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HISTORY AND INDUSTRIAL APPLICATION OF CAROTENOIDS AND VITAMIN A (1)

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Abstract - A review is given of the development of the industrial manufacture of carotenoids and vitamin A by isolation and by synthesis. Special emphasis is placed on the use of carotenoids as a preferred class of colouring matters for food and feed.

INTRODUCTION

A review of the industrial manufacture of carotenoids and vitamin A may be separated into four areas:

First the area of isolation and the structural elucidation of the main compounds, which culminated between 1930 and 1950. Then the development of starting materials and the key intermediates for syntheses, which culminated at the same time. In 1946-1956 9 industrial manufacturing procedures for vitamin A were invented. The period of 1954 - 1968 saw the commercial introduction of 5 carotenoids as colouring matters for food and feed.

ISOLATION AND STRUCTURAL ELUCIDATION

Carotenoids were present in man's food throughout his evolution and are biochemically familiar to our body. The first isolations were described as early as 1817 (paprika) and 1818 (crocin)(2).

TABLE 1 SOME CAROTENOIDS ISOLATED AS COLOURING MATTERS

CLASS	CAROTENOID	NATURAL SOURCE	FURTHER CAROTENOIDS
CAROTENES	β-CAROTENE	CARROTS	α-CAROTENE
		RED PALM OIL	α- & -γ-CAROTENE
		ALFALFA, GRASS MEAL, LEAVES	XANTHOPHYLLS (CHLOROPHYLL)
	LYCOPENE	TOMATO, ROSE HIPS	CAROTENES
XANTHOPHYLLS	CRYPTOXANTHIN	YELLOW MAIZE	ZEAXANTHIN
	ZEAXANTHIN	YELLOW MAIZE	CRYPTOXANTHIN
	LUTEIN	ALFALFA, GRASS MEAL, LEAVES	CAROTENES (CHLOROPHYLL)
	CAPSANTHIN	PAPRICA, RED PEPPER (CAPSICUM ANNUUM)	CAPSORUBIN, ZEAXANTHIN
	ASTAXANTHIN	LOBSTER, SHELLS, SALMON	ASTACENE (METABOLITE)
CAROTENOIC ACIDS	CROCIN, CROCETIN	SAFFRON	β-CAROTENE, ZEAXANTHIN
	BIXIN	SEEDS OF BIXA ORELLANA (ANNATO)	BY-PRODUCTS
	TORULARHODIN	RHODOTORULA RUBRA (YEAST)	TORULENE, β-CAROTENE

Table 1 summarizes some carotenoids which have been used already for centuries as colouring matters (3,4). The carotenes are used in food, the xanthophylls and carotenoid acids in food and feed. Carotenes were first extracted from carrots, later its main source was red palm oil (5,6).

Carotenes and xanthophylls are manufactured together with chlorophyll from alfalfa, grass meal and leaves. Capsanthin, crocin and bixin have a long history as colouring matters. β-Carotene and zeaxanthin have also been produced for a while by fermentation (7). However, this procedure seems to be not economically attractive.

Vitamin A - first called fat soluble growth factor - had been observed in 1909 by Stepp (8) and explored in 1913-16 by the Americans McCollum and Davis (9), and Osborne and Mendel (10), who introduced cod liver oil. Table 2 summarizes the vitamin A content of the liver oils of

TABLE 2 VITAMIN A FROM THE SEA

	COMMON NAME	ZOOLOGICAL NAME	OIL % IN LIVER	VITAMIN A I.U./G LIVER-OIL
FISHES:	COD	GADUS MORRHUA	50 - 75	1'000
	STURGEON	ACIPENSER TRANSMONTANUS	9 - 49	10'000 - 17'000
	TURBOT	RHOMBUS MAXIMUS	15 - 20	50'000
	TUNNY	SCOMBER THYNNUS	15 - 20	50'000
	HALIBUT	HIPPOGLOSSUS HIPPOGLOSSUS	15 - 20	50'000
	HAMMER-HEAD SHARK	SPHYRNA ZYGAENA	-	3'300 - 60'600
	SOUP-FIN SHARK	GALEORHINUS ZYOPTERUS	45 - 65	48'000 - 190'000
WHALES:	FINBACK	PHYSALUS ANTIQUORUM	3.5	45'900
	HUMPBACK	MEGAPTERA LONGIMANA	3.84	130'000
	SPERM	CATODON MACROCEPHALUS	3.80	293'000

some marine animals according to Moore (11). Cod liver oil is a relatively poor source. The oils of turbot, tunny, halibut, sharks and whales are very much richer. The sperm whale liver oil with 293'000 int. units has the highest content of vitamin A.

In 1930-1945 Hickman (12) from DPI, a company belonging to Eastman Kodak, developed the technique of molecular distillation and made DPI the leading manufacturers of vitamin A for that period. He used stills of the centrifugal type with a rotating circular heating element for an even distribution of the oil. During world war II a major contribution of the lend and lease policy of the USA was the provision of rich fish liver oils from the Pacific coast to the United Kingdom, which suffered from a scarcity of the vitamins A and D.

Steenbock from Wisconsin (13) observed in 1919 a growth promoting activity of carotenoids, which was not confirmed by English scientists. In 1929 von Euler and Karrer (14) recognized that β-carotene is a good growth factor and that it is related with vitamin A. Moore (15) elegantly proved the in vivo conversion of β-carotene to vitamin A. 1930-31 Karrer (16) arrived at the structures by oxidative degradation (Fig. 1). On ozonolysis β-carotene gave

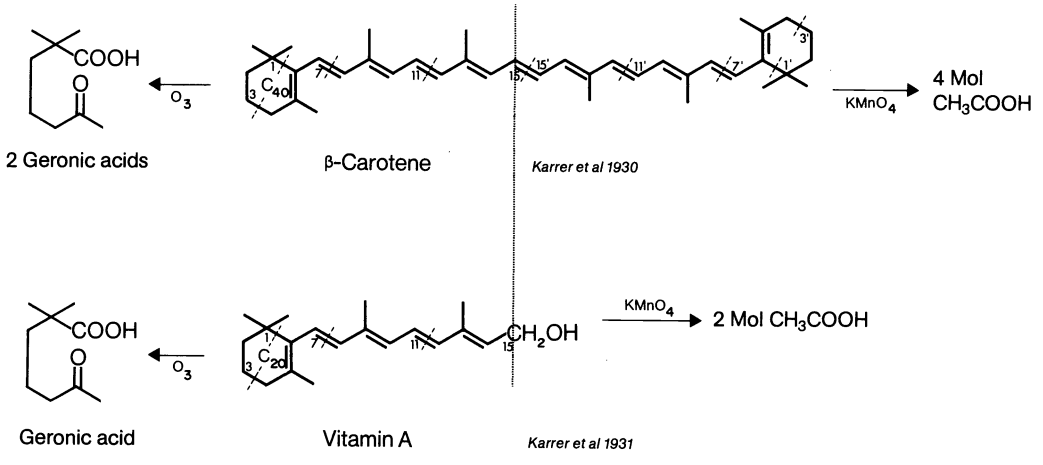

Fig. 1 Structural elucidation of β-carotene and vitamin A

2 moles and vitamin A 1 mole of geronic acid. On permanganate oxidation β-carotene gave 4 moles and vitamin A 2 moles of acetic acid. The symmetrical formulation of β-carotene and the application of the isoprene rule led Karrer to the correct formulae of β-carotene with 8 isoprene units and vitamin A with 4 isoprene units. Vitamin A has the structure of half of the β-carotene molecule with an added molecule of water at C-15. All natural vitamin A is derived from carotenoids. β-Carotene is the most important provitamin A. From 400 carotenoids assembled in Straub's "Key to Carotenoids" (17) about 50 compounds have an unsubstituted β-carotene half and can be converted more or less efficiently into vitamin A in the intestinal wall.

STARTING MATERIALS AND KEY INTERMEDIATES

All industrial syntheses of vitamin A and the carotenoids are based on β-ionone (18,19,20) (Fig. 2). This monocyclic C_{13}-ketone was already available in the 19th century as a perfume

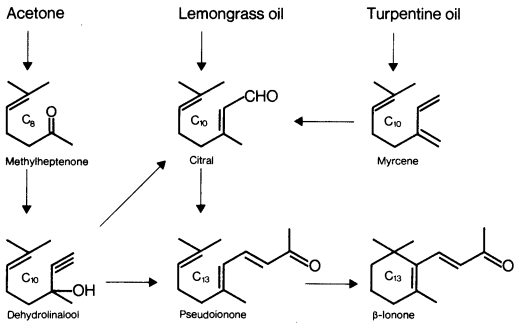

Fig. 2. Manufacture of β-ionone from various scources

agent (21). For 50 years it has been prepared from lemongrass oil (water distillate of Cymbapogon flexnosus and citratus D.C. Napf) containing 70-80% citral. Condensation of citral with acetone gives pseudoionone which is cyclized to β-ionone with strong acid (22). Today lemongrass oil is no longer an economical source for citral and β-ionone.

In 1940 Roche began with the total synthesis of methylheptenone and dehydrolinalool by consecutively lengthening acetone by 2, 3 and again 2 carbons (23). 2 Carbons were added in the form of acetylene and 3 carbons first by acetoacetate, then by diketene (24) and finally with isopropenylether according to a procedure developed by Saucy and Marbet (25). In addition new procedures were devised in 1958 and 1976 for efficient isomerization of dehydrolinalool to citral (26, 27).

In the 1960,s Rhodia Inc. (28) started the production of methylheptenone from isoprene; BASF (29) synthesized iso-methylheptenone from isobutylene; Glidden Co. (30) and A. Broake,Roberts synthesized citral from turpentine oil via myrcene.

Fig. 3 summarizes the scheme used by Roche for the manufacture of β-ionone from acetone.

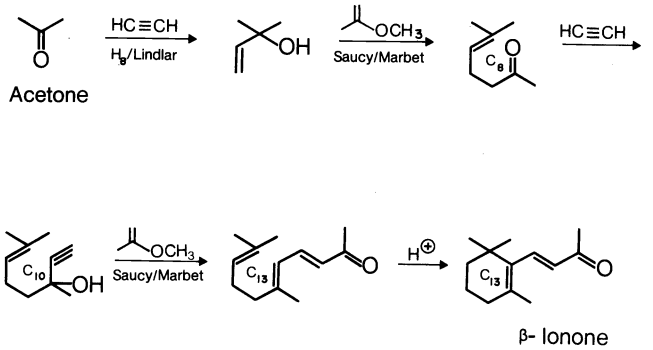

Fig. 3. Total synthesis of β-ionone from acetone

It consists of two double condensations, each one with acetylene and isopropenyl ether. All reactions from acetone to pseudoionone are carried out catalytically.

The key intermediates for the synthesis of vitamin A were prepared for the first time between 1937 and 1949 (Fig. 4). Both β-C_{14}-aldehydes (31-34) are obtained by glycidic ester

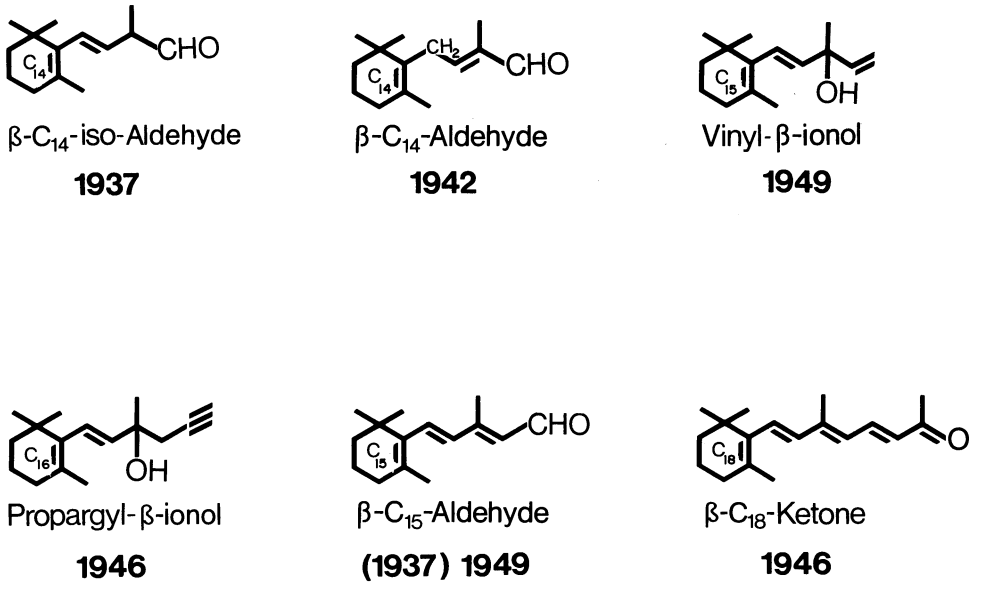

Fig. 4. Key intermediates from β-ionone

synthesis and either one can be obtained in good yield. The β-C_{14}-aldehyde with conjugated double bonds leads to 9-cis compounds and is quite useless. The β-C_{14}-aldehyde with a CH_2-group between ring and side chain was first described in 1942 by Heilbron (32). C_{15}-Vinyl-β-ionol has been prepared by Oroshnik (35) in 1949 by condensation of β-ionone with lithium acetylide followed by partial hydrogenation of the triple bond. C_{16}-Propargyl-β-ionol was synthesized at Roche (36) in 1946 from β-ionone with propargyl bromide and zinc. The β-C_{15}-aldehyde (37), first mentioned in 1937, has been prepared by numerous routes (38,39). Some controversy about this compound was enhanced by the existence of retro-, cis- and trans-forms. β-C_{18}-ketone (38,40) is best obtained by condensation of β-C_{15}-aldehyde with acetone (41). Its first preparation in 1946 was achieved via the β-C_{17}-acid (42,43).

Due to similarity of the structures of vitamin A and the carotenoids these key intermediates have been applied in both fields.

THE MANUFACTURE OF VITAMIN A (44)

The biological functions of vitamin A are general growth, differentiation of epithelial tissue, vision and reproduction. Many in vivo transformations can be achieved in vitro (Fig. 5). Vitamin A can be oxidized with manganese dioxide to vitamin A aldehyde or retinal and the reverse reaction is effected with sodium borohydride.

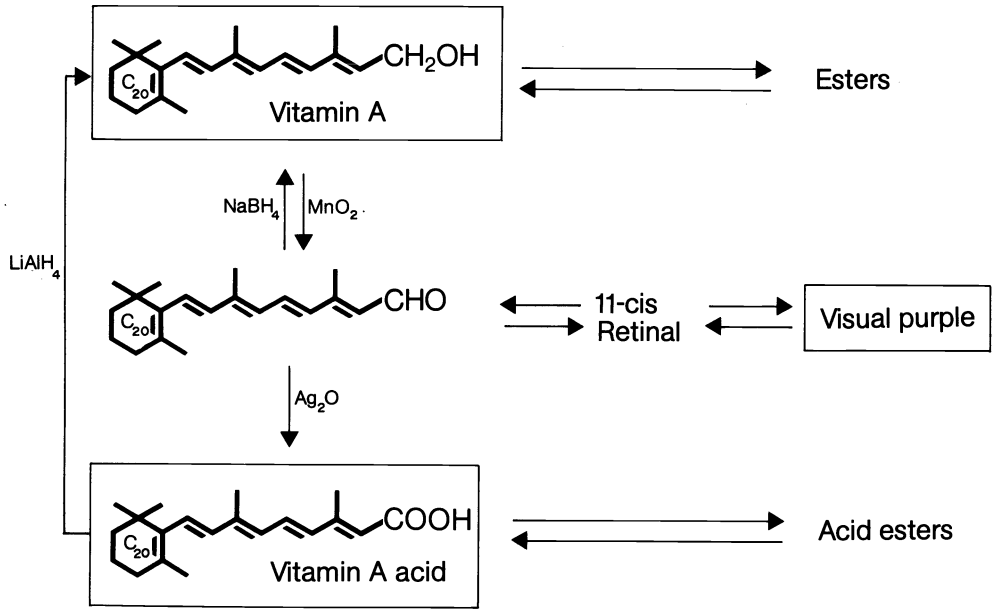

Fig. 5. Transformations of vitamin A compounds

More forceful oxidation of retinal with silver oxide yields vitamin A acid, which can be reduced to vitamin A with lithium aluminium hydride. The esters and acid esters are the market forms. Retinal is isomerized in the retina to the sterically hindered 11-cis-retinal, which on condensation with specific proteins (e.g. opsin) constitutes the visual purple or the photo-receptor system in the rods and cones of the retina. There is no vision in any species without 11-cis-retinal (45).

The four double bonds in the side chain give rise to 16 stereoforms (Fig. 6). The hindered

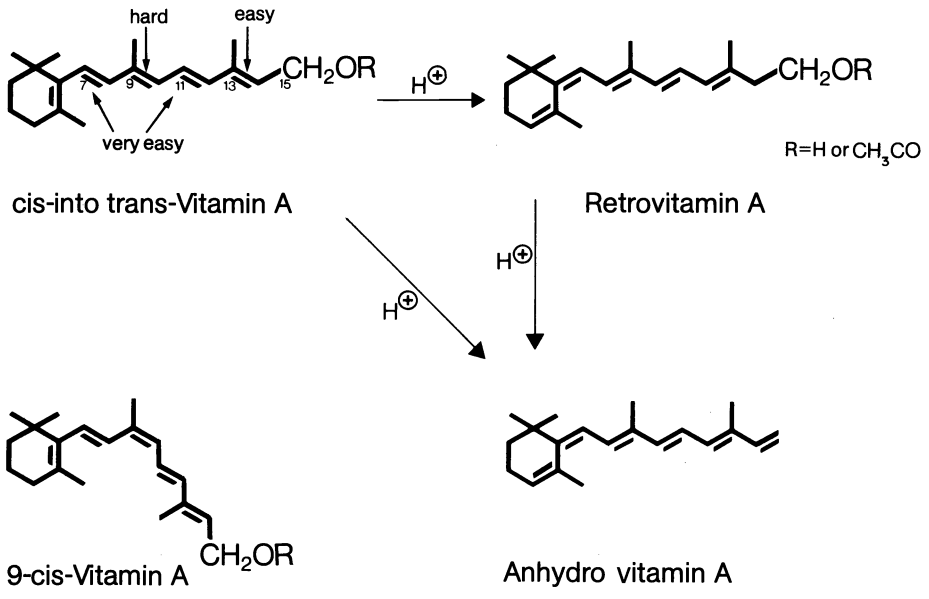

Fig. 6. Stereoforms of vitamin A and retrocompounds

double bonds in the 7- and 11-position isomerize very readily to the trans-form. 13-cis-Vitamin A can be isomerized with iodine, whereas 9-cis-vitamin A is much more stable.

On treatment with acid vitamin A and its acetate give retro-vitamin A and, under more drastic conditions, the hydrocarbon anhydro vitamin A.

In 1937 Kuhn and Morris (46) synthesized via impure β-C_{15}-aldehyde a few drops of an oily preparation with 7,5% biological activity. This was the signal for further attempts in academic and industrial laboratories which did not succeed until 1946. One concept was the condensation of β-ionone with C_7-side chains, which led to 9-cis- and retro compounds (47,48).

In 1945-46 three model experiments at Roche looked promising (Fig. 7): β-C_{14}-aldehyde with

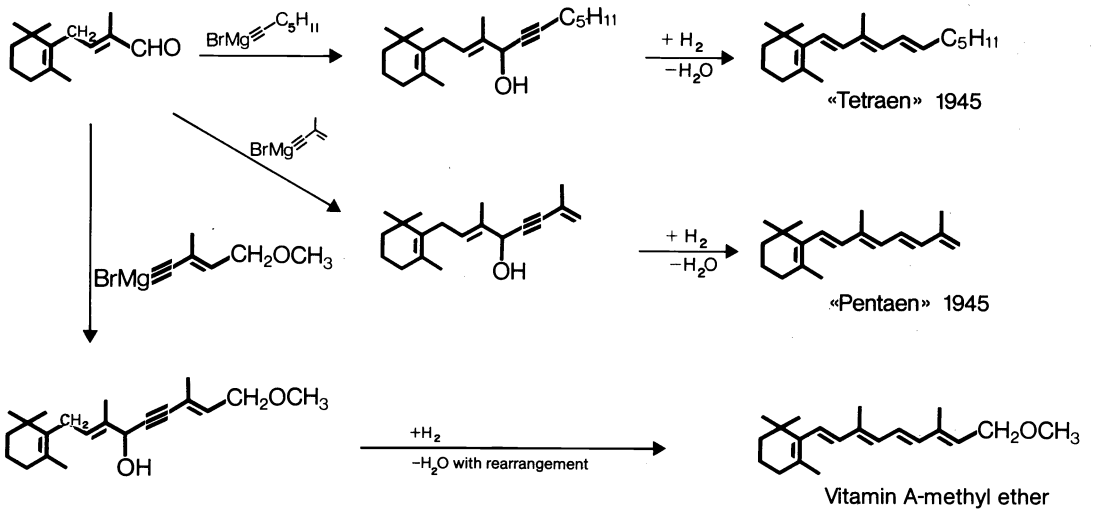

Fig. 7. Model syntheses at Roche in 1945-46

a CH_2-group between ring and side-chain was condensed in a Grignard reaction with 1-heptyne, 2-methyl-but-1-en-3-yne and 1-methoxy-3-methylpent-2-ene-4-yne. The acetylenic carbinols obtained were partially hydrogenated at the triple bond, dehydrated under rearrangement and purified by chromatography. The first product showed absorption as a tetraene and the others as pentaenes. The third product was impure vitamin A methyl ether, showing biological activity of 85% (49). Similar products of Milas (50), who started with the isomeric β-C_{14}-aldehyde with conjugated double bonds, showed only traces of activity.

In 1947 we succeeded in synthesizing cristalline vitamin A (51)(Fig. 8) starting from β-C_{14}-aldehyde and the Grignard compound of 1-hydroxy-3-methyl-pent-2-ene-4-yne, followed by partial hydrogenation of the triple bond, protection of the primary hydroxyl group by acetylation and finally dehydration with rearrangement. This synthesis was gradually improved in all steps. The 1-hydroxy intermediates with a CH_2-group between ring and side chain could be crystallized. The final dehydration step, originally performed with iodine, was improved by boiling with phosphorous oxychloride in pyridine and, finally,by treatment at low temperature with concentrated HBr in methylene chloride. Unilever decided in 1950 to use our synthetic vitamin A in margarine instead of whale liver oils.

Other early syntheses which did not reach the market are shown on the right of Fig. 8. In 1946 Arens and Van Dorp (42) of the Dutch firm Organon described the synthesis of vitamin A acid via β-C_{18}-ketone. In 1947 the same authors (52) announced the synthesis of vitamin A-aldehyde using ethoxy acetylene as a key intermediate. Also in 1947 DPI prepared

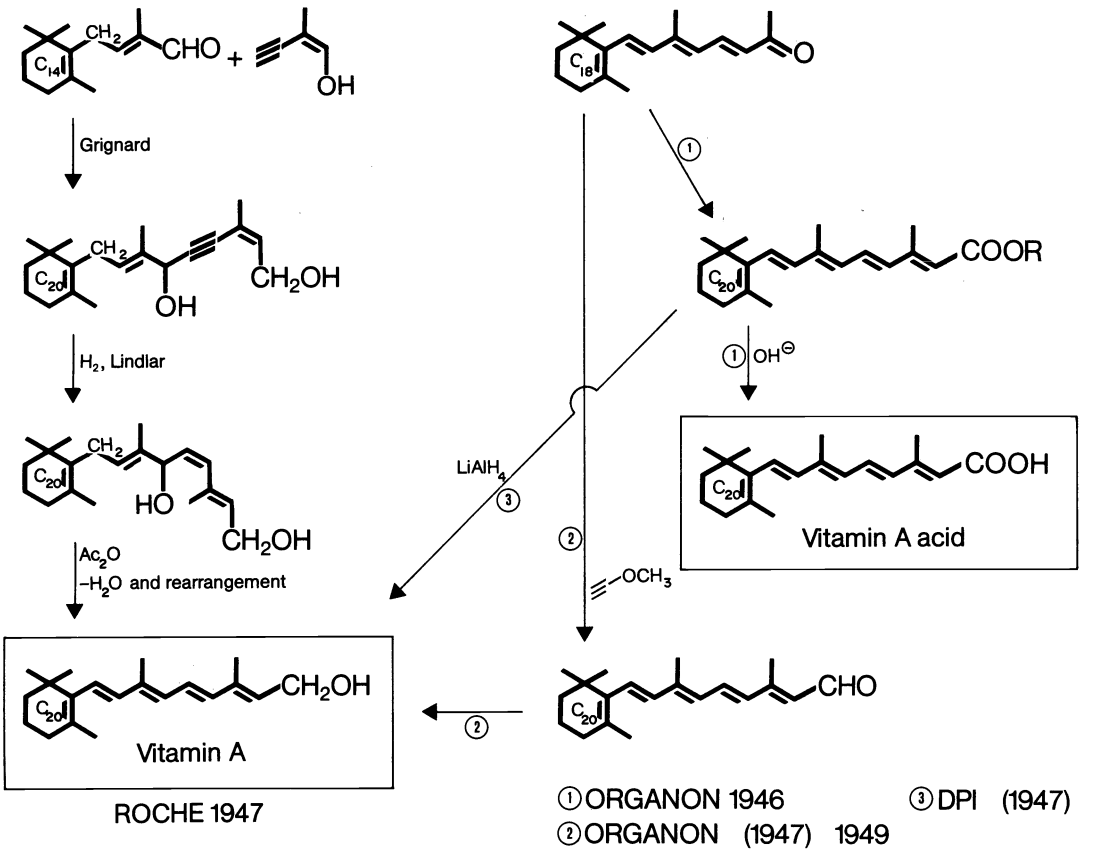

Fig. 8. First vitamin A syntheses in 1946-47

vitamin A from vitamin A acid ester by means of the newly discovered lithium aluminium hydride (53).

The industrial procedures reaching the market are listed in Fig. 9 according to the last

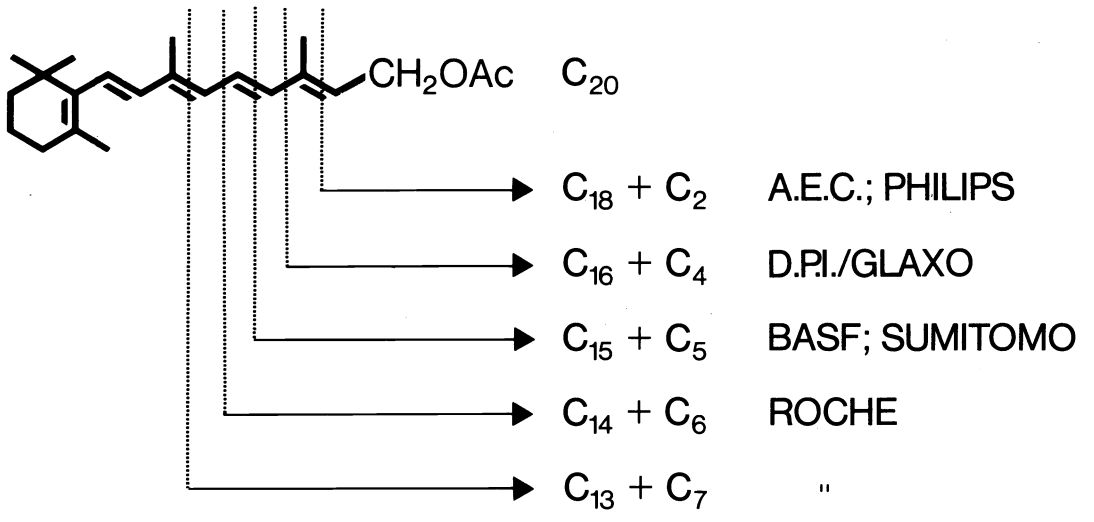

Fig. 9. Vitamin A manufacturing procedures

condensation step in building up the carbon skeleton of 20 C-atoms. In 196Q DPI from Eastman Kodak Co. (54) converted C_{16}-propargyl-β-ionol into vitamin A aldehyde. Glaxo was

allowed to use this procedure in 1963 in India. In 1962 Sumitomo, based on Matsui's research (55), condensed the β-C_{15}-aldehyde to vitamin A acid ester. In 1962 the French firm Alimentation Equilibré (A.E.C.)(39) and in 1963 the Dutch firm Philips-Duphar with Huisman converted β-C_{18}-ketone into vitamin A aldehyde. In these procedures vitamin A acid ester and aldehyde have to be transformed into vitamin A acetate or palmitate by reduction and esterification. The important manufacture of BASF (the Badische Anilin and Sodafabrik) (18), is based on Wittig's elegant olefin synthesis which revolutionized the whole polyene chemistry. In 1964 C_{15}-vinyl-β-ionol was directly transformed to vitamin A acetate (56).

These industrial procedures are shown in Fig. 10 with the formulae of its key intermediates. Roche proceeds via β-C_{14}-aldehyde to vitamin A acetate. DPI and Glaxo proceed via

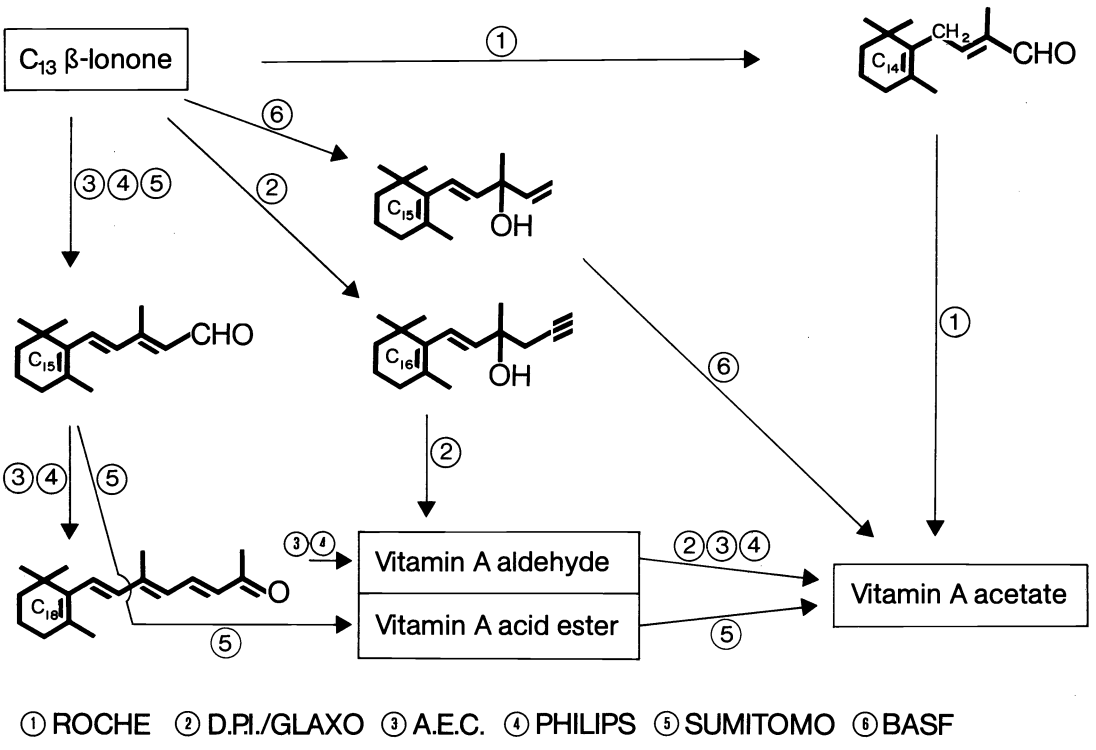

Fig. 10. Key intermediates of vitamin A manufacture

C_{16}-propargyl-β-ionol in a Grignard reaction with ketobutanal acetal to vitamin A aldehyde (54) and acetate. A.E.C. and Philips-Duphar convert β-C_{15}-aldehyde via β-C_{18}-ketone into vitamin A aldehyde and acetate. Lengthening of β-C_{18}-ketone by two carbons is effected by A.E.C. (39) with orthoformate and Grignard reaction and by Philips-Duphar with a cyanoacetic ester syntheses. Sumitomo condenses β-C_{15}-aldehyde with ethyl senecioate into vitamin A acid ester (55). BASF condenses C_{15}-vinyl-β-ionol in a Wittig reaction with a C_5-aldehyde directly to vitamin A acetate (56).

This important Wittig reaction C_{15} + C_5 was developed by Pommer (18, 56, 57) as shown in Fig. 11: C_{15}-Vinyl-β-ionol on treatment with triphenylphosphoniumhalide gives the C_{15}-Wittig salt which is also a building stone in BASF's manufacture of β-carotene and citranaxanthin. The C_{15}-Wittig salt condenses in the presence of base with β-formylcrotylacetate to vitamin A acetate (right) and with the corresponding acid ester to vitamin A acid ester (left) (58).

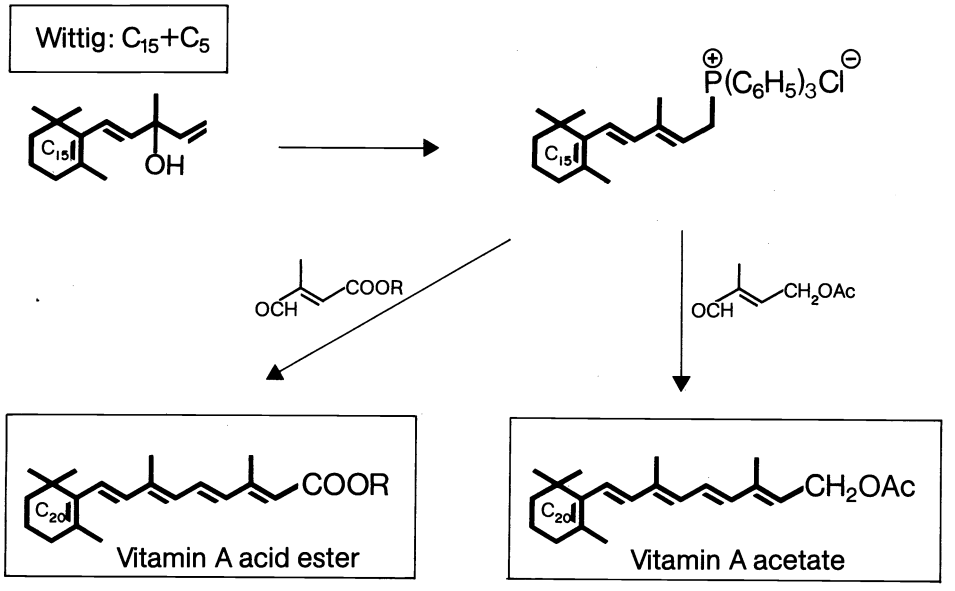

Fig. 11. Vitamin A manufacture by BASF

Each of the known manufacturing procedures leaves something to be desired. The ideal synthesis, which is not yet invented, should start from cheap reagents and use catalytic reactions which cut down the amount of pollutants.

Fig. 12 shows the development of the price and of Roche's capacity from 1948-77. There was

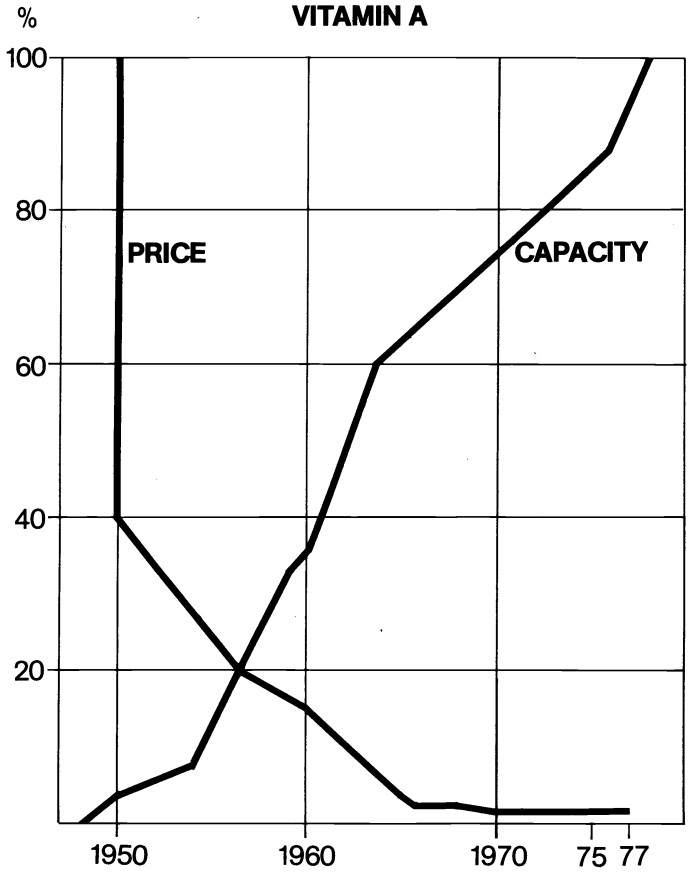

Fig. 12. Price of vitamin A and Roche's capacity

an impressive cheapening of the average price which in 1976 was less than 3% of that in 1948. Roche is manufacturing vitamin A in Switzerland and USA as well as in India. The capacity increased gradually since 1948. The production of all manufacturers reaches several thousand tons per year.

Vitamin A deficiency is today still a very serious problem since every year thousands of children turn blind because of lack of this vitamin.

MANUFACTURE OF CAROTENOIDS (59)

β-Carotene was the first carotenoid to be synthesized and the first to reach the market. Of hundreds of carotenoids, which have been synthesized, only five are at present being manufactured on an industrial scale (Fig. 13).

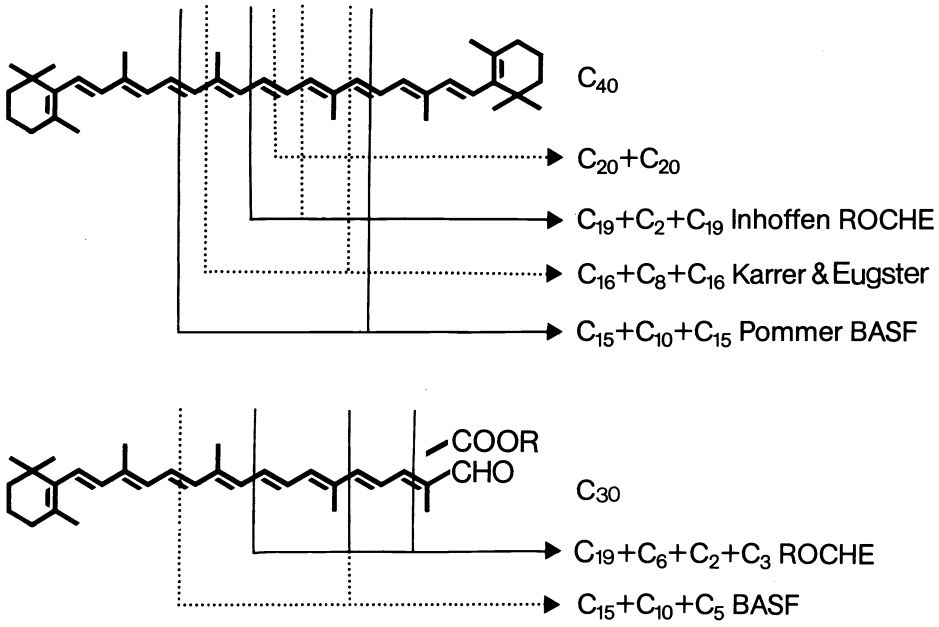

Fig. 13. Carotenoid manufacturing procedures

In 1950 Karrer and Eugster (60) synthesized the first crystals of β-carotene according to the scheme $C_{16} + C_8 + C_{16}$ starting with a Grignard reaction of two C_{16}-propargyl-β-ionols with a symmetrical C_8-diketone. Later, these authors prepared about 40 carotenes in a similar manner. Simultaneously, Inhoffen (61) synthesized in 1950 β-carotene according to the scheme $C_{19} + C_2 + C_{19}$. This scheme was developed by Roche to a manufacturing procedure (62). β-Carotene was introduced on the market in 1954 and Unilever used it in margarine as colouring agent and provitamin A. In 1959 Pommer of BASF (63, 64) applied for patents covering the Wittig condensation $C_{15} + C_{10} + C_{15}$. Some syntheses according to the scheme $C_{20} + C_{20}$ using vitamin A derivatives are also well described (65, 66).

In 1955-58 we tackled the synthesis of some carotenoids like the tomato pigment lycopene and the maize pigment zeaxanthin (67). Lycopene gave no stable market forms and zeaxanthin was too expensive. In 1959 we turned to the C_{30}-β-apo-8'-carotenoids which are very powerful provitamins A standing between β-carotene and vitamin A. Our production of the C_{30}-β-apo-8'-carotenoids (68, 69) begins with a Grignard reaction $C_{19} + C_6 \rightarrow C_{25}$ and is followed by lengthening of the intermediate C_{25}-apoaldehyde by 2 and then by 3 carbons. Later Pommer from BASF (57, 63) employed a Wittig reaction $C_{15} + C_{10} \rightarrow C_{25}$ and continued with a second Wittig reaction $C_{25} + C_5 \rightarrow C_{30}$.

The main features in our own syntheses were intermediates with triple bonds in 15,15'-position and CH_2-groups between ring and side chains (Fig. 14). It was a breakthrough when the β-C_{14}-aldehyde with CH_2-group between ring and side chain was first lengthened by two and by three carbons to the β-C_{19}-aldehyde (62) with the same configuration. For this

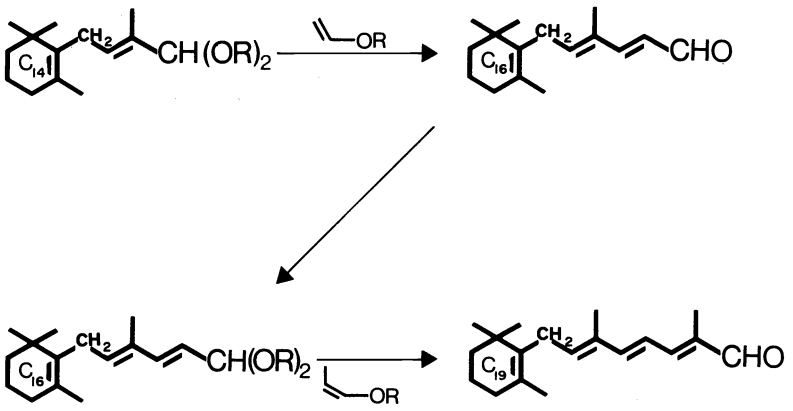

Fig. 14. Lengthening of β-C_{14}-aldehyde to β-C_{19}-aldehyde

purpose β-C_{14}-acetal is condensed with vinyl ether and β-C_{16}-acetal with propenylether.

The manufacture of the butter pigment β-carotene begins with a Grignard or a Wittig reaction (Fig. 15). In the Grignard reaction $C_{19} + C_2 + C_{19}$ two moles of β-C_{19}-aldehyde

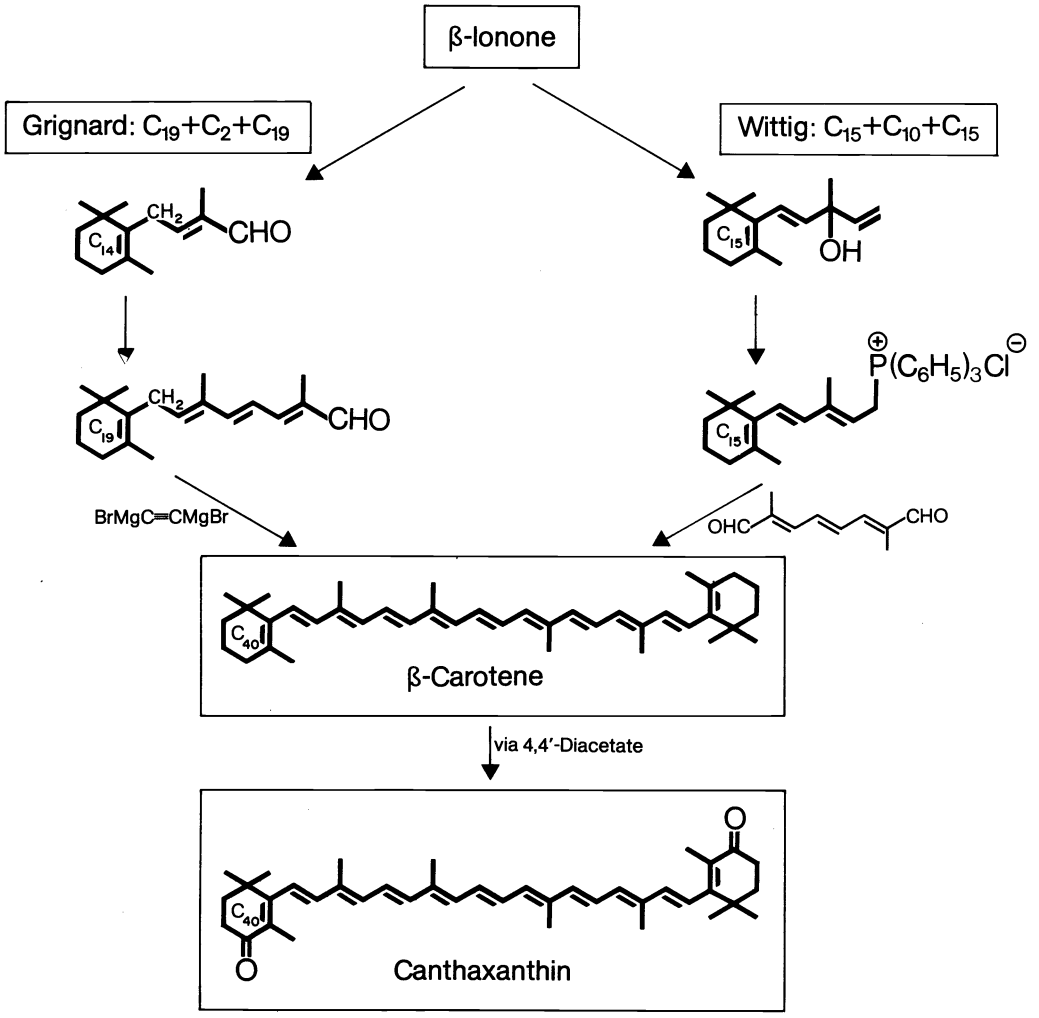

Fig. 15. Manufacture of β-carotene and canthaxanthin

are condensed with acetylene. The C_{40}-compound formed is dehydrated, partially hydrogenated at the 15,15'-triple bond and isomerized to all-trans β-carotene (62). In the Wittig reaction $C_{15} + C_{10} + C_{15}$ developed by BASF (57, 64) two C_{15}-Wittig salts condense on both sides of the symmetrical C_{10}-dialdehyde. As mentioned before this C_{15}-Wittig salt is identical with the C_{15}-building stone in the manufacture of vitamin A and citranaxanthin.

Canthaxanthin is prepared from β-carotene via its 4,4'-diacetate (70, 71) which is saponified and oxidized. Canthaxanthin is more reddish and more stable and can be looked at as a β-carotene metabolite. Canthaxanthin was introduced on the market in 1964. Its main application is in chicken feed.

The manufacture of the C_{30}-β-apo-8'-carotenoids begins also with a Grignard or a Wittig reaction (Fig. 16). In the Grignard reaction the β-C_{19}-aldehyde is condensed with a C_6-side chain to a C_{25}-apocarotenal with a 15,15'-triple bond. This is lengthened first by two carbons with vinyl ether and then by three carbons with propenyl ether - to give - after partial hydrogenation of the 15,15'-triple bond - β-apo-8'-carotenal (68).

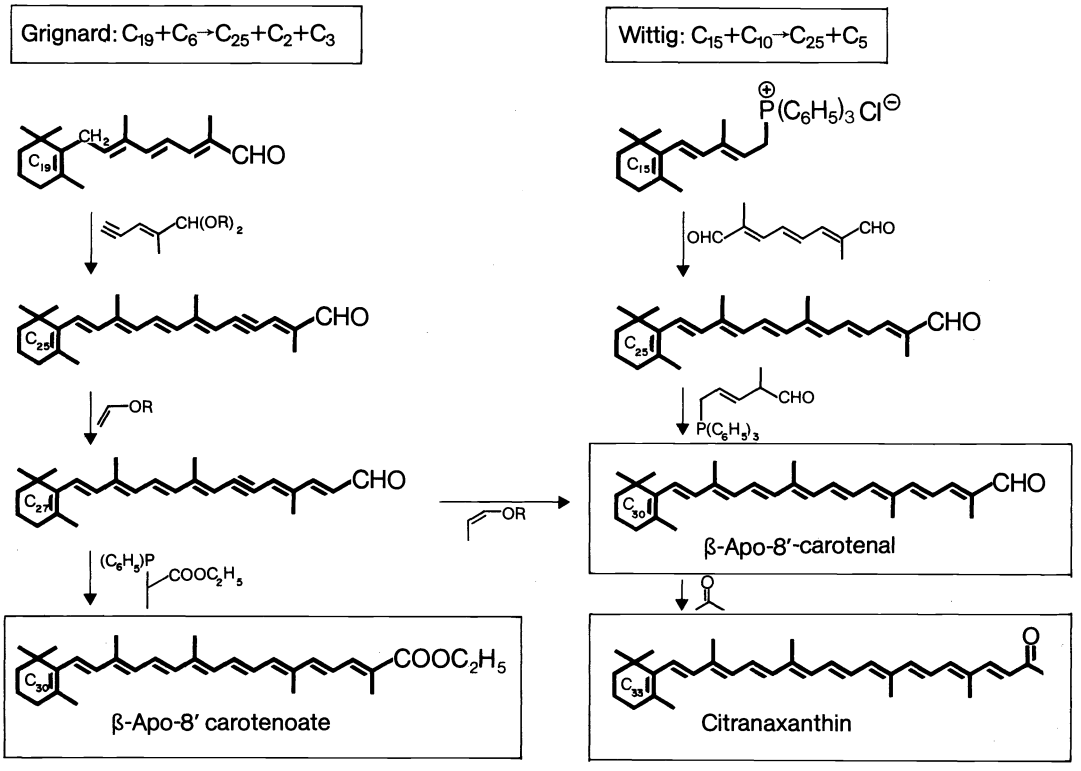

Fig. 16. Manufacture of β-apo-8'-carotenoids

C_{30}-β-apo-8'-carotenoate is obtained from the C_{27}-intermediate in a Wittig reaction with bromopropionate (69).

BASF (57) condenses the C_{15}-Wittig salt with one mole of the symmetrical C_{10}-dialdehyde and is lengthening the C_{25}-aldehyde formed with a C_5-Wittig salt (72) to β-apo-8'-carotenal. Its condensation with acetone leads to citranaxanthin, which is as reddish as canthaxanthin and has been introduced in 1968 by BASF as a feed additive.

The industrial manufacture of all carotenoids reaches several hundred tons per year. This is in contrast to nature, which is producing yearly carotenoids in the order of a hundred million tons.

At present three additional carotenoids are being evaluated for use in food and feed, namely crocetin, zeaxanthin and astaxanthin (Fig. 17).

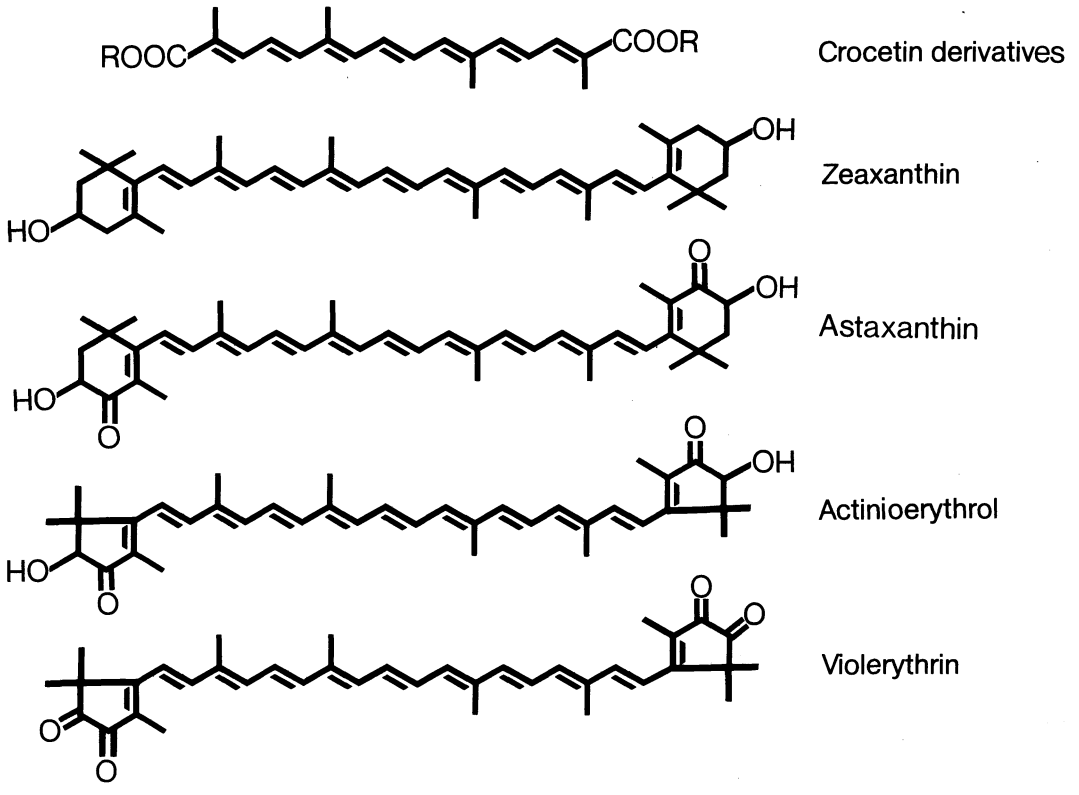

Fig. 17. Products in evaluation

The other interesting carotenoids namely actinioerythrol (73), the pigment of the sea anemone Actinia equina, and its oxidation product violerythrin (74), are members of the class of 2-nor-carotenoids. They possess so far the deepest colours of natural carotenoids. Actinioerythrol exhibits a brilliant violet, violerythrin a deep blue colouration.

Besides their application in food and feed, carotenoids are used in colouring of galenic and cosmetic preparations. As the cones in our retina form a simple trichromatic code it seems to be a challenge to form the whole colour range by combining a few carotenoids with a hue of light yellow to deep red and blue.

CONCLUDING REMARKS

Carotenoids constitute a big class of well tolerated compounds (75). The synthetic carotenoids on the market combine the excellent biological experience in humans for thousands of years with the exact examinations under experimental conditions (including hypersensitivity, cancerogenicity and mutagenicity). The experts of the mixed commission of FAO and WHO (76, 77) classified these pigments into group A(1), i.e. the preferred colours with accepted toxicity tests. Other natural pigments in this group are chlorophyll, riboflavin and caramel colour (Table 3). Betanin (beet red) and curcumin are in group A(2) as they need some further examinations. Anthocyanins and flavonoids, as well as carotenoid extracts, are in group B, because they are concentrates without reliable specifications and biological examination. It is astonishing that some pigments like carminic acid, orcein and alkanet, which are not found in food products, are also in group B. Preference should be given to natural colours occurring in human food (78, 79).

TABLE 3 CLASSIFICATION BY THE JOINT COMMITTEE OF FAO/WHO

GROUP	NATURAL COLORANTS	GOOD SPECIFICATION	BIOCHEMICALLY SAFE
A (1)	β-CAROTENE, β-APO-8'-CAROTENAL, β-APO-8'-CAROTENOATE	YES	YES
	CANTHAXANTHIN	YES	YES
	RIBOFLAVIN	YES	YES
	CHLOROPHYLL, CHLOROPHYLL COPPER COMPLEX, CARAMEL COLOUR	?	YES
A (2)	CHLOROPHYLL (NH_2-PROCESS) CARAMEL (NH_2-PROCESS)	?	YES
	ANNATTO EXTRACTS (BIXA ORELLANA)	?	YES
	BEET RED (BETANIN, BETANIDIN)	?	YES
	TUMERIC AND CURCUMIN	?	?
B	LYCOPENE, MIXED CAROTENES, XANTHOPHYLLS ETC.	NO	YES
	ANTHOCYANINS, FLAVONOIDS (QUERCETIN, RHAMNETIN)	NO	YES
	GLYCYRRHIZINIC ACID, COCHINEAL AND CARMINIC ACID	NO	?
	ORCHIL AND ORCEIN, ALKANET	NO	?

I am convinced that the pure synthetic carotenoids deserve a special status as members of a uniform class of compounds with which man has biochemical experience throughout his evolution. It is my firm belief that they are ideal colouring matters for food and feed, as well as cosmetics and galenic preparations. I think that it is desirable to improve their use and to broaden their colour range.

A group of psychologists believe that the colour sensation was one of the strongest factor in the evolution of man. Traffic lights, modern art, colour television, toys, clothing and hair dressing prove the importance of colourants. However, some people are opposed to the addition of any colours to food, feed and cosmetics. This has a smell of prohibition and seems to tackle the problem from the wrong side. Our efforts should be directed to replace artificial pigments and impure natural extracts by pure safe colourants like pure carotenoids. Most people prefer to eat with eye and taste. They wish to have eggs with a yellow yolk, margarine with butter colour, brown coke, gay candies for children etc. Margarine was a successful food product because it has the colour, flavour and consistency of butter. In our overpopulated world we must create more food and new food products, but this task can only be successful if we give greatest care to colour, smell and taste.

Not only man but also animals depend on synthetic vitamin A. Without synthetic vitamins man would exhaust the natural resources. The fast production of poultry and cattle absolutely depends on the availability of synthetic vitamins. Therefore, besides an aesthetic reasoning which asks for a pleasant appearence of food, the biological necessity for vitamins and provitamins will always force us to make these compounds available on an industrial scale.

I had the privilege to participate in an early stage in the development of this important field for mankind and any success I had, was only possible through the help of many excellent colleagues to whom I am most grateful.

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