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# Catalytic Activity of Diethylene Glycol Dimethyl Ethers in Conversion of 6,7-Dichloro-3-ethyl-2-ethoxynaphthazarine into Echinochrome Trimethyl Ether*

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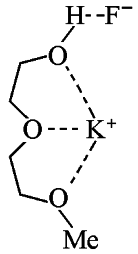
**Abstract**—The nucleophilic substitution of halogen by methoxy groups in 5,8-dihydroxy-2,3-dichloro-1,4-naphthoquinones effected by complex reagent KF–MeOH–$Al_2O_3$ is considerably accelerated in the presence of electron-donor solvents.

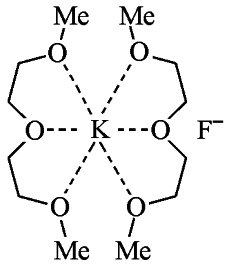
One of the key stages in the synthesis of pharmacologically active naphthazarine polyhydroxy derivatives (5,8-dihydroxy-1,4-naphthoquinone) is the transformation of the chlorinated naphthazarines into the corresponding alkoxy derivatives [1]. We investigated formerly the nucleophilic substitution of halogen atoms by alkoxy groups in the chlorinated juglones (5-hydroxy-1,4-naphthoquinones), naphthazarines [2], and 9,10-anthraquinones effected by methanol or monomethyl ethers of diethylene and triethylene glycols (that simultaneously were the medium) activated with fluoride anion (KF, CsF) on alumina surface [3], and also on the surface of the other metal-containing sorbents [4].

It was shown that the bifunctional nature of polyethylene glycol monoethers (e.g., of diethylene glycol monomethyl ether) led to suppression of the Lewis basicity of the applied metal fluorides resulting in decreased yield of the desired reaction products [4].



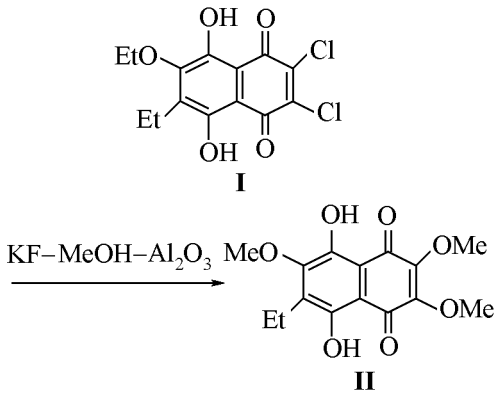
One possible way to increase the basicity of the alkali metal fluoride under these conditions is the use of electron-donor compounds as additional solvent [4, 5].

Unlike anions the cations are well and specifically solvated by solvents with a high Lewis basicity, and therefore their activity grows. Among such solvents that show good solvating properties with respect to cations should be mentioned the polyethylene glycols dialkyl ethers (for example, diethylene glycol dimethyl ether). The solvation of cations abstract them from the existing ion pairs associates.



Looking for the optimal conditions of conversion of 6,7-dichloronaphthazarines into 6,7-dimethoxynaphthazarines in the presence of the complex reagent KF–MeOH–$Al_2O_3$ we investigated the catalytic

**Scheme 1.**



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Catalytic activity of diethylene glycol dimethyl ether and of dioxane in conversion of naphthazarine **I**[a] into echinochrome trimethyl ether **II** effected by KF–MeOH–$Al_2O_3$[b]

| Run no. | Glyme[c] | | Run no. | Diglyme[c] | | Run no. | Dioxane[c] | |
|---|---|---|---|---|---|---|---|---|
| | vol% (mol)[d] | yield of compound **II**, % | | vol% (mol)[d] | yield of compound **II**, % | | vol% (mol)[d] | yield of compound **II**, % |
| *1* | 0 | 52, 68[e] | *9* | 2.5 (0.8) | 56 | *16* | 5.0 (2.8) | 55 |
| *2* | 2.5 (1.1) | 54 | *10* | 5.0 (1.7) | 62 | *17* | 10.0 (5.6) | 58 |
| *3* | 5.0 (2.2) | 57 | *11* | 7.5 (2.5) | 68 | *18* | 15.0 (8.3) | 64 |
| *4* | 7.5 (3.3) | 62 | *12* | 10.0 (3.3) | 75, 74[f] | | | |
| *5* | 10.0 (4.5) | 68 | *13* | 12.5 (4.1) | 65 | | | |
| *6* | 12.5 (5.6) | 64 | *14* | 15.0 (4.9) | 63 | | | |
| *7* | 15.0 (6.7) | 64 | *15* | 17.5 (5.8) | | | | |
| *8* | 17.5 (8.0) | 60 | | | | | | |

[a] Substrate **I** was dried for 5 h at 50°C and 1 mm Hg.

[b] KF was dried for 2 h at 200°C and 1 mm Hg, MeOH was dried and distilled from $Mg(OMe)_2$, $Al_2O_3$ was activated for 2 h at 200°C and 1 mm Hg.

[c] The solvents were dried and distilled over Na.

[d] In parentheses is given the molar ratio solvent : KF.

[e] Yield of compound **II** in 12 h [2].

[f] Yield of compound **II** in 8 h under the treatment with CsF–MeOH–$Al_2O_3$ in the absence of electron-donor solvents.

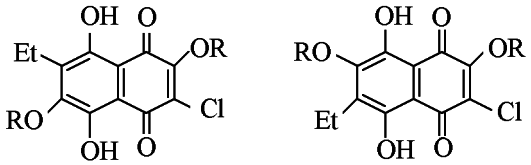
activity of mono- and diethylene glycols dimethyl ethers, and also that of dioxane (Scheme 1). As substrate was used relatively accessible 5,8-dihydroxy-2,3-dichloro-6-ethyl-7-ethoxy-1,4-naphthoquinone (**I**) [1].

Similar to the process without electron-donor solvents [2] the nucleophilic substitution of halogen in substrate **I** was accompanied by transetherification, i.e. by substitution of the ethoxy group by the rest of the alcohol used in the process. The results we obtained investigating the nucleophilic substitution of chlorine in substrate **I** by methanol activated with fluoride anion (KF) on the surface of neutral alumina in the presence of ethylene glycol dimethyl ether (glyme) and diethylene glycol dimethyl ether (diglyme) are presented in the table. In all cases the reaction was carried out for 8 h: in this time was provided the best result without electron-donor solvents with a complex reagent CsF–MeOH–$Al_2O_3$ [2].

As follows from the data in the table addition into the reaction mixture of glyme (runs nos. 2–5) and diglyme (runs nos. 9–12) results in higher yield of trimethyl ether **II** as compared with the control run (run no.1). With ethylene glycol dimethyl ether the highest yield of compound **II** was attained at the molar ratio glyme–metal fluoride 4.5 : 1 (10% of glyme by volume, run no. 5). To obtain similar yield of compound **II** (68%) without addition of electron-donor solvent the reaction should be prolonged to 12 h [2], 1.5 times longer than in run no. 5. The maximum yield of compound **II** (75%, run no. 12) was obtained by adding to the reaction mixture 10 vol% of diethylene glycol dimethyl ether (molar ratio diglyme : KF = 3.3 : 1). This is due to higher solvation capacity of diglyme as compared to glyme (see table). Without electron-donor additives such result was obtained only with the use of complex reagent CsF–MeOH–$Al_2O_3$ [2]. Thus KF in methanol containing 10% by volume of diglyme (run no.12) is formally as strong Lewis base as CsF in methanol. Further increase in content of glyme (runs nos.6–8) and diglyme (runs nos.13–15) in the reaction mixture resulted in reduction of the yield of echinochrome **II** trimethyl ether presumably because of growing strength of the chelate complex that the reaction products formed on the surface of alumina under the given conditions.

The use of dioxane as solvent also accelerated the nucleophilic substitution of halogen with methoxy groups in substrate **I** (runs nos. 16–18). However because of lower solvation capacity of dioxane compared to that of glyme or diglyme the acceptable yield of compound **II** was attained at 15 vol% of dioxane (8.3 mol of dioxane per 1 mol of KF, run no. 18).

As already mentioned, all experiments on the chlorine substitution in substrate **I** were carried out within 8 h. Therefore virtually in all reaction mixtures were detected products of monosubstitution **III** and **IV** (from 3 to 26% depending on the conversion of substrate **I**) that were not chromatographically separable. The monosubstituted products as showed $^1$H NMR spectra formed in the course of reaction in ~4:1 ratio, therefore assignment of signals was easy. Yet the attribution of proton signals to the definite structure **III** or **IV** became possible only on the acid hydrolysis of the isomers mixture and isolation of the respective derivatives **V** and **VI**. The structure of compounds **V** and **VI** was established previously proceeding from the features of their UV and IR spectra [6].




**III, V** **IV, VI**

R = Me (**III, IV**), H (**V, VI**).

Thus by an example of 6,7-dichloro-3-ethyl-2-ethoxynaphthazarine (**I**) we demonstrated that the nucleophilic substitution of halogen with methoxy groups in the system KF–MeOH–$Al_2O_3$ was considerably accelerated at addition of electron-donor solvents. Among the solvents tested, ethylene and diethylene glycols dimethyl ethers, and dioxane, the most efficient was diglyme.

## EXPERIMENTAL

$^1$H NMR spectra were registered on spectrometer Bruker AC-250 at operating frequency 250 MHz from solutions in $CDCl_3$ and acetone-$d_6$, chemical shifts are presented in δ scale relative to TMS, coupling constants in Hz. Mass spectra were measured on LKB-9000 instrument with direct injection, ionizing electrons energy 70 eV. The reaction progress was monitored and the homogeneity of the compounds obtained was checked by TLC on Silufol UV-254 plates, eluent hexane–acetone, 3:1. The individual products were separated on a column packed with silica gel L 40/100 μm ($H^+$), gradient elution with hexane–acetone from 10:1 to 65:1, and also by preparative TLC on plates (20 × 20 cm) with nonfixed silica gel layer 4–40 μm with eluents hexane–acetone, 3:1 or 4:1. Synthesis of the initial 5,8-dihydroxy-2,3-dichloro-6-ethyl-7-ethoxy-1,4-naphthoquinone (**I**) was carried out along procedure described in [1].

**5,8-Dihydroxy-2,3,6-trimethoxy-7-ethyl-1,4-naphthoquinone (II).** A mixture of thoroughly dried 5,8-dihydroxy-2,3-dichloro-6-ethyl-7-ethoxy-1,4-naphthoquinone (**I**) (0.331 g, 1 mmol), anhydrous KF (0.32 g, 5.5 mmol), activated neutral alumina (1.7 g), anhydrous methanol (23.3 ml) and anhydrous glyme, diglyme, or dioxane in amounts indicated in the table were mixed in a pressure reactor at 95±1°C for 8 h. After the end of reaction the reaction mixture was cooled, the sorbent was filtered off, washed with 15 ml of acetone containing 3 ml of 10% HCl. The combined filtrates were concentrated under reduced pressure, the residue was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, with saturated NaCl solution, dried on $Na_2SO_4$, and evaporated. The chromatographically homogeneous 5,8-dihydroxy-2,3,6-trimethoxy-7-ethyl-1,4-naphthoquinone (**I**) was isolated by column chromatography on silica gel, mp 131–132°C (from acetone), (131–132°C [7]). $^1$H NMR spectrum, δ, ppm: 1.17 t (3H, $CH_3$, *J* 7.1), 2.73 q (2H, $CH_2$, *J* 7.1), 4.08 s (3H, $OCH_3$), 4.10 s (3H, $OCH_3$), 4.14 s (3H, $OCH_3$), 12.98 br.s (1H, α-OH), 13.13 s (1H, α-OH). Mass spectrum, *m/z* ($I_{rel}$, %): 308 $M^+$ (100).

Apart compound **II** from the reaction mixture was separated a mixture of monosubstituted products **III** and **IV**.

**5,8-Dihydroxy-2,6-dimethoxy-3-chloro-7-ethyl-1,4-naphthoquinone (III).** $^1$H NMR spectrum, δ, ppm: 1.15 t (3H, $CH_3$, *J* 7.1), 2.69 q (2H, $CH_2$, *J* 7.1), 4.12 s (3H, $OCH_3$), 4.25 s (3H, $OCH_3$), 13.10 br.s (1H, α-OH), 13.14 s (1H, α-OH).

**5,8-Dihydroxy-2,7-dimethoxy-3-chloro-6-ethyl-1,4-naphthoquinone (IV).** $^1$H NMR spectrum, δ, ppm: 1.15 t (3H, $CH_3$, *J* 7.1), 2.71 q (2H, $CH_2$, *J* 7.1) 4.10 s (3H, $OCH_3$), 4.21 s (3H, $OCH_3$), 12.82 br.s (1H, α-OH), 13.33 s (1H, α-OH).

**2,5,6,8-Tetrahydroxy-3-chloro-7-ethyl-1,4-naphthoquinone (V) and 2,5,7,8-Tetrahydroxy-3-chloro-6-ethyl-1,4-naphthoquinone (VI).** A mixture of monosubstituted products **III** and **IV** (100 mg) and 48% HBr (6 ml) was boiled for 0.5 h. The reaction mixture was diluted with water (20 ml), and the products were extracted into ether. The extract was dried with anhydrous $Na_2SO_4$ and evaporated. Compounds **V** and **VI** were isolated by preparative TLC in a ratio 4:1.

**2,5,6,8-Tetrahydroxy-3-chloro-7-ethyl-1,4-naphthoquinone (V) mp 220–223°C (mp 221–224°C [6]).** **$^1$H NMR spectrum ($CDCl_3$, δ, ppm): 1.17 t (3H, $CH_3$,** *J* 7.6); 2.70 q (2H, $CH_2$, *J* 7.6); 12.58 and 12.78 two s (each 1H, α-OH). $^1$H NMR spectrum (acetone-$d_6$, δ, ppm): 1.14 t (3H, $CH_3$, *J* 7.5); 2.69 q (2H, $CH_2$, *J* 7.5); 9.97 br.s (1H, β-OH); 12.92 and 12.95 two s (each 1H, α-OH). Mass spectrum (70 eV), *m/z* ($I_{rel}$, %): 284/286 $[M]^+$ (14), 283/285 $[M-1]^+$ (100), 269/271 (16), 268/270 (12), 241/243 (41).

**2,5,7,8-Tetrahydroxy-3-chloro-6-ethyl-1,4-naphthoquinone (VI).** mp 218–223°C (218–222°C [6]). $^1$H NMR spectrum ($CDCl_3$, δ, ppm): 1.18 t (3H, $CH_3$, *J* 7.5); 2.71 q (2H, $CH_2$, *J* 7.5); 11.76 br.s (1H, α-OH); 13.37 s (1H, α-OH). $^1$H NMR spectrum (acetone-$d_6$, *δ, ppm): 1.14 t (3H, $CH_3$, J* 7.5); 2.70 q (2H, $CH_2$, *J* 7.5); 9.77 br.s (1H, β-OH); 12.11 br.s (1H, α-OH); 13.58 s (1H, α-OH). Mass spectrum, *m/z* ($I_{rel}$, %): 284/286 $[M]^+$ (23), 283/285 $[M-1]^+$ (100), 249 (9), 241 (9).

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