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SYNTHESIS OF ETHERS AND ESTERS OF 1,4-DI-N-OXIDE OF 2,3-BIS(HYDROXYMETHYL)QUINOXALINE UNDER CONDITIONS OF INTERFACIAL CATALYSIS

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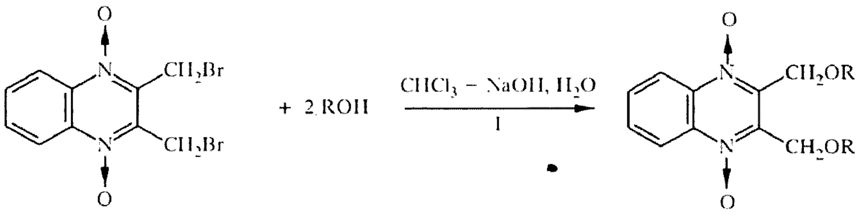
Esters and ethers of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline have been obtained under conditions of interfacial catalysis in a chloroform–water system. The catalytic activities of tetrabutylammonium bromide and cetyltriethylammonium bromide have been compared in the synthesis of the acetate, benzoate, and 4-nitrobenzoate of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline.

Ethers and esters of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline have high biological activities that are used extensively in medical practice for the treatment of acute bacterial infections [1, 2].

The principal method for obtaining these compounds is the interaction of the 1,4-di-N-oxide of 2,3-bis(bromomethyl)quinoxaline with phenolates or salts of the corresponding carboxylic acids [1-3]. The reaction is performed by refluxing the reactants in acetone or anhydrous ethanol; the ether or ester yields vary widely, from 26% to 88%. In many cases, the low yields can obviously be attributed to the fact that these compounds undergo redox conversions in alcohol or water–alcohol media in the presence of bases [4, 5]. It appeared likely that preparation of ethers and esters of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline under conditions of interfacial catalysis would offer a means for avoiding such problems, since it is known that interfacial catalysis is particularly effective in those cases in which the reactants and the reaction products are subject to side conversions [6].

In the work reported here, we investigated the formation of ethers and esters of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline with phenols and with aliphatic and aromatic carboxylic acids. The reaction was performed in a two-phase system consisting of chloroform and an aqueous sodium hydroxide solution, at 56°C. As the interfacial transfer catalyst we used tetrabutylammonium bromide (I). Under these conditions, the corresponding ethers or esters are formed with yields of 62-90%.



IIa–p

II a) R = C_6H_5, b) R = 4-$C_2H_5C_6H_4$, c) R = 4-$OCHC_6H_4$, d) R = 4-BrC_6H_4, e) R = 4-$NO_2C_6H_4$,
f) R = 2-naphthyl g) R = CH_3CO h) R = $C_6H_5CH_2CO$, i) R = C_6H_5CO, j) R = 4-$CH_3C_6H_4CO$,
k) R = 3-$CH_3C_6H_4CO$, *l*) R = 4-ClC_6H_4CO, m) R = 4-BrC_6H_4CO, n) R = 3-BrC_6H_4CO,
o) R = 4-$NO_2C_6H_4CO$, p) R = 3-$NO_2C_6H_4CO$

The comparatively low yield of compound IIf is explained by the slight oxidizability of 2-naphthol, even when the reaction is performed in an inert gas medium. The structures of compounds IIa-p are consistent with the spectral data (Tables 1 and 2) and with the results of elemental analysis.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}		Yield, %
			N—O	CH_2OR (C=O)	
IIa	$C_{22}H_{18}N_2O_4$	175...177	1330	*—	76
IIb	$C_{26}H_{26}N_2O_4$	150...151	1330	1280	64
IIc	$C_{24}H_{18}N_2O_6$	175...177	1335	1275 (1710)	77
IId	$C_{22}H_{16}Br_2N_2O_4$	151...152	1330	1275	75
IIe	$C_{22}H_{16}N_4O_8$	182...184	1330	1285	79
IIf	$C_{30}H_{22}N_2O_4$	175...176	1330	1275	62
IIg	$C_{14}H_{14}N_2O_6$	179...180	1325	(1740)	85
IIh	$C_{26}H_{22}N_2O_6$	151...152	1325	(1740)	81
IIi	$C_{24}H_{18}N_2O_6$	180...181	1330	(1720)	83
IIj	$C_{26}H_{22}N_2O_6$	191...192	1335	(1715)	69
IIk	$C_{26}H_{22}N_2O_6$	157...159	1335	(1720)	66
II*l*	$C_{24}H_{16}Cl_2N_2O_6$	191...193	1330	(1725)	89
IIm	$C_{24}H_{16}Br_2N_2O_6$	198...199	1330	(1720)	85
IIn	$C_{24}H_{16}Br_2N_2O_6$	194...195	1330	(1720)	85
IIo	$C_{24}H_{16}N_4O_{10}$	197...198	1335	(1735)	89
IIp	$C_{24}H_{16}N_4O_{10}$	202...203	1330	(1730)	90

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*Band masked.

TABLE 2. UV and PMR Spectra of Synthesized Compounds*

Compound	λ_{max}, nm (and log ε)	δ, ppm			SSCC (J), Hz	
		5,8-H_2	6,7-H_2	CH_2	5,6 (7,8)	5,7 (6,8)
IIa	233(4,52); 265(4,40); 394(4,05)	8,40	7,60	5,54	9,5	3,00
IIb	232(4,61); 267(4,54); 393(4,02)	8,40	7,60	5,54	10,5	3,50
IIc	232(4,46); 269(4,76); 394(4,08)	—	—	—	—	—
IId	233(4,69); 270(4,46); 394(4,00)	—	—	—	—	—
IIe	233(4,57); 266(4,34); 393(4,05)	8,55	8,08	5,82	12,5	4,00
IIf	231(5,09); 266(4,59); 394(4,05)	—	—	—	—	—
IIg	235(4,46); 267(4,44); 396(4,09)	8,52	7,75	5,60	10,0	3,00
IIh	208(4,41); 232(4,43); 396(4,03)	8,50	7,73	5,50	10,0	3,25
IIi	235(4,58); 267(4,53); 396(4,11)	8,60	7,78	5,90	10,0	3,50
IIj	237(4,69); 269(4,55); 396(4,08)	8,53	7,65	5,78	10,0	3,25
IIk	235(4,70); 268(4,54); 396(4,10)	8,60	7,81	5,80	10,0	3,25
II*l*	237(4,71); 268(4,51); 396(4,04)	8,45	7,70	5,78	12,0	4,00
IIm	240(4,72); 263(4,59); 396(4,09)	8,50	7,75	5,80	10,0	3,00
IIn	235(4,64); 267(4,50); 396(4,09)	8,44	7,75	5,78	10,0	3,25
IIo	236(4,58); 268(4,71); 397(4,08)	8,60	7,86	5,90	10,6	3,60
IIp	233(4,66); 268(4,57); 397(4,08)	—	—	—	—	—

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*PMR spectra of compounds IIa, b, g, h, j, k were recorded in $CDCl_3$, compounds IIe, i, l-o in $DCON(CD_3)_2$. No PMR spectra were obtained for compounds IIc, d, f, p, owing to their low solubilities.

In order to evaluate the influence of the type of interfacial transfer catalyst on the rate of formation of quinoxaline esters, we used cetyltriethylammonium bromide as well as tetrabutylammonium bromide in obtaining compounds IIg, IIi, and IIo.

In the interfacial process, the efficiency of an interfacial transfer catalyst can be evaluated in the first approximation by the magnitudes of the extraction constant and the ion exchange selectivity coefficient

$$K^{\mathrm{sel}}_{Y^-/X^-} = \frac{E_{Q^+Y^-}}{E_{Q^+X^-}} .$$

TABLE 3. Distribution Coefficients of Cetyltriethylammonium Salts in Chloroform–Water System (25°C)

$C_{tot}\cdot 10^4$, M	C_{Q^+} (aq)$\cdot 10^4$, M	$C_{Q^+X^-}$ (org)$\cdot 10^4$, M	K_d
	Cetyltriethylammonium bromide		
1,50	0,13	1,37	10,6
5,37	0,29	5,08	17,5
9,65	0,44	9,21	20,9
15,00	0,61	14,39	24,0
19,50	0,75	18,75	25,9
24,65	0,83	23,82	29,1
30,10	0,93	29.07	31,3
50,00	1,18	48,82	41,8
	Cetyltriethylammonium acetate		
1,00	0,70	0,30	0,43
2,00	1,22	0,78	0,63
3,00	1,65	1,35	0,82
4,00	2,15	1,85	0,87
5,00	2,35	2,65	1,14
5,96	2,70	3,26	1,20
7,00	2,96	4,04	1,36
8,05	3,25	4,80	1,47

where $E_{Q^+Y^-}$ and $E_{Q^+X^-}$ are the respective extraction constants [7]. Values are known for the extraction constants of tetrabutylammonium bromide, acetate, and benzoate in the chloroform–water system [6]. For the extraction constants of cetyltriethylammonium benzoate, tetrabutylammonium 4-nitrobenzoate, and cetyltriethylammonium 4-nitrobenzoate in the same system, we calculated the extraction constants by the method of increments [7]. The extraction constants of cetyltriethylammonium bromide and acetate were calculated on the basis of experimentally determined distribution coefficients (Table 3).

It can be assumed that in a two-phase system consisting of an organic solvent and water, an onium salt (within a certain interval of concentrations) will exist in the organic phase in the form of ion pairs, owing to the low permittivity of the organic solvent; but in the aqueous phase it will exist in the dissociated state.

$$Q^+{}_{(aq)} + X^-{}_{(aq)} \overset{E_{Q^+X^-}}{\rightleftarrows} Q^+X^-{}_{(org)}\,.$$

If these conditions are observed, the extraction constant $E_{Q^+X^-}$ can be found by means of the equation [8]

$$K_d = \frac{C_{Q^+Y^-(org)}}{C_{Q^+X^-(aq)}} = E_{Q^+X^-}\cdot f_{Q^+(aq)}\cdot f_{X^-(aq)}\cdot C_{Q^+X^-(aq)} + \sqrt{E_{Q^+X^-}\cdot K^{dis}_{(org)}}\,. \tag{1}$$

where $E_{Q^+X^-}$ and K_d are the extraction constant and the distribution coefficient, respectively; $C_{Q^+X^-(org)}$ and $C_{Q^+X^-(aq)}$ are the concentrations of salt in the organic and aqueous phases; $f_{Q^+aq)}$ and $f_{X^-(org)}$ are the activity coefficients of the ions in the aqueous phase; $K_{(org)}{}^{dis}$ is the dissociation constant of the salt in the organic phase.

By treatment of the experimental data for cetyltriethylammonium bromide and acetate, we obtain the respective equations for the regression lines:

$$K_d = (2.60 \pm 0.14)\cdot 10^5\cdot f_{Q^+(aq)}\cdot f_{X^-(aq)}\cdot C_{Q^+X^-(aq)} + (9.20 \pm 0.95),$$
$$r = 0.99,\ n = 8,\ S = 0.04;$$
$$K_d = (4.10 \pm 0.10)\cdot 10^3\cdot f_{Q^+(aq)}\cdot f_{X^-(aq)}\cdot C_{Q^+X^-(aq)} + (0.14 \pm 0.02),$$
$$r = 0.99,\ n = 8,\ S = 0.03;$$

TABLE 4. Extraction Constants ($E_{Q^+X^-}$) of Quaternary Ammonium Salts and Selectivity Coefficients (K_{y^-/x^-}^{sel}) Relative to Bromine Ion, in Chloroform–Water System (25°C)

Ammonium cation	Tetrabutyl		Cetyltriethyl	
Anion	$\lg E_{Q^+X^-}$	$\lg K_{y^-/x^-}^{sel}$	$\lg E_{Q^+X^-}$	$\lg K_{y^-/x^-}^{sel}$
Br	1,29	0	5,42	0
CH_3COO^-	-2,12	-3,41	3,61	-1,80
$C_6H_5COO^-$	0,39	-0,90	4,89	-0,52
$4\text{-}NO_2C_6H_5COO$	2,10	0,89	6,61	1,20

The extraction constants for cetyltriethylammonium bromide and acetate in the chloroform–water system are $2.6 \cdot 10^5$ and $4.1 \cdot 10^3$, respectively.

From the data obtained in these experiments (Table 4), we can draw the following tentative conclusions. If the rate of formation of the esters IIg, IIi, and IIo is limited by the equilibrium of ion pair transfer, then, when the change is made from tetrabutylammonium bromide to cetyltriethylammonium bromide, the reaction rate should increase. If the reaction rate is determined by the reactivity of the ion pairs, there should be no acceleration of the process. Thus, the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline acetate, in the presence of tetrabutylammonium bromide, is formed with an 85% yield in 20 h. In comparison, when the tetrabutylammonium bromide is replaced by cetyltriethylammonium bromide, the reaction time is shortened to 14 h. However, in the reaction of the 1,4-di-N-oxide of 2,3-bis(bromomethyl)quinoxaline with the more lipophilic benzoate and 4-nitrobenzoate anions, the process rate is independent of the type of catalyst used for interfacial transport. On the assumption that the formation of the quinoxaline esters takes place in the organic phase, these results signify that in an interfacial catalytic process with the participation of weakly lipophilic anions such as the acetate anion, the equilibrium state of ion transfer is the main factor determining the reaction rate. For lipophilic anions, in contrast, the reaction rate is determined mainly by the reactivity of the ion pairs.

Thus, we have shown that the ethers and esters of the 1,4-di-N-oxide of 2,3-bis(hydroxymethyl)quinoxaline are formed under conditions of interfacial catalysis with higher yields than in the noncatalytic process.

EXPERIMENTAL

The IR spectra were recorded in a UR-20 instrument in KBr tablets; the UV spectra were taken in an SF-46 spectrophotometer in acetonitrile; the analytical concentration of the quinoxaline ethers and esters was $1 \cdot 10^{-5}$ M. The PMR spectra were obtained in a Tesla BS-497 instrument (100 MHz), internal standard HMDS. The distribution coefficients of the cetyltriethylammonium salts were determined by a method that has been described in [9]. The salt concentrations in chloroform and water were determined photocolorimetrically on a complex with bromphenol blue [10].

The distribution coefficients were determined as the average values from three to five parallel measurements. The raw data were worked up by methods of mathematical statistics [11].

The quinoxaline esters and ethers were prepared in a flask that was opaqued by an outside coating of bituminous varnish. Elemental analyses for C, H, and N matched the calculated values.

1,4-Di-N-oxide of 2,3-Bis(2-naphthyloxymethyl)quinoxaline (IIf). To a solution of 2.5 g (0.063 mole) of sodium hydroxide and 8.6 g (0.06 mole) of 2-naphthol in 80 ml of water, there was added a solution of 7 g (0.02 mole) of the 1,4-di-N-oxide of 2,3-bis(bromomethyl)quinoxaline and 0.6 g (0.002 mole) of tetrabutylammonium bromide in 80 ml of chloroform. The mixture was stirred in a flow of nitrogen for 14 h at 56°C, after which it was cooled, the phases were separated, and the organic layer was washed with a 2% (wt.) solution of sodium hydroxide (2 × 50 ml) and dried with magnesium sulfate; the product was isolated by column chromatography (silica gel, chloroform). After crystallization from a 1:3 mixture of chloroform and acetone with the addition of activated carbon, obtained 6.28 g (62%) of compound IIf, mp 175-176°C.

Compounds IIa-e (Table 1) were obtained analogously.

1,4-Di-N-oxide of 2,3-Bis(phenylacetoxymethyl)quinoxaline (IIh). To a solution of 2.5 g (0.063 mole) of sodium hydroxide and 8.2 g (0.06 mole) of phenylacetic acid in 80 ml of water, there was added a solution of 7 g (0.02 mole) of the

1,4-di-N-oxide of 2,3-bis(bromomethyl)quinoxaline and 0.6 g (0.002 mole) of tetrabutylammonium bromide in 80 ml of chloroform. The mixture was stirred for 10 h at 56°C, after which it was cooled, the phases were separated, and the organic phase was washed with water (2 × 50 ml) and dried with magnesium sulfate. After driving off the chloroform, the residue was recrystallized from a 1:2 mixture of acetone and petroleum ether with the addition of activated carbon, obtaining 7.62 g (81%) of compound IIh, mp 151-152°C.

Compounds IIg and IIi-p were obtained analogously; for compound IIg, the reaction time was 20 h.

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