*Studies in the Polyene Series. Part L.** " *Anhydrovitamin A_2.*"

By H. B. Henbest, E. R. H. Jones, T. C. Owen, and V. Thaller.

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" Anhydrovitamin A_2 " is shown to be an ethoxyanhydrovitamin A_1 (IV).

Acid-catalysed dehydration of vitamin A_1 (I) yields a crystalline hydrocarbon, $C_{20}H_{28}$, anhydrovitamin A_1. The structure (III) now accepted for this compound was put forward by Shantz, Cawley, and Embree (*J. Amer. Chem. Soc.*, 1943, **65**, 901) and by Meunier, Dubou, and Vinet (*Bull. Soc. chim. France*, 1943, **25**, 371), and has recently received powerful support from the studies of Oroshnik, Karmas, and Mebane (*J. Amer. Chem. Soc.*, 1952, **74**, 295) on the " retro "-group of dehydration products in the vitamin A_1 series.

Similar treatment of natural vitamin A_2 with hydrochloric acid in ethanol was reported by Shantz (*Science*, 1948, **108**, 417) to yield a crystalline compound, m. p. 89·5°, analysing for $C_{20}H_{26}$ or $C_{20}H_{28}$, named anhydrovitamin A_2. This exhibited ultraviolet light absorption almost identical with that shown by anhydrovitamin A_1, but with antimony trichloride in chloroform vitamin A_1 and its anhydro-compound gave solutions with $\lambda_{max.}$ 6200 Å whereas those of the corresponding A_2 compounds both exhibited $\lambda_{max.}$ 6930 Å—this difference originally led to the detection of vitamin A_2 in fish oils eleven years earlier (Edisbury, Morton, and Simpkins, *Nature*, 1937, **140**, 234; Gillam, Heilbron, Lederer, and Rosanova, *ibid.*, p. 133). Shantz (*loc. cit.*) also observed that seven mols. of hydrogen were absorbed by the anhydro-A_2 compound on microhydrogenation.

When the structure of vitamin A_2 (II) was elucidated by synthesis (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657), it was confirmed that the vitamin was converted by ethanolic hydrochloric acid into a crystalline compound, m. p. 88°, exhibiting ultraviolet absorption identical with that shown by the anhydro-compound derived from the vitamin from natural sources. At this time the analytical data reported earlier for the dehydration product were accepted, and a structure (V) was proposed tentatively in a preliminary communication (*Chem. and Ind.*, 1951, 49).

Later, the infrared spectrum of the compound was determined, and it was found difficult to reconcile the presence of a very strong band near 1100 cm.$^{-1}$ with a hydrocarbon structure. Further study has now shown that the compound contains an alkoxyl group derived from the alcohol in which the reaction is carried out. Thus, " anhydrovitamin A_2 " is really 4′-ethoxyanhydrovitamin A_1 (IV), and use of methanol as reaction medium afforded the analogous methoxy-compound.

The new structure explains the close similarity between the ultraviolet absorption of the compounds (III) and (IV), closer agreement of ε values now being observed with the increased contribution from the molecular weight of the A_2-compound. The relatively strong band at 1100 cm.$^{-1}$ present in the infrared spectrum of (IV) [but not shown by (III)] is now readily explained as a C–O stretching frequency. The earlier hydrogenation

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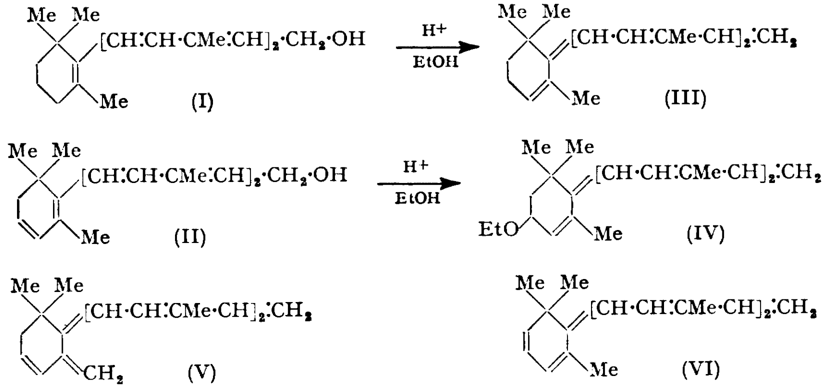
results may be reinterpreted by assuming that hydrogenolysis of the allylic C–O bond occurs, and the new formula also explains the ease of chromatographic separation of the two anhydro-compounds, whereas the parent alcohols are virtually inseparable (cf. Embree and Shantz, *J. Biol. Chem.*, 1940, **132**, 619).

The different course of reaction of the two vitamins upon treatment with dilute mineral acid may be interpreted as follows. In both the A_1- and the A_2-series, initial removal of a hydroxyl group with its bonding electrons should readily occur to give an allylic carbonium ion. In the A_1-series this loses a proton to the medium, yielding a hydrocarbon with a " retro "-structure, the ready formation of which indicates that this arrangement of double bonds represents a relatively stable, unstrained molecular structure. In the A_2-series, stabilisation by loss of a proton would most likely generate structure (V) or (VI). Compared with the analogues (III) or (IV), these would be expected to be strained owing to the enforced coplanarity of the terminal ring, which will cause increases in the internal bond angles of the singly linked carbon atoms. Reaction of the intermediate carbonium atom with solvent therefore takes place to give the unstrained "retro-ether" structure (*e.g.*, IV).



The reaction of anhydrovitamin A_1 with *N*-bromosuccinimide has also been studied as a possible route to compounds of a true anhydrovitamin A_2 structure (*e.g.*, V or VI). Reaction between the hydrocarbon and the bromo-imide occurred readily, even at —40°; the product at this stage showed little characteristic ultraviolet absorption and the presence of carbonyl bands in the infrared spectrum indicated that addition of reagent to the polyene system was the major reaction. However, if the reaction product was treated with *N*-phenylmorpholine some unsaturated hydrocarbon ($\sim$5%) could be isolated, and this on further chromatography gave a fraction exhibiting a main absorption maximum at 4080 Å, with subsidiary maxima at 3870 and 4330 Å. The absorption data are not inconsistent with the dehydro-structure (VI), but the small yield (1%) of this compound and its great sensitivity to oxygen rendered further investigation unattractive.

EXPERIMENTAL

General directions are as given in Part XLIII (*J.*, 1952, 2657).

4′-Ethoxyanhydrovitamin A_1 (IV).—A solution of vitamin A_2 (0·35 g.) (prepared as in the following paper) in ethanol (5 c.c.) was treated with anhydrous ethanolic hydrogen chloride (40 c.c.; M/30). After being kept at 20° for 20 min., the mixture was poured into water, and the product isolated with pentane, and then chromatographed on alumina (200 g.). Elution with pentane (400 c.c.) afforded a golden-yellow oil (0·2 g.) which was dissolved in pentane (2 c.c.) and filtered through alumina (0·1 g.) into a small tube. This was sealed with a bung, cooled to $-30°$, and then allowed to warm to $-10°$. During 2 days a crystalline product separated. The supernatant liquid was decanted and the material crystallised twice in a similar manner, to give the *ethoxy-compound* as thick yellow needles, m. p. 86—88° (Found: C, 84·55; H, 10·35; OEt, 14·5. $C_{22}H_{32}O$ requires C, 84·55; H, 10·3; OEt, 14·4%). Ultraviolet absorption: $\lambda_{max.}$ 3520, 3700, and 3910 Å (ε 63,800, 95,000, and 85,600 respectively).

Infrared spectrum: peaks at 2980, 2940, 2870, 1450, 1362, 1200, 1085, 1102, 985, 968, and 885 cm.$^{-1}$.

The *methyl ether*, prepared similarly, had m. p. 76—77° (Found: C, 84·4; H, 10·35; OMe, 10·7. $C_{21}H_{30}O$ requires C, 84·5; H, 10·15; OMe, 10·4%).

Reaction of Anhydrovitamin A_1 with N-*Bromosuccinimide.*—*N*-Bromosuccinimide (0·858 g., 1·18 mol.) was added to a stirred solution of the hydrocarbon (1·09 g.) in chloroform (25 c.c.; freshly distilled from P_2O_5) at −45° in a nitrogen atmosphere. The solution was warmed to −20° during 30 min. *N*-Phenylmorpholine (2·2 g.) was then added. The mixture was heated under reflux for 2 min., cooled, poured into dilute hydrochloric acid, and extracted with light petroleum. After the usual processing the organic extract was evaporated under reduced pressure. The tarry residue was extracted with light petroleum; the soluble material (62 mg.) showed $\lambda_{max.}$ 3700 and 4070 Å. Chromatography on alumina (150 g.; P. Spence, grade O) with light petroleum as developing solvent gave three yellow zones. The most readily eluted showed $\lambda_{max.}$ 3700 Å, the next showed $\lambda_{max.}$ 3700 and 4080 Å, and the last exhibited $\lambda_{max.}$ 3870, 4080, and 4330 Å. All of these fractions were orange, very oxygen-sensitive gums.

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THE UNIVERSITY, MANCHESTER, 13.

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