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# SYNTHETIC STUDIES ON VITAMIN A III. CRYSTALLINE CIS-ISOMERS OF VITAMIN A PALMITATE

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It was previously reported that four geometric isomers of vitamin A, *i.e.*, all-trans, 2-cis, 6-cis and 2,6-di-cis were prepared from cis- and trans- $\beta$ -ionylideneacetaldehydes and senecioate via intermediate vitamin A acids (1).



Synthesized all-trans- and neo-vitamin A were acetylated and all-trans-vitamin A acetate was obtained in a crystalline form, while another one was an oily product.

Among the geometric isomers of vitamin A acetate and palmitate, two esters, i. e., all-trans-vitamin A acetate (mp 57-58°) and all-trans-vitamin A palmitate (mp  $27-28^{\circ}$ ) had been isolated in a crystalline form (2, 3).

Robeson et. al. (4) reported the preparation and properties of four isomers of vitamin A acetate from vitamin A acids obtained by another method. However, these vitamin A acetates were all non-crystallizable oils except an all-trans form. The same authors described the synthesis of non-crystallizable neo-vitamin A palmitate (5). The other isomers of vitamin A palmitate have not been reported yet.

This paper is concerned with the synthesis and properties of geometric isomers of vitamin A palmitate.

Physical Properties of Vitamin A Palmitates						
Isomer	Vitamin A			Vitamin A palmitate		
	mp	$\lambda_{max}$	ε	mp	λmax	8
	°C	mμ		°C	mμ	
all-trans neo 6-cis 2,6-di-cis	$61-62 \\ 57-58 \\ 83-84.5 \\ 59-60$	325 329 321.5 324	$52,500 \\ 48,750 \\ 40,900 \\ 38,000$	27–28 oil 40–41 29–30	327 331 322.5 325	$51,000 \\ 43,600 \\ 40,400 \\ 36,000$

TABLE I



FIG. 1 Ultraviolet Absorptions Spectra of Vitamin A Palmitates I, all-trans; II, neo-; III, 6-cis-; IV, 2,6-dicis.

Two isomers, 6-*cis*- and 2,6-di-*cis*vitamin A palmitate, as well as all-*trans*, was isolated in a pure crystalline form, while only *neo*-vitamin A palmitate was an oily product. The physical properties (Table I) and ultraviolet and infrared absorption spectra (Fig 1 and 2) of these compounds are given. The corresponding vitamin A acetates were prepared by the similar method, but neither of them was obtained in a crystalline form except an all-*trans* one.

These esters of vitamin A were prepared from each crystalline vitamin A which had been synthesized from vitamin A acid. Crystallization of vitamin A was successfully carried out by using *n*-hexane or ethyl formate as a solvent. 6-*cis*-Vitamin A is more crystallizable and more stable than the other isomers.

## EXPERIMENTAL<sup>1</sup>

## 1. Crystalline 6-cis-Vitamin A

A concentrate of 6-cis-vitamin A was obtained from 6-cis-vitamin A acid

methyl ester by the previously reported method (1), and a modified method of "Organic Reactions" (6). As an antioxidant 0.1 % weight of butylated hydroxy toluene was added.

The above concentrate (18 g) was readily solidified on standing in a refrigerator. It was allowed to dissolve in *n*-hexane (72 ml) at  $50-55^{\circ}$  under a stream of nitrogen. A solution was slowly cooled to  $0^{\circ}$  for an hour and then cooled to  $-25^{\circ}$  for 4 hours. The crystals which separated were filtered and washed on a cold glass-filter and dried *in vacuo*. The crystal of 6-*cis*-vitamin A (15.6 g, yield 87 %) was brilliant pale yellow needles, and melted at 83-84.5°:  $\varepsilon$  (258, 321.5 m $\mu$ ), 10,400; 40,900. Analysis: C, 83.97; H, 10.70 %. Calculated for C<sub>20</sub>H<sub>30</sub>O: C, 83.86; H, 10.56 %. From the mother liquor a small quantity of the second crop was obtained.

#### 2. Crystalline 2,6-di-cis-Vitamin A

A concentrate of 2,6-di-*cis*-vitamin A (4.7 g), which had been obtained from 2,6-di-*cis*-vitamin A acid methyl ester by the method described for 6-*cis*-vitamin A, was dissolved in ethyl formate (5 ml), and cooled to  $-60^{\circ}$ . After several hours a crystalline solid was separated by filtration on a cold glass-filter. This solid, which

<sup>&</sup>lt;sup>1</sup> Melting points are not corrected. All ultraviolet absorption spectra were determined in ethanol.



FIG. 2 Infrared Absorption Spectra of all-trans-, neo-, 6-cis- and 2,6-di-cis-Vitamin A Palmitates (in 1% CS<sub>2</sub> Solution)

melted at room temperature, was dissolved in *n*-hexane, and concentrated *in vacuo*. The residual oil (2.2 g) was dissolved in *n*-hexane (10 ml), and cooled to  $-60^{\circ}$  for several hours. The crystals of 2,6-di-*cis*-vitamin A (1.2 g) were pale yellow needles, and melted at 59-60°;  $\varepsilon$  (262, 324 m $\mu$ ), 8,500; 38,000. Analysis: C, 83.91; H, 10.30 %. Calculated for C<sub>20</sub>H<sub>30</sub>O: C, 83.86; H, 10.56 %.

## 3. Crystalline 6-cis-Vitamin A Palmitate

Crystalline 6-cis-vitamin A (5.6 g) was dissolved in a mixture of *n*-hexane (60 ml) and pyridine (5 ml) and cooled to  $-15^{\circ}$ . A solution of distilled palmitoyl chloride (5.7 g) in *n*-hexane (20 ml) was slowly added with stirring under a stream of nitrogen. After standing overnight at the same temperature, protected from light, the reaction mixture was acidified with 5% sulfuric acid and was extracted with *n*-hexane. The extract was successively washed with water, 2% potash-aqueous methanol and water, and then dried over anhydrous sodium sulfate. After distillation of hexane under reduced pressure, the palmitate was obtained as a pale yellow oil (9.8 g yield 95.5%).

The residue was absorbed from *n*-hexane solution on a column (diameter 3 cm) of alumina<sup>2</sup> (100 g), and eluted with more *n*-hexane. The unesterified vitamin A and other impurities were separated as a sharp yellow band. The eluate was concentrated *in vacuo* and a nearly pure 6-*cis*-vitamin A palmitate (8.5 g) was obtained as a pale yellow oil which solidified in a refrigerator;  $\varepsilon$  (323 m $\mu$ ), 39,300.

The solidified ester was triturated with cold methanol (10 ml), filtered and washed with the same solvent. After three recrystallizations from acetone (10 ml) at 0°, 6-*cis*-vitamin A palmitate crystalls were white needles and melted at 40-41°;  $\varepsilon$  (260, 322.5 m $\mu$ ), 10,300; 40,400. Analysis: C, 82.45; H, 11.64 %. Calculated for C<sub>36</sub>H<sub>60</sub>O<sub>2</sub>; C, 82.38; H, 11.52 %.

## 4. Crystalline 2,6-di-cis-Vitamin A Palmitate

Crystalline 2,6-di-*cis*-vitamin A (1 g) was dissolved in mixture of *n*-hexane (30 ml) and pyridine (0.6 ml), and was esterified with palmitoyl chloride (1.1 g) in *n*-hexane (15 ml) in the same way. The palmitate, after purification by alumina chromatography, had  $\varepsilon$  (325 m $\mu$ ), 35,950 (1.7 g) and solidified in a cold state. After washing with methanol and recrystallization from acetone at 0°, the crystals of 2,6-di-*cis*-vitamin A palmitate were obtained as white needles, and melted at 29–C<sub>36</sub>H<sub>60</sub>O<sub>2</sub>: 30°;  $\varepsilon$  (264, 325 m $\mu$ ) 8,100; 36,000. Analysis: C, 82.54; H, 11.60 %. Calculated for C, 82.38; H, 11.52 %.

## SUMMARY

New two crystalline isomers of vitamin A palmitate are reported. These isomers are: 6-*cis*- and 2,6-di-*cis*-vitamin A palmitates. Only *neo*-vitamin A palmitate was non-crystallizable. The corresponding vitamin A acetates were all oily products except all-*trans*. These esters were prepared from each crystalline vitamin A isomer.

<sup>&</sup>lt;sup>2</sup> Alumina had been previously immersed in ethyl acetate overnight, filtered and dried at 80°.

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