SYNTHESIS OF SULFUR-CONTAINING ANALOGS OF THE K GROUP VITAMINS BY AN ELECTROCHEMICAL METHOD

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An efficient electrochemical method is proposed for obtaining structural analogues of the K group vitamins (3-alkylthio and 3-arylthio ethers of 2-methyl-1,4-naphthoquninone).

Keywords: *2-methyl-1,4-naphthoquinone, vitamin K_1, mercaptans, electrochemical synthesis.*

The thioethers of 2-methyl-1,4-naphthoquinone (**1**) occupy an important place among the numerous structural analogues of the K group vitamins. Antibacterial, fungicidal, and antitubercular activities [3-5] are inherent for similar derivatives as well as marked antihemorrhagic activity [1, 2].

The preparation of such compounds is based usually on the reaction of 2-methyl-1,4-naphthoquinone (MNQ) (**1**) with thiols of various structure capable of actively generating thiolate anion under the reaction conditions. The alkylthiolation process occurs through the formation of a thiosubstituted 2-methyl-1,4-naphthohydroquinone which is then partially oxidized by the initial MNQ to the desired compound. The yield from various thiols is 30-40% [2, 6]. The reaction requires significant consumption of time [6, 7] even at elevated temperatures [8]. An increase in the yield is achieved by introducing an additional stage of oxidizing the reduced form of the thioether, such as with iron chloride [7] or copper sulfate [8].

It has recently been shown possible to generate thiolate anion electrochemically by direct fission of the S–H bond of the thiol [9, 10] on the cathode and to add the thiolate anion generated to an epoxy compound [11] or to an activated olefin [12].

It has been shown in the present study that the electrically generated thiolate anion efficiently initiates the addition of thiols to MNQ. The process is catalytic and is described by a scheme comprising cathodic generation of the thiolate anion (**3**)

TABLE 1. Physicochemical and Analytical Characteristics of 2-Methyl-2,4-naphthoquinone Thioethers

Compound	Appearance	Yield, %	Mp, °C	Empirical formula	Found / Calculated, %		
					C	H	S
6a	Yellow crystals	89	70–72	$C_{19}H_{24}O_2S$	70.10 70.30	7.29 7.40	11.30 11.12
6b	Ditto	91	78–81	$C_{22}H_{30}O_2S$	75.64 75.64	9.47 9.42	7.36 7.48
6c	Ditto	87	84–86	$C_{25}H_{36}O_2S$	74.95 75.01	9.05 9.02	7.71 7.99
6d	Dark-red crystals	85	75–77	$C_{21}H_{20}O_2S$	75.13 75.01	6.02 5.91	9.26 9.26
6e	Orange crystals	88	79–81	$C_{15}H_{12}O_2S$	63.42 62.91	4.97 4.88	12.86 12.90

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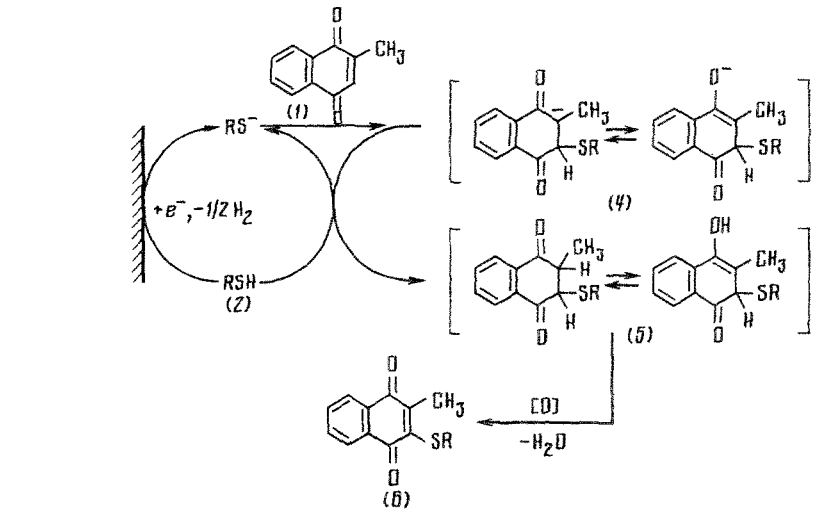
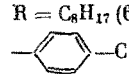
Scheme 1



R = C_8H_{17} (6a); $C_{14}H_{29}$ (6b); $C_{16}H_{33}$ (6c);

(6d); CH_2CH_2OH(6e).

from the thiol (**2**) with subsequent nucleophilic addition of it to the double bond of MNQ. The resulting anion (**4**) is fairly basic and is protonated by the thiol (**2**) in the bulk of the solution with the formation of the sulfide (**5**) and thiolate anion (**3**) (Scheme 1).

The use of absolute MeCN as solvent and tetraethylammonium bromide as base electrolyte, the cations of which tend to form ion pairs with the thiolate anion formed at the electrode, enables alkylthiolation of MNQ (**1**) to be effected rapidly under mild conditions (~20°C, in the absence of strong base). In addition the indicated conditions increased the efficiency of carrying out the oxidation of the reduced form of (**5**) to the desired compound (**6**) by oxygen of the air.

Essentially complete conversion of thiol (**2**) occurred on passing 0.02-0.05 $F \cdot mole^{-1}$ of electricity, which confirms the electrocatalytic character of the process. Yields of the final product (**6**) were 85-90% after working up the reaction mixture.

Derivatives of MNQ with unbranched alkyl mercaptans containing 8, 14, and 16 carbon atoms and with 4-*t*-butylphenylmercaptan and 2-mercaptoethanol were obtained according to Scheme 1. Using spectroscopic and analytical methods the compounds obtained were identified as 2-methyl-3-octylthio-1,4-naphthoquinone (**6a**), 2-methyl-3-tetradecylthio-1,4-naphthoquinone (**6b**), 3-hexadecylthio-2-methyl-1,4-naphthoquinone (**6c**), 3-(4-*t*-butylphenylthio)-2-methyl-1,4-naphthoquinone (**6d**), and 3-(2-hydroxyethylthio)-2-methyl-1,4-naphthoquinone (**6e**). The physicochemical and analytical characteristics of the compounds obtained are given in Tables 1 and 2.

TABLE 2. Spectroscopic Characteristics of 2-Methyl-1,4-naphthoquinone Thioethers

Compound	UV spectrum, λ_{max}, nm ($E_1^{1\%}$cm)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, J, Hz
6a	257(402.14) 330(75.99) 420(36.94)	1660, 1640, 1580, 1564, 1310, 1273, 694	1.3 m (12H, 2-7-CH_2); 1.6 s (3H, 8-CH_3); 2.45 s (3H, 2-CH_3); 3.2 t (2H, 1-CH_2, J=5); 7.7-8.1 s (4H, aromatic protons)
6b	257(407.74) 330(76.78) 423(35.71)	1670, 1650, 1590, 1560, 1320, 1335, 1280, 700	1.2 m (24H, 2-13-CH_2); 1.5 s (3H, 14-CH_3); 2.3 s (3H, 2-CH_3); 3.2 t (2H, 1-CH_2, J=5); 7.6-8.1 m (4H, aromatic protons)
6c	256(414.97) 331(76.1) 416(29.19)	1670, 1650, 1590, 1560, 1320, 1325, 1280, 700	1.25 m (28H, 2-15-CH_2); 1.5 s (3H, 16-CH_3); 2.35 s (3H, 2-CH_3); 3.15 t (2H, 1-CH_2, J=5); 7.15-8.05 m (4H, aromatic protons)
6d	249(835.05) 330(114.69) 427(65.72)	1658, 1590, 1560, 1320, 1300, 1275, 700	1.3 s (9H, $-C(CH_3)_3$); 2.35 s (3H, 2-CH_3); 7.7-8.15 m (4H, aromatic protons)
6e	258(658.97) 314(126.21) 416(76.55)	3545, 1660, 1590, 1550, 1320, 1335 1060, 700	2.4 s (3H, 2-CH_3); 3.3 t (2H, CH_2-OH, J=5); 3.75 t (2H, S-CH_2, J=5; 7.65-8.15 m (4H, aromatic protons)

Attention must be paid to the fact that no reaction of MNQ with the alkanethiols was observed under these experimental conditions without passing a current. In the two remaining cases the conversion of the starting materials, although it occurred, was extremely slow. All reactions ceased after 30 min under electrolysis conditions. It must be noted that the generation of thiolate ions in the electrochemical process is probably the limiting stage due to their high reactivity. Consequently, the rate of alkylthiolation of MNQ will be determined by the size of the electrolysis current.

The data given above show the possibility of efficient electrochemical synthesis of various thioethers of 2-methyl-1,4-naphthoquinone. We suggest that the approach described will be extremely useful when functionalizing MNQ not only with thiols (S−H acids) but also with various organic O−H, P−H, N−H, and C−H acids.

EXPERIMENTAL

Thin layer chromatography on Silufol UV-254 plates and column chromatography on silica gel L 100/250 μm were used for checking the course of a reaction and for identifying and isolating the compounds synthesized. IR spectra were taken on a Shimadzu IR-435 spectrometer in Nujol, UV spectra were taken on a Shimadzu UV-240 spectrometer in methanol, ^{1}H NMR spectra were taken on a Bruker WM-250 Fourier transform NMR spectrometer of operating frequency 250.13 MHz (TMS was the internal standard), mass spectra were taken on a Varian MAT 311-A chromato-mass spectrometer. Peaks for molecular ions were present in the mass spectra of all compounds.

General Method for Electrolysis. 2-Methyl-1,4-naphthoquinone (1.72 g: 0.01 mole) and an equimolar quantity of the mercaptan in 0.02-0.03 *N* Et_4NBr solution in absolute MeCN (40 ml) were placed in the cathode compartment of a "glass in glass" electrolyzer. A solution (40 ml) of the base electrolyte was placed in the anode compartment (Mg anode). Electrolysis was carried out at 20°C with stirring on a platinum cathode (S = 35 cm^2) in the galvanostatic mode at a current density of 0.5-1.0 mA · cm^{-2} until the passage of 0.05 F · mole^{-1} electricity. The reaction was stopped after complete conversion of the starting materials (check by TLC). After the end of the process air was passed through the catholyte for 1 h.

When carrying out electrolysis and preparing compounds (**6a-c**) the precipitated solid was removed, when preparing (**6d**) and (**6e**) the MeCN was evaporated, the residue was extracted with hexane (3 × 300 ml) in the case of (**6d**) or ether (4 × 250 ml) in the case of (**6e**). The substance obtained as a solid or extract was purified by column chromatography in the following systems: (**6a**) hexane−acetone (2:1), (**6b**) and (**6c**) hexane−$CHCl_3$ (4:1), (**6d**) hexane−ether (6:1), and (**6e**) hexane−$CHCl_3$ (2:1).

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