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# OXIDATION OF VITAMIN A ALCOHOL WITH PERACETIC ACID*

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**Abstract**—Oxidation of vitamin A alcohol (1) by peracetic acid in tetrahydrofuran at room temperature affords an amorphous product, which on purification by the column chromatography gives 11,12-epoxy vitamin A aldehyde (5; 45%) whose structure was determined on the basis of IR, UV, NMR and mass spectra. This reaction is compared with oxidations with other oxidants.

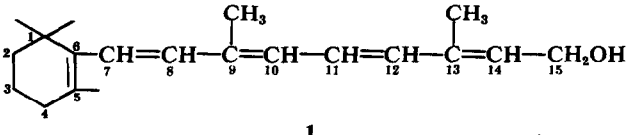
It is known that vitamin A alcohol (1) gives various oxidation products depending on the mode of oxidation including autoxidation. For example, it is reported that the oxidation with $MnO_2$[1] and the $PtO_2$-catalysed autoxidation[2] result in the conversion of its $CH_2OH$ to CHO, yielding vitamin A aldehyde (2). Troitskii[3] reported that monoperphthalic acid results in epoxidation of the 11,12-double bond to form 11,12-epoxy vitamin A alcohol (3), which was named chromogen 574 by Karrer.[4] But Karrer[5] claimed that the epoxidation occurs at the 7,8-double bond, leading to the 7,8-epoxy vitamin A alcohol, because $\lambda_{max}^{EtOH}$ 275 nm suggests a 7,8-epoxy system. In our previous paper[6] we showed that 3 was produced in the cobalt-catalysed autoxidation, which is similar to the monoperphthalic acid oxidation. In some cases, oxidation of the OH group to aldehyde together with epoxidation of the double bond followed by cyclisation takes place, e.g., the $MnO_2$ oxidation of 1 gives 3-methyl-7-(2,4,5,6,7,7a-hexahydro-4,4,7a-trimethyl-2-benzofuryl)-2,4,6-octatrienal (4).[7]

Because of the complex structure of 1 the structural analysis of the product is difficult, but modern tools may enable more accurate analysis. The present paper concentrates on the structure of the product obtained by the peracetic acid oxidation of 1, which is compared with the products formed by the other oxidants.

*Contribution No. 189.

## RESULTS AND DISCUSSION

The peracetic acid oxidation of 1 proceeds over 50% conversion after ca 10 hr. Its conversion was measured by a decrease of the absorbance at the characteristic UV maximum of 1 ($\lambda_{max}^{MeOH}$ 324·5 nm), the results being shown in Table 1. The product precipitated as dark yellow solid after THF and excess peracetic acid had been removed. The solid



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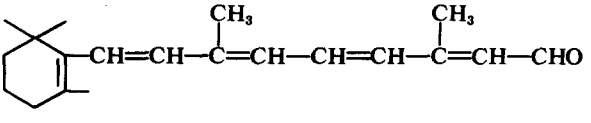

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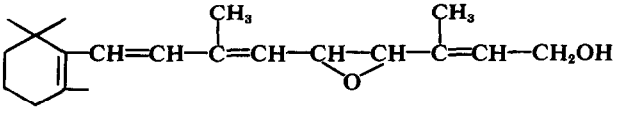

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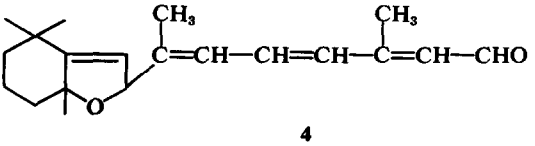

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Table 1. The yield and conversion percentage for peracetic acid oxidation of vitamin A alcohol (1) in THF at 25·3°: initial concentration, I: $9{\cdot}33 \times 10^{-3}$ M; peracetic acid: $4{\cdot}14 \times 10^{-2}$ M. Solvent (THF): 10 ml

| Reaction time (hr) | Yield ($\times 10^{-3}$ M)* | Conversion (%) |
|---|---|---|
| 0 | 0 | 0 |
| 2 | 1·81 | 19·4 |
| 4 | 2·46 | 26·4 |
| 7 | 3·93 | 42·2 |
| 10 | 5·44 | 58·3 |

*The yield was calculated by the UV spectrophotometric determination of epoxide 5 at 282 nm.

was purified by means of an alumina column using light petroleum and a mixture of light petroleum and methanol as eluents. On passing 1 through the column under air, slight change of 1 occurs, giving unknown products. Since the conversion of 1 was 58·3% and Fraction 6 was obtained in 45% yield, it is obvious that Fraction 6 is a main product. The other products are due to dehydration of 1 in the column and/or to other side reactions.

The product has characteristic UV peaks at 230 and 282 nm. According to the corrected relation[8] between the absorption maximum and a number of conjugated double bonds, $n$, in polyene, H—(CH=CH)$_n$—H, $1/\lambda_{max} = 0{\cdot}55/n + 0{\cdot}192$, ($n \leqq 5$), $\lambda_{max}$ should be 268 nm for $n = 3$ and $\lambda_{max}$ 304 nm for $n = 4$. Therefore, $\lambda_{max}$ of 282 nm in this product suggests a $n$ value of 3 rather than 4. Moreover, it is known that 11,12-epoxy vitamin A (3), which is obtained by monoperphthalic acid oxidation[3] or cobalt-catalysed autoxidation[6] of 1, has a UV peak at $\lambda_{max}^{EtOH}$ 275 nm. Hence, our product should have a structure with a similar number of the conjugated double bonds to that of 3 and the number is less than that of 1. The meaning of peak 230 nm will be discussed below.

The IR band at 3000 cm$^{-1}$ of the product is assigned to an epoxy ring methine in open chain or unstrained ring compounds, the strong IR band 1260 cm$^{-1}$ to $\nu_{sym}$ of an epoxy ring, and the IR bands 860 and 805 cm$^{-1}$ to $\nu_{unsym}$ of an epoxy ring. As apparent from Fig 1, the intensity of 965 cm$^{-1}$ band (out-of-plane hydrogen bending vibration of a *trans* —CH=CH—) of 1 decreases by proceeding of the oxidation of 1 which has two *trans* —CH=CH— at 7,8- and 11,12-positions. Therefore, the double bond at either 7,8-position or 11,12-position seems to be oxidised. As reported,[3,6] it is known that epoxidation of 1 occurs at 11,12-position rather than 7,8-position on account of the larger steric hindrance of the latter position. Furthermore, a report[3] that 7,8-epoxide has $\lambda_{max}$ at 320 nm supports that our product has an epoxide ring at 11,12-position because of its $\lambda_{max}$ at 282 nm.

The IR peak at 3500–3400 cm$^{-1}$ for OH in 1 disappears and a strong band at 1715 cm$^{-1}$ appears

Table 2. Isolation of oxidation products of 1 by a column packed with alumina deactivated with 10% water

| Fr. No. | Yield (%) | $\lambda_{max}^{MeOH}$ nm | Remark |
|---|---|---|---|
| 1 | 3 | 330, 348, 367, 388 | anhydrovitamin A[10] |
| 2 | 5 | 330, 348, 367 | |
| 3 | 14 | 324·5 | I |
| 4 | 5 | 315 (broad) | |
| 5 | 3 | 290, 450 | |
| 6 | 45 | 230, 282 | product |
| 7 | — | — | |

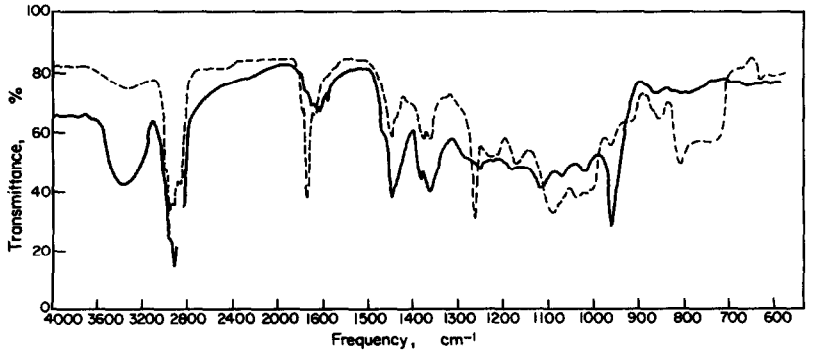



Fig 1. IR spectra of vitamin A alcohol (1) (full line) and 11,12-epoxy vitamin A aldehyde (5) (broken line).

in the product. Since the latter band corresponds to the CO group, oxidation of primary alcohol to aldehyde should have occurred.

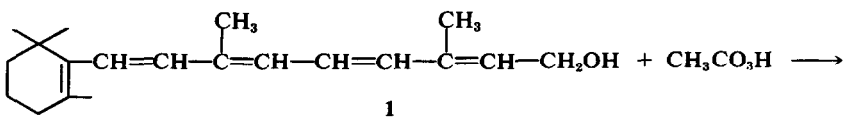
The UV absorption of $\lambda_{max}$ 230 nm suggests that the position of the CO group is terminal and that CO is conjugated with a double bond in view of the following reasoning. The known relation[9] between the absorption maximum and a number of conjugated double bonds, $m$, in polyene aldehyde, Me—(CH=CH)$_m$—CHO, suggests that $\lambda_{max}$ should be 220 nm for $m = 1$ and 270 nm for $m = 2$ and thus $m$ must be 1 in this case.

Complex NMR spectra were observed with the product. The assignment of peaks are shown in Table 3 in view of the reports on the NMR spectra of 1 and related compounds.[11–14] It is seen that the main skeleton of 1 is retained, with appearance of epoxy ring proton at 11- and 12-positions (2·41 and 3·35 ppm, respectively) and furthermore the protons of aldehyde and of its α-position (—CHO, =CH—CHO) 7·91 and 5·50 ppm, respectively. Therefore, it is apparent that 1 is oxidised to a product having both epoxide and aldehyde groups.

Moreover, the CO group was confirmed by the reaction with 2,4-dinitrophenylhydrazine. In the IR spectra of the corresponding 2,4-dinitrophenylhydrazone, a strong CO band at 1715 cm$^{-1}$ of original aldehyde disappears and a >C=N— band appears at 1620 cm$^{-1}$ and the —NH— band at 3300 and 3100 cm$^{-1}$.

The mass spectra of the oxidation product is shown in Table 4. The observed molecular weight of the product is 300 because the $M^+$ is 300 and observed fragmentation ($m/e$ = 29, 42, 69) is convincing by assuming structure 5; hence the structure 5 is most probable, in which the alcohol group of 3 is converted to aldehyde group.

In conclusion, the IR, UV, NMR and mass spectra together with the formation of 2,4-dinitrophenylhydrazone suggest that the peracetic acid oxidation of 1 affords 11,12-epoxy vitamin A aldehyde (5) as shown in Eq. 2.



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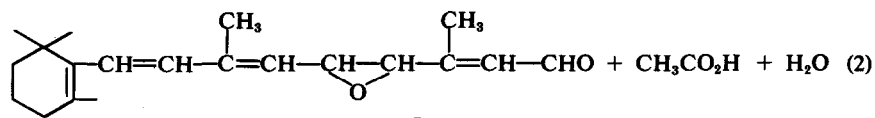

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The preferential attack of peracid on the 11,12-position may be explained as follows. The electrophilic nature of peracid favours the attacking site to be as far as possible from the electron-attracting OH (or CO) group, but the steric requirement, as apparent from the molecular model, hinders the attack at 5,6- and 7,8-positions. The reaction is similar to the $MnO_2$ oxidation, where both the epoxidation and the oxidation to aldehyde group occur to form 4, but the epoxidation position is different and rapid epoxidation occurs.

Table 3. The assignment of NMR signals of the peracetic acid oxidation product of vitamin A alcohol (1) in $CCl_4$ (1% TMS as an internal standard)

| Peaks, ppm | Assignment |
|---|---|
| 1·00 | —$CH_3$ ($C_1$) |
| 1·40, 1·68 | —$CH_2$— |
| 1·79, 1·91, 2·00 | —$CH_3$ ($C_5$, $C_9$, $C_{13}$) |
| 2·41, 3·35 | —CH—CH— (epoxide) |
| 5·50 | =CH—CHO |
| 4·75, 6·43 | =CH— |
| 7·91 | —CHO |

Table 4. The assignment of fragment ions in mass spectra from the peracetic acid oxidation product of vitamin A alcohol (1)

| $m/e$ | Percentage (%) | Assignment |
|---|---|---|
| 29 | 50 | —CH=O |
| 42 (base peak) | 100 | =CH—CHO |
| | | $CH_3$ |
| 69 | 17 | —C=CH—CHO |
| $M^+ - 18$ (272) | 5 | 5 − $H_2O$ |
| $M^+ - 1$ (299) | 5 | 5 − H |
| $M^+$ (300) | 4 | 5 |

## EXPERIMENTAL

M.p.'s measured by a Yanagimoto micromelting point apparatus are corrected. IR spectra were measured by a Perkin-Elmer Model 337 grating infrared spectrometer. UV spectra were measured by a Hitachi double beam instrument Model 124. NMR spectra were recorded by a Japan Electron Optic Laboratory Co., C60 HL NMR instrument. Electron impact fragmentation was carried out on a Mattauch type (JMS-OSG) mass spectrometer.

*Materials.* Vitamin A alcohol (1) was obtained by hydrolysis of vitamin A acetate (300,000 I.U./g) dissolved

in soybean oil (Sankyo Pharmaceutical Co.) and qualified by IR (Fig 1) and UV spectra, $\lambda_{max}^{MeOH}$, 324·5 nm.

Peracetic acid was obtained by the reaction of $Ac_2O$ (205 g) with 60% $H_2O_2$ (50 g) added with conc $H_2SO_4$ (0·5 ml) at 35–40°. THF was purified by distillation over Na, b.p. 66° (760 mm).

*Oxidation.* For the reaction of **1** with peracetic acid, **1** (initial concentration, $9·33 \times 10^{-3}$ M) was treated with peracetic acid (initial concentration, $4·14 \times 10^{-2}$ M) in THF (10 ml) at 25·3°. The product was concentrated by the removal of solvent and excess reagent.

Reaction of **5** with 2,4-dinitrophenylhydrazine.[15] **5** (0·1077 g) was dissolved in EtOH (6 ml) and was added with 2,4-dinitrophenylhydrazine (0·0730 g) and HCl (0·0133 g), refluxed for 10 min and cooled. The ppt of 2,4-dinitrophenylhydrazone was recrystallised from EtOH, m.p. 150–160°.

*Column chromatography.* A concentrated aliquot (1 g) of the product was passed through a column of 60 cm × 1·5 cm$^{\phi}$ packed with alumina deactivated with 10% water. The 1st, 2nd and 3rd elutions were done by light petroleum (500 ml) and the 4th, 5th and 6th elutions by a mixture (500 ml) of light petroleum and MeOH (90:10) and the 7th by a mixture (100 ml) of light petroleum and MeOH (50:50). A fraction collector was set to collect each 5 g fraction.

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