J.C.S. Снем. Сомм., 1972

New Synthesis of Vitamin K

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Summary A new and effective synthesis of vitamin K_1 (1) and $K_{2(5)}$, (2; n = 1), is described, using a π -allylic nickel(I) complex; solvent effects and the *trans*-stereo-selectivity have been investigated.

VITAMIN K_1 , (1) and $K_{2(5n)}$, (2), are quinones involved in the normal clotting of the blood, each containing an isoprenoid side chain. All the double bonds in the side chain have the *trans* configuration in the naturally occurring compounds.

The usual methods for introducing the side chain into the 3-position of menadione consist of acid-catalysed condensation of phytol or polyprenyl alcohols with 2-methyl-1,4-naphthohydroquinone or the 1-mono-ester derivatives in dioxan followed by oxidation with silver oxide.^{1,2} These methods, however, yield many by-products which are difficult to remove.



We report here a new and effective synthesis of vitamin K_1 and $K_{2(6)}$ using π -allylic nickel(I) bromide (5 or 6) and derivatives of 3-bromo-2-methyl-1,4-naphthoquinone. Vitamin $K_{2(5)}$, considered as the most fundamental structure of both vitamin K_1 and $K_{2(5\pi)}$, was synthesized successfully in the following manner.

Treatment of (3) with excess of nickel carbonyl in benzene at 50 °C under nitrogen for 3 h gave the 1,1dimethyl- π -allylnickel(I) bromide (5). After the removal of benzene under reduced pressure, the crude nickel complex (5) was dissolved in dimethylformamide and treated with (7a) or (7b) at 50—70 °C for several hours.

Dihydrovitamin $K_{2(5)}$ bis-methoxymethyl ether (8a) or the diacetate (8b) was obtained in good yield (ca. 75%).

Hydrolysis of (8a) and (8b) with acid or alkali, respectively, followed by ferric chloride oxidation gave vitamin $K_{2(5)}$ in quantitative yield.

We extended this reaction to the synthesis of vitamin K_1 . Treatment of (4) with nickel carbonyl at 52 °C for 3 h in benzene under nitrogen gave the π -complex (6). After changing the solvent to hexamethylphosphoramide, (7b) was added and reacted for 5 h at 50 °C. The reaction

² R. Hirschmann, R. Miller, and N. L. Wendler, J. Amer. Chem. Soc., 1954, 76, 4592.

mixture was chromatographed on silica gel to give (9) (85%).

Hydrolysis of (9) was carried out with alkali and ferric chloride oxidation afforded vitamin K_1 (1) in 93% yield after purification by silica gel chromatography.





The n.m.r. spectrum of (1) showed two singlet peaks at δ 1.72 and 1.62, assignable to the *trans* and *cis* olefinic methyl groups, respectively, attached to the double bond in the side chain. The ratio of *trans* to *cis* isomers was determined quantitatively by calculation of the area of these two peaks.

To obtain a higher yield and higher *trans* stereoselectivity, solvent effects and temperature dependence of this reaction were investigated. It was found that a strongly coordinating solvent gives the product in excellent yield, but with poor stereoselectivity, *i.e.*, in hexamethylphosphoramide at 50 °C, yield 85%, *trans*: cis = 51:49. On the other hand, a less co-ordinating solvent shows good stereoselectivity, *i.e.*, in *N*-methylpyrrolidone at 30 °C, yield = 44% trans: cis = 80:20.

(Received, 4th May 1972; Com. 752.)

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¹ L. F. Fieser, J. Amer. Chem. Soc., 1939, 61, 3467.