30. *The Action of the Oppenauer Reagent on Primary Alcohols, including Vitamin-A.*

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Attempts to obtain the aldehyde corresponding to vitamin-A by the oxidation of the latter with aluminium *tert.*-butoxide in the presence of acetone have resulted in the isolation of a ketone, $C_{23}H_{32}O$, characterised by a semicarbazone, m. p. 193°, a

p-tolylsemicarbazone, m. p. 217—218°, and a *p*-chlorobenzoylhydrazone, m. p. 198—199°. That this ketone is a secondary condensation product of the originally produced vitamin-A aldehyde with acetone has been established by a series of analogous reactions, *viz.*, oxidation of geraniol to ψ-ionone, cinnamyl alcohol to cinnamylideneacetone, benzyl alcohol to benzylideneacetone, and furfuryl alcohol to furfurylideneacetone. As neither tetrahydrogeraniol, β-phenylethyl alcohol, nor γ-phenylpropyl alcohol undergoes oxidation under these conditions, it would appear that the reaction is specific, in the case of primary alcohols, for those containing an activated hydroxyl group.

HOLMES and CORBET (*J. Amer. Chem. Soc.*, 1937, **59**, 2042) have described the preparation of crystalline vitamin-A and while it would appear that spectroscopically this material is virtually pure ($\varepsilon_{max.} = 60{,}000$), the low melting point (7·5—8°) would seem to indicate that it is a mixture of geometrical isomers [cf. δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylic acid; Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878]. This view, that vitamin-A (I), when obtained as a single entity free from geometrical isomers, will have a moderately high melting point, is based on the facts that the polyene aliphatic alcohols are high-melting solids ($\Delta^{\beta\delta\zeta}$-octatrien-α-ol, m. p. 100°; γη-dimethyl-$\Delta^{\beta\delta\zeta}$-octatrien-α-ol, m. p. 46—47°; $\Delta^{\beta\delta\zeta\theta}$-decatetraen-α-ol, m. p. 122—124°; $\Delta^{\beta\delta\zeta\theta\kappa}$-dodecapentaen-α-ol, m. p. 204°; and γηλ-trimethyl-$\Delta^{\beta\delta\zeta\theta\kappa}$-dodecapentaen-α-ol, m. p. 136—137°) and that even β-*cyclo*geraniol (II) has a melting point of 43—44°. (Kuhn and Hoffer, *Ber.*, 1934, **67**, 357). We have ourselves made many attempts, using rich vitamin-A concentrates prepared from halibut liver-oil, to obtain the vitamin in crystalline form, but have never met with the success achieved by Holmes and Corbet (*loc. cit.*), nor have we been more fortunate in our efforts to obtain a crystalline derivative by the method of Hamano (*Sci. Papers Inst. Phys. Chem. Research, Tokyo*, 1935, **28**, 69; 1937, **32**, 44), who claims to have prepared a β-naphthoate, m. p. 76°, and an anthraquinone-2-carboxylate, m. p. 124°.

In view of our unpromising results, we turned our attention to the possibility of converting the vitamin into its corresponding aldehyde (III), from which we hoped, after its purification *via* a suitable crystalline derivative, to regenerate the pure vitamin by reduction with aluminium *iso*propoxide. Oppenauer (*Rec. trav. chim.*, 1937, **56**, 141) has described an elegant method of oxidising secondary alcohols, *e.g.*, ergosterol, to the corresponding ketones by refluxing with aluminium *tert.*-butoxide in benzene solution in the presence of a large excess of acetone as hydrogen acceptor; in view of the mild conditions employed, we have investigated the application of this reaction to vitamin-A and other primary alcohols.

It was found that oxidation of a rich vitamin-A concentrate ($E^{1\%}_{1cm.}$ 3280 A. = 1300)* under these conditions gave a crude product exhibiting a new absorption band at 4010 A. ($E^{1\%}_{1cm.} = 950$) together with that at 3280 A. due to unchanged vitamin-A ($E^{1\%}_{1cm.} = 300$). After successive purifications by chromatographic adsorption on alumina and by

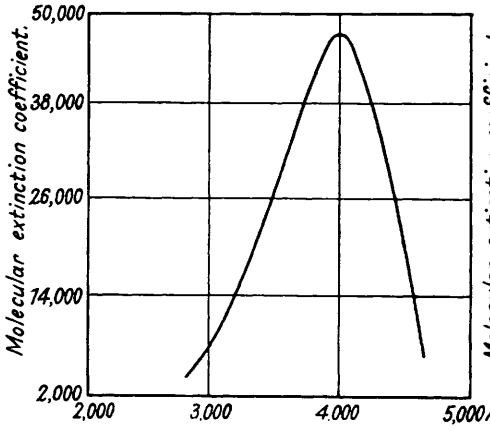
Compound.	Solvent.	$\lambda_{max.}$, A.	$\epsilon_{max.}$
(a) Carbonyl compound	EtOH	4010	48,900
(b) Semicarbazone of (a)	EtOH	3970	86,100
(c) *p*-Tolylsemicarbazone of (a)	$CHCl_3$	4140	84,200
(d) *p*-Chlorobenzoylhydrazone of (a)	$CHCl_3$	4135	80,800

treatment with the Girard Reagent P (Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095), a carbonyl compound was isolated exhibiting a single well-defined absorption maximum at 4010 A., the extinction coefficient ($E^{1\%}_{1cm.} = 1450$) of which remained unchanged after distillation in high vacuum. The compound formed a *semicarbazone*, m. p. 193°, a p-*tolylsemicarbazone*, m. p. 217—218°, and a p-*chlorobenzoylhydrazone*, m. p. 198—199°, the analyses of which revealed that they were derived, not from the anticipated aldehyde $C_{20}H_{28}O$, but from a substance of molecular formula $C_{23}H_{32}O$. The

* $E^{1\%}_{1cm.}$ is defined as the extinction coefficient ($\log I_0/I$) of a 1 cm. layer of a 1% solution of a substance at a particular wave-length, I_0 being the intensity of the light incident on the solution, and I the intensity of the transmitted light.

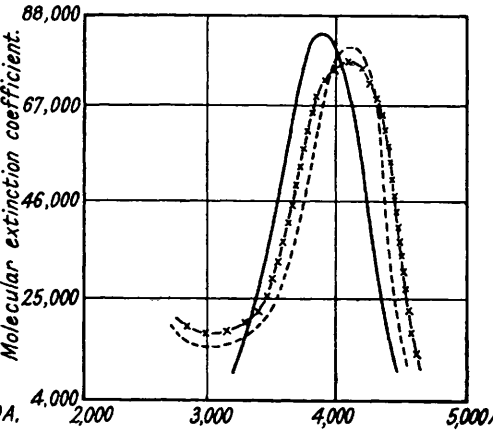
only feasible explanation of the production of such a compound is that it is the ketone (IV), formed by the subsequent condensation of the initially produced vitamin-A aldehyde with the acetone present. This is strongly supported by the spectrographic data (Table; Figs. 1 and 2), since the position of the absorption maximum of the carbonyl compound (4010 A.) lies mid-way between those of α-aldehydo-$\Delta^{\alpha\gamma\text{-enyl}}$-undecapentaene (V) and α-aldehydo-$\Delta^{\alpha\gamma\text{-enyl}\cdot\delta\varepsilon}$-pentadecaheptaene (VI), which absorb respectively at 3850 A. and 4120 A. (unpublished work).

FIG. 1.



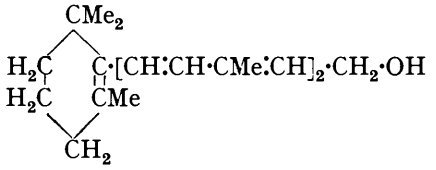
C_{23} *Ketone* (IV) *in* EtOH.

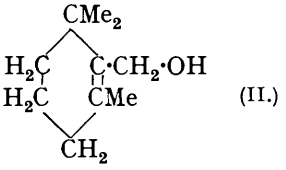
FIG. 2.

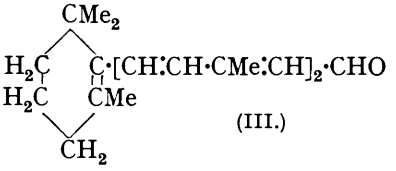


——— *Semicarbazone of* (IV) *in* EtOH.
– – – – p-*Tolylsemicarbazone of* (IV) *in* $CHCl_3$.
–×–×– p-*Chlorobenzoylhydrazone of* (IV) *in* $CHCl_3$.

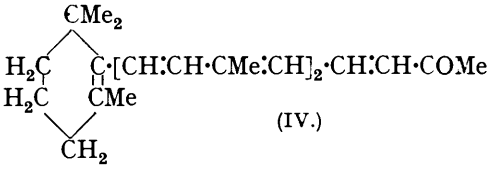
With a view to establishing the validity of this suggested reaction mechanism, the action of the Oppenauer reagent upon a selection of other primary alcohols was next investigated. We have found that, whereas geraniol gives a good yield of ψ-ionone and

(I.) 

(II.) 



(III.)



(IV.)

(V.) Me·[CH:CH]$_5$·CHO

(VI.) Me·[CH:CH]$_7$·CHO

cinnamyl, furfuryl and benzyl alcohols give respectively cinnamylidene-, furfurylidene-, and benzylidene-acetone, tetrahydrogeraniol, β-phenylethyl alcohol, and γ-phenylpropyl alcohol on the other hand are completely unreactive. It thus follows that, at any rate in the case of primary alcohols, an activating centre, such as an αβ-double bond or an aromatic nucleus contiguous to the CH_2·OH group, is necessary for oxidation to proceed.

While in none of the cases cited has it been possible to determine whether the aldehyde exists as such during the reaction, the ability of aluminium *tert.*-butoxide to effect condensation has been established by the conversion of citral into ψ-ionone by condensation with acetone under the standard conditions.

With the object of avoiding the complications due to the presence of the acetone, the reaction is now being studied with other ketones, such as di*iso*propyl ketone, which contain no reactive methylene groups.

Experimental.

Oxidation of Vitamin-A.—A solution of a vitamin-A concentrate (18·5 g., $E^{1\%}_{1cm.}$ 3280 A. = 1300) in a mixture of dry A.R. benzene (500 c.c.) and acetone (200 c.c., distilled from potassium permanganate and dried over potassium carbonate) was refluxed on the steam-bath in a stream of nitrogen for 30 hours together with freshly prepared aluminium *tert.*-butoxide (20 g.). The deep red suspension was diluted with water and filtered; the benzene layer was removed, washed with water, and dried over sodium sulphate. After removal of solvent under reduced pressure the residual red viscous oil was dissolved in light petroleum and adsorbed on a column of alumina. The dark reddish-brown zone, which passed slowly down the column on washing with solvent, was elutriated with light petroleum–methyl alcohol, and the elutriate washed with water and dried. After removal of solvent the product, which still contained vitamin-A, was dissolved in a mixture of absolute alcohol (200 c.c.) and glacial acetic acid (20 c.c.) and refluxed with Girard Reagent P (20 g.) for 1 hour. The whole was poured into water and, after neutralisation of 90% of the acetic acid with sodium bicarbonate, was repeatedly extracted with ether. The aqueous layer was warmed at 50—60° for ½ hour with a saturated solution of oxalic acid (20 g.), and the regenerated ketone extracted with ether. After removal of solvent from the washed and dried solution, the residual deep red oil was distilled in a high vacuum (bath temp. 135°, 10^{-4} mm.), giving β-*keto*-μ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-ζκ-*dimethyl*-$\Delta^{\gamma\epsilon\eta\lambda}$-*dodecapentaene* (IV) as a viscous orange-yellow oil which resisted all attempts at crystallisation. The ketone was characterised by a well-defined absorption maximum at 4010 A. ($E^{1\%}_{1cm.}$ = 1450) and with chloroformic antimony trichloride gave a blue-green colour with a maximum at 6460 A. (Found : C, 84·8; H, 9·6. $C_{23}H_{32}O$ requires C, 85·2; H, 9·9. Calc. for $C_{20}H_{28}O$: C, 84·5; H, 9·9%). The *semicarbazone*, prepared in the normal manner, crystallised from aqueous acetone in pale yellow micro-needles, m. p. 193° (Found : C, 75·6; H, 9·0; N, 11·2. $C_{24}H_{35}ON_3$ requires C, 75·6; H, 9·2; N, 11·0. Calc. for $C_{21}H_{31}ON_3$: C, 73·9; H, 9·1; N, 12·3%). The p-*tolylsemicarbazone* was prepared by heating a solution of the ketone (1·1 g.) in alcohol (30 c.c.), containing a few drops of glacial acetic acid, with *p*-tolylsemicarbazide acetate (0·8 g.) on the steam-bath for 10 minutes. The product, which separated on cooling, crystallised from ethyl acetate in golden-yellow needles, m. p. 217—218° (Found : C, 78·7; H, 8·6; N, 8·8. $C_{31}H_{41}ON_3$ requires C, 78·9; H, 8·7; N, 8·9. Calc. for $C_{28}H_{37}ON_3$: C, 77·9; H, 8·6; N, 9·7%). The p-*chlorobenzoylhydrazone* was obtained by refluxing the ketone (2 g.) with *p*-chlorobenzoylhydrazine (1 g.) in alcohol (15 c.c.), containing two drops of glacial acetic acid, for 1 hour. The product which separated from the hot solution crystallised from ethyl acetate in orange-red micro-crystals, m. p. 198—199° (Found : C, 75·3; H, 7·8; N, 5·9; Cl, 7·1. $C_{30}H_{37}ON_2Cl$ requires C, 75·5; H, 7·8; N, 5·9; Cl, 7·4. Calc. for $C_{27}H_{33}ON_2Cl$: C, 74·2; H, 7·6; N, 6·4; Cl, 8·1%).

Oxidation of Geraniol.—Geraniol (14 g.) was oxidised with aluminium *tert.*-butoxide (20 g.) in a mixture of acetone (200 c.c.) and benzene (500 c.c.) for 30 hours exactly as described above for vitamin-A. The crude product on distillation gave a main fraction, b. p. 155—165°/23 mm., consisting of almost pure ψ-ionone as shown by its absorption maximum at 2910 A. ($\varepsilon_{max.}$ = 22,800) in alcohol. Yield, 70%. The 2 : 4-dinitrophenylhydrazone, m. p. 141°, showed no depression in melting point on admixture with an authentic specimen.

Condensation of Citral with Acetone.—A solution of aluminium *tert.*-butoxide (20 g.) in a mixture of acetone (200 c.c.) and dry benzene (500 c.c.) was refluxed with citral (15 g.) for 30 hours. After dilution with water, filtration from alumina, and removal of the solvent from the dried benzene solution, distillation of the residue gave a 75% yield of ψ-ionone, b. p. 150—163°/25 mm., identified as above.

Cinnamylideneacetone.—Cinnamyl alcohol (10 g.) was oxidised with aluminium *tert.*-butoxide (20 g.) in a mixture of benzene (500 c.c.) and acetone (200 c.c.) for 24 hours at 90—95°. Distillation of the crude product gave two fractions : (a) b. p. 130—160°/20 mm. (2·1 g.), which did not solidify at 0°, and (b) b. p. 160—180°/20 mm. (6·2 g.). The solid which separated on cooling was freed from oil by pressure between porous tiles and crystallised from light petroleum (b. p. 40—60°), giving cinnamylideneacetone in pale yellow prisms, m. p. 68° (Diehl and Einhorn, *Ber.*, 1885, **18**, 2322, give m. p. 68°). For further characterisation the ketone was converted into its oxime, which crystallised from aqueous alcohol in needles, m. p. 152°.

Furfurylideneacetone.—Furfuryl alcohol (16 g.) was oxidised with aluminium *tert.*-butoxide (10 g.) in acetone (100 c.c.) and benzene (250 c.c.) as above for 24 hours. Distillation of the product gave a fraction (3·3 g.), b. p. 140—150°/50 mm., which solidified on cooling (m. p.

37—38°) and showed no depression in melting point on admixture with authentic furfurylideneacetone, m. p. 39°. Its phenylhydrazone, prepared in alcoholic acetic acid, crystallised from alcohol in yellow needles, m. p. 128—129°, no depression in melting point being observed on admixture with a specimen of furfurylideneacetonephenylhydrazone, m. p. 131°.

Benzylideneacetone.—Benzyl alcohol (8 g.) was oxidised by the standard method with aluminium *tert.*-butoxide (10 g.) in acetone (100 c.c.) and benzene (250 c.c.) for 24 hours. Distillation of the product gave two fractions: (a) b. p. 80—140°/25 mm. (2 g.); (b) b. p. 142—150°/25 mm. (3 g.). The latter, which solidified on standing to colourless plates, m. p. 40°, was characterised as benzylideneacetone by conversion into its oxime, m. p. 115° (Marshall, J., 1915, **107**, 521, gives m. p. 116°).

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