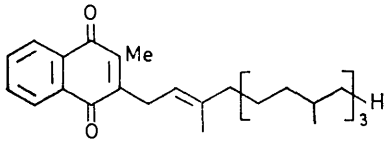
A New Synthesis of Vitamin K *via* π-Allylnickel Intermediates

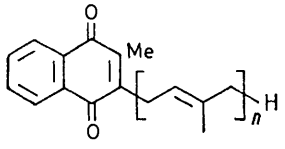
By **Kikumasa Sato,* Seiichi Inoue, and Kenji Saito,** Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Ooka, Minami-ku, Yokohama, 233, Japan

A new synthesis of vitamins K_1 (1), and $K_{2(5n)}$ (2) is described. Reaction of bis-(1—3-η-3-alkylbut-2-enyl)di-μ-bromodinickel complexes (8a—c) with 2-bromo-3-methylnaphthalene-1,4-diyl bis(methoxymethyl) ether (6a) or diacetate (6b) in a polar, co-ordinating solvent gave the corresponding vitamin K derivatives (9a—d) in high yield, which were converted into vitamin K analogues also in high yield. The stereoselectivity decreases as the donor strength of the solvent increases. All-*trans*-vitamin $K_{2(45)}$ (2b) was isolated from the *trans–cis*-mixture (70:30) prepared by this method.

VITAMINS K_1 (1) and $K_{2(5n)}$ (2) are quinones distributed widely amongst species of higher plants and algae, and bacteria and some fungi, respectively. They are used



(1)



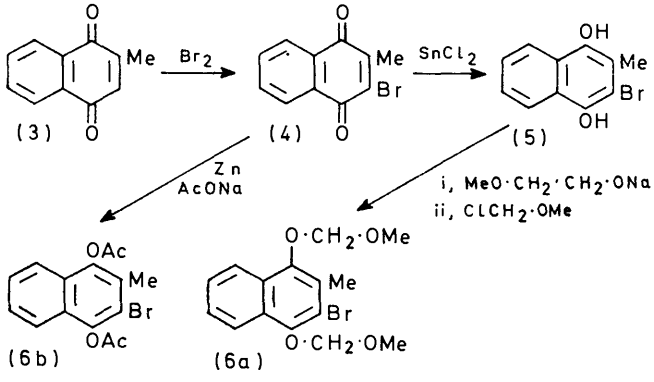
(2) a; n = 1
b; n = 9

in therapy to promote normal clotting of the blood. All the double bonds in the isoprenoid side chain have the *trans*-configuration in the naturally occurring compounds. Methods generally used for introducing the isoprenoid side chain into the 3-position of 2-methyl-1,4-naphthoquinone (3) have involved Friedel–Crafts alkylation of 2-methylnaphthalene-1,4-diol or 1-monoester derivatives with phytol or polyprenyl alcohols.[1–4] These procedures, however, suffer from the disadvantages of chromanol formation and side-chain cyclisation, which make product isolation difficult. In 1967, Corey and Semmelhack reported that η-allylnickel complexes react with aliphatic or aromatic halides in polar co-ordinating media to afford cross-coupling products in good yield.[5] We have been studying the utilisation of this reaction in the synthesis of polyprenyl alcohols [6] and isoprenoid quinones like coenzyme Q_n [7] and vitamin K.[8]

We now describe a new synthesis of the vitamins (1) and (2) by use of allylnickel complexes; we also describe the effects of solvent on the stereoselectivity of the reaction, and the isolation of all-*trans*-vitamin $K_{2(45)}$ (2b). We first attempted the synthesis of vitamin $K_{2(5)}$ (2a). Although several protected quinones were considered as starting materials, the bis(methoxymethyl) ether (6a) and the diacetate (6b) were chosen because of their ease of hydrolysis.†

Bromination of the quinone (3) in acetic acid at 50 °C gave 2-bromo-3-methyl-1,4-naphthoquinone (4), which was reduced by tin(II) chloride to the corresponding hydroquinone (5).[9] This was treated with sodium 2-methoxyethoxide and chloromethyl methyl ether in 2-methoxyethanol under nitrogen to afford the diether (6a). The diacetate (6b) was prepared by reductive acetylation of (4) with zinc dust in boiling acetic anhydride.[9]

Treatment of 1-bromo-3-methylbut-2-ene (7a) with excess of tetracarbonylnickel in benzene under nitrogen



at 50 °C for 3 h gave the η-3-methylbut-2-enylnickel bromide (8a). The crude complex in a polar solvent was treated with compound (6a or b) at 50—75 °C for several hours to give the cross-coupling product (9a or b) in high yield (see Table 1).

Hydrolysis of (9a) in boiling acidic methanol for 1 h, then oxidation by iron(III) chloride yielded vitamin $K_{2(5)}$ (2a) quantitatively. Deacetylation of (9b) was achieved by shaking with aqueous methanolic potassium

† While this work was in progress, L. S. Hugedus, E. L. Waterman, and J. Catlin (*J. Amer. Chem. Soc.*, 1972, **94**, 7155) reported that allylnickel complexes react with conjugated enone systems to produce 1,4-adducts. They applied this reaction to the synthesis of coenzyme Q_1 and plastoquinone-1.

[1] L. F. Fieser, *J. Amer. Chem. Soc.*, 1939, **61**, 3467.
[2] R. Hirschmann, R. Miller, and N. L. Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4592.
[3] H. Lindlar, B.P. 752,420/1956 (*Chem. Abs.*, 1957, **51**, 9699).
[4] O. Isler, R. Rüegg, L. Chopard-dit-Jean, A. Winterstein, and O. Wiss, *Helv. Chim. Acta*, 1958, **41**, 786.
[5] E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, 1967, **89**, 2755.
[6] K. Sato, S. Inoue, S. Ota, and Y. Fujita, *J. Org. Chem.*, 1972, **37**, 462.
[7] K. Sato, S. Inoue, and R. Yamaguchi, *J. Org. Chem.*, 1972, **37**, 1899.
[8] Preliminary communication, K. Sato, S. Inoue, and K. Saito, *J.C.S. Chem. Comm.*, 1972, 953.
[9] R. Adams, T. A. Geissmann, B. R. Baker, and T. M. Teeter, *J. Amer. Chem. Soc.*, 1941, **63**, 528.

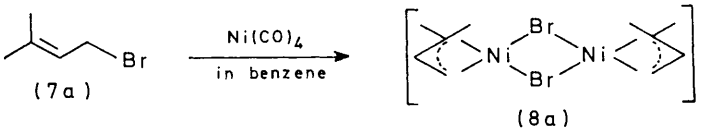
hydroxide followed by oxidation with iron(III) chloride to give the same product (2a) in quantitative yield.

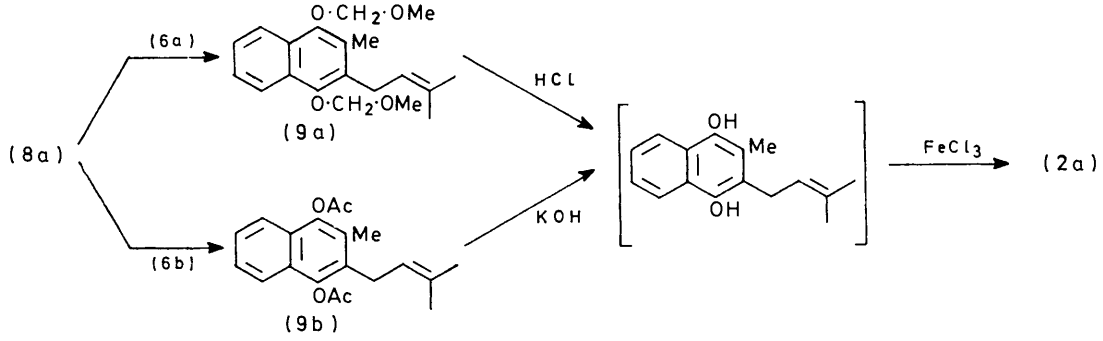
TABLE 1

Reaction conditions and yields in vitamin $K_{2(5)}$ synthesis

Quinone derivative	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
(6a)	DMF	75	14	(9a)	75
(6b)	DMF	65	13	(9b)	73
(6b)	HMPA	50	5	(9b)	80

We then extended this reaction to the synthesis of vitamin K_1 (1). *trans*-Phytol, isolated from natural products, was treated with phosphorus tribromide to

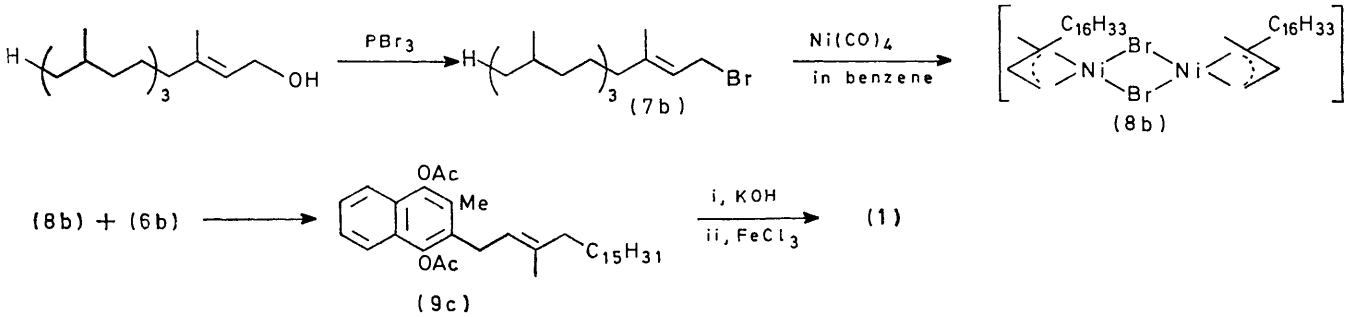




give phytyl bromide (7b). Reaction of (7b) with an excess of tetracarbonylnickel in benzene under nitrogen at 52 °C for 4 h afforded the phytylnickel complex (8b), which was treated with the diacetate (6b) in several aprotic polar solvents. No by-products were found by t.l.c. of the crude product except for hydrocarbons, arising from the thermal decomposition of the complex

The ratio of *trans*- to *cis*-isomers was determined from the areas of these peaks (Table 2). Gutmann has defined the donor number, which expresses the donor strength of a molecule.[10] The donor numbers of the solvents used here decrease in the following order: hexamethylphosphoramide (HMPA) > *NN*-dimethylacetamide (DMA) > *NN*-dimethylformamide (DMF) > *N*-methylpyrrolidone (MPD). In our experiments, the *trans*-stereoselectivity increases in the order: HMPA < DMA < DMF < MPD. Thus a strongly co-ordinating solvent gives the product in excellent yield, but with poor stereoselectivity, whereas use of a less strongly co-ordinating solvent results in good stereoselectivity.

The method was then applied to the synthesis of vitamin $K_{2(45)}$ (2b). Solanesyl bromide (7c), prepared from the natural all-*trans*-solanesol by treatment with phosphorus tribromide in petroleum, reacted with an excess of tetracarbonylnickel in benzene under nitrogen at 52 °C for 4 h to give the solanesylnickel complex (8c). After changing the solvent to DMA, the diacetate (6b)



(8b). Pure dihydrovitamin K_1 diacetate (9c) was obtained by silica gel chromatography. Hydrolysis of (9c) as for (9b) gave vitamin K_1 (1) in quantitative yield.

The n.m.r. spectrum of vitamin K_1 (1) showed two singlets at δ 1·72 and 1·62, assignable to *trans*- and *cis*-olefinic methyl groups, respectively, in the side chain.

was added and the mixture heated at 50 °C for 16 h to give dihydrovitamin $K_{2(45)}$ diacetate (9d) in 52% yield. Hydrolysis and oxidation as before gave vitamin $K_{2(45)}$ (2b) in 85% yield.

The *trans* : *cis* ratio of the double bond nearest to the

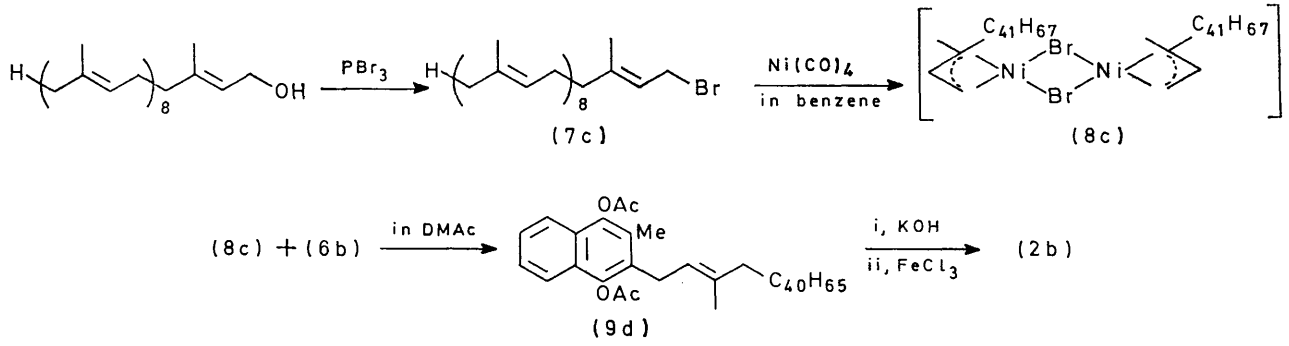
[10] V. Gutmann, *Angew. Chem. Internat. Edn.*, 1970, **9**, 843.

ring in the product (2b) was 70 : 30 as evidenced by 100 MHz n.m.r. spectroscopy. The proportion of all-*trans*-vitamin $K_{2(45)}$ was increased by low-temperature recrystallisation from acetone (ratio 87 : 13). In a large-scale experiment, repeating this procedure would give the all-*trans* compound. Small-scale separation was achieved by column chromatography.

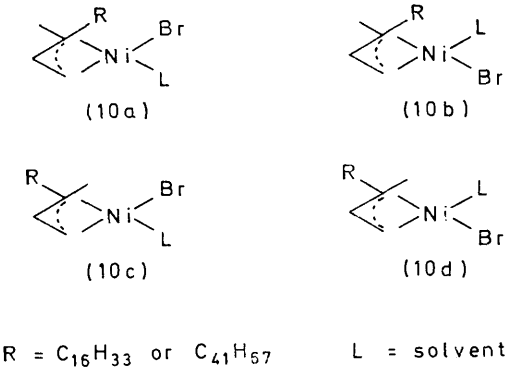
TABLE 2

Reaction conditions and yields in vitamin K_1 synthesis

Solvent	Donor no.	Temp. (°C)	Time (h)	Yield (%)	*trans* : *cis*
HMPA	38·8	50	5	85	51 : 49
HMPA		20	42	53	64 : 36
DMA	27·8	50	9	79	69 : 31
DMA		35	20	71	72 : 28
DMF	26·6	65	9	69	72 : 28
DMF		50	24	55	71 : 29
MPD		50	5	75	80 : 20
MPD		30	30	44	80 : 20
MeCN	14·1	50	6	0	



The mechanism of the coupling reaction has not been clarified; however we consider the four isomeric structures (10a—d) to be present in the co-ordinating solvent. The relation between the equilibration of these structures and the *trans–cis*-isomer distribution in the product is under investigation. The methods described here can be extended to provide a general synthesis of isoprenoid quinones.



EXPERIMENTAL

I.r. spectra were recorded on a Hitachi 215 spectrophotometer. N.m.r. spectra were obtained on a JEOL C-60 spectrometer for solutions in carbon tetrachloride or deuteriochloroform with tetramethylsilane as internal reference. 2-Methyl-1,4-naphthoquinone (3),[11] 2-bromo-3-methyl-1,4-naphthoquinone (4),[9] 2-bromo-3-methylnaphthalene-1,4-diol (5),[9] 2-bromo-3-methylnaphthalene-1,4-diyl diacetate (6b),[9] and 1-bromo-3-methylbut-2-ene (7a)[12] were obtained by the methods described in the literature, and their physical properties agreed with those reported. Phytyl bromide (7b) and solanesyl bromide (7c) were prepared from the alcohols with phosphorus tribromide in petroleum, and used without further purification.[13] Reactions involving η-allylnickel complexes were carried out under a stream of nitrogen.

2-Bromo-3-methylnaphthalene-1,4-diyl Bis(methoxymethyl) Ether (6a).—To a stirred solution of the diol (5) (9·2 g) in ethylene glycol monomethyl ether (120 ml) were added, dropwise, 12 ml of a solution of sodium (3·65 g) in the same solvent (48 ml) and then chloromethyl methyl ether (3·2 g), with the temperature of the mixture maintained at −10 to 0 °C, under nitrogen. The remaining alkoxide solution was added in three equal portions, each addition being followed by dropwise addition of 3·2 g of chloromethyl methyl ether. The mixture was then stirred for 1 h at −10 to 0 °C, and the precipitate was filtered off. The filtrate was concentrated *in vacuo*, and treated with water, and the precipitate was collected. The crystals were combined, washed with water, and dried *in vacuo*. Recrystallisation from petroleum gave the *ether* (6a) (10·1 g, 81%) as needles, m.p. 76—77°; $\nu_{max.}$ (KBr) 2920, 2830, 1580, 1165, and 965 cm^{-1}; δ (CCl_4) 8·20 (m) and 7·58 (m) (ring protons, total 4H), 5·18 (s) and 5·07 (s) (O·CH_2·O, total 4H), 3·71 (s) and 3·64 (s) (OMe, total 6H), and 2·52 (3H, s, ring Me) (Found: C, 52·35; H, 5·3. $C_{15}H_{17}BrO_4$ requires C, 52·8; H, 5·0%).

Vitamin $K_{2(5)}$ (2a) via *Dihydrovitamin $K_{2(5)}$ Bis(methoxymethyl) Ether* (9a).—To a stirred solution of tetracarbonylnickel (12·0 g) in dry benzene (68 g), the bromide (7a) (7·0 g) in dry benzene (35 g) was added dropwise at 50 °C during 1·5 h under nitrogen. Stirring was continued for a further 2 h and the mixture was cooled. Benzene was removed *in vacuo*, and DMF (40 ml) was added to the residue, followed by the ether (6a) (9·7 g) in DMF (80 ml) at 10 °C. The mixture was then heated to 75 °C and kept there for 14 h, poured into water containing a small quantity of ammonia and ammonium chloride, and extracted with chloroform. The extract was washed with water, dried

[11] L. F. Fieser, 'Experiments in Organic Chemistry,' D. C. Heath & Co., New York, 1955, p. 207.

[12] J. Tanaka, T. Katagiri, and S. Yamada, *Nippon Kagaku Zasshi*, 1966, **87**, 877.

[13] P. Karrer, A. Geiger, H. Rentschler, E. Zbinden, and A. Kugler, *Helv. Chim. Acta*, 1943, **26**, 1741.

($MgSO_4$), and concentrated *in vacuo*. The residual oil (9·5 g) consisted of 25% of (6a) and 75% of (9a) (n.m.r. assay), but the latter could not be completely purified by silica gel column chromatography.* Partially purified (9a) (3·25 g; 95% pure by n.m.r.), was dissolved in methanol (30 ml) containing a few drops of conc. hydrochloric acid, and the solution was boiled for 1 h, cooled, neutralised with potassium hydroxide, and concentrated *in vacuo*. The product was dissolved in ether (30 ml), aqueous iron(III) chloride was added, and the mixture was stirred for 3 h at room temperature, and extracted with ether. The extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel [elution with n-hexane–di-isopropyl ether (90 : 10)] to afford vitamin $K_{2(5)}$ (2a) (2·10 g, 90%) as a yellow oil, n_D^{20} 1·5860 (lit.,[14] 1·5840); $\nu_{max.}$ (neat) 2910, 1650, 1615, 1440, 1370, 1325, 1290, and 710 cm^{-1}; δ (CCl_4) 7·99 (m) and 7·60 (m) (ring protons, total 4H), 4·97 (1H, t, CH=), 3·28 (2H, d, CH_2), 2·15 (3H, s, ring Me), and 1·78 (s) and 1·68 (s) (olefinic methyls, total 6H) (Found: C, 80·35; H, 6·95. Calc. for $C_{16}H_{16}O_2$: C, 79·95; H, 6·7%).

Dihydrovitamin $K_{2(5)}$ Diacetate (9b).—Di-μ-bromobis-(1—3-η-3-methylbut-2-enyl)dinickel (8a) was prepared from the bromide (7a) (5·1 g) and tetracarbonylnickel (8·7 g) as already described. After the removal of benzene, the diacetate (6b) (6·8 g) was added. The mixture was dissolved in HMPA (80 ml), stirred at 50 °C for 5 h, and, after treatment with water containing a little hydrochloric acid, extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residual oil was readily crystallised by treatment with ethanol; recrystallisation from ethanol afforded the *diacetate* (9b) (5·3 g, 80%), m.p. 106—107°; $\nu_{max.}$ (KBr) 2925, 1750, 1595, 1365, 1210, 1170, 1050, and 755 cm^{-1}; δ (CCl_4) 7·40 (4H, m, ring protons), 4·96 (1H, t, CH=), 3·35 (2H, d, CH_2), 2·42 (6H, s, Ac), 2·20 (3H, s, ring Me), and 1·75 (s) and 1·67 (s) (olefinic methyls, total 6H) (Found: C, 73·55; H, 6·95. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

When DMF was used as solvent, recrystallisation was not a suitable method for isolation of (9b), because of the faster crystallisation of (6b). In this case, silica gel column chromatography was successful [eluant n-hexane–di-isopropyl ether (75 : 25)].

Hydrolysis of the Diacetate (9b).—The diacetate (9b) (1·1 g) in ether (30 ml) was well shaken in a separating funnel with potassium hydroxide (3·5 g) in water–methanol (1 : 3; 10 ml) and a little freshly prepared saturated aqueous sodium hydrogen sulphite. The ether layer was separated, and the aqueous layer was neutralised with dilute hydrochloric acid, then re-extracted with ether. The combined ethereal extract was washed with water, and oxidised with aqueous iron(III) chloride. The mixture was worked up as before, giving vitamin $K_{2(5)}$ (2a) (0·73 g, 91%), identical (spectral data) with that derived from (9a).

Dihydrovitamin K_1 Diacetate (9c).—Di-μ-bromodi-η-phytyldinickel (8b) was prepared from the bromide (7b) (3·9 g) and tetracarbonylnickel (2·5 g) in benzene at 52 °C for 3 h under nitrogen. After the removal of benzene, the diacetate (6b) (2·5 g) and polar solvent (40 ml) were added and the mixture was treated as indicated in Table 2. It was then poured into water containing a little hydrochloric acid, and extracted with n-hexane–ether (1 : 1). The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The oily residue was chromatographed on silica gel [eluant n-hexane–di-isopropyl ether (80 : 20)] to afford the *diacetate* (9c) as a waxy solid; $\nu_{max.}$ (neat) 2920, 1760, 1595, 1460, 1355, 1202, and 1175 cm^{-1}; δ (CCl_4) 7·25 (4H, m, ring protons), 4·89 (1H, t, CH=), 3·22 (2H, d, CH_2 nearest ring), 2·27 (6H, s, Ac), 2·11 (3H, s, ring Me), 1·66br (3H, s, olefinic Me), 1·16br (21H, s, methylene chain), and 0·85 (12H, d, side chain Me) (Found: C, 78·35; H, 10·0. $C_{35}H_{52}O_4$ requires C, 78·3; H, 9·75%).

When the yield of (9c) was below 70%, unchanged diacetate (6b) could easily be separated by treatment with n-hexane and filtration [m.p. 209—210° (from benzene) (lit.,[9] 209°)].

Vitamin K_1 (1).—The diacetate (9c) (0·70 g) was hydrolysed and oxidised as described for the diacetate (9b). The crude product was chromatographed on silica gel [eluant n-hexane–di-isopropyl ether (95 : 5)] to give *vitamin K_1* (1) (0·55 g, 93%), as a yellow oil, n_D^{25} 1·5249; $\nu_{max.}$ (neat) 2920, 1655, 1618, 1595, 1460, 1375, 1325, 1295, and 715 cm^{-1}; δ (CCl_4) 7·75 (m) and 7·40 (m) (ring protons, total 4H), 4·82 (1H, t, CH=), 3·20 (2H, d, CH_2 nearest ring), 2·08 (3H, s, ring Me), 1·72 (s, *trans* olefinic Me), 1·62 (s, *cis* olefinic Me), 1·16br (21H, s, methylene chain), and 0·85 (12H, d, side chain Me) (Found: C, 82·4; H, 10·45. $C_{31}H_{46}O_2$ requires C, 82·6; H, 10·3%).

Dihydrovitamin $K_{2(45)}$ Diacetate (9d).—Di-μ-bromodi-η-solanesyldinickel (8c) was prepared from the bromide (7c) (10·2 g) and tetracarbonylnickel (3·8 g) in benzene at 52 °C for 4 h under nitrogen. After the removal of benzene, the diacetate (6b) (3·8 g) and DMA (80 ml) were added below 10 °C. Then the temperature was raised to 50 °C and kept there for 16 h. The mixture was poured into water containing a little hydrochloric acid, and extracted with n-hexane–ether (1 : 1). The extract was washed with water, dried ($MgSO_4$), and evaporated. n-Hexane (50 ml) was added to the crude product (13·9 g) and after cooling the precipitated diacetate (6b) was filtered off (m.p. 198—199°). A portion (2·01 g) of the crude solid obtained by concentration was chromatographed on silica gel [elution with n-hexane–di-isopropyl ether (80 : 20)] to give the *diacetate* (9d) (0·82 g) (estimated yield 52%) as a waxy solid, $\nu_{max.}$ (neat) 2920, 1765, 1660, 1602, 1450, 1360, 1205, and 1175 cm^{-1}; δ ($CDCl_3$) 7·40 (4H, m, ring protons), 5·20 (9H, mt, olefinic protons), 3·48 (2H, d, CH_2 nearest ring), 2·50 (6H, s, Ac), 2·30 (3H, s, ring Me), 2·06br (32H, s, methylene chain), and 1·78 (s, *trans* olefinic Me nearest ring) and 1·60 (s, other olefinic methyls) (total of these two peaks 30H) (Found: C, 82·45; H, 10·1. $C_{60}H_{86}O_4$ requires C, 82·7; H, 9·95%).

Vitamin $K_{2(45)}$ (2b).—The diacetate (9d) was hydrolysed and oxidised like the diacetate (9b). The crude product was chromatographed on silica gel [elution with n-hexane–isopropyl ether (90 : 10)] to afford *vitamin $K_{2(45)}$* (0·93 g, 85%) as yellow crystals (mixture of isomers), m.p. 44—45°; $\nu_{max.}$ (KBr) 2920, 1660, 1615, 1595, 1450, 1380, 1330, 1295, and 712 cm^{-1}; δ ($CDCl_3$) 8·09 (m) and 7·67 (m) (ring protons, total 4H), 5·08 (9H, mt, olefinic protons), 3·36 (2H, d, CH_2 nearest ring), 2·16 (3H, s, ring Me), 1·98br (32H, s, methylene chain), and 1·78 (s, *trans* olefinic Me nearest ring), 1·68 (s,

* From comparison with the n.m.r. spectrum of (6a), the chemical shifts of (9a) were deduced: δ (CCl_4) 7·85 (m) and 7·30 (m) (ring protons, total 4H), 5·05 (1H, t, CH=), 4·91 (4H, s, O·CH_2O), 3·54 (6H, s, OMe), 3·50 (2H, d, CH_2), 2·32 (3H, s, ring Me), and 1·73 (s) and 1·63 (s) (olefinic methyls, total 6H).

[14] O. Isler, R. Rüegg, A. Studer, and R. Jurgens, *Z. physiol. Chem.*, 1953, **295**, 290.

cis olefinic Me nearest ring and end *cis*-Me), and 1·58 (s, other *trans* olefinic methyls) (total of these three peaks 30H) (Found: C, 85·55; H, 10·4. $C_{56}H_{80}O_2$ requires C, 85·65; H, 10·25%).

Recrystallisation of the 70 : 30 *trans–cis*-mixture from acetone at −20 °C (20 min) gave an 87 : 13 mixture (n.m.r.), m.p. 50—51°. This was chromatographed on a silica gel column [eluant hexane–dibutyl ether (85 : 15)] to give first the *cis*-isomer, and then the all-*trans*-compound, m.p. 59—60° (lit.,[15] 56—57°; lit.,[16] 60—61°).

[3/1046 *Received*, 18*th May*, 1973]

[15] H. Noll, R. Rüegg, U. Gloor, G. Ryser, and O. Isler, *Helv. Chim. Acta*, 1960, **43**, 433.

[16] C. H. Shunk, R. E. Erickson, E. L. Wong, and K. Folkers, *J. Amer. Chem. Soc.*, 1959, **81**, 5000.