ACTA CHEMICA SCANDINAVICA 10 (1956) 1035—1037

Short Communication

Synthesis of Racemic Methyl C_{27}-Phthienoate. Part II.

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A synthesis of racemic methyl *erythro*-2,4,6-trimethyl-$\Delta^{2:3}$-tetracosenoate was described in a previous communication [1]. The route which was used gave, as major product, the *cis*-isomer. The *trans*-isomer also obtained had the same infra-red absorption curve as the methyl ester of C_{27}-phthienoic acid isolated from tubercle bacilli [2,3].

In the present communication, a new method of synthesizing racemic methyl *erythro*-2,4,6-trimethyl-$\Delta^{2:3}$-tetracosenoate is described, which gives almost solely the *trans*-isomer. The starting material, the monomethyl ester of *meso*-3,5-dimethylpimelate (I), is the same as that used in the previous synthesis [1]. The sequence of reactions involved is shown in the following chart.

The acid chloride of (I) was treated with the calculated amount of CH_3MgI in the cold, and the neutral product obtained (II) was acetylated by boiling with acetic anhydride: methyl 3,5,7-trimethyl-7-acetoxyoctanoate (III) was isolated as a colourless liquid, b. p. 92—94°, 0.2 mm, $n_D^{25} = 1.4358$, $d_4^{25} = 0.965$. By cautious saponification, the acid (IV) was obtained. Kolbe reaction [4] of 3,5,7-trimethyl-7-acetoxyoctanoic acid (IV) with stearic acid and isolation of the reaction products by distillation gave 2,4,6-trimethyltetracosene-1 (V), m. p. 10.2—10.6°, $n_D^{20} = 1.4549$, $d_4^{20} = 0.811$ ($C=CH_2$ I.R. out of plane deformation vibration at 11.26 μ).

The formation of the unsaturated hydrocarbon (V) (instead of the expected long-chain acetoxy-compound) is due to thermal decomposition of an intermediary trimethyltetracosanyl-2 stearate arising from a transesterification of trimethyltetracosanyl-2 acetate (X) when distilled in the presence of free stearic acid. 2,4,6-Trimethyl-2-acetoxytetracosane (X) can be distilled without decomposition, whereas slow distillation of a mixture of the same acetoxy-compound (X) together with free stearic acid gives trimethyltetracosene-1 in excellent yield.

The same hydrocarbon (V) was also prepared from methyl hydrogen 3,5-dimethylpimelate (I) by bromine degradation of its silver salt according to Hunsdiecker [5], hydrolysis of the bromo-ester (VI) thus obtained to the bromo-acid (VII) (colourless liquid, $n_D^{21} = 1.4750$, $d_4^{21} = 1.298$), and transformation of this bromo-acid through Kolbe reaction with stearic acid * into 2,4-dimethyldocosanyl bromide (VIII) (colourless liquid, $n_D^{20} = 1.4635$, $d_4^{20} = 0.950$). 2,4-Dimethyldocosanyl magnesium bromide was obtained in low yield by the

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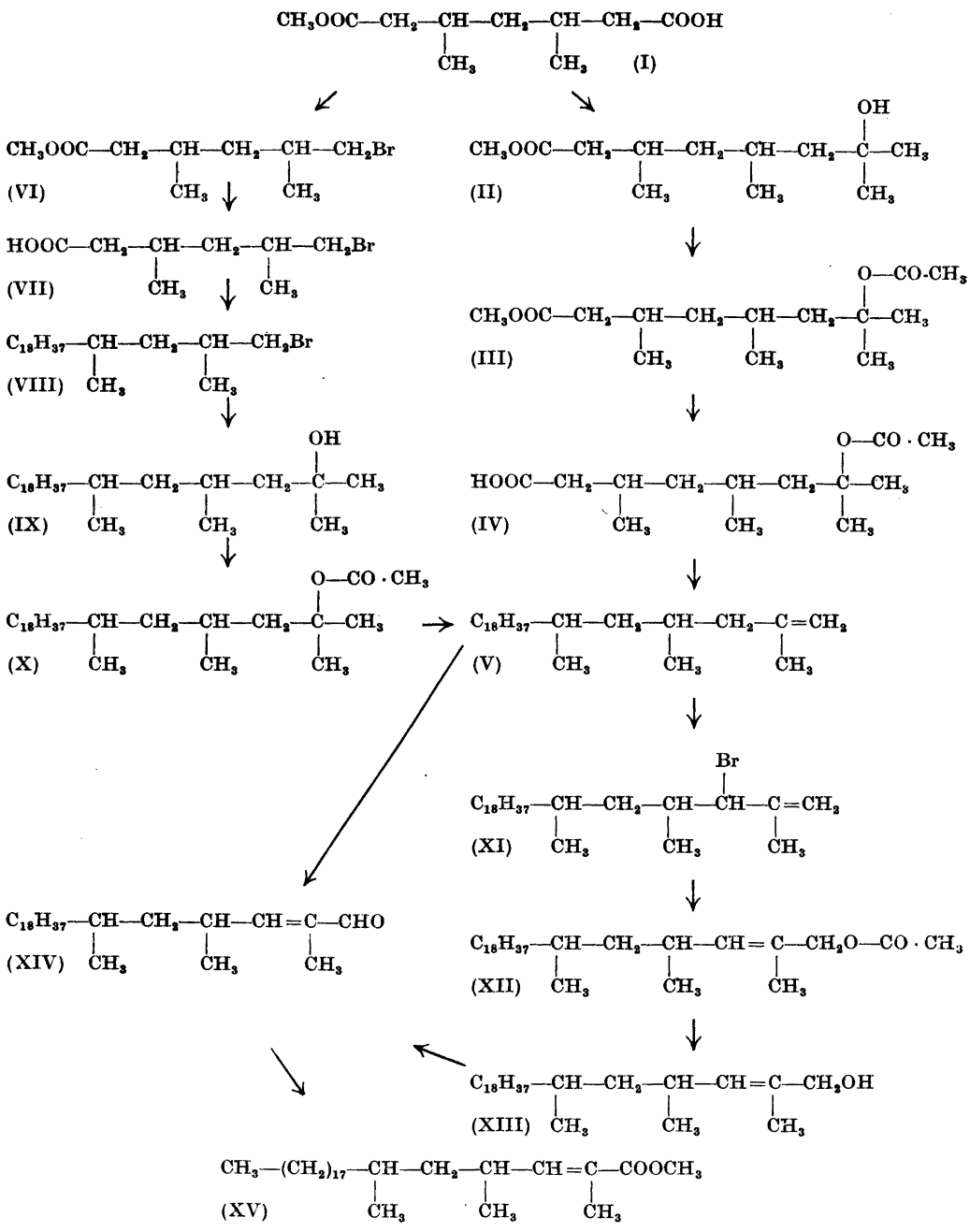
* In a recent paper [10], the behaviour of straight chain ω-halogenocarboxylic acids in the Kolbe reaction was studied; it was concluded that "only with a chain length of eleven or greater did normal coupling occur". In our case, the main chain consisted of only six carbon atoms.


CH3OOC—CH2—CH(CH3)—CH2—CH(CH2)—CH2—COOH (I)
CH3OOC—CH2—CH(CH3)—CH2—CH(CH2Br)—CH3 (VI)
HOOC—CH2—CH(CH3)—CH2—CH(CH2Br)—CH3 (VII)
C18H37—CH(CH3)—CH2—CH(CH3)—CH2Br (VIII)
C18H37—CH(CH3)—CH2—CH(CH3)—CH2—C(OH)(CH3)—CH3 (IX)
C18H37—CH(CH3)—CH2—CH(CH3)—CH2—C(O—CO·CH3)(CH3)—CH3 (X)
CH3OOC—CH2—CH(CH3)—CH2—CH(CH3)—CH2—C(OH)(CH3)—CH3 (II)
CH3OOC—CH2—CH(CH3)—CH2—CH(CH3)—CH2—C(O—CO·CH3)(CH3)—CH3 (III)
HOOC—CH2—CH(CH3)—CH2—CH(CH3)—CH2—C(O—CO·CH3)(CH3)—CH3 (IV)
C18H37—CH(CH3)—CH2—CH(CH3)—CH2—C(=CH2)—CH3 (V)
C18H37—CH(CH3)—CH2—CH(CH3)—CHBr—C(=CH2)—CH3 (XI)
C18H37—CH(CH3)—CH2—CH(CH3)—CH=C(CH2O—CO·CH3)—CH3 (XII)
C18H37—CH(CH3)—CH2—CH(CH3)—CH=C(CH2OH)—CH3 (XIII)
C18H37—CH(CH3)—CH2—CH(CH3)—CH=C(CHO)—CH3 (XIV)
CH3—(CH2)17—CH(CH3)—CH2—CH(CH3)—CH=C(COOCH3)—CH3 (XV)

method of Geiger-Berschandy [6] and after reaction with acetone, 2,4,6-trimethyltetracosanol-2 (IX) was isolated (m. p. 23.1—24.1° and 27.5—29.0° (dimorphism)), $n_D^{24} = 1.4554$, $d_4^{24} = 0.842$. 2,4,6-Trimethyl-2-acetoxytetracosane (X) (m. p. 8.6—9.2°, $n_D^{23} = 1.4498$, $d_4^{23} = 0.853$) was prepared by boiling the free alcohol with acetic anhydride. Distillation of this acetate with stearic acid gave 2,4,6-trimethyltetracosene-1 (V) ($n_D^{23} = 1.4533$, $d_4^{23} = 0.808$).

Allylic bromination of the unsaturated hydrocarbon (V) with N-bromo-succinimide [7] gave a bromo-compound (XI) which was transformed into 2,4,6-trimethyl-1-acetoxytetracosene (XII) under conditions which favoured the allylic transposition. The free primary alcohol (XIII) was obtained after $LiAlH_4$ reduction of its acetate. CrO_3-pyridine oxidation [8] gave the unsaturated aldehyde (XIV) (phthienoic aldehyde) (crude product: λ_{max} 225 mμ, $\varepsilon = 7\,280$ in hexane; I.R. spectrum: aldehydic C—H stretching vibration at 3.72 μ and C=O stretching vibration at 5.92 μ). Silver oxide oxidation [9] of the unsaturated aldehyde and chromatographic purification of the acidic fraction as methyl ester gave the *trans*-isomer of methyl *erythro*-2,4,6-trimethyl-$\Delta^{2:3}$-tetracosenoate (XV) (m. p. 14.1—14.6°, $n_D^{25} = 1.4598$, λ_{max} 216 mμ, $\varepsilon = 12\,850$ in hexane); no *cis*-isomer could be detected.

The transformation of 2,4,6-trimethyltetracosene-1 (V) into C_{27}-phthienoic aldehyde (XIV) was also directly performed by SeO_2 oxidation [11]; the α,β-unsaturated aldehyde chromatographically purified had m. p. 29.5—35.0°, λ_{max} 225 mμ, $\varepsilon = 15\,550$ (hexane). Silver oxide oxidation lead to a sample of slightly impure *trans*-isomer of methyl *erythro*-2,4,6-trimethyl-$\Delta^{2:3}$-tetracosenoate (XV): m. p. 16.8—17.6°, $n_D^{25} = 1.4597$, λ_{max} 217 mμ, $\varepsilon = 11\,900$ in hexane.

The infra-red absorption curves of both preparations of the *trans*-form of racemic methyl *erythro*-2,4,6-trimethyl-$\Delta^{2:3}$- tetracosenoate described in the present paper are identical with that of the *trans*-isomer described previously [1], and with that of the methyl ester of naturally occurring C_{27}-phthienoic acid.

In this synthetic route, the carboxyl group of phthienoic acid is introduced on the side of the free acid group of the methyl hydrogen 3,5-dimethylpimelate (I) whereas in the route previously described [1] it is introduced on the ester side of the half ester (I). For the synthesis of the optically active natural acid it is therefore necessary to start with different enantiomorphs of (I) in the two routes.

We are indebted to Dr. I. Fischmeister for the infra-red spectra. The expenses involved in this work were defrayed by grants from *the Swedish Medical Research Council* to S. Ställberg-Stenhagen.

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Received July 31, 1956.