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STUDIES ON TOCOPHEROLS II[1]. CONVENIENT SYNTHESIS OF TOCOPHEROLS

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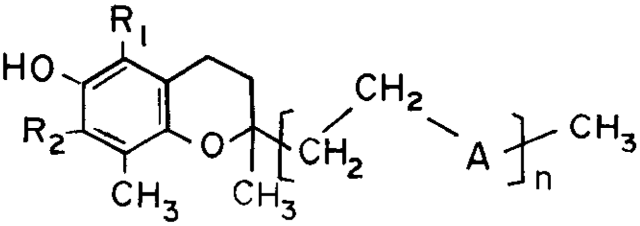
Summary : A convenient synthesis of tocopherols from methylbenzoquinone and isoprenyl alcohol in high yield is described.

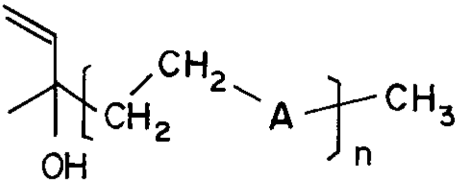
In recent years, tocopherol[2] (vitamin E) as the biological antioxidant and free radical scavenger in lipid peroxidation have received considerable attention in both chemical reactivity studies and investigations for clinical and nutritional applications in human health. Many methods of synthesizing α-tocopherol[3] have already been described, but tocopherols are given to colored material by the autoxidation during condensative reaction. The separation of tocopherol and colored material are difficult by simple methods such as distillation. An attempt has not yet been undertaken for the synthesis of α-tocopherol in reductive condition, although the conversion of 5-methyl-2,3-dimethoxy-1,4-benzoquinone to hexahydro-coenzyme Q_4 chromanol was reported by Weinstock[4].

Here, we wish to report our short and efficient routes applicable to preparation of the tocopherols. We have been utilizing the methylbenzoquinone and isoprenyl alcohol as starting materials for a simple method to synthesize tocopherols under reductive condition. We have now found that the condensation of methylbenzoquinone (2) and isoprenyl alcohol[1,2] (3 or 4 or 5) in the presence of copper-zinc and formic acid was accomplished in good yield. The structures of (1) were established by their spectral data, and purity was checked by H.P.L.C. and T.L.C. Compounds (2) were easily prepared from p-hydroquinone or relative amine compounds by Jones oxidation.

Our results are summarized in Table 1.



(1)



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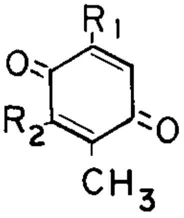

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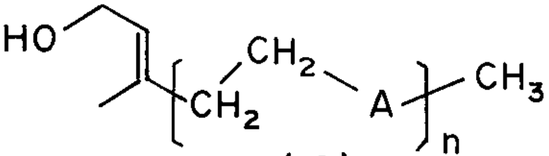

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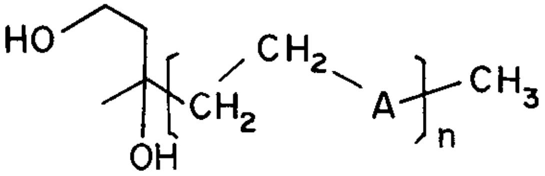
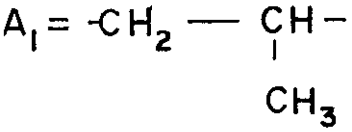


(5)

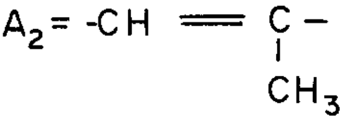
R_1 = H or CH_3

R_2 = H or CH_3

A :



$A_1 = -CH_2-\underset{\displaystyle CH_3}{\underset{|}{C}}H-$



$A_2 = -CH=\underset{\displaystyle CH_3}{\underset{|}{C}}-$

n = 0, 1, 2, 3

Table 1. Preparation of tocopherols and it's relative compounds

Benzoquinone (2)			Isoprenyl alcohol (3) or (4) or (5)			Product (1)					
	R_1	R_2		A	n		R_1	R_2	A	n	%
2	CH_3	CH_3	3	A_1	3	1	CH_3	CH_3	A_1	3	83
2	CH_3	CH_3	4	A_1	3	1	CH_3	CH_3	A_1	3	81
2	CH_3	CH_3	3	A_2	3	1	CH_3	CH_3	A_2	3	66
2	H	CH_3	4	A_1	3	1	H	CH_3	A_1	3	72
2	CH_3	CH_3	3	A_2	2	1	CH_3	CH_3	A_2	2	71
2	CH_3	CH_3	4	A_2	1	1	CH_3	CH_3	A_2	1	78
2	H	H	4	A_1	3	1	H	H	A_1	3	20
2	CH_3	CH_3	5	A_1	3	1	CH_3	CH_3	A_1	3	20

General Procedure for Tocopherol

A well-stirred suspension of trimethylbezoquinone (15 g. 0.1 mole) and 2% copper-zinc powder (1.0 g) in formic acid (200 ml) under nitrogen atomosphere is warmed. The reaction mixture is kept at 85°C throughout the addition and 2% copper-zinc powder (14 g) is added in portions. The isophytol (58.6 g. 0.19 mole) is slowly added at 90° C. After addition, the reaction mixture is refluxed for 2 h, cooled, filtered, and extracted with methylene chloride. The methylene chloride extract is washed with water, dried over anhydrous sodium sulfate and concentrated to give crude product. The crude product is filtered through silica gel (benzene) to yield the desired α-tocopherol as pale yellow oil; yield 35.7 g (83%). The spectral data of α-tocopherol are in good agreement with that reported[5].

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References

1. M.Kajiwara, O.Sakamoto, H.Katsura, and S.Ohta, *Heterocycles*, 1980 , in the press.

2. a) L.E.Machlin, Ed. ' Vitamin E ', Marcel Dekker: New York, 1979.; b) J.G.Bieri and P.M.Farrell, *Vitam. Horm.* (N.Y.), 1976, **34**, 31.

3. a) H.Mayer and O.Isler, *Methods Enzymol.*, 1971, **18C**, 241.; b) P.Schudel, H.Mayer, and O.Isler, In ' The Vitamins ', Vol. V, W.H.Sebrell Jr., R.S.Harris Ed., Academic Press, New York, 1972, p168.

4. L.M.Weinstock, R.Tull, B.Handelsmen, and E.F.Schoenewaldt, *J. Chem. Eng. Data*, 1967, **12**, 154.

5. M.Kofler, P.F.Sommer, H.R.Bolliger, B.Schmidli, and M.Vecchi, *Vitam. Horm.* (N.Y.), 1962, **20**, 407.

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