985. *Studies in the Polyene Series. Part LII.* Oxidation of Vitamin A_1 and Retinene$_1$ by Manganese Dioxide.*

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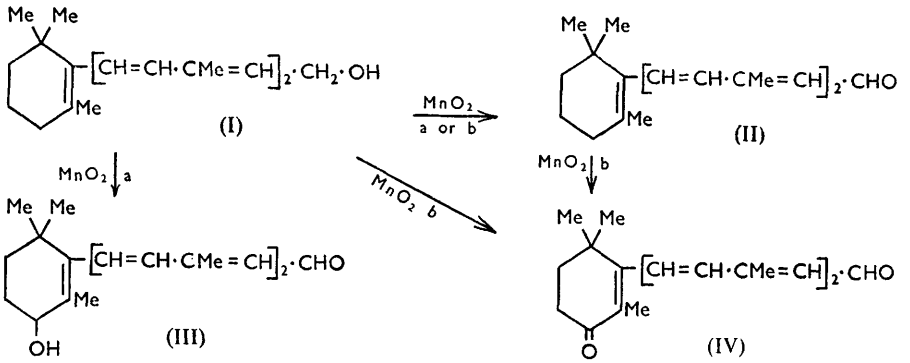
From a study of oxidation by manganese dioxide, it has been shown that oxygenation of the methylene group at the 3-position in the terminal ring may occur with β-ionylidene compounds, and oxo-derivatives of vitamin A_1 and retinene$_1$ have thus been prepared.

The best procedure for preparing retinene$_1$ (II) is by oxidation of vitamin A_1 (I) by the elegant and convenient manganese dioxide method.[1,2] In agreement with Wald [3] it was found that reaction was fast enough to be effected by merely filtering a solution of the alcohol in light petroleum through a tube containing the oxidising agent, and most of the experiments described below were carried out by this technique. Various samples of manganese dioxide gave different yields of retinene$_1$. The use of dioxide prepared by a modification of the procedure described by Attenburrow *et al.*[4] (see p. 4911) afforded almost quantitative yields of the aldehyde by the percolation technique. " Precipitated manganese dioxide " (B.D.H.) [MnO_2(a) on the chart] gave about an 80% yield of retinene together with 15% of a compound which was more difficult to elute. The latter was purified by chromatography but did not crystallise. Its ultraviolet absorption ($\lambda_{max.}$ 3700 Å in EtOH) was similar to that given [5] for a product (" 545 mμ chromogen "—antimony trichloride colour) obtained in a similar manner, and for which a 3-hydroxyretinene$_1$ structure (III) was favoured. This has been confirmed since (*a*) the infrared spectrum shows the presence of a hydroxyl group, (*b*) $\lambda_{max.}$ in the ultraviolet is displaced 100 Å to shorter wavelength from that of the parent aldehyde retinene$_1$—a similar shift was observed [6] with the simpler compounds, β-ionone and 3-hydroxy-β-ionone—and (*c*) interconversion with 3-oxoretinene$_1$ (IV) was achieved (see below).

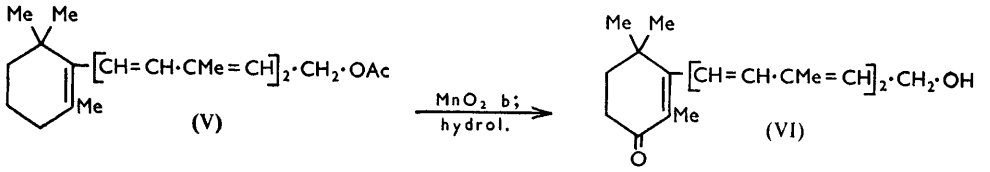


Another commercial sample of manganese dioxide (supplied by J. Woolley, Sons & Co. Ltd., and prepared under acidic conditions: see p. 4911) gave even more unusual results. When a pentane solution of vitamine A_1 was filtered through this material [MnO_2(b) on the chart], only a 30% yield of retinene$_1$ was eluted. A second product was eluted with ether, which on further purification gave a 25% yield of a crystalline compound. From

* Part LI, *J.*, 1955, 2765.

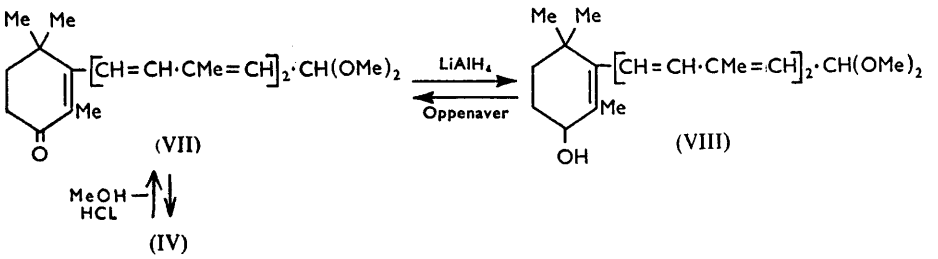
[1] Ball, Gordon, and Morton, *Biochem. J.*, 1948, **42**, 516.
[2] Farrer, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.
[3] Wald, *J. Gen. Physiol.*, 1947, **31**, 489.
[4] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[5] Wald, *J. Gen. Physiol.*, 1948, **31**, 489.
[6] Henbest, *J.*, 1951, 1074.

its physical properties and reactions this must be formulated as 3-oxoretinene$_1$ (IV). Similar treatment of retinene$_1$ also gave the 3-oxo-compound. As far as we are aware, oxidation of an allylic methylene group to an unsaturated ketone has not been effected previously by an insoluble reagent at room temperature, although the oxidation of *N*-methyl to *N*-formyl groups in mono- and di-methylanilines by the same manganese dioxide may be considered to be an analogous process.[7] The remarkable specificity of this oxidation occurring in the presence of the polyene chain prompted a preliminary examination of its generality.



Treatment of vitamin A$_1$ acetate (V) with a 20-fold weight of this manganese dioxide afforded some unchanged material and an acetoxy-ketone, which on hydrolysis gave 3-oxovitamin A$_1$ (VI) as golden plates ($\lambda_{max.}$ 3510 Å). This experiment proved therefore that a terminal carbonyl group in conjugation with the polyene system was not necessary to promote oxidation in the ring. However, an attempt to insert an oxo-group into anhydrovitamin A$_1$ was unsuccessful, the hydrocarbon being rapidly transformed into material displaying no characteristic ultraviolet absorption. β-Ionone is oxidised relatively slowly, the product apparently being 3-oxo-β-ionone. There are thus indications that in β-ionylidene compounds the rate of allylic oxidation by this type of manganese dioxide will parallel the rate of reaction of *N*-bromosuccinimide at the same position, *i.e.*, increasing rate with increasing unsaturation.

Not sufficient is as yet known about the course of reactions occurring by adsorption from solution on to the surface of an oxidising agent to warrant further discussion of the results obtained with the various batches of manganese dioxide. However, the fact that the material capable of oxidising an allylic methylene group to a ketone was prepared



under acidic conditions may be relevant for further work. Previous work [7] has shown that the oxidising power of manganese dioxide depends on the substrate. For the oxidations of retinene$_1$ and vitamin A$_1$ acetate to 3-oxo-compounds, approximately 9000 and 4600 g. of manganese dioxide are required respectively to give 16 g. of "available oxygen"—these figures may be compared with those given for the other oxidations in which the same commercial oxide was employed.

During this work it has also been shown that, in acidic methanol, retinene$_1$ and related compounds very readily form dimethyl acetals, from which the parent aldehydes are regenerated by acidic hydrolysis in aqueous acetone. The oxo-aldehyde (IV) affords an acetal (VII) in high yield, which on reduction by lithium aluminium hydride gives the hydroxy-acetal (VIII), converted by hydrolysis into 3-hydroxyretinene$_1$ (III), identical

[7] Henbest and Thomas, *J.*, 1957, 3032.

with that obtained by oxidation of vitamin A_1 by manganese dioxide. The hydroxyretinene (III) has also been prepared from retinene$_1$ by a modification of the route employed [6] to transform β-ionone into 3-hydroxy-β-ionone; the hydroxy-acetal (VIII) was an intermediate and could be oxidised by the Oppenauer method to the keto-acetal (VII) and thence converted into the keto-aldehyde (IV).

Light absorption of 3-substituted vitamin A_1 compounds

Compound	$\lambda_{max.}$ (Å)	ε
Vitamin A_1 (I)	3280	54,000
3-Oxovitamin A_1 (VI)	3510, 2780	34,000, 21,300
Retinene$_1$ (II)	3850	40,000
3-Hydroxyretinene$_1$ (III)	3750	40,000
3-Oxoretinene$_1$ (IV)	3800, 2930	42,500, 10,000
Retinene$_1$ dimethyl acetal	3280	47,000
3-Hydroxyretinene$_1$ dimethyl acetal (VIII)	3280	45,000
3-Oxoretinene$_1$ dimethyl acetal (VII)	3520, 2770	41,000, 22,000

The ultraviolet absorption characteristics of these 3-substituted vitamin A_1 compounds are listed in the accompanying Table. The three 3-oxo-compounds are characteristic in giving subsidiary maxima at shorter wavelengths.

Experimental

Formation of Retinene$_1$ (II) *and 3-Hydroxyretinene$_1$* (III).—A pentane solution (25 c.c.) of vitamin A_1 (prepared from vitamin A_1 acetate, 0·6 g.) was percolated through " precipitated " manganese dioxide (10 g.; B.D.H.). Washing with pentane (1 l.) afforded 80% of retinene$_1$. Further elution with ether–methanol (10 : 1) gave 3-hydroxyretinene$_1$ (0·1 g.) as a yellow oil, which was purified by further chromatography. Infrared spectrum on liquid: OH band at 3430 cm.$^{-1}$, C=O band at 1660 cm.$^{-1}$.

Repetition of this oxidation with manganese dioxide prepared by Haslam and Quibell's method (unpublished work at Manchester) gave an almost quantitative yield of retinene$_1$. In brief, this method involves treatment of a stirred solution of manganous sulphate tetrahydrate (200 g.) in water (200 c.c.) at 20° with potassium hydroxide solution (20 g. in 50 c.c. of water), followed immediately with potassium permanganate (130 g.) in water (2 l.). After 5 min. the solid was filtered off, and washed with water, and then sodium hydrogen carbonate solution until the pH of the washings was 5—7. The oxide was dried overnight at 100—120° in air. The average activity was $13·5 \times 10^{-4}$ g.-atoms of oxygen per g.

3 : 7-*Dimethyl*-9-(3-*oxo*-2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*nona*-2 : 4 : 6 : 8-*tetraen*-1-*al* (3-*Oxoretinene$_1$*) (IV) —A solution of vitamin A_1 (from vitamin A_1 acetate, 5 g.) in pentane (60 c.c.) was poured on manganese dioxide (100 g.; supplied by J. Woolley, Sons & Co. Ltd., and prepared by T. Tyrer & Co. Ltd., by addition of potassium permanganate solution to manganese sulphate solution followed by washing the product with water). Elution with pentane (3 l.) gave retinene$_1$ (1·13 g., 25%), and then further elution with ether afforded an orange oil (2 g.), which was rechromatographed on deactivated alumina (250 g.). The product from the main band crystallised from light petroleum–benzene (5 : 2) at −10°, to give 3-*oxoretinene$_1$* (1·0 g.) as thick orange needles, m. p. 117—118° (Found: C, 81·0; H, 8·75. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%), C=O band at 1655 cm.$^{-1}$.

Retinene$_1$ (0·6 g.) in pentane (10 c.c.) was filtered through the same manganese dioxide (10 g.). Elution with pentane (700 c.c.) gave starting material (0·3 g.). Elution with ether provided crude 3-oxoretinene$_1$ (0·25 g.), which after purification as before had m. p. 116—117°.

3 : 7-*Dimethyl*-9-(3-*oxo*-2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*nona*-2 : 4 : 6 : 8 -*tetraen*-1-*ol* (3-*Oxovitamin A_1*) (VI).—Vitamin A_1 acetate (0·5 g.) in pentane (20 c.c.) was percolated through manganese dioxide (10 g.; Woolley). Starting material (0·21 g.) was recovered by elution with pentane (700 c.c.). Ether eluted a product which was chromatographed on deactivated alumina (100 g.). The main yellow band gave material which was heated in methanol (10 c.c.) containing potassium hydroxide (100 mg.) for 45 min. The product (isolated with ether), dissolved in ether–pentane (1 : 1) was cooled to −10°; the 3-*oxovitamin A_1* (90 mg.) crystallised as orange-yellow

cubes, m. p. 140—141° (Found: C, 79·55; H, 9·25. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), having an OH band at 3400 and a C=O band at 1655 cm.$^{-1}$.

Alternatively, a pentane solution (50 c.c.) of vitamin A_1 acetate (1 g.) and manganese dioxide (20 g.; Woolley) was rolled for 20 hr. Chromatography gave starting material (0·27 g.), and pure oxo-acetate (0·20 g.), which did not crystallise but gave a good yield of solid oxo-vitamin on hydrolysis. If the proportion of manganese dioxide was doubled only a trace of starting material was obtained but the yield of oxo-acetate was not substantially improved. Manganese dioxide (Haslam and Quibell) did not oxidise vitamin A_1 acetate.

Conversion of Retinene$_1$ into 3-Oxoretinene$_1$ by N-Bromosuccinimide.—Pure, finely powdered *N*-bromosuccinimide (0·5 g.) was added at 0° to a solution of retinene$_1$ (0·64 g.) in freshly purified chloroform (20 c.c.), and the mixture stirred vigorously in air for 20 min. Light petroleum (40 c.c.) was added to the brown solution, and the mixture filtered into a solution of sodium formate (1·25 g.) in 90% formic acid (15 c.c.). After evaporation under reduced pressure to remove the light petroleum and most of the chloroform, dioxan (30 c.c.) was added and the mixture stirred at 20° for 2 hr. The formyloxy-aldehyde ($\lambda_{max.}$ 3710 Å) was isolated with ether, and dissolved in methanol (20 c.c.), and treated with concentrated hydrochloric acid (0·1 c.c.), the dimethyl acetal being formed ($\lambda_{max.}$ 3270 Å, see below). Hydrolysis of this with potassium hydroxide (0·55 g.) in 80% methanol (20 c.c.), followed by isolation and chromatography, afforded 3-hydroxyretinene$_1$ dimethyl acetal (0·2 g.) (see below). This was dissolved in dry benzene (3 c.c.), added to a solution of aluminium *tert.*-butoxide (0·24 g.) in dry benzene (4 c.c.) and acetone (1 c.c.), and heated for 24 hr. After isolation with ether, the acetal was hydrolysed with hydrochloric acid (0·01 c.c.) in acetone (5 c.c.), and the crude product purified by chromatography and crystallisation to give pure oxoretinene$_1$ (30 mg.), m. p. and mixed m. p. 116—117°.

Retinene$_1$ Dimethyl Acetal and 3-Oxoretinene$_1$ Dimethyl Acetal (VII).—Concentrated hydrochloric acid (0·1 c.c.) was added to retinene$_1$ (0·5 g.) dissolved in methanol (50 c.c.). After 10 min. the acid was neutralised by addition of triethanolamine (0·2 g.) in methanol (2 c.c.), and the product isolated with ether and purified by chromatography. The *acetal* (0·5 g.) was obtained as a pale yellow oil (Found: C, 80·5; H, 9·9. $C_{22}H_{34}O_2$ requires C, 80·0; H, 10·35%). C–O bands at 1055 and 1130 cm.$^{-1}$.

Similar treatment of 3-oxoretinene$_1$ (0·175 g.) gave the monoacetal (0·14 g.) as a yellow oil, with C=O band at 1660 cm.$^{-1}$ and C–O bands at 1060 and 1130 cm.$^{-1}$.

3-Hydroxyretinene$_1$ from 3-Oxoretinene$_1$.—A solution of lithium aluminium hydride (30 mg.) in dry ether (10 c.c.) was added with shaking to a solution of 3-oxoretinene$_1$ dimethyl acetal (0·14 g.) in dry ether at −30°. After 40 min. at −30° the solution was treated with ethyl acetate, and the product isolated as usual. The acetal (0·11 g.) was a pale yellow oil, having C–O bands at 1055 and 1130 cm.$^{-1}$. Hydrolysis of the acetal was effected by dissolving it in acetone (5 c.c.) containing concentrated hydrochloric acid (0·02 c.c.). Water was added after 5 min., and after chromatography 3-hydroxyretinene$_1$ was obtained as a yellow oil (0·1 g.), whose ultraviolet and infrared absorptions were identical with those of the product from manganese dioxide oxidation of vitamin A_1.

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