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Synthesis of Vitamin A

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A preliminary account of this synthesis was reported recently in a Communication to THIS JOURNAL.[1] This work was undertaken originally with the objective in mind of exploring novel variations of certain synthetic approaches to vitamin A. To this end β-ionylideneacetaldehyde was chosen as a key intermediate and consequent hereto considerable effort was devoted to a study of this substance. As a result of this investigation, it has been possible to elucidate for the first time the exact character of β-ionylideneacetaldehyde implicit with its stereochemical relationship as a structural unit in vitamin A and vitamin A precursors.

The literature concerning β-ionylideneacetaldehyde has, until very recently,[2] been extremely confused. Many claims[3] to the synthesis of this compound have proven incapable of being duplicated and in no instance heretofore has β-ionylideneacetaldehyde *per se* been characterized as a pure substance (see below). In 1937 Kuhn and Morris[4] described the first synthesis of β-ionylideneacetaldehyde through the reduction of the toluidide of β-ionylideneacetic acid by means of chromous chloride. The product was characterized as its semicarbazone derivative m.p. 193–195° exhibiting maximum absorption at 3200 Å. This much disputed synthesis however, has never been successfully duplicated.[2,3] In 1947, Ahrens and van Dorp[5] and shortly thereafter Preobrazhenskii and Rubtsov[6] reported independently a successful synthesis of β-ionylideneacetaldehyde through the reaction of β-ionone with the Grignard reagent prepared from ethoxyacetylene followed by partial reduction and subsequent allylic rearrangement of the intermediate carbinol. The apparent identity of the semicarbazone derivative obtained by Ahrens and van Dorp with that of Kuhn and Morris substantiated the prior claim of the German workers to the synthesis of this compound. More recently, Ahrens and van Dorp[7] were able to prepare and isolate β-ionylideneacetaldehyde in very small amount as its semicarbazone derivative through the condensation of β-ionone with hydroxymaleic anhydride followed by decarboxylation and hydrolysis of the intermediate β-ionylidenepyruvic acid anil.

β-Ionylideneacetaldehyde as prepared by Ahrens and van Dorp was described as a clear yellow oil b.p. 118–122° at 10^{-2} mm. forming a semicarbazone derivative m.p. 194.5–196°. Our investigation on the synthesis of this compound has revealed that two stereoisomeric forms of this substance are normally to be anticipated from synthetic preparations, differing from each other in the disposition of groups (*cis* or *trans*) about the α,β-double bond. Both of these isomers have been isolated in pure form and in substantially equal amounts from our synthetic preparations and conclusively characterized.

Our synthesis was initiated from β-ionone (I). The latter was converted to ethyl β-ionylideneacetate (II) through the Reformatsky reaction with zinc and ethyl bromoacetate essentially according to the method of Karrer, Morf and Walker[8] as modified by Young, Andrews and Cristol.[9] Reduction of ethyl β-ionylideneacetate with lithium aluminum hydride according to Milas and Harrington[10] yielded β-ionylideneëthyl alcohol (III). This alcohol exhibited maximum absorption, however, at 2850 Å. in contrast to the value of 2740 Å. reported by these authors.[11] This alcohol, furthermore, was found to be extremely sensitive to air oxidation, absorbing exactly one mole of oxygen over a 24-hour period to form a moloxidic product which exhibited only end-absorption. β-Ionylideneëthyl alcohol formed a trityl ether derivative m.p. 132–134° $\lambda_{max}^{isooctane}$ 2850 Å. which proved to be surprisingly stable, thus resisting pyrolysis at 200° or prolonged refluxing with dimethylaniline and being recovered from both treatments essentially unchanged. It had been anticipated, moreover, that the trityl ether on pyrolysis would disproportionate into β-ionylideneacetaldehyde and triphenylmethane.[12]

Oxidation of β-ionylideneëthyl alcohol with manganese dioxide in petroleum ether, according to the recent method employed to convert vitamin A to vitamin A aldehyde,[13] produced a mixture of two stereoisomeric β-ionylideneacetaldehydes (IV) ($\lambda_{max}^{isooctane}$ 3165 $E_{1\,cm}^{1\%}$ 655),[14] in 60% yield which could be separated by chromatography into essentially equal amounts of the pure *trans* and *cis* isomers possessing spectra shown in Fig. 1. The *trans*-isomer was converted quantitatively to its **semicarbazone,** obtained as yellow plates from methanol m.p. 195–196°, whereas the *cis*-isomer formed a **semicarbazone,** quantitatively as yellow needle-like prisms from methanol m.p. 175–176°. The absorption spectra of the isomeric **semicarbazone** derivatives are shown in Fig. 2.

(1) Wendler, Slates and Tishler, THIS JOURNAL, **71**, 3267 (1949).

(2) For an excellent and comprehensive review and evaluation of the chemistry of vitamin A see O. Isler, *Chimia*, **4**, 103 (1950).

(3) Milas, "Vitamins and Hormones," Vol. 5, Academic Press, New York, N. Y., 1947, p. 1.

(4) Kuhn and Morris, *Ber.*, **70**, 853 (1937); *J. Chem. Soc.*, 613 (1938).

(5) Ahrens and van Dorp, *Nature*, **160**, 189 (1947); *Rec. trav. chim.*, **67**, 973 (1948).

(6) Preobrazhenskii and Rubtsov, *J. Gen. Chem. (U. S. S. R.)*, **18**, 1719 (1948).

(7) Ahrens and van Dorp, *Rec. trav. chim.*, **67**, 459 (1948).

(8) Karrer, Morf and Walker, *Helv. Chim. Acta*, **15**, 878 (1932).

(9) Young, Andrews and Cristol, THIS JOURNAL, **66**, 520 (1944).

(10) Milas and Harrington, *ibid.*, **69**, 2247 (1947).

(11) This alcohol has also been prepared recently by Inhoffen, Bohlmann and Bohlmann (*Ann.*, **565**, 35 (1949)). These authors report the absorption of this compound at 2700–2800 Å. In this connection it is interesting to note that Karrer and Benz (*Helv. Chem. Acta*, **31**, 1048 (1948)) report maximum absorption for β-ionylideneëthane at 2820 Å.

(12) See for example Norris and Young, THIS JOURNAL, **52**, 753 (1930).

(13) Ball, Goodwin and Morton, *Biochem. J.*, **42**, 516 (1948).

(14) At a recent meeting of the Metropolitan-Long Island Subsection of the New York Section of the American Chemical Society at the Hotel Granada, Brooklyn, N. Y. on March 17, 1950, Schwartzkopf and Levine reported the preparation of β-ionylideneacetaldehyde by Rosenmund reduction of β-ionylidene acetyl chloride.

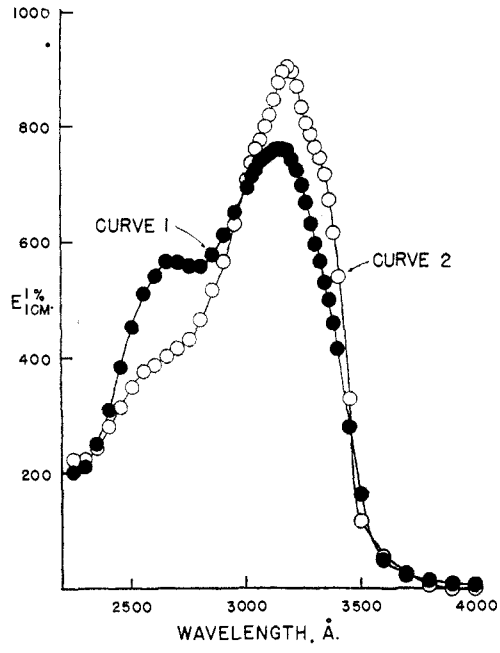


Fig. 1.—Absorption spectra in isoöctane of *trans*-β-ionylideneacetaldehyde (Curve 1) and *cis*-β-ionylideneacetaldehyde (curve 2).

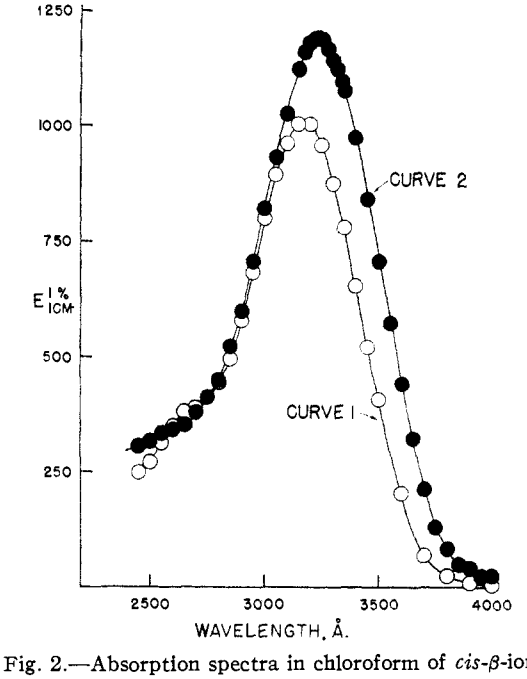


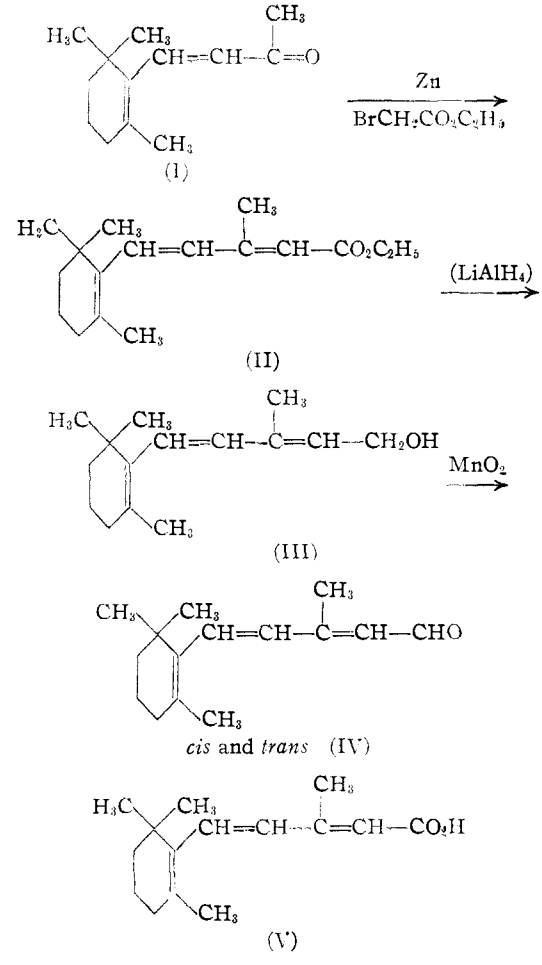
Fig. 2.—Absorption spectra in chloroform of *cis*-β-ionylideneacetaldehyde semicarbazone (curve 1) and *trans*-β-ionylideneacetaldehyde semicarbazone (curve 2).

The prefixes *nor-* and *iso-* were employed earlier (see ref. 1) to differentiate the two isomeric β-ionylideneacetaldehydes, since at that time the exact assignment of configuration was somewhat in doubt. Recently, however, the isomer previously designated as *nor-* has been identified with β-ionylideneacetaldehyde obtained from the oxidation of β-carotene[15]; to the latter is ascribed an all *trans* configuration.[16]

(15) Wendler, Rosenblum and Tishler, THIS JOURNAL, **72**, 234 (1950).

(16) Zechmeister, LeRosen, Schroeder, Polgár and Pauling, *ibid.*, **65**, 1940 (1943); Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

Both isomeric aldehydes were oxidized by alkaline silver oxide to yield the same crystalline β-ionylideneacetic acid (V) m.p. 126–127° found to be identical with the crystalline acid obtained from the saponification of ethyl β-ionylideneacetate.[8,9] Whereas the *trans*-aldehyde was oxidized rapidly and in fair yield, the oxidation of the *cis*-aldehyde proceeded at a markedly slower rate to give a somewhat lower yield of crystalline acid.



The isomerism arising in β-ionylideneacetaldehyde undoubtedly originates during the formation of ethyl β-ionylideneacetate as evidenced from the spectrum of this compound as well as from the mixture of crystalline and liquid acids obtained from its saponification.[8,9] The persistence of this isomerism in β-ionylidene ethyl alcohol is indicated by the lack of sharpness in melting point of its trityl ether derivative. The energy differences existing between the isomeric forms must be small since the conditions of formation of ethyl β-ionylideneacetate are ideal for producing the more stable isomer and yet essentially equal amounts of the two isomeric C_{15}-aldehydes were invariably realized from this compound.[16a]

(16a) Shortly after this work had been submitted for publication, a communication appeared by H. O. Huismann (*Rec. trav. chim.*, **69**, 851 (1950)). It was stated therein that, in contrast to our own findings, only one isomer (*trans*, (nor-)) of β-ionylideneacetaldehyde could be obtained. In the absence of experimental detail or any direct reference to the procedure employed it is difficult to evaluate this inconsistency with regard to isomer formation.

Both the *cis-* and *trans-* forms of β-ionylideneacetaldehyde were independently submitted to the succeeding steps of the synthesis and were found to give essentially one and the same vitamin A acid (X). Thus in the course of succeeding reaction phases, all apparent isomeric differences appeared to have vanished.

The two β-ionylideneacetaldehydes were independently submitted to condensation with acetone in the presence of aluminum *t*-butylate[17] to produce the C_{18}-ketone (VI). The C_{18}-ketone preparation obtained from the *trans-* series was well characterized by its single band at 3350 Å. and its **semicarbazone** m.p. 186–188°, both of which were in agreement with values reported.[18] The C_{18}-ketone preparation obtained from the *cis-* series, however, possessed a broad flat band in the 3360 Å. region which was not greatly improved in character by chromatography or fractional distillation in high vacuum. The analysis of this ketone preparation, however, was in substantial agreement with a C_{18}-ketone structure (VI) although it failed to give a well-defined semicarbazone derivative. Careful chromatography of the latter, however, did yield a small amount of material m.p. 141–143° with a $\lambda_{max.}$ 3400 Å., $E^{1\%}_{1\,cm.}$ 1500, in excellent agreement with the values reported by Ahrens and van Dorp[19] for their *cis*-C_{18}-ketone obtained by another route. These authors also experienced difficulties with this compound. Our results appear to indicate that a partial inversion of the *cis*-structure occurred during the condensation to give a mixture of isomeric C_{18}-ketones.[20]

The two C_{18}-ketone preparations were converted independently to the known Reformatsky ester (VII)[18,21] and thence to vitamin A ester (IX) by dehydration with iodine in high-boiling petroleum ether according to the technique employed by Isler, Huber, Ronco and Kofler[22] in another synthetic series. The crude vitamin A ester (IX) was given a preliminary purification on alumina and then saponified to vitamin A acid (X). Identical vitamin A acid (Fig. 3) as revealed by melting point and mixed melting point determinations was obtained from both the *cis-* and *trans-*series and in nearly the same yield (20–25% over-all from β-ionylideneacetaldehyde). This acid possessed physical characteristics in substantial agreement with those reported[18] (see however experimental section, ref. 24). This same acid was also produced in somewhat lower yield by initial saponification of the Reformatsky ester (VII) to the corresponding C_{20}-hydroxy acid (VIII) followed by iodine dehydration of the latter. By this procedure, however,

(17) Milas and Harrington (THIS JOURNAL, **69**, 2247 (1947)) reported the conversion of β-ionylideneethyl alcohol to the C_{18}-ketone by the Oppenauer oxidation of the former in the presence of acetone and aluminum *t*-butylate. We repeated this preparation many times and invariably recovered 75–80% of unchanged β-ionylidene ethyl alcohol together with a small fraction of material absorbing at 3350 Å. The latter failed in our hands to give a crystalline semicarbazone and probably represented a mixture (see above).

(18) Ahrens and van Dorp, *Rec. trav. chim.*, **65**, 338 (1946).

(19) Ahrens and van Dorp, *ibid.*, **66**, 759 (1947).

(20) For an example of geometrical inversion produced by aluminum alkoxides see Lutz and Gillespie, THIS JOURNAL, **72**, 344 (1950).

(21) Schwartzkopf, Cahnmann, Lewis, Swidinsky and Wuest, *Helv. Chim. Acta*, **32**, 443 (1949).

(22) Isler, Huber, Ronco and Kofler, *ibid.*, **30**, 1911 (1947).

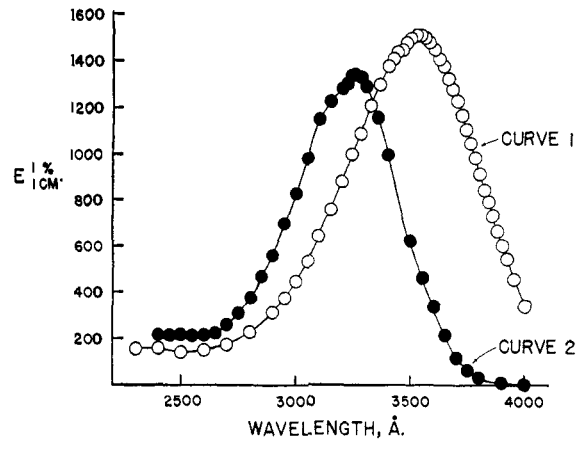


Fig. 3.—Absorption spectra of vitamin A acid in ethanol (curve 1) and vitamin A in isoöctane (curve 2).

there was isolated in addition to vitamin A acid a neutral fraction with an absorption spectrum (Fig. 4) identical with that of desmethylaxerophthene (XI).[23] This hydrocarbon was obviously formed as a result of decarboxylation during the dehydration process.

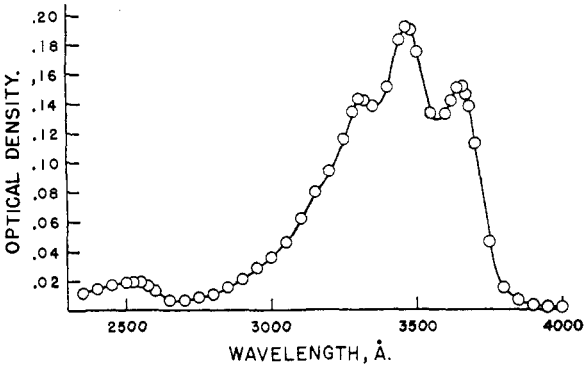


Fig. 4.—Absorption spectrum in isoöctane of desmethylaxerophthene (XI) obtained from I_2-dehydration of the C_{20}-hydroxy acid (VIII).

Crystalline vitamin A acid was reduced with lithium aluminum hydride to vitamin A with an absorption spectrum shown in Fig. 3.

Experimental

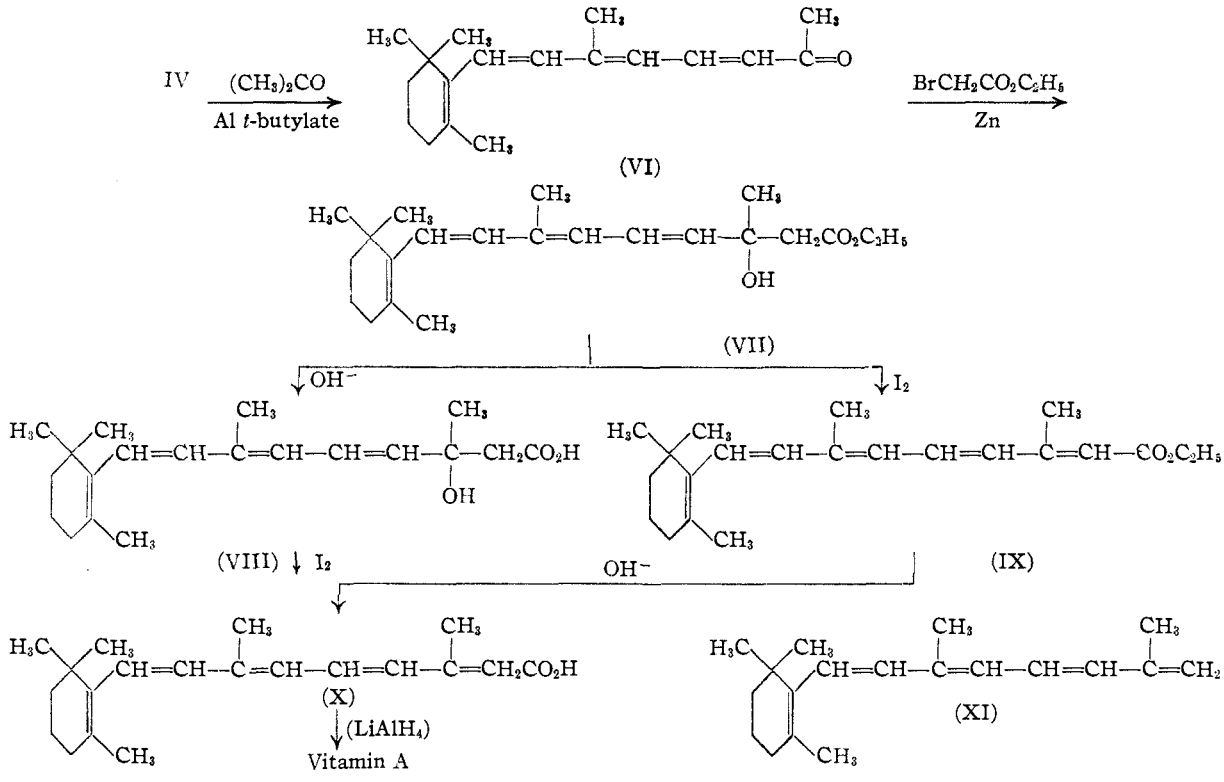
Ethyl β-Ionylideneacetate (II).—This ester was prepared according to the modified procedure of Young, Andrews and Cristol[9] using highly purified β-ionone of λ_{max} 2960 Å., ε 10,700. The ester was obtained as a colorless oil b.p. 164–166° at 6 mm. $\lambda^{C_2H_5OH}_{max.}$ 2850 Å., $E^{1\%}_{1\,cm.}$ 1045.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.97; H, 10.06.

Saponification of a sample of this ester according to Karrer, Solomon, Morf and Walker[8] afforded a small amount of crystalline **β-ionylideneacetic acid**, m.p. 125–126°, found to be undepressed on admixture with the crystalline acid obtained by silver oxide oxidation of β-ionylideneacetaldehyde (see below).

β-Ionylideneethyl Alcohol[10] **(III).**——In a 1-liter 3-necked flask equipped with mercury-seal stirrer, addition funnel and condenser with drying tube were placed 200 ml. of ether (dried over calcium hydride) and 5 g. of lithium aluminum hydride. The solution was stirred with cooling in an ice-bath while a solution of 26 g. of ethyl β-ionylidene-

(23) Schantz, THIS JOURNAL, **68**, 2553 (1946); see also Karrer and Benz, *Helv. Chim. Acta*, **31**, 1607 (1948).



acetate in 100 cc. of anhydrous ether was added dropwise. After the addition was complete, the mixture was stirred at 0° for 1.5 hours. The excess lithium aluminum hydride was decomposed by dropwise addition of 50 cc. of water. The ether layer was separated and the aqueous layer extracted thoroughly with additional ether. The combined ether extracts were washed with 5% aqueous potassium hydroxide and finally with water until no longer basic, and dried over anhydrous sodium sulfate. A few crystals of hydroquinone were added to the ether solution and the solvent removed *in vacuo*. Distillation of the residue after removal of solvent through a short Vigreux column in a nitrogen atmosphere afforded 18 g. (83%) of β-ionylideneethyl alcohol b.p. 112–114° at 0.4 mm. $\lambda_{max.}^{isooctane}$ 2850 Å., $E_{1\,cm.}^{1\%}$ 1330.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.52; H, 11.20.

β-Ionylideneëthyl Alcohol Trityl Ether.—A solution of 18.5 g. of β-ionylideneëthyl alcohol in 125 cc. of anhydrous pyridine was treated in the cold with 28 g. of triphenylmethyl chloride (m.p. 111–113°). The reaction mixture deposited pyridine hydrochloride copiously after the first hour and was allowed to stand at room temperature for 24 hours. At the end of this period the pyridine hydrochloride was removed by filtration and washed with ether. The combined filtrate and ether washings were extracted with 1% aqueous hydrochloric acid and finally washed with dilute aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The dried ether solution was concentrated and crystallization of triphenylcarbinol effected by addition of petroleum ether. After removal of the triphenylcarbinol by filtration, the filtrate was concentrated to a small volume whereupon the trityl ether of β-ionylideneethyl alcohol crystallized. Recrystallization from ether–acetone afforded 12–13 g. (30%), m.p. 132–134° $\lambda_{max.}^{C_2H_5OH}$ 2850 Å. $E_{1\,cm.}^{1\%}$ 733.

Anal. Calcd. for $C_{34}H_{38}O$: C, 88.31; H, 8.22. Found: C, 88.13; H, 8.47.

Pyrolysis of the trityl ether of β-ionylideneëthyl alcohol at 200° for 2 hr. or refluxing for the same time in dimethylaniline, resulted only in the recovery of unchanged starting material.

β-Ionylideneacetaldehydes (IV).—A solution of 10 g. of β-ionylideneëthyl alcohol in 500 cc. of petroleum ether (b.p. 30–60°) was mechanically stirred for 7 days at room temperature and in a nitrogen atmosphere with 100 g. of precipitated manganese dioxide. The reaction mixture was protected from light. At the end of this digestion period the manganese dioxide was removed by filtration and washed thoroughly with petroleum ether and ether. The combined filtrate and washings were concentrated *in vacuo* to an orange oil weighing 7.7 g. This oil was dissolved in 800 cc. of low boiling petroleum ether and the solution passed through a column of 240 g. of weakly adsorbing acid-washed alumina. The column was eluted with mixtures of petroleum ether–benzene until the orange color produced with antimony trichloride in chloroform (characteristic color produced by β-ionylideneacetaldehyde) was no longer distinct. The eluates were combined and evaporated to dryness *in vacuo* thus affording a mixture of the isomeric aldehydes as an oil $\lambda_{max.}^{isooctane}$ 3165 Å., $E_{1\,cm.}^{1\%}$ 655. The mixture of aldehydes was dissolved in 800 ml. of low boiling petroleum ether and resolved into its components on 240 g. of more tightly-adsorbing alumina by fractional elution into 10 (or more fractions) with petroleum ether–benzene. Semicarbazone derivatives were prepared from 50–100-mg. aliquots of each fraction. From the melting point values of the crude derivatives, the cut-point where separation was effective could be readily ascertained at that position on the melting point curve where depression became manifest.

***cis*-β-Ionylideneacetaldehyde.**—Fractions 1 through 3 from the above chromatography, consisting of three 500-cc. petroleum ether eluates, were combined and concentrated to an oil *in vacuo*. This oil was evaporatively distilled in high vacuum at 80–85° (10^{-2} mm.) affording *ca.* 3 g. of essentially pure *cis*-β-ionylideneacetaldehyde as a pale yellow oil; n_D^{25} 1.5780; $\lambda_{max.}^{isooctane}$ 3180 Å., $E_{1\,cm.}^{1\%}$ 904 (Fig. 1).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.57; H, 10.09. Found: C, 82.14; H, 10.33.

The yields varied in several experiments from 25–30% of theory.

cis-β-Ionylideneacetaldehyde was dissolved in aqueous ethanol and treated with an equal weight each of semicarbazide hydrochloride and anhydrous sodium acetate. Slow crystallization of ***cis*-β-ionylideneacetaldehyde semicarbazone**, m.p. 171–173.5°, occurred which was quantitative after several hours. The material was recrystallized from methanol and obtained as yellow needle-like prisms m.p. 175–176° $\lambda_{max.}^{CHCl_3}$ 3175 Å., $E_{1\,cm.}^{1\%}$ 1000 (Fig. 2).

Anal. Calcd. for $C_{16}H_{25}ON_3$: C, 69.82; H, 9.09; N, 15.27. Found: C, 70.16; H, 9.07; N, 15.03.

***trans*-β-Ionylideneacetaldehyde.**—Fractions 6 through 10 from the above chromatography consisting of eluates 5% benzene in petroleum ether through 100% benzene were combined and concentrated to an oil *in vacuo*. This oil was evaporatively distilled in high vacuum at 90–95° (10^{-2} mm.) affording *ca.* 3 g. of essentially pure *trans*-β-ionylideneacetaldehyde as a pale yellow oil; n_D^{25} 1.5780; $\lambda_{max.}^{isooctane}$ 2650 Å., $E_{1\,cm.}^{1\%}$ 567 and 3150 Å., $E_{1\,cm.}^{1\%}$ 760 (Fig. 1).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.57; H, 10.09. Found: C, 82.14; H, 10.35.

The yields varied in several experiments from 25–30% of theory.

trans-β-Ionylideneacetaldehyde was treated in aqueous ehtanol with an equal weight each of semicarbazide hydrochloride and anhydrous sodium acetate. Immediate and quantitative crystallization of ***trans*-β-ionylideneacetaldehyde semicarbazone** m.p. 193–195° occurred. The material was recrystallized from methanol and obtained as yellow plates m.p. 195–196° $\lambda_{max.}^{CHCl_3}$ 3230, $E_{1\,cm.}^{1\%}$ 1330 (Fig. 2).

Anal. Calcd. for $C_{16}H_{25}ON_3$: C, 69.82; H, 9.09; N, 15.27. Found: C, 69.56; H, 8.82; N, 15.29.

A mixed melting point of this semicarbazone with β-ionylideneacetaldehyde semicarbazone obtained from the oxidation of β-carotene[15] showed no depression. A mixed melting point of the *cis*- and *trans*-β-ionylideneacetaldehyde semicarbazones was strongly depressed.

β-Ionylideneacetic Acid (V) from β-Ionylideneacetaldehyde.—A solution of 0.5 g. of *trans*-β-ionylideneacetaldehyde in 10 ml. of ethanol was added to a vigorously stirred suspension of silver oxide freshly prepared by addition of 0.35 g. of potassium hydroxide in 15 cc. of 95% ethanol to 1 g. of silver nitrate dissolved in 10 cc. of distilled water. The mixture was stirred vigorously for 30 minutes at room temperature and then the reaction mixture was filtered, diluted with 200 cc. of water and extracted thoroughly with ether. The aqueous layer was acidified to congo paper with dilute aqueous hydrochloric acid and extracted thoroughly with ether. The ether solution of the acid was dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a buff-colored crystalline residue which was recrystallized from ether–petroleum ether affording 250 mg. of *trans*-β-ionylideneacetic acid as colorless needles m.p. 126–127°; $\lambda_{max.}^{isooctane}$ 2550 Å., $E_{1\,cm.}^{1\%}$ 525 and 3000 Å., $E_{1\,cm.}^{1\%}$ 660; $\lambda_{max.}^{C_2H_5OH}$ 2550 Å., $E_{1\,cm.}^{1\%}$ 575 and 3000 Å., $E_{1\,cm.}^{1\%}$ 660.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.98; H, 9.46.

A solution of 0.5 g. of *cis*-β-ionylideneacetaldehyde was treated similarly with alkaline silver oxide in aqueous ethanol. (No crystalline acid was obtained on working up the reaction mixture after 30 minutes or 1 hour.) The oxidation was allowed to proceed in a nitrogen atmosphere for 16 hours and the product was worked up as previously described. There was obtained after crystallization from ether–petroleum ether 100 mg. of *trans*-β-ionylidene acetic acid m.p. 124.5–126° which was neither depressed on admixture with the acid obtained from the *trans*-aldehyde nor with the crystalline acid formed from the saponification of ethyl β-ionylidene acetate (see above).

C_{18}-Ketone (VI).—(A) In a 500-cc. flask were placed 4.3 g. of *cis*-β-ionylideneacetaldehyde, 12 g. of aluminum *t*-butylate, 60 cc. of dry acetone and 120 cc. of dry benzene. The mixture was refluxed in an atmosphere of nitrogen for 24 hours. At the end of this period the reaction mixture was cooled, shaken with 75 cc. of water to decompose the aluminum alkoxides and filtered. The benzene layer was separated from the filtrate, washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, finally at 0.1 mm. and 50° to afford 6.2 g. of crude product as an orange oil. This oil was purified by adsorption from petroleum ether solution on 150 g. of acid-washed alumina followed by elution with benzene–petroleum ether of that fraction giving a wine-red color with antimony trichloride in chloroform. Concentration of the eluates afforded 4.3 g. of a pale orange oil $\lambda_{max.}^{isooctane}$ 3360–3380 Å., $E_{1\,cm.}^{1\%}$ 968. The oil was submitted to evaporative distillation at 90–95° (10^{-2} mm.) affording a product absorbing with greater intensity although the flat peak persisted, $\lambda_{max.}^{isooctane}$ 3340–3370 Å., $E_{1\,cm.}^{1\%}$ 1100.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.71; H, 10.14. Found: C, 83.13; H, 10.08.

Chromatography of this material failed to improve substantially the character of the maximum absorption. A **semicarbazone** was obtained in low yield m.p. 141–143°; $\lambda_{max.}^{C_2H_5OH}$ 3400 Å., $E_{1\,cm.}^{1\%}$ 1500 in excellent agreement with the *cis*-C_{18}-ketone prepared by Ahrens and van Dorp.[19]

Anal. Found: C, 71.60; H, 9.13; N, 13.64.

(B) In a similar manner 1.5 g. of *trans*-β-ionylideneacetaldehyde in 25 cc. of acetone and 50 cc. of dry benzene together with 5 g. of aluminum *t*-butylate afforded 2.7 g. of crude C_{18}-ketone as an oil. The latter after purification on 70 g. of alumina gave 1.6 g. of purified material $\lambda_{max.}^{C_2H_5OH}$ 3360 Å., $E_{1\,cm.}^{1\%}$ 839. This material afforded a **semicarbazone** as yellow crystals from methanol m.p. 186–88° $\lambda_{max.}^{CHCl_3}$ 3490 Å., $E_{1\,cm.}^{1\%}$ 1680 (reported: m.p. 188.6–189.6°; $\lambda_{max.}^{CHCl_3}$ 3490 Å., log $E_{max.}$ 4.69).[18]

Anal. Calcd. for $C_{19}H_{29}ON_3$: C, 72.38; H, 9.21; N, 13.33. Found: C, 72.64; H, 9.11; N, 13.00.

C_{20}-Hydroxy Ester (VII).—(A) The above C_{18}-ketone preparation from the *cis*-series, 4.3 g., together with 75 cc. of anhydrous benzene, 3.04 g. of ethyl bromoacetate and 1.24 g. of activated zinc were refluxed with stirring in a nitrogen atmosphere. Reaction set in shortly after refluxing began and the color of the reaction mixture changed from light orange to red-brown. Refluxing and vigorous stirring were continued for 1 hour. The reaction mixture was then cooled, poured onto ice-cold 10% aqueous acetic acid and agitated thoroughly. The product was extracted with petroleum ether and the petroleum ether–benzene solution was washed successively with 10% aqueous acetic acid, dilute aqueous sodium bicarbonate solution and finally water. The solution was dried over anhydrous sodium sulfate, filtered and the solvents removed *in vacuo*. Last traces of solvent were removed at 50° and 0.1 mm. for 1 hour. There was thus obtained 5.6 g. of crude C_{20}-hydroxy ester (IX) as a light orange oil $\lambda_{max.}^{C_2H_5OH}$ 2925 Å., $E_{1\,cm.}^{1\%}$ 587 (reported: $\lambda_{max.}$ 2900 Å., ϵ 28050).[21]

(B) In a like manner 2.8 g. of the C_{18}-ketone preparation from the *trans*-series in 20 ml. of benzene together with 2.1 g. of ethyl bromoacetate and 0.85 g. of zinc was converted to 4 g. of crude C_{20}-hydroxy ester obtained as a light orange oil $\lambda_{max.}^{isooctane}$ 2890 Å., $E_{1\,cm.}^{1\%}$ 648.

Vitamin A Acid Ethyl Ester (IX).—(A) A solution of 4.5 g. of crude C_{20}-hydroxy ester from the *cis*-series in 50 cc. of petroleum ether (b.p. 95–100°) was refluxed for 5 minutes with 50 mg. of iodine. The reaction mixture was cooled and washed several times with 10% aqueous sodium thiosulfate solution. The organic layer was washed with water, dried over sodium sulfate and the solvents removed *in vacuo*. The residue was taken up in low-boiling petroleum ether and chromatographed on 125 g. of acid-washed alumina. Elution was effected with petroleum ether–benzene and that fraction collected which gave a red color with antimony trichloride in chloroform. Removal of the solvents *in vacuo* and finally at 50° and 1 mm. for 1 hour afforded 3 g. of crude vitamin A acid ester as a pale orange oil $\lambda_{max.}^{isooctane}$ 3472 Å., $E_{1\,cm.}^{1\%}$ 763 (reported: $\lambda_{max.}$ 3470 Å., ϵ 44500).[21]

(B) In a similar fashion crude C_{20}-hydroxy ester from the *trans*-series, 4 g. was converted to vitamin A acid ester and saponified directly to vitamin A acid without isolation (see below).

Vitamin A Acid (X).—(A) Vitamin A acid ester from the *cis*-series, 3 g., was dissolved in 22 ml. of ethanol and treated with 0.84 g. of potassium hydroxide dissolved in 3 cc. of distilled water. The reaction mixture was allowed to stand for 72 hours at room temperature in the dark in an atmosphere of nitrogen. At the end of this time the major share of the solvents was removed *in vacuo* at room temperature and the residue treated with water. The aqueous solution was extracted thoroughly with ether. The ether-washed aqueous layer was acidified carefully to congo paper with dilute hydrochloric acid and the material which sepa-

rated taken up in ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* yielded 2.1 g. of crude oily acid $\lambda_{max.}^{C_2H_5OH}$ 3460 Å., $E_{1\,cm.}^{1\%}$ 882. On the basis of an $E_{1\,cm.}^{1\%}$ of 1510 for the pure acid (see below), this material was estimated to contain *ca.* 1.2 g. of pure vitamin A acid, representing an over-all conversion of *ca.* 25%, from *cis*-β-ionylideneacetaldehyde.[24] The crude oily acid crystallized on addition of ether. Recrystallization from ether afforded the acid as fine, yellow needles, m.p. 180.5-181.5°, $\lambda_{max.}^{C_2H_5OH}$ 3530 Å., $E_{1\,cm.}^{1\%}$ 1510 (Fig. 3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.36. Found: C, 80.26; H, 9.55.

(B) In an identical manner crude vitamin A acid ethyl ester obtained from 4 g. of C_{20}-hydroxy ester in the *trans*-series was saponified to give *ca.* 1.1 g. of crude vitamin A acid as a yellow semi-sold $\lambda_{max.}^{C_2H_5OH}$ 3475–3500 A., $E_{1\,cm.}^{1\%}$ 905[24] (*ca.* 20% over-all from *trans*-β-ionylideneacetaldehyde). The latter was crystallized from ether affording the acid as yellow needles m.p. 179–180° $\lambda_{max.}^{C_2H_5OH}$ 3500 Å., $E_{1\,cm.}^{1\%}$ 1415.

Anal. Found: C, 80.39; H, 9.09.

A mixed melting point of this acid with the one obtained from the *cis*-series melted at 180–181°.

Vitamin A Acid from the C_{20}-Hydroxy Acid (VII).—A solution of 3 g. of C_{20}-hydroxy ester preparation from the *trans*-series was saponified as already described for vitamin A acid ester. There was obtained in this way crude **C_{20}-hydroxy acid** as an orange oil $\lambda_{max.}^{isooctane}$ 2920 Å., $E_{1\,cm.}^{1\%}$ 595. This oil was dehydrated by refluxing with 50 mg. of iodine in 50 cc. of petroleum ether (b.p. 95–110°) in the manner already described. The cooled reaction product was extracted with 5% aqueous sodium carbonate solution. The sodium carbonate extract was washed in turn with ether. Acidification of the aqueous layer precipitated an oil which was taken up in ether, washed with water and evaporated to a residue of 1.5 g. of crude vitamin A acid $\lambda_{max.}^{C_2H_5OH}$ 3470 Å., $E_{1\,cm.}^{1\%}$ 750. The crude acid crystallized on seeding and was recrystallized from ether m.p. 179–180°.

The neutral extracts from the iodine dehydration were combined and concentrated *in vacuo* to a dark brown oil (wt. 1 g.). This oil was chromatographed on 25 g. of acid-washed alumina. The eluate giving a purple color with antimony trichloride in chloroform was concentrated to an orange oil identified as desmethylaxerophthene (XI) by its absorption spectrum (Fig. 4); $\lambda_{max.}^{isooctane}$ 3310, 3460 and 3660 Å.

Vitamin A from Vitamin A Acid.—In a 100-cc. 3-necked flask, equipped with stirrer, reflux condenser, dropping funnel and nitrogen inlet was placed a solution of 300 mg. of lithium aluminum hydride in 50 cc. of anhydrous ether. The contents of the flask were cooled to 0°, stirred and maintained under a nitrogen atmosphere while a solution of 65 mg. of crystalline vitamin A acid in anhydrous ether was added dropwise over a period of 15 minutes. After addition was complete, the reaction mixture was stirred an additional 30 minutes. The reaction mixture was then decomposed by the cautious addition of 15 cc. of water. The ether layer was separated and 100 cc. of 5% aqueous potassium hydroxide was added to the aqueous layer and the latter extracted several times with small portions of ether. The combined ether extracts were washed with water until neutral to litmus and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded 62 mg. of a pale yellow oil $\lambda_{max.}^{isooctane}$ 3260 Å., $E_{1\,cm.}^{1\%}$ 1340 (80%) (Fig. 3).

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Summary

1. The synthesis of β-ionylideneacetaldehyde and its resolution into two stereoisomeric forms is described.

2. The independent conversion of the two isomeric forms to the same vitamin A acid and thence to vitamin A has been effected.

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(24) Ahrens and van Dorp[18] reported for pure Vitamin A acid: m.p. 181.5°, $\lambda_{max.}^{C_2H_5OH}$ 3470 Å., log $E_{max.}$ 4.64. The position of maximum absorption observed by these authors for their pure acid approximates what we observed for our crude product. The absorption spectral curve reported by these authors, however, possessed a considerable band spread in the region of maximum absorption. In this connection, Schwartzkopf, *et al.*,[21] reported for the ethyl ester of vitamin A acid, $\lambda_{max.}^{hexane}$ 3470 Å., ε 44500; the methyl ester obtained from crystalline vitamin A acid with diazomethane, however, was reported to absorb at 3540-3550 Å., ε 43600. The exact significance of these discrepancies in the absorption spectra is not clear, but very probably are associated with stereomutations in solution about the center of α,β-unsaturation (see the discussion of this point with regard to vitamin A aldehyde by Wendler, Rosenblum and Tishler[15]).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Octahydrocoumarins and their Reaction with Phosphorus Pentoxide

BY ROBERT L. FRANK AND RUTH C. PIERLE

The reaction of γ-lactones with phosphorus pentoxide[1,2,3] or similar reagents[4] has been shown to result in the formation of substituted cyclopentenones, a transformation analogous to the formation of cyclopentenones by ring closure of unsaturated acids.[4-8] In the present investigation the reaction has been extended to a group of δ-lactones, the four octahydrocoumarins XIV, XV, XVI and XVII.

Preparation of Octahydrocoumarins.—Direct hydrogenation of coumarins, if feasible, would yield a wide variety of octahydro derivatives, due to the many excellent methods for substituted coumarins.[9] de Benneville and Connor[10] have studied such hydrogenations and have found that, although octahydrocoumarin can be obtained in good yield from coumarin, the product is contaminated by dihydrocoumarin,[11] a by-product difficult to separate. Exhaustive hydrogenation to eliminate this impurity results in cleavage of the

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(5) Haberland and Heinrich, *Ber.*, **72B**, 1222 (1939); Chuang, Tien and Ma, *ibid.*, **69B**, 1494 (1936).

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(7) Nenitzescu and Przemetzky, *Ber.*, **74B**, 676 (1941).

(8) Johnson, Davis, Hunt and Stork, THIS JOURNAL, **70**, 3021 (1948).

(9) Sethna and Shah, *Chem. Revs.*, **36**, 1 (1945).

(10) de Benneville and Connor, THIS JOURNAL, **62**, 283, 3067 (1940).

(11) Preparation of a completely pure sample of octahydrocoumarin by another method in this investigation and determination of its refractive index ($n^{20}D$ 1.4912) indicates that the purest octahydrocoumarin yet obtained by hydrogenation still contains 10-12% of the dihydro derivative.