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Conversion of Phytol into Dihydrophytol and Phytanic Acid

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When phytol is hydrogenated over Raney-nickel at room temperature and atmospheric pressure of hydrogen, dihydrophytol is obtained in quantitative yield. With palladium on charcoal as catalyst, phytene and phytane are formed, and almost no dihydrophytol is produced. Platinum on charcoal catalyst yields a mixture of dihydrophytol and phytane.

Oxidation of dihydrophytol with chromic oxide yields phytanic acid. A method suitable for macro- as well as microscale preparation of this biologically important acid is described.

In 1963 Klenk and Kalhke [1] demonstrated the occurrence of large amounts of 3,7,11,15-tetramethyl hexadecanoic acid (phytanic acid) in lipid fractions from a patient with Refsum's disease.[2] Recent studies by Eldjarn, Try and Stokke [3] suggest that this accumulation of phytanic acid reflects an inborn error of metabolism in an alternative pathway for the degradation of branched-chain fatty acids. In view of the rapidly increasing interest in the biochemistry of Refsum's disease,[1,3–5] considerable quantities of phytanic acid, or related compounds such as phytol and dihydrophytol, may often be required. Moreover, ^{14}C-labelled or ^{3}H-labelled phytanic acid, if available, may give valuable information in tracer studies.

Dihydrophytol and phytanic acid have been synthesized by several authors [1,5–10] from the unsaturated alcohol phytol, which is commercially available. The simplest procedures have involved hydrogenation of phytol over a platinum catalyst to give dihydrophytol, and subsequent oxidation of the latter alcohol with chromic oxide to yield phytanic acid. Although other synthetic procedures have been described,[6,7] there is probably only one alternative pattern of practical importance, namely the following three step synthesis:[5,8] oxidation of phytol with manganese dioxide to yield the corresponding aldehyde, oxidation of the aldehyde to phytenic acid with silver oxide, and hydrogenation of phytenic acid to give phytanic acid. Direct oxidation of phytol to phytenic acid with chromic oxide is not recommended, because the yield is poor and several by-products are formed.[6]

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When phytol is hydrogenated over platinum catalysts at room temperature and atmospheric pressure, some phytane is usually formed in addition to the dihydrophytol, as first pointed out by Willstätter, Mayer and Hüni in 1911 [6] and later confirmed by others.[11,12] This unwanted side-reaction can apparently be avoided if the hydrogenation of phytol instead is carried out at 175° for one hour in the presence of Raney-nickel catalyst and a hydrogen pressure of 2800 lb/sq. in.[13] Although the latter method seems to be satisfactory, it requires the use of a hydrogenation bomb, which is not a common apparatus in a biochemical laboratory.

In the present report we have investigated the hydrogenation of phytol more closely, in order to arrive at simple methods for obtaining dihydrophytol and phytanic acid in good yield without the use of special equipment. We have found that dihydrophytol may be obtained from phytol in quantitative yield, and completely free from phytane, when Raney-nickel is used as catalyst at room temperature and atmospheric pressure of hydrogen. With palladium on charcoal as catalyst, phytol is first converted into phytene and then into phytane, and almost no dihydrophytol is formed. Platinum on charcoal catalyst acts in an intermediary way, yielding a mixture of dihydrophytol and phytane.

EXPERIMENTAL

Palladium catalysts. According to newer literature [14] palladium on charcoal appears to the best catalyst to use for hydrogenation of olefins at room temperature and atmospheric pressure. Attempts were therefore made to prepare dihydrophytol by means of this catalyst. Phytol (15 g in 250 ml of ethanol) was hydrogenated over 1 g of 10 % Pd on charcoal (prepared as described by Augustine [14]) at 22° and 1 atm. of hydrogen. Small aliquots were withdrawn from the reaction flask at intervals and analysed by gas-chromatography (for details see Fig. 1). From this figure it is evident that the reaction followed the line: phytol → phytene → phytane, *i.e.* the alcohol group was hydrogenated in preference to the double bond. Thus, with palladium on charcoal as catalyst, phytol was almost quantitatively converted into the saturated hydrocarbon phytane, and only very little dihydrophytol was formed.

This rather unusual reaction sequence is apparently due to the activating effect of the double bond on the alcohol group of phytol. This could be demonstrated by repeating the experiment described above, but starting with pure dihydrophytol instead of phytol. The gas-chromatographic results clearly showed that even after hydrogenation for 24 h in presence of the palladium catalyst, the dihydrophytol was completely unchanged and virtually no phytane had been formed.

Further hydrogenation experiments with palladium on charcoal, palladium on barium sulphate, other solvents than ethanol, as well as experiments where the alcohol group of the phytol was protected by an acetyl group, suggest that palladium catalysts are not suitable for the preparation of dihydrophytol. On the other hand, these catalysts offer a most convenient method to obtain pure phytane.

Platinum catalyst. With 10 % platinum on charcoal (obtained from Koch-Light Laboratories, England) as catalyst, the results were somewhat different. This time considerable amounts of dihydrophytol were formed, but the product was heavily contaminated with phytane. The overall yield of dihydrophytol was not better than 60—70 %. Platinum on charcoal, therefore, is apparently also unsuitable as catalyst for the synthesis of dihydrophytol.

Raney-nickel catalyst. We have found, however, that dihydrophytol can be obtained in quantitative yield from phytol, when Raney-nickel is used as catalyst at room temperature and atmospheric pressure of hydrogen. This is shown in Fig. 2, which also clearly demonstrates that no by-products such as phytene or phytane are formed. The following

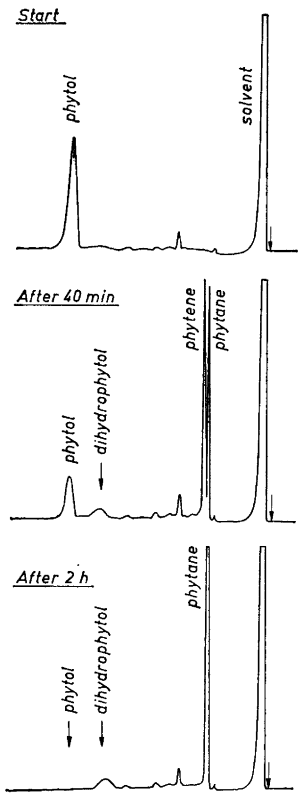

Fig. 1. Hydrogenation of phytol with palladium on charcoal as catalyst at room temperature and one atmosphere. Gas-chromatography columns of stainless steel, 6 ft. 1/8 in. o.d., 8 % butanediol succinate on chromosorb W. Column temperature programmed from 100 to 190° at the rate of 26.7°/min. Injection block at 240°; detector at 190°.

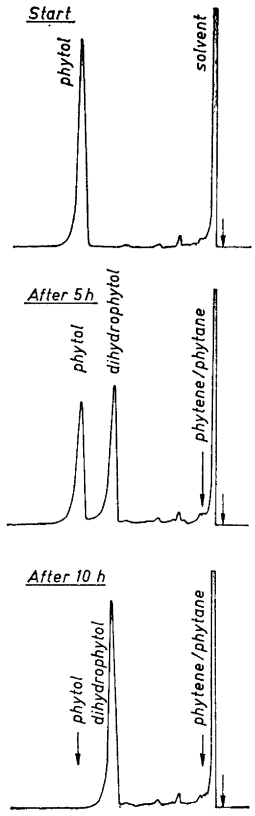

Fig. 2. Hydrogenation of phytol with Raney-nickel as catalyst at room temperature and one atmosphere. Column temperature: 190°.

method is now in practise in our laboratory for the synthesis of dihydrophytol and phytanic acid:

To a solution of phytol (30 g, supplied by E. Merck, Darmstadt) in ethanol (350 ml) is added 2—3 g of Raney-nickel catalyst (gebrauchsfertig, obtained from Fluka A.G., Switzerland). The flask is connected to a hydrogen supply and is mechanically shaken for about 10—12 h at room temperature. The hydrogen pressure is atmospheric or slightly above. The reaction is followed by withdrawing a sample from time to time and analysing it by gas-chromatography (see Fig. 2). When the phytol peak has disappeared from the chromatogram (or when the mixture no longer decolorizes bromine in carbon tetrachloride), the reaction is stopped. After removal of the catalyst by filtration, the solvent is evaporated, leaving the pure dihydrophytol (yield: 30 g). Phytanic acid is then prepared according to a modification of the method of Karrer, Epprecht

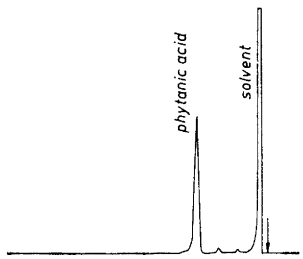

Fig. 3. Gas-chromatogram of methylated phytanic acid. The methyl ester was prepared with diazomethane. Column temperature: 190°.

and König.[7] Chromic oxide (15 g) is dissolved in 80 % acetic acid saturated with potassium hydrogen sulphate (250 ml), and this mixture is added dropwise to a solution of dihydrophytol (30 g) in glacial acetic acid (200 ml) in the course of 30 min. After 90 min at room temperature, water (500 ml) is added to the mixture, which subsequently is extracted twice with one volume of petroleum ether (30°—60°). The extract is placed on a water bath at 65°, and the ether as well as the dissolved acetic acid is removed under suction. The remaining yellow oil is dissolved in alcoholic potassium hydroxide (0.5 N, 400 ml) and refluxed for 90 min. This treatment saponifies the dihydrophytyl-phytanate which was formed during the oxidation (see Ref. 7). After complete hydrolysis one volume of water is added, and the alkaline mixture is washed twice with one volume of petroleum ether. If the organic phase is collected, some impure dihydrophytol may be recovered from it. The alkaline, aqueous solution of potassium phytanate is acidified with 5 N sulphuric acid (100 ml) and the liberated phytanic acid is extracted twice with one volume of petroleum ether. The combined extracts are washed once with one volume of water. To the yellow coloured solution of phytanic acid in petroleum ether is added 5—10 g of activated carbon powder. After shaking for 5 min, the carbon is filtered off, giving an almost colourless filtrate. When the solvent is removed under vacuum, phytanic acid remains as a very pale yellow, oily liquid (yield 15 g = 48 %). Fig. 3 shows the gas-chromatogram of the final product (as methyl ester). The described method has also been employed in reduced scale for the synthesis of ^{14}C-labelled phytanic acid. The starting material ^{14}C-phytol, was a generous gift from Professor Patton of Pennsylvania State University. After hydrogenation and oxidation of the labelled phytol according to the method described above, the resulting radioactive phytanic acid was purified by preparative thin-layer chromatography on plates of Silica gel G, with petroleum ether (60—80°)/diethyl ether/glacial acetic acid (85/15/1 v/v) as solvent.

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