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THERMAL REORGANISATION REACTIONS—II

THERMAL CYCLIZATION OF METHYL KAMLOLENATE*†

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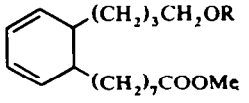
Abstract—Sulphur-catalysed intramolecular thermal cyclization of conjugated trienes, discovered with methyl eleostearate, has now been extended to its ω-hydroxy analogue, *viz.* methyl kamlolenate. The primary cyclic monomer (III) has been isolated and characterised. Two cyclokamlolenate-derived macrocyclic lactones (VI) and (VII) have also been prepared.

KAMLOLENIC acid (I) is the well-characterised ω-hydroxy analogue of eleostearic acid, and, it also exists in two forms: the natural α-form (*cis, trans, trans*) and the isomerised all-*trans* β-variety. The acid is readily accessible from *kamala* (seed oil) (*Mallotus philippinensis*) which is indigenous to India.[1] Sulphur-catalysed intramolecular thermal cyclization, optimized earlier[2] for methyl eleostearates has now been extended to methyl kamlolenate. It was surmised that cyclokamlolenic acid or its simple modifications could be further transformed into macrocyclic lactones of an interesting type—a macrocycle fused to a common ring—of possible interest in perfumery. This has also been achieved.

Total *kamala* oil methyl esters (λ_{max} 268 mμ, $a = 90{\cdot}5$; ~50% methyl kamlolenate) on being heated at 160°/5 hr, in presence of sulphur, in a sealed evacuated tube, furnished, after distillation in a falling film molecular still, ~70% monomeric distillate. This product, was segregated into cyclic (~50%) and acyclic portions by the urea-inclusion technique. The cyclic product was further purified as the acetate by chromatography over silica gel to finally give a homogenous material. From its spectral characteristics (λ_{max} 261 mμ, $\varepsilon = 6900$; IR: C=O 1750 cm^{-1}; OAc 1240 cm^{-1}; PMR: $OCOC\underline{H}_3$, 3H singlet at 118 c/s; $COOC\underline{H}_3$, 3H singlet at 217 c/s; $C\underline{H}_2OAc$, 2H triplet centred at 240 c/s, $J = 6$ c/s; four vinylic protons, essentially an ill-defined singlet at 345 c/s) and mode of synthesis and isolation, the product is assigned‡ structure II.

$HOCH_2.(CH_2)_3.(CH{=}CH)_3.(CH_2)_7.COOH$



I: R = Ac
III: R = H

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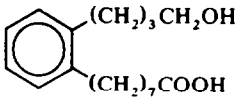
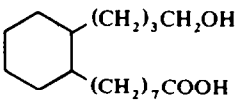
‡ For a close analogy see the detailed work on methyl eleostearate.[2]

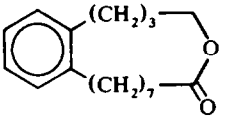


IV

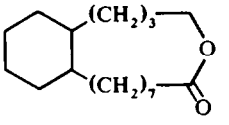


V

When the thermal treatment (in presence of S) was carried out at 240°/1 hr, considerable complications arose due to intermolecular esterification, and several unexpected side reactions, such as elimination reactions (Experimental). However, the cyclic monomeric mixture (yield ~40% based on methyl kamlolenate) was considered suitable for conversion to *ar*-cyclokamlolenic acid (IV) and the fully saturated analogue V by standard methods of catalytic dehydrogenation (10% Pd—C, 240°) and catalytic hydrogenation (Raney Ni) respectively. A minor by-product of catalytic dehydrogenation has been characterised (IR, PMR) as δ-phenyl-n-butanol,* resulting from elimination of the bigger side chain during dehydrogenation.[3]



VI



VII

It appeared of interest to effect lactonization of both IV and V as the resulting products (VI and VII) would be macrocyclic lactones having 15 members in the macro ring, a necessary structural feature for certain macrocyclic musks.[4] Both hydroxy acids (IV, V) could be readily cyclized with *p*-toluenesulphonic acid under high dilution conditions, using a set up described elsewhere,[5] to furnish respectively VI and VII, which were suitably characterized. The lactone VI was evaluated† to have a weak musk odour, while lactone VII showed practically no such character.

EXPERIMENTAL

For general remarks see Part I of this series.

Methyl kamlolenate

Methanolysis[6] of kamala oil (90 g) followed by distillation in a 2″-rotafilm molecular still at 180°/50μ furnished total methyl esters (56·8 g); λ_{max} 268 mμ [a = 90·5 (conc g/l.); pure ester a = 153].

Sulphur catalyzed thermal treatment

(a) *At* 160°. The above ester (56 g) and S (112 mg) were taken in an evacuated pyrex glass tube and immersed in a preheated oil bath (160°). After 5 hr, the thermal product was distilled (180°/50μ). The distillate (38 g) was adducted with urea (190 g) in dry MeOH (760 ml). After 24 hr at 0°, the filtrate was worked up in the usual manner to yield 17·0 g of urea non-complexing material. This was acetylated with Ac_2O (50 ml) and dry pyridine (10 ml) at room temp for 2 hr and the product distilled and further treated as described below.

(b) *At* 240°. Total kamala oil esters (3 × 70 g) were thermally processed at 240° for 1 hr as described in (a). The distillate (85 g) was fractionated by urea-inclusion to furnish the filtrate monomer (40·5 g). This was chromatographed on SiO_2 gel (450 g, 22 × 8 cm). Elution with light petroleum gave a non-aromatic

* Some amount of this compound is also formed during the thermal (240°/1 hr) treatment of methyl kamlolenate, described earlier.

† Authors are grateful to Dr. E. T. Theimer (International Flavors and Fragrances, Union Beach) for this evaluation.

hydrocarbon (0·52 g) while light petroleum-benzene (1 : 1) and neat benzene eluted out a material (15·47 g) transparent in the OH-stretching region but revealed strong absorptions for COOMe (1750 cm^{-1}) and monosubstituted benzenoid moiety (1600, 1500, 750 and 700 cm^{-1}). Finally Et_2O—MeOH (9 : 1) eluted out the cyclokamlolenate mixture (21·9 g) having IR bands at 3400 and 1060 cm^{-1} in addition to the above aromatic bands.

Methyl cyclokamlolenate-I (II)

The acetate mixture (5·78 g) from (a) (TLC, one major spot and three minor spots; solvent, 5% EtOAc in light petroleum) was chromatographed on SiO_2 gel (200 g, 21 × 4 cm) by the "dry column" technique[7] using the TLC solvent system. A central cut (2·8 g) on further purification by rechromatography over $AgNO_3$-SiO_2 using benzene as solvent furnished II as a yellowish liquid. (Found: C, 72·14; H, 9·88. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%).

ar-Cyclokamlolenic acid (IV)

The cyclic monomer concentrate (5·05 g) from (b) and 10% Pd-C (1·0 g) were heated at 240° while dry N_2 was bubbled into the liquid. After 2 hr the product (5·01 g) was chromatographed[7] over SiO_2 gel (150 g, 15 × 3·5 cm) using benzene as developer to yield the aromatized material (3·32 g). Hydrolysis of this product (3·0 g) with aqueous methanolic KOH gave a small amount (130 mg) of neutral compound identified as δ-phenyl n-butanol: colourless liquid b.p. 130° (bath)/2·0 mm; IR spectrum: CH_2OH (3300, 1060 cm^{-1}), benzene monosubstitution (1600, 1500, 750 and 700 cm^{-1}), C=O region transparent; PMR spectrum: *ar*-H (5H, s 426 c/s), CH_2OH (2H, tr, 210 c/s, J = 7 c/s), CH_2OH (s 168 c/s, D_2O-exchange), *ar*-CH_2 (tr 155 c/s) and aliphatic CH_2 (m 90–100 c/s). (Found: C, 79·00; H, 9·33. $C_{10}H_{14}O$ requires: C, 79·95; H, 9·39%).

The acid (2·501 g), a pale yellow gum, was further purified by chromatography[7] on SiO_2 gel (80 g, 20 × 2·5 cm) using 15% EtOAc-C_6H_6. A central cut (1·181 g) was now TLC-pure IV but still did not crystallize; IR spectrum: CH_2OH (3300, 1060 cm^{-1}), COOH (3300, 2600, 1710 cm^{-1}), benzene-1,2-substitution (1500, 760 cm^{-1}). *Methyl ar-cyclokamlolenate* (CH_2N_2-method) had b.p. 200° (bath)/0·1 mm; IR spectrum: CH_2OH (3400, 1060 cm^{-1}), COOMe (1750, 1180 cm^{-1}) and 1,2-disubstituted benzene (1610, 1500, 760 cm^{-1}); PMR spectrum: CH_2 of C-chain (broad s 84 c/s), CH_2OH (149 c/s, superimposed on *ar*-CH_2 resonance, located by D_2O-exchange), COOMe (s 217 c/s), CH_2OH (apparent poor tr, main resonance swamped by COOMe signal) and *ar*-H (4H-sharp s 422 c/s). (Found: C, 74·54; H, 10·21. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%).

ar-Cyclokamlolactone (VI)

ar-Cyclokamlolenic acid (IV, 913 mg) in dry benzene (200 ml) was added very slowly (*ca* 15 microdrops/5 min) through a Hershberg dropping funnel into a flask containing dry benzene (1 l.) and *p*-toluenesulfonic acid (0·5 g) through the intermediacy of a high-dilution still-head. After refluxing for 22 hr, during which period the addition was complete, the reaction mixture was washed successively with water (100 ml), Na_2CO_3 aq (150 ml × 3) and brine. Evaporation and distillation of residue (0·72 g) at 180° (bath)/0·1 mm afforded VI as a pale yellow liquid; IR spectrum: lactone (1750, 1250 cm^{-1}), *o*-disubstituted benzene (1600, 1500 and 760 cm^{-1}); PMR spectrum: aliphatic CH_2 (broad s 87 c/s), *ar*-CH_2 (essentially tr 155 c/s), CH_2—O—CO (broad tr 247 c/s) and *ar*-H (sharp s 422 c/s). (Found: C, 79·07; H, 9·59. $C_{18}H_{26}O_2$ requires: C, 78·79; H, 9·55%).

Saturated cyclokamlolactone (VII)

The cyclic monomer concentrate (10·1 g) from (b) in EtOH (300 ml) was subjected to high pressure hydrogenation (550 psi) at 105° for 10 hr in presence of Raney Ni (8·0 g) in a stainless steel autoclave equipped with a stirrer. The hydrogenated product (9·61 g) had slight aromatic contamination (IR). This material (6·91 g) on hydrolysis with aqueous methanolic KOH gave V as a pale yellow gum (6·26 g); the neutral impurity (0·592 g) was identified as δ-phenyl n-butanol.

V (1·02 g) in dry benzene (200 ml) was intramolecularly lactonized in a high-dilution apparatus as described earlier (addition time = 32 hr). The product (0·987 g) was purified by chromatography[7] on $AgNO_3$-SiO_2 gel (150 g, 17 × 2 cm) using hexane-benzene (3 : 7) as developer. A central cut (286 mg) furnished the pure saturated lactone (VII): pale yellow liquid b.p. 160° (bath)/0·05 mm; IR spectrum: lactone (1750, 1260 cm^{-1}); PMR spectrum: aliphatic CH_2 (broad s 80 c/s), CH_2CO (broad tr 135 c/s) and CH_2·O·CO (broad tr 245 c/s). (Found: C, 77·49; H, 11·61. $C_{18}H_{32}O_2$ requires: C, 77·09; H, 11·50%).

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KEY WORDS

Methyl kamlolenate—sulphur-catalysed intramolecular thermal cyclization of.
Methyl cyclokamlolenate-I.
Macrocyclic lactones (*ar*-cyclokamlolactone and saturated cyclokamlolactone).