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Convenient Synthesis of 4-Acetyl-2-methoxy-5-methyl-triacontane and 23-Hydroxytriacontan-2-one, the Constituents of *Curculigo orchioides*

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Unambiguous syntheses of the two title compounds (I) and (II), recently isolated by Mehta *et al.* and Misra *et al.* from *Curculigo orchioides* are reported. The syntheses use the Grignard coupling of undecenyl bromide with cetyl bromide (2) and monobromo-pyranyl ether (10) of dodecanediol, respectively as one of the key reactions. Further elaboration of the products in each case leads to the desired compounds (I) and (II). Complete identity of the synthetic products with the natural ones, however, could not be established.

RECENTLY Mehta *et al.*[1] and Misra *et al.*[2] have isolated two solid compounds having m.ps. 87-88° and 109-110°, respectively from the petroleum extract of *Curculigo orchioides* and established their identities as I and II on the basis of spectroscopic data. With a view to obtain I and II in sufficient quantities for biological evaluations, the synthesis of these compounds has been achieved from easily accessible materials which is reported here.

Following the conventional procedure, undecenoic acid was converted into its methly ester which was subsequently reduced with $LiAlH_4$ to the corresponding alcohol. This was brominated[3] using triphenylphosphonium dibromide to afford the bromide (1) in high yield. Cetyl alcohol was also converted into its bromide by using aq. 48% HBr. The Grignard coupling[4] between undecenylmagnesium bromide and the cetyl bromide (2) in the presence of catalytic amount of Li_2CuCl_4 furnished the alkene (3) in good yield. Under the condition of phase transfer catalysis[5], hydrobromic acid was added to the carbon-carbon double bond to obtain the secondary bromide (4). Alkylation of sodioethyl acetoacetate in THF with allyl bromide afforded the corresponding allyl β-keto ester (5). The carbonyl group of 5 was protected as its ethylene ketal (6). This was subjected to a oxymercuration-demercuration reaction in anhydrous methanol[6] to furnish the methoxy compound (7). Deketalisation provided the β-keto ester (8) which on alkylation with secondary bromide (4) provided the requisite skeleton (9). Due to the weak reactivity of the substrates, the reaction was conducted in a polar medium (DMF) and was catalysed by the addition of sodium iodide to optimise the yield. This was followed by decarbethoxylation *in situ* to furnish the desired compound (I).

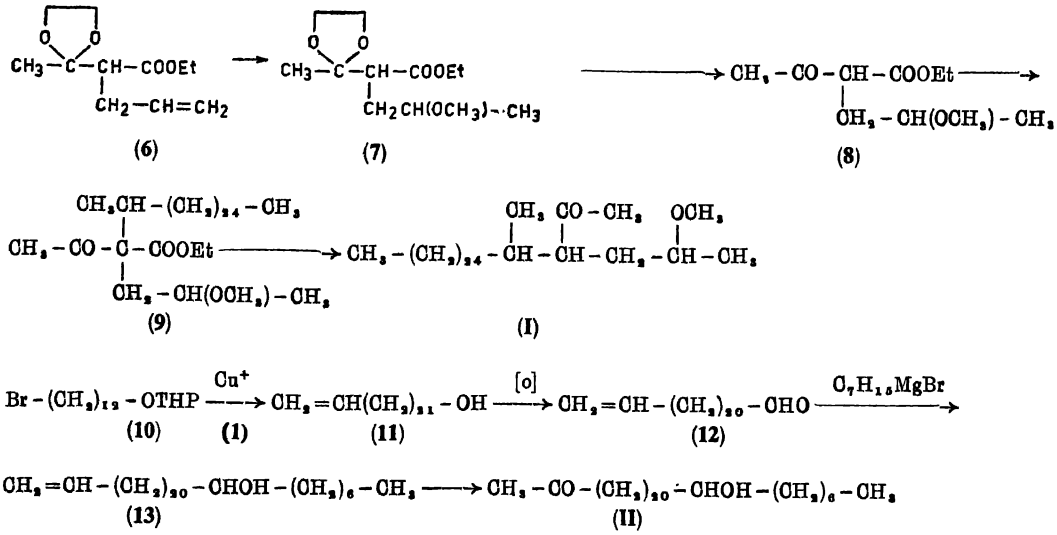
For the synthesis of II, dodecanediol was converted to its bromopyranyl ether (10)[7] by subjecting it to a partial bromination and subsequently pyranylating the free hydroxyl group. The next step involved a Grignard coupling[4] of undecenylmagnesium bromide and the bromopyranyl ether (10) to afford an intermediate which on depyranylation afforded the coresponding alkenol (11). It was oxidised with pyridinium chlorochromate[8] to yield the corresponding alkenal (12). A Grignard reaction of heptylmagnesium bromide with 12 gave a secondary hydroxy compound (13). Functionalisation of the terminal methylene group was achieved by subjecting 13 to a $PdCl_2$ oxidation[9] in aqueous DMF in the presence of oxygen to furnish the desired compound (II).

The mass spectral data of our synthetic I and II are in agreement with those reported. The ir spectrum of I is almost superimposable with the spectrum of the authentic sample (kindly supplied by Dr. Mehta). However, there are variations in relative absorbance bands in ir and *m/e* fragments for I. The m.ps. reported for I and II by these authors are not in agreement with those of our synthetic samples. These discrepancies appear to cast doubt on the purity of the isolated products. We failed in our attempts to get authentic samples of the natural I and II.

$$\underset{(1)}{CH_2{=}CH-(CH_2)_8-Br(Mg)} + \underset{(2)}{CH_3-(CH_2)_{15}-Br} \xrightarrow{Cu^+} \underset{(3)}{CH_2-(CH_2)_{24}-CH{=}CH_2} \longrightarrow \underset{(4)}{CH_3-(CH_2)_{24}-CHBr-CH_3}$$

$$CH_3-CO-CH_2-COOEt \xrightarrow[CH_2=CH-CH_2Br]{B^-} CH_3-CO-\underset{\displaystyle CH_2-CH=CH_2}{\underset{|}{CH}}-COOEt \longrightarrow$$

(5)



Experimental

All the melting points and boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord 137-B spectrophotometer using KBr discs for solids. Only prominent and/or characteristic bands are reported. Pmr spectra were recorded on a Varian A-60A spectrometer using $SiMe_4$ as internal reference. Mass spectra were recorded on a VG Micromass 7070F instrument. Glc was carried out on a 3% OV-17 column using nitrogen (30 lb in^{-2}) as the carrier gas. All the reactions requiring anhydrous conditions were conducted under argon atmosphere. Solvents THF and ether were distilled from sodium benzophenone ketyl and then distilled over LAH immediately prior to use. Tlc was performed on silica gel plates.

Undecenyl bromide (**1**) : To a stirred and cooled solution of triphenylphosphine (26.3 g, 0.1 mol) in anhydrous dichloromethane (100 ml), was added bromine (20 ml of 5.5 *M* solution in CCl_4, 0.1 *M*) during 10 min. The resulting thick white suspension was treated with a solution of undecenyl alcohol (17.1 g 0.1 mol) in pyridine (9 ml). A mildly exothermic reaction ensued, which was completed by stirring the mixture for 1 h at ambient temperature. The contents of the flasks were carefully distilled under reduced pressure and the distillate was fractionated to obtain undecenyl bromide (**1**) (19.9 g, 85.0%), b p 114-115°/5 mm Hg (lit[10], 103°/4 mm Hg) ; ν_{max} 2 940, 1 660, 1 450, 1 000 and 910 cm^{-1} ; δ 1.33 (16H, m, $(CH_2)_8$), 3.53 (2H, t, *J* 7Hz), 4.86-5.95 (3H, m, $CH=CH_2$) ; glc showed a single peak.

1-Heptacosene (3) : The Grignard reagent was prepared from Mg (1.8 g, 0.075 g-atom) and the bromide (**1** ; 14.0 g, 0.06 mol) in anhydrous tetrahydrofuran (75 ml). The flask was then immersed in an ice-salt bath, and a solution of the bromide (**2**) (15.3 g, 0.05 mol) in THF (25 ml) was introduced. The reaction mixture was cooled to −5 to 0° and the catalyst dilithium tetrachlorocuplate in THF (11.5 ml, 0.1 mol) was added dropwise through the funnel. The reaction mixture was stirred for 3 h below 5° and then left overnight. A black colloidal suspension of copper indicated the formation of the coupling product. The reaction was quenched by the addition of a saturated solution of ammonium chloride (6 ml), diluted with petroleum ether (100 ml) and filtered through a short (3 inch) pad of silica gel. The solvent was evaporated and the residue was crystallised from petroleum ether to afford the alkene (**3**) as a low melting solid (13.6 g, 72%) (Found : C, 85.30 ; H, 14.50. Calcd. for $C_{27}H_{54}$; C, 85.71 ; H, 14.28%) ; ν_{max} 2 940, 1 460, 990 and 910 cm^{-1} ; δ 1.3 (48H, m, $(CH_2)_{24}$), 4.86-5.90 (3H, m, $CH=CH_2$) ; *m/e* 378 (M^+).

2-Heptacosanyl bromide (4) : A mixture of 1-heptacosene (**3** ; 11.3 g, 0.03 mol), 48% aqueous HBr (16.7 ml, 0.15 mol) and cetyltributylammonium bromide (1.5 g, 0.003 mol) was treated under stirring at 115° (bath temperature) for 3 h. The organic layer was separated and the aqueous phase was extracted with ether (4×25 ml). The combined ether extracts was washed once with brine (25 ml) and dried over anhydrous sodium sulphate. Removal of solvent afforded the desired bromide (**4**) as a low melting solid in quantitative yield (13.2 g) (Found : Br, 17.5. Calcd. for $C_{27}H_{55}Br$, 17.43%). Its ir spectrum was devoid of the absorption bands due to the terminal double bond (990 and 900 cm^{-1}) indicating the conversion of the olefin to bromide.

4-Carbethoxy-5-acetoxypent-1-ene (5) : A three-necked flask (250 ml) was charged with sodium hydride (4.8 g as 50% dispersion in oil, 0.1 mol) and anhydrous THF (25 ml). The suspension was stirred and a solution of ethyl acetoacetate (13.0 g, 0.1 mol) in THF (50 ml) was added dropwise over a period of 30 min. An instantaneous reaction took place with vigorous evolution of hydrogen.

Stirring was continued till all the sodium hydride disappeared, and a clear solution resulted (1 h). A solution of allyl bromide (12.1 g, 0.1 mol) in THF (25 ml) was then added dropwise over a period of 30 min. A mildly exothermic reaction took place. The reaction mixture was stirred for 1 h and then left overnight. It was then diluted with water (50 ml) and extracted thoroughly with ether (4×50 ml). The combined ether extracts was washed with water (25 ml), saturated brine and dried over anhydrous sodium sulphate. Evaporation of the solvent and distillation of the residue under reduced pressure gave the desired β-ketoester (5) (13.6 g, 80%), b.p 102-106°/5 mm ; ν_{max} 2 950, 1 740, 1 650, 1 010 and 910 cm^{-1} ; δ 1.31 (3H, d,d, *J* 8Hz, CH_3), 2.25 (3H, s, $COCH_3$), 2.61 (2H, t, $CH_2=CHCH_2CH$), 3.58 (1H, m, C*H*), 4.2 (2H, q, OCH_2CH_3) and 4.95-6.05 (3H, m, $CH=CH_2$) ; glc showed a single peak.

4-Carbethoxy-5,5'-ethylenedioxyhex-1-ene (6) : A mixture of the monoalkylated product (5 ; 8.5 g, 0.05 mol), ethylene glycol (4.7 g, 0.075 mol), a few crystals of *p*-toluenesulphonic acid and dry benzene was refluxed in a Dean-Stark apparatus until no more aqueous phase separated (6 h). After neutralisation with anhydrous sodium carbonate, the reaction mixture was filtered and concentrated. The residue was distilled under reduced pressure to give the ketal ester (6) (9.0 g, 85%), b.p 104-108°/ 5 mm Hg ; ν_{max} 2 960, 1 740, 1 660, 1 050, 1 010, 950 and 910 cm^{-1} ; δ 1.25 (2H, t, *J* 7 Hz, OCH_2CH_3), 1.4 (3H, s, CH_3), 2.13-2.90 (3H, m, $CH-CH_2-CH=CH_2$), 4.0 (4H, s, $(CH_2O)_2$), 4.17 (2H, q, OCH_2CH_3), 4.90-6.20 (3H, m, $CH=CH_2$).

4-Carbethoxy-5,5'-ethylenedioxy-2-methoxyhexane (7) : To a stirred suspension of mercuric acetate (9.6 g, 0.03 mol) in anhydrous methanol (30 ml), the ketal ester (6 ; 6.4 g, 0.03 mol) was added in one lot. The mixture was stirred at room temperature for 10 min to complete oxymercuration. Then 3.0 *M* NaOH (15 ml) was added followed by a solution of 0.5 mol sodium borohydride in 3.0 *M* NaOH (15 ml). Reduction of oxymercurial was almost instantaneous. Methanol was removed on a rotatory evaporator. Mercury was allowed to settle down. It was diluted with ether. The ether layer was separated and washed with saturated brine, dried and concentrated to afford the corresponding methoxy compound (7) which was used as such in the next step, (6.6 g, 90%), ν_{max} 2 960, 1 740, 1 060 and 955 cm^{-1} ; δ 1.17 (3H, t, *J* 7 Hz, OCH_2CH_3), 1.26 (d, *J* 7 Hz, $CH(OCH_3)CH_3$), 1.38 (3H, s, CH_3), 3.97 (4H, s, $(CH_2O)_2$) and 4.2 (2H, q, OCH_2CH_3).

Ethyl-2-acetoxy-4-methoxypentanoate (8) : To a solution of the ketal ester (7 ; 4.9 g, 0.02 mol) in aqueous acetone (5%, 40 ml), a few crystals of *p*-toluenesulphonic acid was added and the mixture was refluxed on a water-bath for 2 h. Most of the acetone was distilled off, the residue diluted with water and extracted with ether. The extract was washed with a solution of bicarbonate, saturated brine and dried over anhydrous sodium sulphate. Removal of solvent followed by distillation of the residue under reduced pressure afforded the desired compound (8) in almost quantitative yield (4.0 g), b.p. 71-72°/0.6 mm Hg ; ν_{max} 2 960, 1 750, 1 460, 1 380 and 1.100 cm^{-1} ; δ 1.17 (3H, t, *J* 7 Hz, OCH_2CH_3), 1.34 (d, *J* 7 Hz, $CH(OCH_3)CH_3$), 1.88(2H, t, *J* 7 Hz, $CHCH_2CH$), 2 18 (3H, s, $COCH_3$), 3.23 (3H, s, OCH_3), 3.5-3.7 (2H, m, $CHCH_2CH$) and 4.18 (2H, q, OCH_2CH_3).

2 Methoxy-4-acetoxy-5-methyltriacontane (I) : A three-necked flask (100 ml) charged with sodium hydride (0.24 g as 50% dispersion in oil, 0.005 mol) was washed with dry hexane and suspended in anhydrous dimethylformamide (5 ml). To the magnetically stirred suspension, a solution of 8 (1.0 g, 0.005 mol) was added dropwise over a period of 10 min. An instantaneous reaction ensued with vigorous evolution of hydrogen. Stirring was continued till all sodium hydride disappeared and a clear solution resulted (~30 min). The bromide (4 ; 2.3 g, 0.005 mol) and a catalytic amount of sodium iodide (0.075 g, 0.5 mmol) were added and the reaction mixture was stirred at 70-75° (bath temperature) for 8 h. It was then diluted with water (20 ml), extracted with ether and washed with saturated brine. Removal of solvent afforded an intermediate (9) which was suspended in 2 *N* NaOH (10 ml) and stirred at 50° for 3 h. The reaction mixture was acidified with 50% H_2SO_4 and stirred for further 2 h. It was then diluted with water, and extracted with ether. The combined ether extracts was washed with water, saturated brine and dried over anhydrous sodium sulphate. The crude product after evaporation of the solvent was subjected to column chromatography (silica gel, 20% ether in petroleum ether) followed by crystallisation from petroleum ether to afford I (0.760 g, 30%), m.p. 71-72° (Found : C, 80.25 ; H, 13.60. Calcd. for $C_{34}H_{68}O_2$: C, 80.3 ; H, 13.3%) ; ν_{max} 2 980, 1 730, 1 490 and 720 cm^{-1} ; δ 0.9 (6H, distored t and d typical of long chain CH_2CH_3 and $CHCH_3$), 1.2 (3H, d, $CH(OCH_3)CH_3$), 1.23 (48H, m, $(CH_2)_{24}$), 1.68 (1H, s, $CHCH_3$), 2.12 (3H, s, $COCH_3$), 3.06 (3H, s, OCH_3), 3.23 (1H, m, $CHOCH_3$) and 3.93 (1H, m, $CHCOCH_3$) ; *m/e* 508 (M^+), 448, 493, 477 (by α-cleavage) determined the position of methoxy group and 465 (M^+CH_3CO) indicated the presence of acetyl group. It showed a single spot on tlc, DNPH +ve, solvent system (EtOAc-petroleum ether, 1 : 9) Rf 0.7.

Tricosen-1-ol (11) : The Grignard reagent prepared from Mg (1.5 g, 0.06 g-atom) and the bromide (1 ; 12.8 g, 0 055 mol) in THF (60 ml), was cooled (−5 to −10°) and treated with a solution of the bromopyranyl ether (10)[7] (17.5 g, 0.05 mol) in THF (40 ml) followed by a 0.1 *M* solution of dilithium tetrachlorocuprate in THF. Usual workup followed by crystallisation of the residue from petroleum ether afforded the alkenol (11) (10.1 g, 60%), m.p.

65-67°; ν_{max} 3 350, 2 940, 1 660, 1 460, 1 060, 1 010 and 910 cm^{-1}; δ 1.27 (40H, m, $(CH_2)_{20}$), 3.67 (2H, t, J 6 Hz, CH_2OH) and 4.80-5.20 (3H, m, $CH=CH_2$); *m/e* 338 (M^+); showed single spot on tlc, solvent benzene, Rf 0.3.

Tricosen-1-al (**12**): To a stirred suspension of pyridiniumchlorochromate (3.2 g, 0.015 mol) in anhydrous methylene chloride (15 mol) a solution of the alkenol (**11**; 3.4 g, 0.01 mol) in methylene chloride (5 ml) was rapidly added at room temperature. After being stirred for 2 h at room temperature the reaction mixture was diluted with 5 volumes of anhydrous ether and passed through a small bed of florosil and concentrated in vacuum to afford the alkenal (**12**) and was used as such in the next step, (3.0 g, 90.0%); ν_{max} 2 940, 2 720, 1 725, 1 660, 1 460, 1 010 and 910 cm^{-1}; showed single spot on tlc, solvent benzene, Rf 0.8; gave DNPH +ve test.

8-Hydroxytriacont-29-ene (**13**): Following the conventional procedure, a Grignard reagent was prepared from Mg (0.3 g, 0 012 g-atom) and heptyl bromide (1.8 g, 0.01 mol) in THF (10 ml). The solution was cooled to 0° and treated with a solution of the alkenal (**12**; 3.0 g, 0.09 mol) in THF (10 ml). The reaction mixture was stirred for 2 h at 0° and left overnight. Usual workup afforded a residue which was crystallised from methanol to furnish the desired alkenol (**13**) (2.3 g, 60%), m.p. 68-70°; ν_{max} 3 350, 2 940, 1 660, 1 460, 1 010 and 910 cm^{-1}.

8-Hydroxytriacontan-29-one (**II**): To a mixture of palladium chloride (28 mg, 0.16 mmol) and cupric chloride (22 mg, 0.16 mmol) in aqueous dimethylformamide (DMF, 1.0 ml, H_2O, 0.1 ml), alkenol (**13**; 0.440 g, 1 mmol) was gradually added in 1 h while oxygen was bubbled through the reaction mixture. Thereafter temperature of the reaction mixture was raised to 60-70° and maintained for 1 h after the introduction of the olefin. The mixture was poured in dilute cold HCl and extracted with ether. The ether extract was subsequently washed with water and brine and dried over anhydrous sodium sulphate. Removal of solvent followed by crystallisation of the residue from methanol furnished the compound **II** (0.29 g, 65%), m.p. 61-62° (Found: C, 79.44; H, 13.90. Calcd. for $C_{30}H_{60}O_2$. C, 79.65; H, 13.27%); ν_{max} 3 350, 2 940, 1 710 and 1 460 cm^{-1}; δ 0.9 (3H, m, CH_3), 1.3 (52H, m, $(CH_2)_{26}$), 2.15 (3H, s, CH_3CO) and 3.3-3.7 (1H, m, CH); single spot on tlc, DNPH +ve and stains with 5% alkaline $KMnO_4$, solvent system (EtOAc-petroleum ether, 1 : 9) Rf 0.6; *m/e* 452 (M^+), 353, 308, 143, 129, 99, 57 and 43.

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