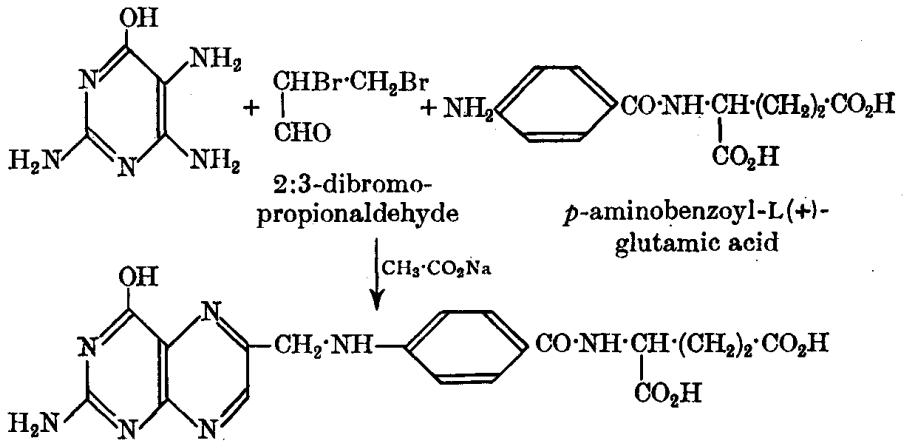
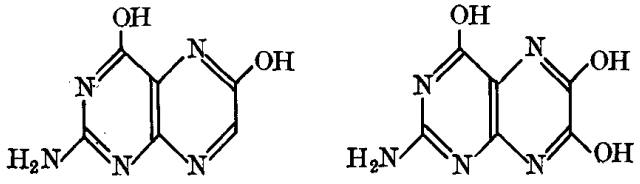
(ii)



liver *L. casei* factor

It might be noted, in passing, that the **pterins** are pigments of butterfly wings, wasps, etc.; they were first isolated from butterfly wings.



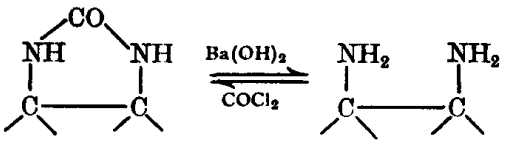
xanthopterin leucopterin

§9. **Biotins** (vitamin H). Bios, an extract of yeast, was shown to be necessary for the growth of yeast (Wildiers, 1901). It was then found that bios consisted of at least two substances (Fulmer *et al.*, 1922), and two years later, Miller showed that three substances were present in bios. The first of these was named Bios I, and was shown to be *meso*inositol (Eastcott, 1928; see also §13). The second constituent, named Bios IIA, was then shown to be β-alanine (Miller, 1936) or pantothenic acid (Rainbow *et al.*, 1939). The third substance, named Bios IIB, was found to be identical with *biotin*, a substance that had been isolated by Kögl *et al.* (1936) as the methyl ester from egg-yolk. Subsequently other factors present in bios have been isolated, *e.g.*, pyridoxin (see §10) and nicotinic acid (§11).

Biotin is a vitamin, being necessary for the growth of animals. In 1940, du Vigneaud *et al.* isolated from liver a substance which had the same biological properties as biotin. Kögl *et al.* (1943) named their extract from egg-yolk α-biotin, and that from liver β-biotin. Both compounds have the same molecular formula $C_{10}H_{16}O_3N_2S$.

β-Biotin (Bios IIB or biotin), m.p. 230–232°, behaves as a saturated compound (the usual tests showed the absence of an ethylenic double bond). β-Biotin forms a monomethyl ester $C_{11}H_{18}O_3N_2S$ which, on hydrolysis, gives an acid the titration curve of which corresponds to a monocarboxylic acid; thus the formula of β-biotin may be written $C_9H_{15}ON_2S{\cdot}CO_2H$. When heated with barium hydroxide solution at 140°, β-biotin is hydrolysed to carbon dioxide and diaminocarboxylic acid $C_9H_{18}O_2N_2S$ which, by the action of carbonyl chloride, is reconverted into β-biotin (du Vigneaud *et al.*, 1941). These reactions suggest that β-biotin contains a cyclic ureide structure. Furthermore, since the diaminocarboxylic acid condenses with phenanthraquinone to form a quinoxaline derivative, it follows that the two amino-

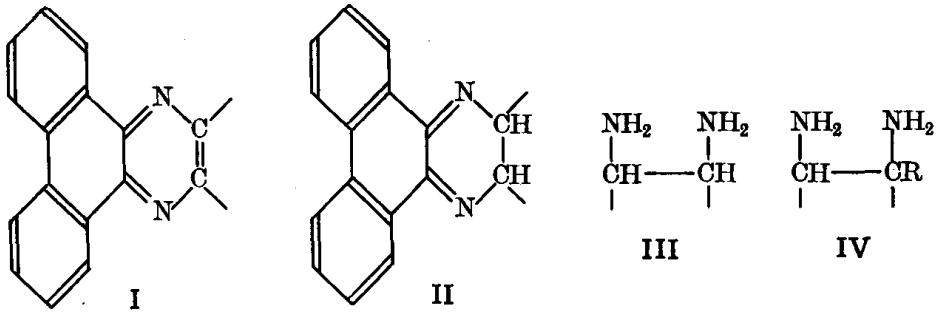
groups are in the 1 : 2-positions (*cf.* §19. XII), and thus the cyclic ureide is five-membered. Hence we may write the foregoing reactions as follows:



β-biotin diamino-compound

When this diaminocarboxylic acid is oxidised with alkaline permanganate, adipic acid is produced (du Vigneaud *et al.*, 1941). One of the carboxyl groups in adipic acid was shown to be that originally present in β-biotin as follows. When the carbomethoxyl group of the methyl ester of β-biotin was replaced by an amino-group by means of the Curtius reaction (ester → hydrazide → azide → urethan → NH_2; see Vol. I), and the product hydrolysed with barium hydroxide solution, a triamine was obtained which did not give adipic acid on oxidation with alkaline permanganate (du Vigneaud *et al.*, 1941, 1942). It was therefore inferred that β-biotin contains a $-(CH_2)_4{\cdot}CO_2H$ side-chain (*n*-valeric acid side-chain).

The absorption spectrum of the quinoxaline derivative (formed from phenanthraquinone and the diaminocarboxylic acid) showed that it was a quinoxaline, I, and not a dihydroquinoxaline, II; thus the diaminocarboxylic could be III but not IV.



It therefore follows that the *n*-valeric acid side-chain cannot be attached to a carbon atom joined to an amino-group.

The nature of the sulphur atom in β-biotin was shown to be of the thioether type (*i.e.*, C—S—C) since:

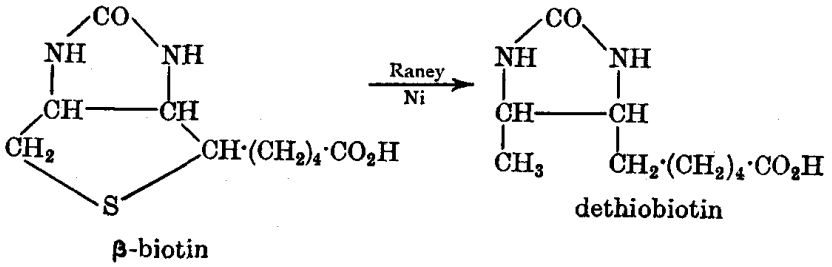
(i) Oxidation of β-biotin with hydrogen peroxide produced a sulphone.

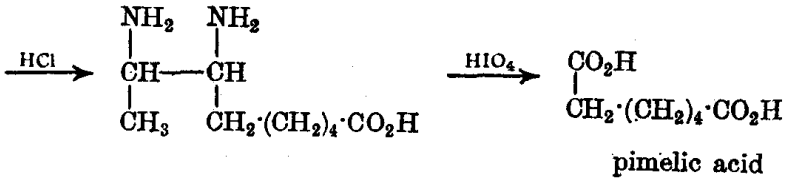
(ii) When the methyl ester of β-biotin was treated with methyl iodide, a sulphonium iodide was formed.

As we have seen, β-biotin does not contain a double bond; hence, from its molecular formula, it was deduced that β-biotin contains two rings (du Vigneaud *et al.*, 1941; Kögl *et al.*, 1941). The sort of argument that may be used is as follows. The molecular formula of β-biotin is $C_{10}H_{16}O_3N_2S$. The carboxyl group may be regarded as a substituent group, and so the parent compound will be $C_9H_{16}ON_2S$. Also, since two NH groups are present, these may be replaced by CH_2 groups; thus the parent compound is $C_{11}H_{18}OS$. The CO group may be replaced by a CH_2 group and the sulphide atom also by a CH_2 group. This gives a compound of formula $C_{13}H_{22}$ which has the same "structure" as β-biotin. Now the formula $C_{13}H_{22}$ corresponds to the general formula C_nH_{2n-2}, and this, for a *saturated* compound, corresponds to a system containing two rings.

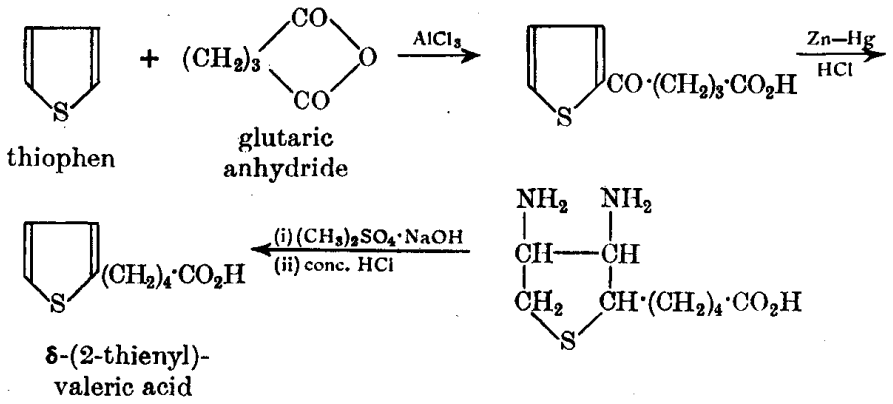
When heated with Raney nickel, β-biotin formed *dethiobiotin* by elimination of the sulphur atom (this is an example of the *Mozingo reaction*, 1943).

Dethiobiotin, on hydrolysis with hydrochloric acid, gave a diaminocarboxylic acid which, on oxidation with periodic acid, gave pimelic acid (du Vigneaud *et al.*, 1942). These results can be explained by assuming that the sulphur atom is in a five-membered ring and the *n*-valeric acid side-chain is in the position shown.

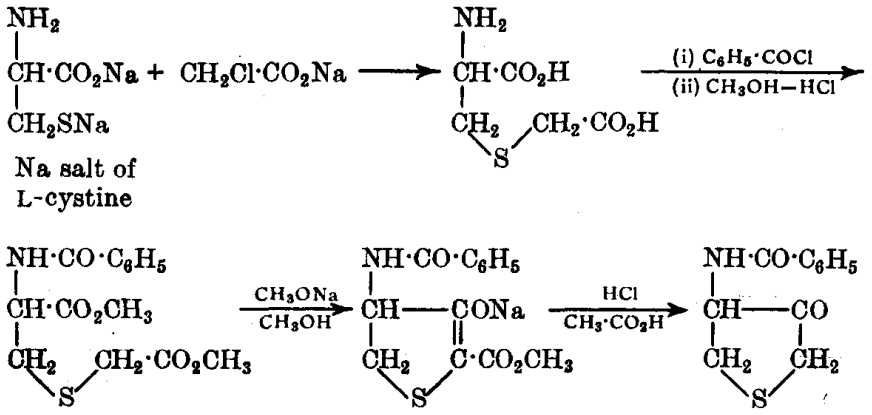


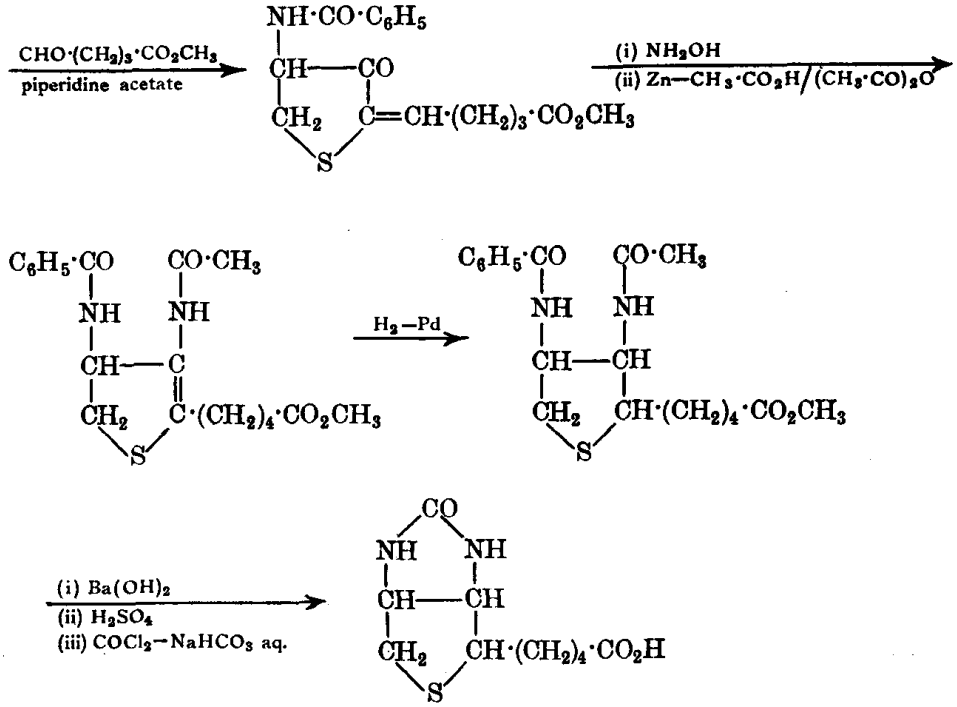


Further evidence for this structure is given by the fact that the exhaustive methylation of the diaminocarboxylic acid (produced from β-biotin), followed by hydrolysis, gave δ-(2-thienyl)-valeric acid (du Vigneaud *et al.*, 1942); the structure of this compound was confirmed by synthesis.



The above structure for β-biotin has been confirmed by synthesis (Harris *et al.*, 1943, 1944).





Two racemates were isolated, one of which was (±)-β-biotin; this was resolved *via* its esters with (−)-mandelic acid.

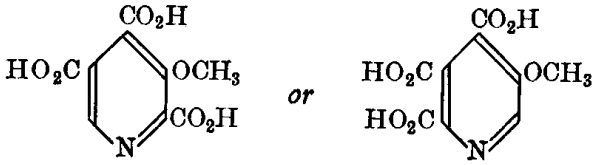
Examination of the β-biotin formula shows the presence of three asymmetric carbon atoms; the rings are fused in the *cis*-position in β-biotin and the orientation of the side-chain is also *cis*, as shown by X-ray analysis (Traub, 1956).

The structure of α-biotin is uncertain.

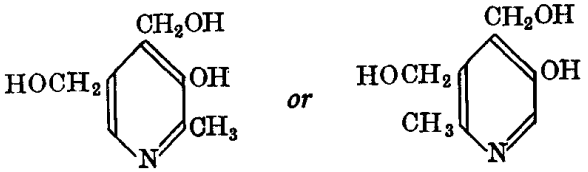
§10. Pyridoxin (Adermin, vitamin B_6), $C_8H_{11}O_3N$, is obtained from rice bran and yeast; it cures dermatitis in rats. Pyridoxin behaves as a weak base, and the usual tests showed the absence of methoxyl and methylamino-groups. Application of the Zerewitinoff method showed the presence of three active hydrogen atoms. When treated with diazomethane, pyridoxin formed a monomethyl ether which, on acetylation, gave a diacetyl derivative (Kuhn *et al.*, 1938). It therefore appears that the three oxygen atoms in pyridoxin are present as hydroxyl groups, and since one is readily methylated, this one is probably phenolic. This conclusion is supported by the fact that pyridoxin gives the ferric chloride colour reaction of phenols. Thus the other two hydroxyl groups are alcoholic.

Examination of the ultraviolet absorption spectrum of pyridoxin showed that it is similar to that of 3-hydroxypyridine. It was therefore inferred that pyridoxin is a pyridine derivative with the phenolic group in position 3. Since lead tetra-acetate has no action on the monomethyl ether of pyridoxin, this leads to the conclusion that the two alcoholic groups are not on adjacent carbon atoms in a side-chain (Kuhn *et al.*, 1939). When this methyl ether is *very carefully* oxidised with alkaline potassium permanganate, the product is a methoxypyridinetricarboxylic acid, $C_9H_7O_7N$. This acid gave a blood-red colour with ferrous sulphate, a reaction which is characteristic of pyridine-2-carboxylic acid; thus one of the three carboxyl groups is in the 2-position. When the methyl ether of pyridoxin was oxidised with alkaline permanganate under the usual conditions, the products were carbon dioxide and the anhydride of a dicarboxylic acid, $C_8H_5O_4N$; thus these two carboxyl groups are in the *ortho*-position. Furthermore, since this anhydride, on

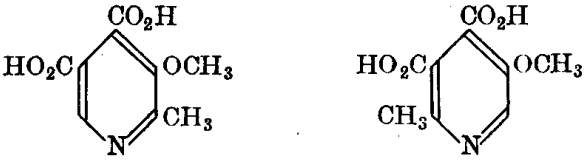
hydrolysis to its corresponding acid, did not give a red colour with ferrous sulphate, there is no carboxyl group in the 2-position. It therefore follows that, on decarboxylation, the tricarboxylic acid eliminates the 2-carboxyl group to form the anhydride; thus the tricarboxylic acid could have either of the following structures.



Now pyridoxin methyl ether contains three oxygen atoms (one as methoxyl and the other two alcoholic); it is therefore possible that two carboxyl groups in the tricarboxylic acid could arise from two CH_2OH groups, and the third from a methyl group, *i.e.*, pyridoxin could be either of the following:

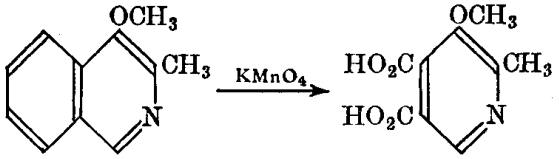


A decision between the two structures was made on the following evidence. When pyridoxin methyl ether was oxidised with barium permanganate, the product was a dicarboxylic acid, $C_9H_9O_5N$, which did not give a red colour with ferrous sulphate; thus there is no carboxyl group in the 2-position. Also, since the dicarboxylic acid formed an anhydride and gave a phthalein on fusion with resorcinol, the two carboxyl groups must be in the *ortho*-position. Furthermore, analysis of both the dicarboxylic acid and its anhydride showed the presence of a methyl group. Thus the structure of this dicarboxylic acid is either I or II.

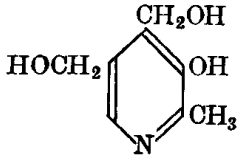


I II

Kuhn *et al.* (1939) showed that the anhydride was that of I from its formation by the oxidation of 4-methoxy-3-methyl-*iso*quinoline (a synthetic compound of known structure).

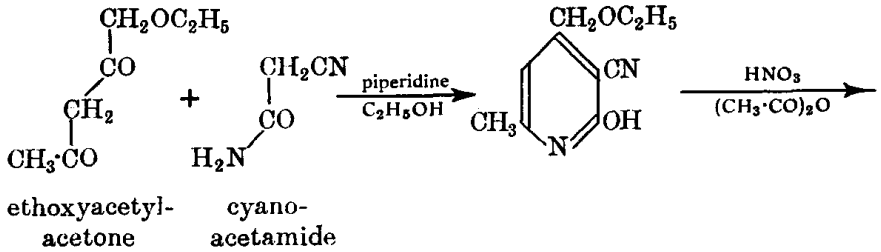


Hence, on the foregoing evidence, pyridoxin is

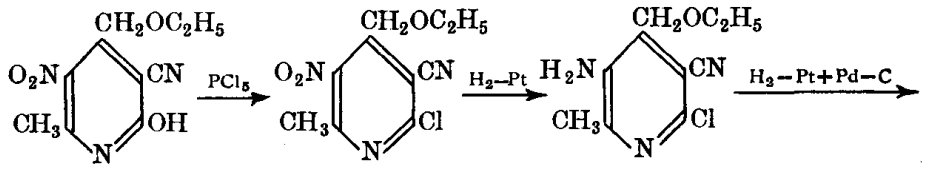


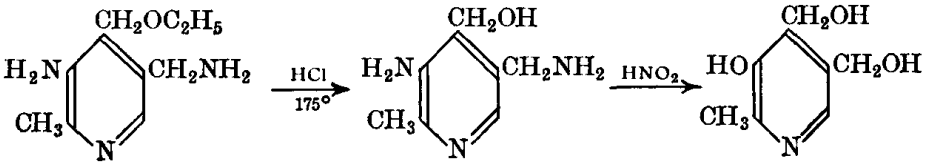
pyridoxin

This structure has been confirmed by synthesis, *e.g.*, that of Harris and Folkers (1939):



ethoxyacetyl-acetone cyano-acetamide

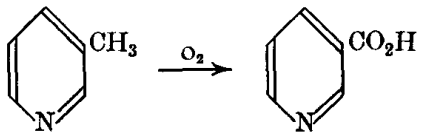




pyridoxin

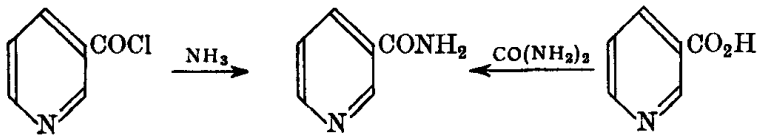
§11. Nicotinic acid and nicotinamide. These two compounds have been shown to be the human pellagra-preventing (P.P.) factor. Nicotinamide is part of the co-enzymes codehydrogenase I and II, which play a part in many biological oxidations.

Nicotinic acid (*Niacin*) was first prepared by the oxidation of nicotine (§21. XIV). This is now used as a commercial method; another commercial method for the preparation of nicotinic acid is the vapour-phase oxidation of 3-methylpyridine (β-picoline) in the presence of a vanadium and iron catalyst.



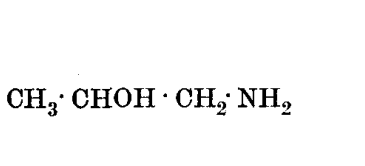
Still another commercial method is the oxidation of quinoline to quinolinic acid, which is then decarboxylated to nicotinic acid (see also §21. XIV).

Nicotinamide, m.p. 131°, is manufactured by various methods, *e.g.*, by the action of ammonia on nicotinyl chloride, or by heating nicotinic acid with urea in the presence of a molybdenum catalyst.

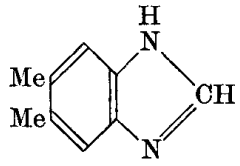


§12. Vitamin B_{12}, Cyanocobalamin. This is the anti-pernicious anæmia factor, and has been isolated from liver extract. Folic acid (§8) also has anti-anæmic properties. Vitamin B_{12} has been obtained as a red crystalline substance (Folkers *et al.*, 1948; Smith *et al.*, 1948, 1949), and the elements present have been shown to be C, H, O, N, P, Co; this vitamin is the first natural product found to contain cobalt. The cobalt has been shown to

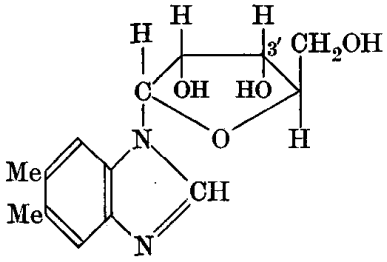
be attached to a cyano group. The hydrolysis of vitamin B_{12} with hydrochloric acid under different conditions produces ammonia, 1-aminopropan-2-ol (I), 5 : 6-dimethylbenzimidazole (II), 5 : 6-dimethylbenzimidazole-1-α-D-ribofuranoside (III) and the 3′-phosphate of III (Folkers *et al.*, 1949, 1950; Todd *et al.*, 1950). Compound IV (a succinimide derivative) has also been isolated by the chromic acid oxidation of hydrolysed vitamin B_{12} (Folkers, 1955).



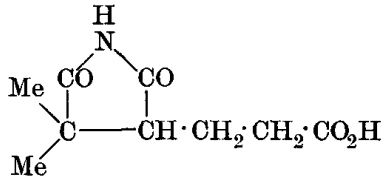
I



II

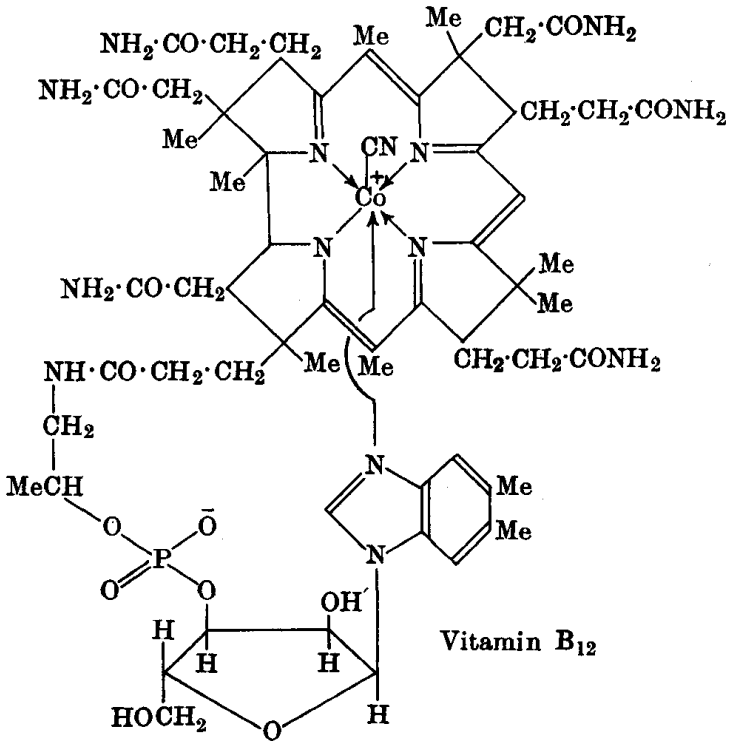


III



IV

Other work has shown that six amido groups are present in the molecule. Also, alkaline hydrolysis of vitamin B_{12} gives a mixture consisting mainly of a penta- and a hexacarboxylic acid, in both of which the nucleotide fragment is absent. As the result of a detailed X-ray analysis of the hexacarboxylic acid, vitamin B_{12} has been assigned the structure shown.



Vitamin B_{12}

A point of interest is that the arrangement of the four pyrrole nuclei is somewhat similar to that in the natural porphin derivatives such as hæm and chlorophyll (§§2, 7. XIX).

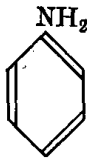
A number of vitamin B_{12} compounds have now been isolated which differ only in the nature of the basic component of the nucleotide. The remainder of the molecule, which is referred to as **Factor B,** is common to all the members of the vitamin B_{12} group. A partial synthesis of vitamin B_{12} (starting from factor B) has now been carried out by Bernhauer *et al.* (1960).

§13. Other compounds of the vitamin B complex. Three other compounds which have definitely been isolated from the vitamin B complex are:

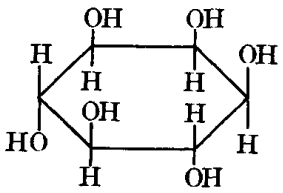
(i) *p*-Aminobenzoic acid; this is a growth factor for bacteria.

(ii) *meso*Inositol (m.p. 225–226°). This is a growth factor in animals, and its configuration has been elucidated by Posternak (1942; see also §11 iv. IV).

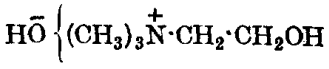
(iii) Choline. The absence of this compound leads to the formation of a fatty liver in animals.



p-amino-benzoic acid



*meso*inositol



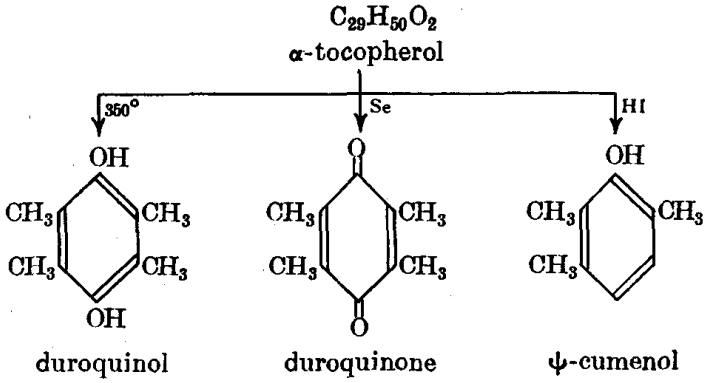
choline

Other vitamins of the vitamin B complex that have been said to exist are vitamins B_3, B_4, B_5, B_{10}, B_{11}, B_{13}, B_{14} and others.

VITAMIN E GROUP

§14. Introduction. Vitamin E is the anti-sterility factor; it occurs in seed germ oils. It is now known that there are three closely related compounds comprising " vitamin E "; all three are biologically active, and are known as α-, β- and γ-tocopherol. The main source of α- and β-tocopherol is wheat germ oil; the γ-compound is obtained from cotton seed oil. Wheat germ oil was first subjected to chromatographic analysis to remove sterols, etc., and then the α- and β-tocopherols were purified by conversion into their crystalline allophanates (see §12. XII) or 3 : 5-dinitrobenzoates. Hydrolysis of these derivatives gave the tocopherols as pale yellow oils.

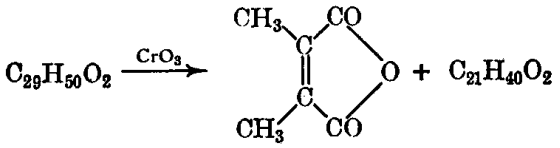
§15. α-Tocopherol, $C_{29}H_{50}O_2$. When α-tocopherol is heated at 350°, duroquinol is obtained (Fernholz, 1937). On the other hand, when heated with selenium, α-tocopherol forms duroquinone (McArthur *et al.*, 1937). Finally, when heated with hydriodic acid, ψ-cumenol is formed (John *et al.*, 1937).



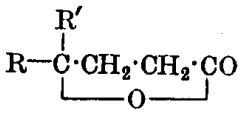
duroquinol duroquinone ψ-cumenol

The formation of these products led to the suggestion that α-tocopherol was the monoether of duroquinol; the possibility that it might be the diether was ruled out by the fact that α-tocopherol forms an allophanate, which indicates the presence of one free hydroxyl group. This monoether structure was shown to be incorrect by the fact that the ultraviolet absorption spectra of various monoethers of duroquinol were different from that of α-tocopherol (Fernholz, 1938).

Oxidation of α-tocopherol with chromic acid forms dimethylmaleic anhydride and a compound $C_{21}H_{40}O_2$.

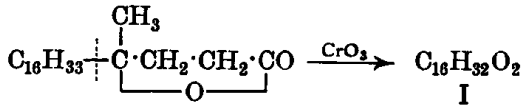


This latter compound was shown to be an optically active saturated lactone. This lactone was then shown to be derived from a γ-hydroxyacid in which the hydroxyl group is tertiary, *e.g.*, the acid lactonised immediately its salt was acidified, and also could not be oxidised to a keto-acid. Thus the structure of this lactone may be written (R + R′ = 17C):

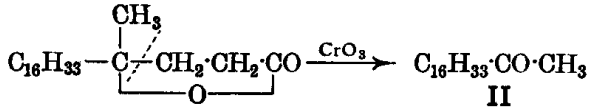


Now α-tocopherol acetate, on oxidation with chromic acid, forms an acid, $C_{16}H_{32}O_2$, I, and a ketone, $C_{18}H_{36}O$, II. Both of these compounds must be produced by the oxidation of the lactone at different points in the chain. Fernholz therefore suggested that if in the lactone R = $C_{16}H_{33}$ and R′ = CH_3, then the products I and II can be accounted for; thus:

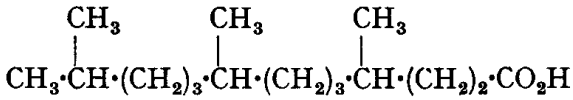
(i)



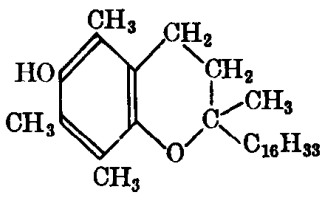
(ii)



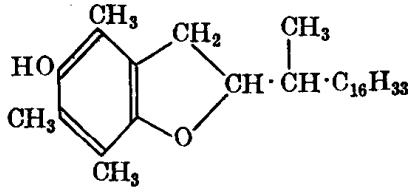
Fernholz then showed that the acid (I) contained methyl groups (*cf.* §3. IX), and was led to propose a structure based on the isoprene unit, *viz.*



The evidence obtained so far indicates the presence of a substituted benzene ring and a long side-chain in α-tocopherol. When the monoethers of duroquinol (see above) were oxidised with silver nitrate solution, the action took place far more slowly than for α-tocopherol when oxidised under the same conditions. Furthermore, whereas the former compounds were oxidised to duroquinone, the latter compound gave a red oil which appeared to have approximately the same molecular weight as α-tocopherol (Fernholz, 1938). Since duroquinone is not split off during this oxidation, it suggests that the side-chain is connected to the aromatic ring by a carbon bond as well as an ether link. In this case α-tocopherol is either a chroman or coumaran derivative:



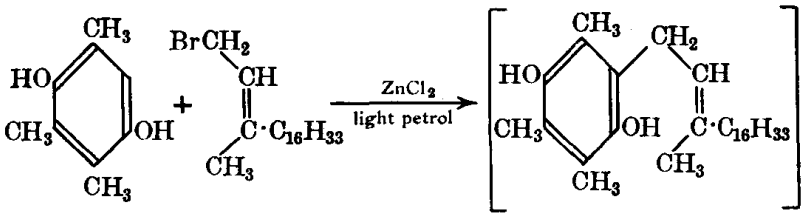
chroman structure

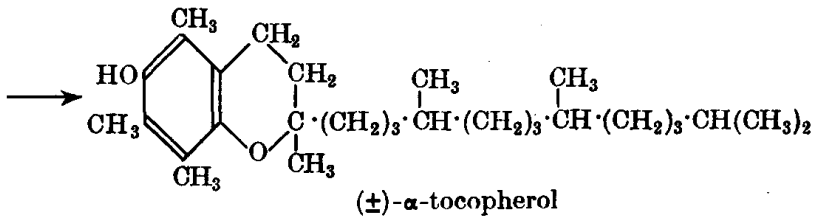


coumaran structure

According to Fernholz, the oxidation products are best explained on the chroman structure. This has been supported by ultraviolet absorption measurements of α-tocopherol (John *et al.*, 1938).

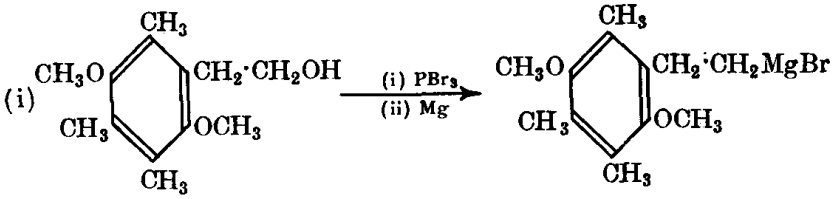
Karrer *et al.* (1938) have synthesised (±)-α-tocopherol by condensing trimethylquinol with phytyl bromide (§30. VIII).

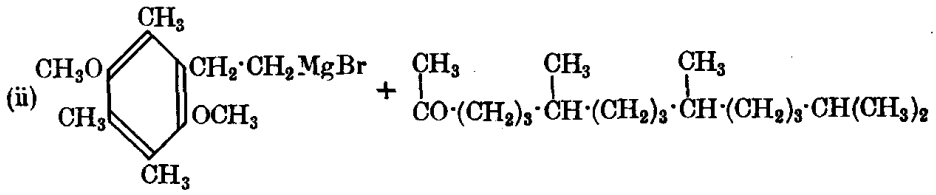


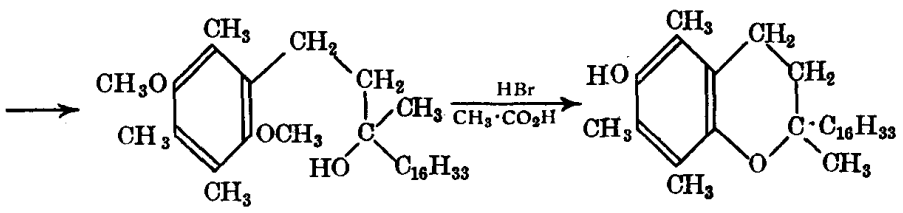


(±)-α-tocopherol

This synthesis, however, is not completely unambiguous, since phenols may condense with allyl compounds to form coumarans. Smith *et al.* (1939) have shown that $\gamma:\gamma$-disubstituted halides form only chromans, and since phytyl bromide is a halide of this type, this strengthens the course of the synthesis given above. Finally, Smith *et al.* (1942) have carried out an unambiguous synthesis of α-tocopherol as follows:



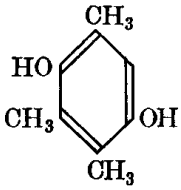




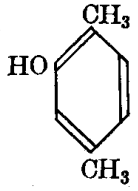
(±)-α-tocopherol

Smith *et al.* prepared the methyl ketone by ozonolysis of phytol, and also by oxidation of phytol with chromic acid.

§16. β-Tocopherol, $C_{28}H_{48}O_2$. This formula differs from that of α-tocopherol by CH_2. Thermal decomposition of β-tocopherol gives trimethylquinol, I, and heating with hydriodic acid *p*-xylenol, II (John *et al.*, 1937).

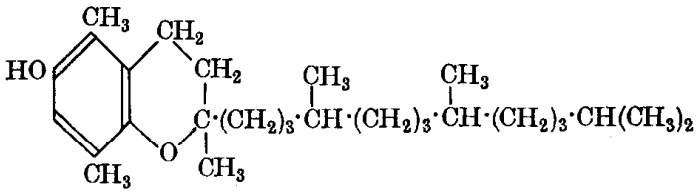


I



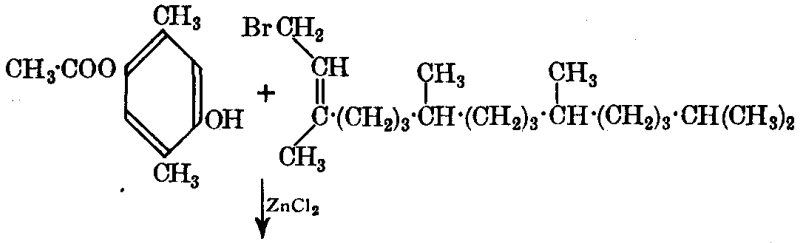
II

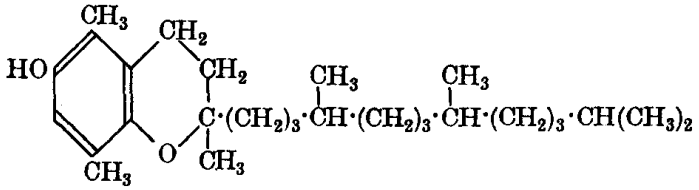
When oxidised with chromic acid, β-tocopherol gives the same lactone ($C_{21}H_{40}O_2$) as that obtained from α-tocopherol. Thus the only difference between the two tocopherols is that the α-compound has one more methyl group in the benzene ring than the β-; hence the latter is



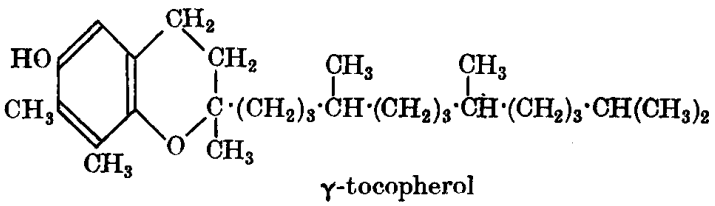
β-tocopherol

This has been confirmed by synthesis, starting from the monoacetate of *p*-xyloquinol and phytyl bromide.



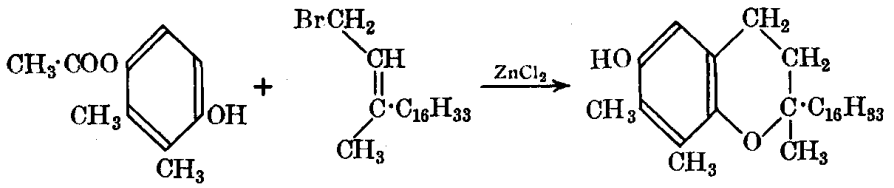


§17. γ-Tocopherol, $C_{28}H_{48}O_2$. This is isomeric with β-tocopherol; the only difference is the positions of the two methyl groups in the benzene ring, *e.g.*, when heated with hydriodic acid, γ-tocopherol gives *o*-xyloquinol. Thus γ-tocopherol is

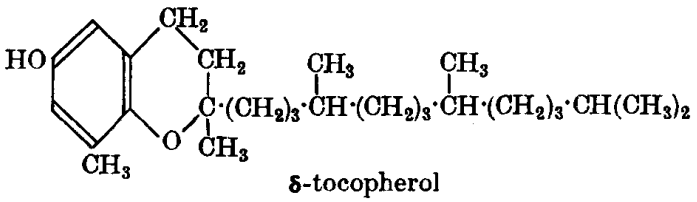


γ-tocopherol

This structure has been confirmed by synthesis, starting from the monoacetate of *o*-xyloquinol and phytyl bromide.



§18. **δ-Tocopherol,** $C_{27}H_{46}O_2$. This was isolated from soya bean oil by Stern *et al.* (1947); it is a yellow oil, and is inactive physiologically. The structure of δ-tocopherol is

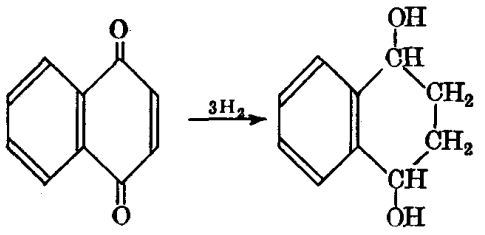


δ-tocopherol

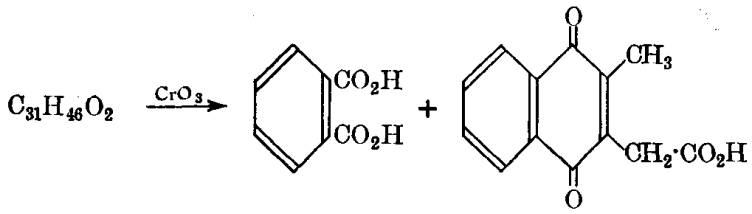
VITAMIN K GROUP

§19. **Introduction.** Dam *et al.* (1939) and Doisy *et al.* (1939) isolated vitamin K from alfalfa, and called it vitamin K_1 to distinguish it from a substance called vitamin K_2 which had been isolated from putrefied fish meal by Doisy *et al.* (1939). Both are antihæmorrhagic vitamins; they are connected with the enzymes involved in blood clotting, a deficiency of them lengthening the time of blood clotting. Kegel *et al.* (1962) have obtained chemical evidence for the presence of vitamin K_1 in extracts from spinach chloroplasts.

§20. **Vitamin K_1** (α-phylloquinone), $C_{31}H_{46}O_2$, is a light yellow oil. The redox potential of vitamin K_1 is very similar to that of 1 : 4-quinones (Karrer *et al.*, 1939), and its absorption spectrum is very similar to that of 2 : 3-disubstituted 1 : 4-naphthaquinones (McKee *et al.*, 1939). Thus vitamin K_1 appears to be a 1 : 4-naphthaquinone derivative, and this is in keeping with the fact that the vitamin is very sensitive to light and to alkalis. Now the catalytic hydrogenation of vitamin K_1 causes the addition of four molecules of hydrogen (McKee *et al.*, 1939); the product is a colourless compound. Since it is known that three molecules of hydrogen are added when 1 : 4-naphthaquinone is reduced under these conditions, the addition of a fourth molecule of hydrogen to the vitamin suggests the presence of an ethylenic double bond in a side-chain.

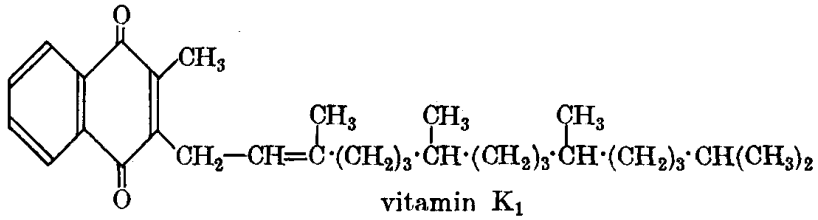


When subjected to reductive acetylation (*i.e.*, acetylated under reducing conditions), vitamin K_1 is converted into the diacetate of dihydrovitamin K_1 (Binkley *et al.*, 1939). This diacetate is difficult to hydrolyse; this is a property characteristic of 2 : 3-disubstituted 1 : 4-naphthaquinones. When oxidised with chromic acid, vitamin K_1 gives phthalic acid, but when the oxidation is carried out under controlled conditions, the product is a compound with the molecular formula $C_{13}H_{10}O_4$. This latter compound was subsequently shown to be 2-methyl-1 : 4-naphthaquinone-3-acetic acid (Binkley *et al.*, 1939).



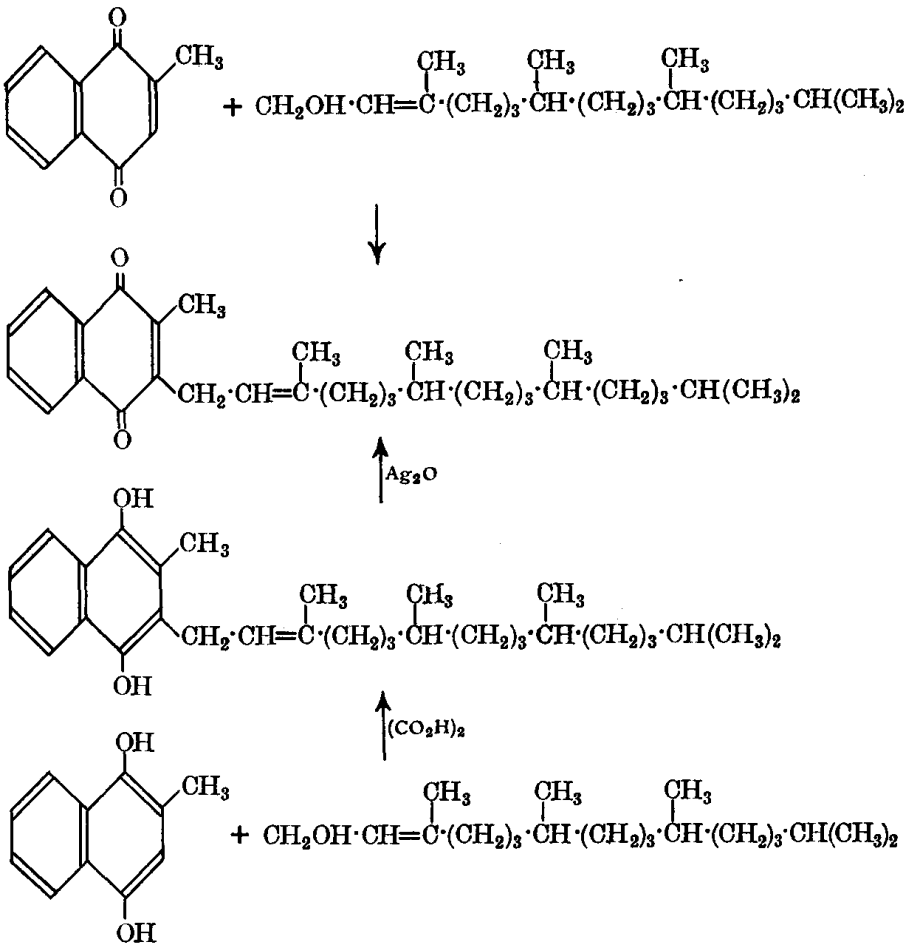
Thus the presence of the 1 : 4-naphthaquinone structure is confirmed, and at the same time these products show that one ring is unsubstituted and that the other (the quinonoid ring) has substituents in the 2- and 3-positions.

When the diacetate of dihydrovitamin K_1 (see above) was subjected to ozonolysis, a compound $C_{18}H_{36}O$ was obtained, which was then shown to be identical with the ketone produced by the oxidation of phytol (McKee *et al.*, 1939; *cf.* Smith's synthesis of α-tocopherol, §15). Hence, on the evidence obtained above, vitamin K_1 is 2-methyl-3-phytyl-1 : 4-naphthaquinone.



vitamin K_1

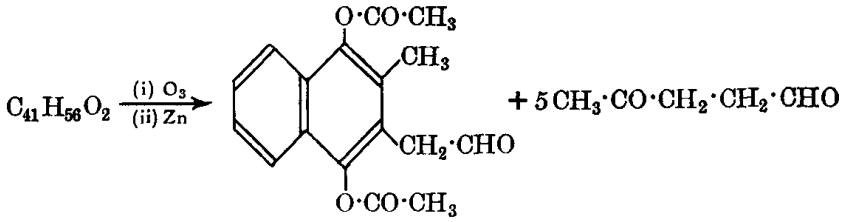
This structure has been confirmed by synthesis: Almquist *et al.* (1939) obtained vitamin K_1 by condensing 2-methyl-1 : 4-naphthaquinone with phytol; Fieser *et al.* (1939) obtained a better yield by heating 2-methyl-1 : 4-naphthaquinol with phytol in dioxan solution in the presence of anhydrous oxalic acid, and then oxidising the product, dihydrovitamin K_1, with silver oxide in ether.



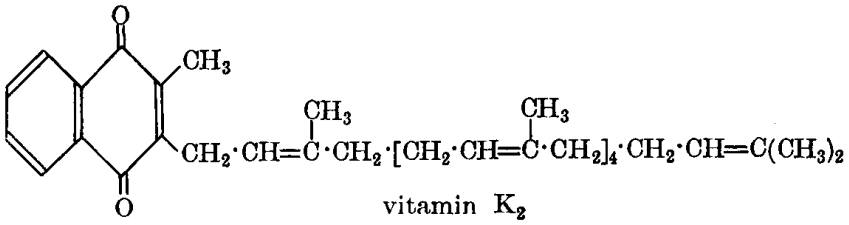
Wendler *et al.* (1954) have obtained vitamin K_1 in good yield by condensing the 1-acetyl derivative of 2-methyl-1 : 4-naphthaquinol with phytol in the presence of boron trifluoride.

§21. Vitamin K_2, $C_{41}H_{56}O_2$, is a yellow solid, m.p. 54°; it is less potent than vitamin K_1. It was shown to contain a 1 : 4-naphthaquinone nucleus by the facts that it is sensitive to light and to alkalis, and that it has an absorption spectrum similar to that of vitamin K_1 (McKee *et al.*, 1939). When catalytically reduced, vitamin K_2 adds on nine molecules of hydrogen, and since three of these are absorbed by the naphthaquinone nucleus (see §20), it therefore suggests that there is a side-chain present which contains six double bonds. Furthermore, since vitamin K_2 does not form an adduct with maleic anhydride, no conjugation is present (McKee *et al.*, 1939). That these six double bonds are ethylenic is shown by the fact that on reductive acetylation, vitamin K_2 forms the diacetate of dihydrovitamin K_2, which can add on six molecules of bromine.

The oxidation of vitamin K_2 with permanganate produces phthalic acid; therefore one ring is unsubstituted. On the other hand, when ozone is passed into a solution of vitamin K_2 in acetic acid, and the product then treated with zinc dust in ether, 1 : 4-diacetoxy-2-methylnaphthalene-3-acetaldehyde is produced. At the same time there is obtained lævulaldehyde in a yield of 93 per cent. calculated on the basis that one molecule of vitamin K_2 can produce five molecules of the aldehyde.



Acetone is also formed in this reaction, and is obtained in a yield of 56 per cent. based on the assumption that one molecule of acetone is produced from one molecule of vitamin K_2 (McKee *et al.*, 1940). On this evidence, it has been suggested that vitamin K_2 is 3-difarnesyl-2-methyl-1 : 4-naphthaquinone (Binkley *et al.*, 1940).



vitamin K_2

§22. Other compounds possessing antihæmorrhagic properties. It has been shown that simple 1 : 4-naphthaquinones have blood-clotting properties. 2-Methyl-1 : 4-naphthaquinone is more active than either vitamin K_1 or K_2 (Fernholz *et al.*, 1939); it is therefore used instead of the natural vitamins. *Phthiocol* (3-hydroxy-2-methyl-1 : 4-naphthaquinone) is also an active compound, and is water-soluble. It is also interesting to note that many quinones other than 1 : 4-naphthaquinones have also been found to be active, *e.g.*, some *p*-benzoquinones.

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(ii) Todd *et al.*, *Nature*, 1955, **176**, 330.
(iii) *Chem. Soc. Special Publ.*, No. 3, 1955.