only 4.5 tonnes of pure triacontanol would be needed for India's 132 million hectares of arable land[20].

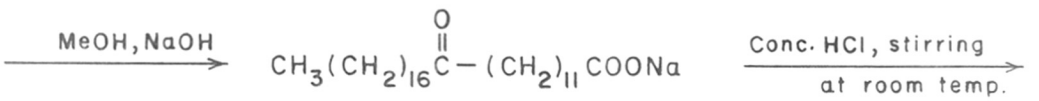
A project has been undertaken in these laboratories for the industrial preparation of n-triacontanol by using comparatively inexpensive starting materials. In the present strategy it is anticipated to prepare triacontanol in large scale by a modified literature[16,21] procedure from easily available cyclododecanone and stearic acid (Scheme-13) in pure form.

Accordingly, 1-morpholinocyclododecene[21](1) was prepared in 93% yield (on the basis of the consumed cyclododecanone) by vigorously refluxing a mixture of cyclododecanone, morpholine and toluene p-sulfonic acid using Dean-Stark apparatus for 32 hrs. 1 was then acylated with stearoyl chloride using triethylamine as a base at room temperature for 18 hrs. The colourless crystals obtained were identified as 2-hexadecyl-1,3-cyclotetradecane dione(2) by comparing with the available data. IR spectrum showed a carbonyl absorption at 1700 cm^{-1}

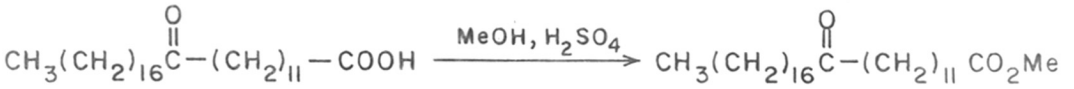
SCHEME 13



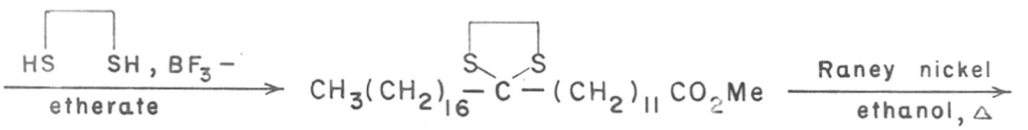
1 2



3



4 5



6

7 8

while mass spectrum revealed molecular ionpeak at m/e 448.

When this cyclic product 2 was treated with sodium hydroxide in methanol at reflux temperature, sodium-13-oxotriacontanoate 3 was obtained in 90% yield. IR spectrum showed two absorptions at 1720 and 1575 cm^{-1} corresponding to C=O and COONa groups. The sodium salt was hydrolysed to 13-oxo-triacontanoic acid(4)by stirring with conc. hydrochloric acid at room temperature (85% yield). Mass spectrum revealed its molecular ion peak at m/e 466. IR spectrum showed the carbonyl absorption at 1700 and 1710 cm^{-1}.

Esterification of 4 with methanol and sulfuric acid at reflux temperature gave the keto ester 5 in 90% yield. m.p. 74-75°. In IR spectrum the C=O of the ketone appeared at 1700 cm^{-1} and the C=O of the ester appeared at 1730 cm^{-1}. Molecular ion peak appeared at m/e 480,confirmed the structure 5. The ester 5 was smoothly converted into dithiane 6 in almost quantitative yield by treating with ethanedithiol in presence of BF_3-etherate in chloroform at room temperature. The characteristic dithiane absorption at 920 cm^{-1} and the carbonyl (C=O of ester) absorption at 1745 cm^{-1} were observed in IR spectrum. Molecular ion peak revealed at m/e 556 while in NMR spectrum the chemical shifts appeared

at the expected positions.

Reductive desulfurisation of the dithiane group with Raney nickel in refluxing ethanol furnished methyl triacontanoate 7 in almost quantitative yield. Compound 7 was then subjected to LAH reduction in THF to give n-triacontanol whose physical and spectral data were identical with reported sample[15].

EXPERIMENTAL

1-Morpholino-1-cyclododecene[21] (1)

A mixture of cyclododecanone (182 g, 1 mole), morpholine (174 g, 2 moles, freshly distilled), toluene-p-sulfonic acid (5 g) and toluene (300 ml, dried over sodium) was vigorously refluxed for 24 hr using a Dean-Stark water separator. When there was no separation of water the reaction mixture was cooled to 50°C and added a second lot of toluene-p-sulfonic acid (3 g) and refluxed for 12 hr more, till there was no separation of water. The Dean-Stark apparatus was replaced by a distillation condenser. Toluene and the excess morpholine were distilled under vacuum and the residual brown viscous oil was distilled under vacuum, b.p. 125-30°/ 2 mm, 72 g of cyclododecanone, b.p. 150-60° at 1 mm, 120 g (93.8%) of morpholino cyclodecene.

Stearoyl chloride

A solution of thionyl chloride (119 g, 1 mol) and dry benzene (100 ml) was added dropwise at room temperature to a stirred suspension of stearic acid (142 g; 500 m.mol) in dry benzene (250 ml) during 30 min. After the addition, the reaction mixture was stirred at room temperature for another 30 min. and slowly the temp. was raised to 75°C and heated at that temp. for 2 hr and then refluxed at 90°C for 2 hr. Excess thionyl chloride and benzene were removed under reduced pressure and the residue on distillation

provided stearic acid chloride 150 g (99%), b.p. 185°/2 mm (lit.[22] b.p. 215°/13-15 mm). IR (liquid film) 1805 cm^{-1} (C=O of acid chloride).

2-Hexadecyl-1,3-cyclotetradecane dione (2)

To a well stirred solution of 1 (100.4 g, 400 m.mol) and triethylamine (80.8 g, 800 m.mol) in chloroform (100 ml), cooled at 0°C, was added dropwise stearoyl chloride (121.4 g; 400 m.mol) in chloroform (100 ml) during a period of 1 hr. After the addition, the reaction mixture was brought to room temperature and stirred for 18 hr. Added 100 ml more of chloroform and washed the reaction mixture twice with 1.2N HCl (150 ml), sodium bicarbonate and finally with water. The chloroform layer was dried (anhyd. Na_2SO_4) and the solvent was evaporated on a rotavapour. The thick reddish brown oil obtained was solidified and weighed to give 178 g (quantitative yield) of 2, m.p. 60° (lit.[21] m.p. 62-3°) was pure enough to proceed with the next step. ^{1}H-NMR (CCl_4): δ 0.96 (t, 3H, $-CH_3$), 1.26 (br.s,48H, 24X $-CH_2$), 2.26 - 2.93 (m, 4H, 2X $-COCH_2$), 3.18 - 3.22 (t, 1H, -CH). IR: 1700 cm^{-1} (carbonyl of the cyclic dione). M^+ : 448.

Sodium-13-oxotriacontenoate (3)

Sodium hydroxide (90 g, 2.25 mol) was dissolved in methanol (300 ml) by heating and stirring at 55-60°C. To this was added a hot solution of 1,3-cyclotetradodecene dione (2) (112 g, 250 m.mol) in methanol (500 ml) and refluxed for

1 hr. The reaction mixture was cooled, precipitated sodium salt was filtered and pressed as dry as possible. This moist salt was again suspended in methanol, filtered and dried to give 110 g (90%) of 3. IR: 1710 and 1575 cm^{-1} (C=O and COONa).

13-Ketotriacontanoic acid (4)

Sodium salt (3) (48.8 g, 100 m.mol) was suspended in dilute hydrochloric acid (500 ml, 1:1) and stirred for 5 hr at room temperature. The fluffy white amorphous solid was filtered, washed thoroughly with water, dried and crystallised from benzene to give 40 g, (90%) of 4 in colourless plates m.p. 99-100°, ^{1}H-NMR ($CDCl_3$): δ 0.96 (br.s, 3H, $-CH_3$), 1.4 (br.s, 54H, 27X CH_2-), 2.13 - 2.4 (br.s, 1H, OH); IR: 1700, 1710 cm^{-1} (C=O and COOH).

Methyl-13-oxotriacontanoate (5)

13-Ketotriacontanoic acid (23, 3 g, 50 m.mol) in methanol (500 ml) and sulfuric acid (catalytic amount) were refluxed for 10-12 hr. Methanol was distilled and the residue was taken in water, filtered, washed with water, dried and crystallised from petroleum ether to give 18 g (75%) of 5 as colourless needles, m.p. 78-80°C, ^{1}H-NMR ($CDCl_3$): δ 0.90 (dist. t, 3H, $-CH_3$), 1.3 (br.s, 48H, 24X $-CH_2$-), 2.1 - 2.5 (m, 6H, 3X $COCH_2$-), 3.70 (s, 3H, -OMe); IR: 1740 and 1705 cm^{-1} (ester and ketone carbonyl); M^+ 480.

Analysis: Calc. for $C_{31}H_{60}O_3$: C, 77.5; H, 12.5; Found: C, 77.41; H, 12.48%.

Methyl 11-(octadecan-1,2-dithiolane-2-yl) undecanoate (6)

To a stirred solution of the keto ester (5) (4.80 g, 10 m.mol) and 1,2-ethanedithiol (0.94 g,10 m.mol) in dry chloroform (25 ml),was added gradually borontrifluoride-etherate (1.56 g, 10 m.mol) in dry chloroform (5 ml) over a period of 20 min. at room temperature. The reaction mixture was stirred at room temperature for 24 hr quenched with water and extracted with chloroform, the organic layer was washed successively with water, 5% aqueous potassium hydroxide, brine and dried over (Na_2SO_4). The residue obtained after the removal of solvent under reduced pressure, furnished 6 (quantitatively) as yellowish brown viscous oil. ^{1}H-NMR: δ 0.90 (dist.t, 3H, $-CH_3$), 1.33 (br.s, 52H, 26X CH_2-), 1.97 (dist.t, 2H, $-CH_2$ CO_2Me), 2.1 - 2.3 (m, 2H, $-CH_2$), 2.6 - 2.9 (m, 4H, 2X $-SCH_2$-), 3.66 (s, 3H, -OMe); IR: 915 cm^{-1}, 1740 cm^{-1}; M^+ 556.

Methyl triacontanoate (7)

A solution of (6) (2.78 g, 5 m.mol) in ethanol (50 ml) was heated at reflux with a suspension of active Raney nickel (6g, 12 ml of settled suspension) for 6 hr. The reaction mixture was cooled, the suspension was filtered and washed thoroughly with hot ethanol. Ethanol was removed under reduced pressure to furnish 2.09 g (90%) of (7) as a

solid, which was crystallised from ethanol into colourless plates, m.p. 71° (lit.[15] m.p. 71.5°). ^{1}H-NMR ($CDCl_3$): δ 0.91 (dist.t, 3H, $-CH_3$), 1.33 (br.s, 56H, 28X $-CH_2-$), 2.1 - 2.4 (m, 2H, $-CH_2-$), 3.70 (s, 3H, $-OCH_3$); IR: 1740 cm^{-1}; M^+ 466.

Analysis: Calculated for $C_{31}H_{62}O_2$: C, 79.82; H, 13.30; Found: C, 79.78; H, 13.26%.

1-Triacontanol (8)

A solution of ester (7) (1.120 g, 2.4 m.mol) in dry THF (15 ml) was added dropwise to a stirred suspension of lithiumaluminium hydride (0.047 g, 1.25 m.mol) in dry THF (5 ml) at -10° and slowly brought to room temperature and stirred for 4 hr. After usual work up with aqueous sodium hydroxide, fine precipitate was filtered, and washed with THF. The filtrate was dried (anhyd. Na_2SO_4), solvent was removed on a rotary evaporator to give a solid which on crystallisation from hexane furnished 1.01 g (95%) of 7 as colourless plates, m.p. 87° (lit.[15] m.p. 87-88°). It was found to be identical in all respects with the authentic sample. ^{1}H-NMR ($CDCl_3$): δ 0.90 (dist.t, 3H, CH_3); 1.30 (br.s, 56H, 28X $-CH_2-$), 3.50 (t, 2H, $-CH_2OH$); IR: 3300 cm^{-1} (OH), M^+ 438.

Analysis: Calculated for: $C_{30}H_{62}O$: C, 82.19; H, 14.15; Found: C, 82.14; H, 14.20%.

REFERENCES

1 R.J. Weaver
"Plant Growth Substances in Agriculture"
W.H. Freeman and Company, San Francisco, 1972, pp.2

2 D. Gross
Phytochemistry 14, 2105 (1975).

3 L.G. Nickell
Chem. & Engg. News 56(41), 18 (1978).

4 S.K. Ries, V. Wert, C.C. Sweeley and R.A. Leavitt
Science, 195, 1339 (1977).

5 S.K. Ries, W. Violet
Planta 135, 77 (1977).

6 R. Hangerter and S.K. Ries
Plant Physiol. 61, 855 (1978).

7 W. Bleyberg and H. Ulrich
Chem. Ber. 64B, 2504 (1931).

8 H.A. Schuette, R.M. Christenson and H.A. Vogel
Oil and Soap, 20, 263 (1943).

9 G.M. Robinson
J. Chem. Soc., 1543 (1934).

10 A. Watanabe
Bull. Chem. Soc. Japan, 34, 398 (1961).

11 Huang-Minlon
J. Am. Chem. Soc., 68, 2487 (1946).

12 R.G. Jones
J. Am. Chem. Soc., 69, 2350 (1947).

13 H. Schildknecht and G. Renner
Fette, Seifen, Anstrichmittel 66,176 (1964);
C.A. 61, 15966h (1964).

14 H. Oura, J. Hase, K. Honda and S. Fukai
J. Pharm. Soc. Japan 76, 1433 (1956); C.A. 51, 6515b (1957).

15 A.V. Rama Rao, M.N. Deshmukh and M. Kamalam
Tetrahedron 37, 227 (1981).

16 N.R. Hunter, J.L. Charlton, N.A. Green, W.J. Fritz and
B.M. Addison
Organic Preparations and Procedure Int. 13(1), 19 (1981).

17 K. Maruyama, K. Terada and Y. Yamamoto
J. Org.Chem., 45, 737 (1980).

18 T. Gibson
Tetrahedron Lett. 23, 157 (1982).

19 A.V. Rama Rao, J.S. Yadav and G.S.Annapurna
Synth.Commun., 13(4) 331 (1983).

20 Chander Uday Singh
India Today, Sept. 16 (1981).

21 S. Hunig, H.-J Buysch, H.Hock & W. Lendle
Chem. Ber., 100, 4006 (1967).

22 A.W. Ralston and W.M. Selby
J. Am.Chem. Soc., 61, 1079 (1939).