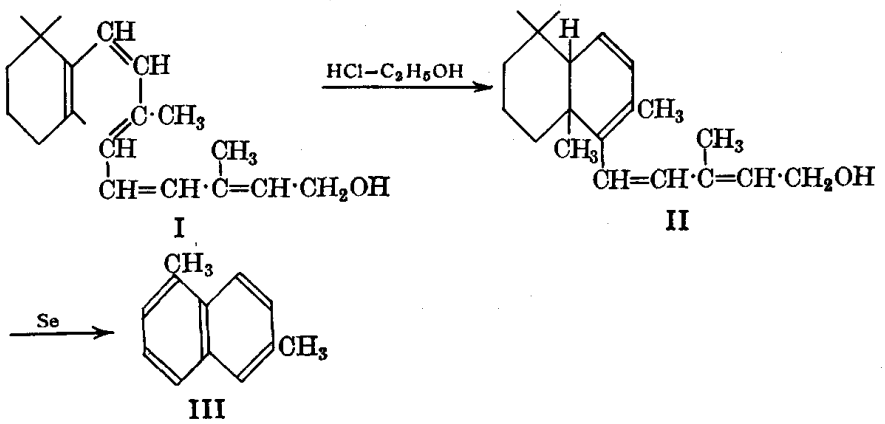
A δ-carotene has also been isolated, and this has been shown to be the α-ionone analogue of γ-carotene (Kargel *et al.*, 1960).

§7. **Vitamin A,** $C_{20}H_{30}O$. Vitamin A is also known as **Axerophthol,** and is also usually referred to as vitamin A_1 since a second compound, known as vitamin A_2, has been isolated.

Vitamin A_1 influences growth in animals, and also apparently increases resistance to disease. Night blindness is due to vitamin A_1 deficiency in the human diet, and a prolonged deficiency leads to xerophthalmia (hardening of the cornea, etc.). Vitamin A_1 occurs free and as esters in fats, in fish livers and in blood. It was originally isolated as a viscous yellow oil, but later it was obtained as a crystalline solid, m.p. 63–64° (Baxter *et al.*, 1940). Vitamin A_1 is estimated by the blue colour reaction it gives with a solution of antimony trichloride in chloroform (the Carr–Price reaction; *cf.* §1); it is also estimated by light absorption (vitamin A_1 has a maximum at 328 mμ).

Carotenoids are converted into vitamin A_1 in the intestinal mucosa, and feeding experiments showed that the potency of α- and γ-carotenes is half that of β-carotene. This provitamin nature of β-carotene led to the suggestion that vitamin A_1 is half the molecule of β-carotene.

On catalytic hydrogenation, vitamin A_1 is converted into perhydrovitamin A_1, $C_{20}H_{40}O$; thus vitamin A_1 contains five double bonds. Since vitamin A_1 forms an ester with *p*-nitrobenzoic acid (this ester is not crystallisable), it follows that vitamin A_1 contains a hydroxyl group. Thus the parent hydrocarbon of vitamin A_1 is $C_{20}H_{40}$, and consequently the molecule contains one ring. Ozonolysis of vitamin A_1 produces one molecule of geronic acid (§3) per molecule of vitamin A_1, and so there must be one β-ionone nucleus present (Karrer, 1931, 1932). Oxidation of vitamin A_1 with permanganate produces acetic acid; this suggests that there are some $-C(CH_3)=$ groups in the chain. All of the foregoing facts are in keeping with the suggestion that vitamin A_1 is half the β-carotene structure. When heated with an ethanolic solution of hydrogen chloride, vitamin A_1 is converted into some compound (II) which, on dehydrogenation with selenium forms 1 : 6-dimethylnaphthalene, III (Heilbron *et al.*, 1932). Heilbron *assumed* I as the structure of vitamin A_1, and explained the course of the reaction as follows:

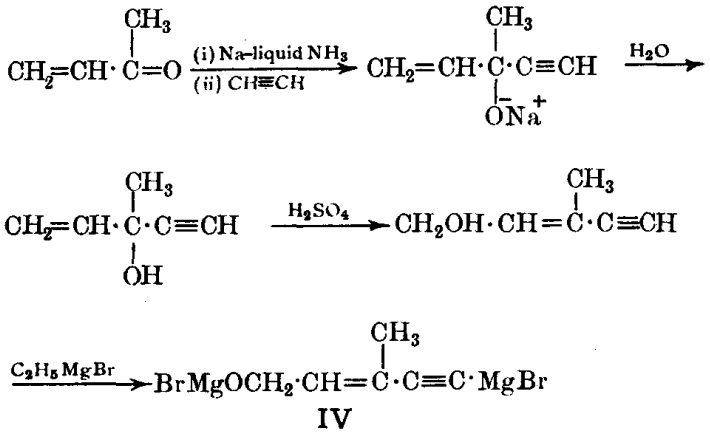


I II III

Perhydrovitamin A_1 has been synthesised from β-ionone (Karrer, 1933), and was shown to be identical with the compound obtained by reducing vitamin A_1; thus there is evidence to support the structure assigned to vitamin A_1. Final proof of structure must rest with a synthesis of vitamin A_1 itself, and this has now been accomplished by several groups of workers.

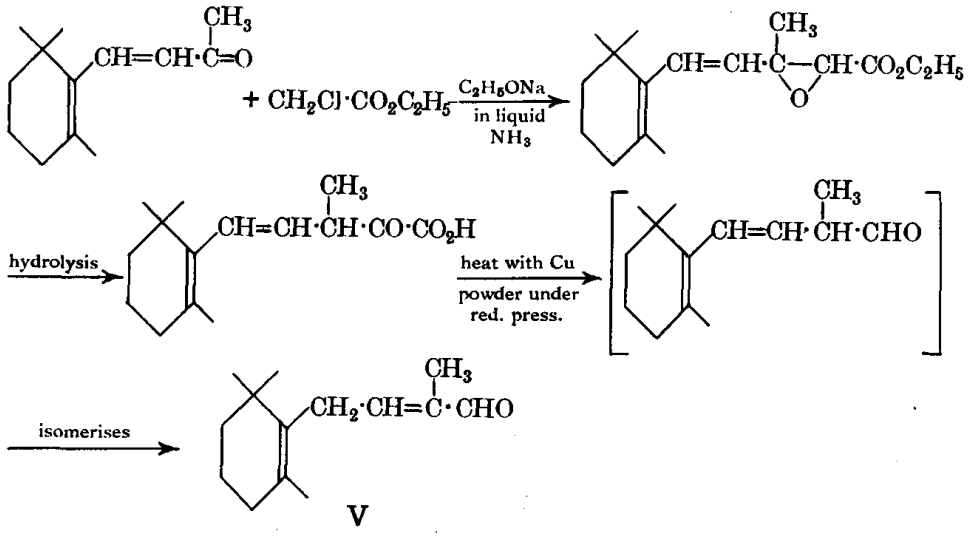
The following synthesis is that of Isler *et al.* (1947). This starts with methyl vinyl ketone to produce compound IV, one stage of the reactions involving

Preparation of IV.



IV

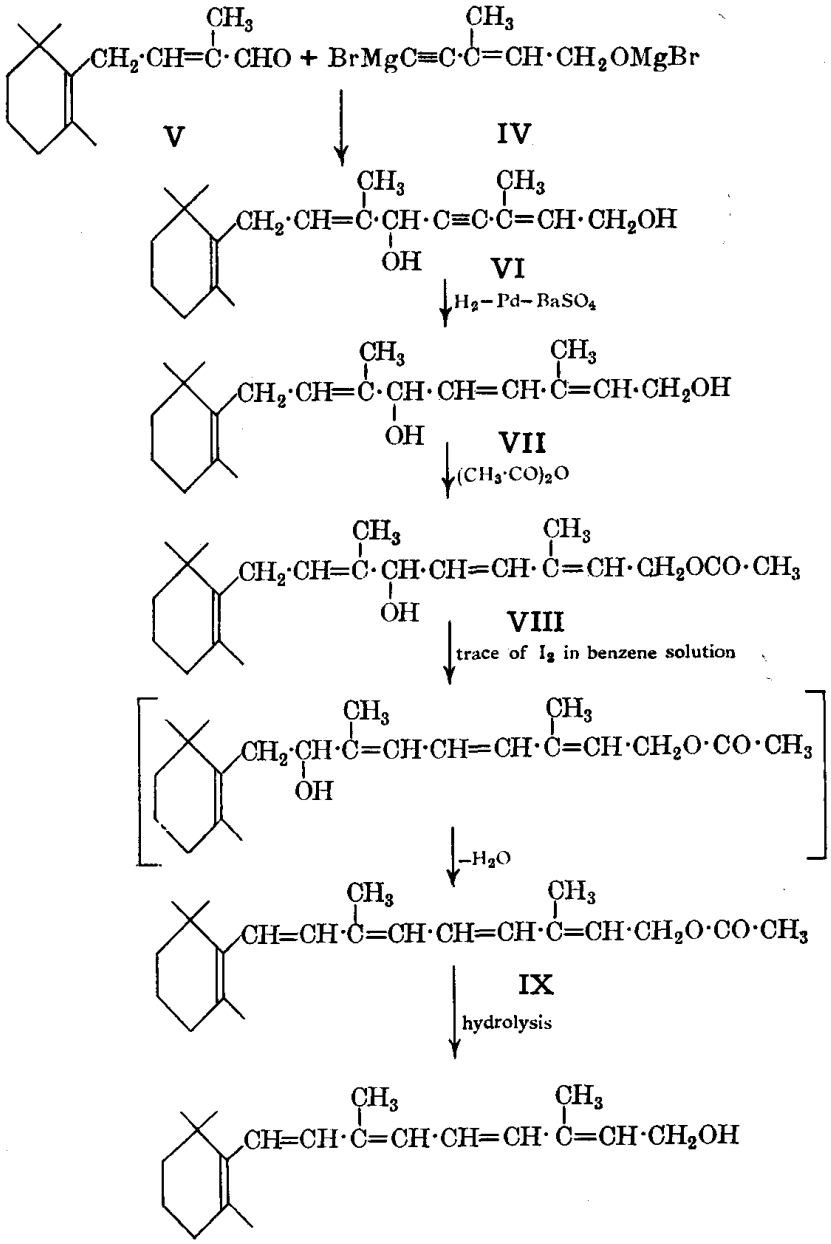
Preparation of V.



V

an allylic rearrangement (*cf.* §8. VIII). Compound V is prepared from β-ionone by means of the Darzens glycidic ester reaction (see also Vol. I). The following chart shows the steps of the synthesis, and it should be noted that another allylic rearrangement is involved in one of the later steps.

Combination of IV and V, etc.

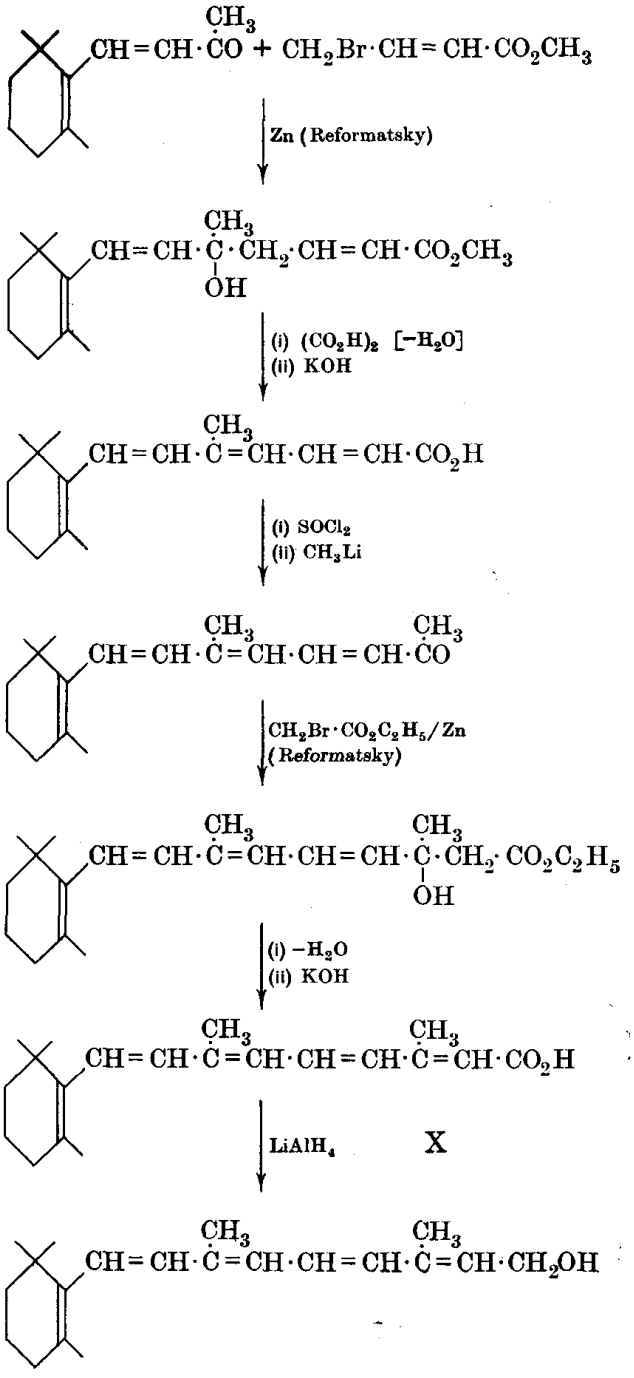


In the hydrogenation of VI to VII, barium sulphate is used to act as a poison to the catalyst to prevent hydrogenation of the *double* bonds. Partial acetylation of VII (primary alcoholic groups are more readily acetylated than secondary) protects the terminal group from an allylic rearrangement in the conversion of VIII to IX.

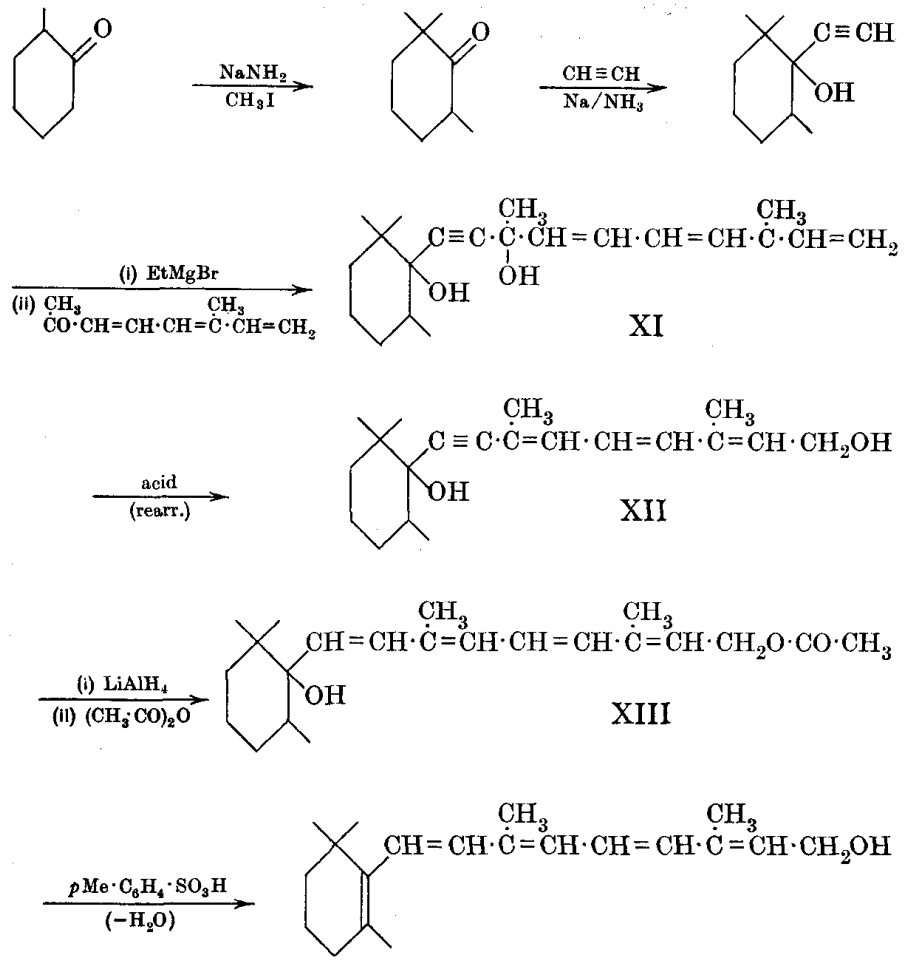
The crude vitamin A_1 obtained in the above synthesis was purified *via* its ester with anthraquinone-2-carboxylic acid, and was thereby obtained in a crystalline form which was shown to be identical with natural vitamin A_1.

Lindlar (1952) has shown that triple bonds may be partially hydrogenated in the presence of a Pd—$CaCO_3$ catalyst that has been partially inactivated by treatment with lead acetate; better results are obtained by the addition of quinoline. Thus the hydrogenation of VI gives VII in 86 per cent. yield when the Lindlar catalyst is used.

Another method of synthesising vitamin A_1 is due to van Dorp *et al.* (1946) who prepared vitamin A_1 acid (X), which was then reduced by means of lithium aluminium hydride to vitamin A_1 by Tishler (1949); β-ionone and methyl γ-bromocrotonate are the starting materials.



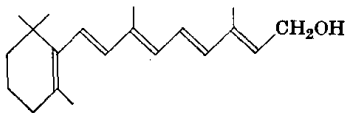
Attenburrow *et al.* (1952) have also synthesised vitamin A_1 starting from 2-methyl*cyclo*hexanone.



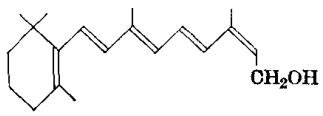
Acid causes rearrangement of XI to XII in which all multiple bonds are in complete conjugation, and the reduction of XII to XIII by lithium aluminium hydride is possible because of the presence of the propargylic hydroxyl grouping (§3).

Synthetic vitamin A_1 is now a commercial product.

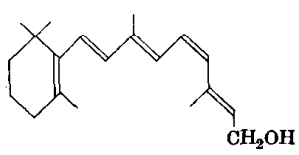
Two biologically active geometrical isomers of Vitamin A_1 (all-*trans*) have also been isolated: **neovitamin a** from rat liver (Robeson *et al.*, 1947) and **neovitamin b** from the eye (Oroshnik *et al.*, 1956). Vitamin A_1 is the most active form in curing " vitamin A " deficiency.



vitamin A_1



neovitamin a



neovitamin b