Studies in the Polyene Series. Part LI. Conversion of Vitamin A_1 into Vitamin A_2.*

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A method for converting vitamin A_1 into vitamin A_2 has been devised which makes the latter readily accessible. Crystalline vitamin A_1 acid nitrile is also described.

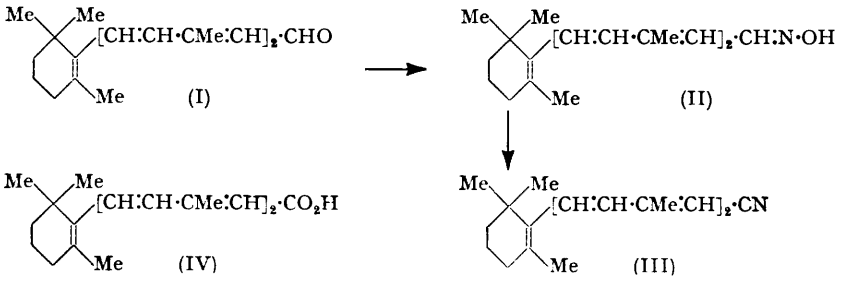
WHEN the structural problem of " anhydrovitamin A_2 " was reinvestigated a supply of vitamin A_2 was required. The difficulty of obtaining the pure vitamin from natural sources and the considerable length of the synthesis (from β-ionone) employed to establish its structure (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657) led to the consideration of other routes. Since vitamin A_1 acid (IV) was an intermediate in the previous synthesis the conversion of (commercially available) vitamin A_1 acetate into this acid was investigated, but various attempts to oxidise the vitamin itself or to oxidise further the corresponding aldehyde retinene$_1$ (I) were abortive. However, an indirect oxidation of retinene$_1$ was accomplished by dehydration of its oxime (II) with phosphorus oxychloride in pyridine to yield vitamin A_1 acid nitrile (III). This was obtained crystalline, exhibited $\lambda_{max.}$ 3580 Å in the ultraviolet region, and gave a C≡N stretching frequency (2210 cm.$^{-1}$) in the expected position in the infrared spectrum. However, hydrolysis to the acid by dilute alkali proceeded extremely slowly and use of more drastic conditions led to much decomposition, thus rendering this route to the acid impracticable. The difficulty encountered with the hydrolysis step is probably connected with delocalisation of the charge separation in the nitrile group by conjugation with the extended unsaturated system, the effect being augmented by hyperconjugation with attached alkyl groups.

Introduction of the extra double bond in the terminal ring in the previous A_2 synthesis was carried out on the methyl ester of the acid (IV), bromination with *N*-bromosuccinimide being followed by treatment with *N*-phenylmorpholine. Vitamin A_1 acetate reacted readily with *N*-bromosuccinimide, but allylic attack appeared to take place at either end of the

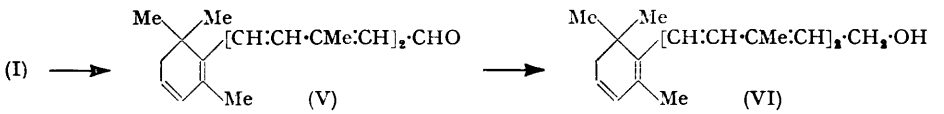
* Part L, preceding paper.

unsaturated system, for the light-absorption properties of the product obtained after dehydrobromination indicated the presence of a mixture of vitamin A_1 and A_2 acetates and the two retinenes.

Trial experiments (with benzaldehyde) had shown that an aldehyde group does not



react readily with *N*-bromosuccinimide, and this offered promise for bromination of retinene$_1$ (I) at the allylic position in the terminal ring. Under carefully controlled conditions (see Experimental section) this reaction proceeded smoothly, to yield an unstable bromo-compound, which on dehydrobromination afforded retinene$_2$ in more than 60% overall yield. The retinene$_2$ obtained was clearly a mixture of two or more stereoisomers for although it showed an ultraviolet absorption almost identical with that of the crystalline (all-*trans*-)aldehyde, it could not be induced to crystallise satisfactorily even after careful chromatography. The all-*trans*-form was, however, the chief isomer present for it could be separated as its oxime (30% overall yield from retinene$_1$) by treatment of the mixture with hydroxylamine acetate. The formation in the bromination–dehydrobromination



procedure of a mixture of geometrical isomers starting with crystalline all-*trans*-retinene$_1$ parallels our previous observations in the C_{20} ester series where a high yield of spectroscopically pure dehydro-ester was obtained from crystalline A_1-ester, but from which only a 30% yield of crystalline all-*trans*-acid was obtained on hydrolysis. The interconversion of isomers probably occurs during the bromination; an intermediate complex radical or ion may be produced, which by resonance stabilisation with the unsaturated system may cause the ultimate formation of new geometrical arrangements in the side-chain.

Reduction of retinene$_2$ (stereoisomeric mixture) by lithium aluminium hydride yielded vitamin A_2, characterised as in the earlier work by its ultraviolet absorption spectrum, preparation of a *p*-phenylazobenzoate, and by conversion into crystalline "anhydrovitamin A_2." This route to vitamin A_2 is the first based on vitamin A_1, and provides a more convenient route to the rarer vitamin.

Experimental

1-*Cyano*-2 : 6-*dimethyl*-8-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*octa*-1 : 3 : 5 : 7-*tetraene* (III).—Phosphorus oxychloride (0·25 c.c.) in pyridine (1 c.c.) was added to a solution of retinene$_1$ oxime (200 mg.) in pyridine (2 c.c.) cooled to −70°. On being allowed to warm to 0° the solution became deep red. The product was then isolated with light petroleum and chromatographed on alumina. The most easily eluted material was crystallised from methanol to give the *nitrile* (70 mg.) as yellow prisms, m. p. 50—50·5° (Found: C, 85·0; H, 9·45. $C_{20}H_{27}N$ requires C, 85·35; H, 9·6%). Ultraviolet spectrum (in EtOH): $\lambda_{max.}$ 3580 Å (ε = 47,200). Infrared spectrum: strong bands at 965, 1580, 2210, and 2920 cm.$^{-1}$.

Conversion of Retinene$_1$ into Retinene$_2$ (V).—Retinene$_1$ (2·2 g.) was dissolved in dry chloroform (50 c.c.; freshly distilled from P_2O_5) at 0°, and finely powdered *N*-bromosuccinimide (1·6 g.) was added with vigorous stirring. After 10 min. dissolution of the bromo-imide was complete

and a dark brown colour developed. Stirring was continued for a further 5 min. and *N*-phenylmorpholine (2 g.) was then added. The solution was heated under reflux for 5 min. and then poured into dilute hydrochloric acid, and the polyene isolated with pentane. Chromatography on deactivated alumina (400 g.) gave a main orange band which was eluted with pentane–ether (50 : 1) to give retinene$_2$ (1·4 g.), $\lambda_{max.}$ 4000 Å (ε = 35,000); the infrared spectrum was almost identical with that of the crystalline material. Further chromatography and fractional separation from cold pentane failed to give satisfactory crystalline material. The non-crystalline retinene$_2$ (1·4 g.) was converted into its oxime (cf. *J.*, 1952, 2657). The crude crystalline oxime (0·78 g.) gave on crystallisation from methanol the pure oxime as orange needles, m. p. 147—148° (Found: C, 81·0; H, 9·1. Calc. for $C_{20}H_{27}ON$: C, 80·75; H, 9·15%). M. p. given in our previous paper, 141—143°.

Vitamin A$_2$ (VI) *and its* p-*Phenylazobenzoate.*—Finely powdered lithium aluminium hydride (0·3 g.) was added to a solution of retinene$_2$ (0·75 g.; stereoisomeric mixture prepared as in the previous experiment) in dry ether (30 c.c.) at −30°. The mixture was kept at −30° for 30 min. with occasional agitation. Ethyl acetate was then added, and the vitamin isolated with ether and chromatographed on deactivated alumina (200 g.). Two minor products were eluted with pentane, and the main band was then eluted with ether, to give the vitamin (0·52 g.) as a yellow oil, extremely reactive to oxygen. It was dissolved in methylene dichloride (0·8 c.c.) and pyridine (0·8 c.c.); *p*-phenylazobenzoyl chloride (0·6 g.) was added and the mixture was shaken for 4 hr. Ether was added and the *p*-phenylazobenzoic anhydride filtered off. The solution was washed with dilute acid and dilute alkali, and the product chromatographed on deactivated alumina (200 g.). The single orange band was eluted with light petroleum to afford an orange oil (0·55 g.) which was dissolved in pentane (3 c.c.) and kept at −5° for 72 hr. The solid product was crystallised several times from pentane at −5°, to give vitamin A$_2$ *p*-phenylazobenzoate (0·2 g.) as thick orange-red needles, m. p. 74—77° (Shantz, *loc. cit.*, records m. p. 76—77°.).

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