the color characteristic of nickel salicyladehydrate appears. Then add in sequence 1.12 g (20 mmoles) of KOH in 15 ml of methanol and 1 g (10 mmoles) of 3,4-diaminofurazan in 10 ml of methanol. After boiling the solution for 10 h, filter off the precipitated complex compound, wash it repeatedly with hot methanol, and dry it in vacuum at 120°C. Yield 2.95 g (82%), black crystals with mp 350°C. IR spectrum: 1615 (C=N, azomethine), 1630 $cm^{-1}$ (furazan ring). Found: C 52.8; H 2.7; N 15.5; Ni 16.5%. Calculated for $C_{16}H_{10}N_4NiO_3$: C 52.6; H 2.8; N 15.4; Ni 16.1%.

B. Dissolve 0.5 g (2.5 mmoles) of azomethine VII in 30 ml of methanol and add 0.26 g (1.25 mmoles) of nickel acetate tetrahydrate in 10 ml of the same solvent. After boiling the solution for 4 h, filter off the black crystals, wash three times with methanol, and dry in vacuum at 120°C.

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# CROWN ETHERS BOUND TO SULFANILAMIDE PREPARATIONS


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Complexes with a 1:2 composition were obtained by the reaction of 8-crown-6 ethers with 4-aminobenzenesulfonamide and 4-aminobenzensulfoguanidine. Crown ethers containing a sulfanilyl group were obtained in the reaction of azacrown ethers with 4-acetylaminobenzenesulfonyl chloride.


Interest has recently arisen in crown ethers containing pharmacophoric groups [1, 2]. To change the hydrophilic-hydrophobic properties of sulfanilamide preparations (SFAP), we carried out reaction of 4-aminobenzenesulfonamide, 4-aminobenzenesulfoguanidine, 2-(4-aminobenzenesolfonamido)thiazole, 4-aminobenzenesulfonylurea, 2-(4-aminobenzenesulfonamido)-4,6-dimethylpyridimidine, 2-(4-aminobenzenesulfonamido)-3-methoxypyrazine, 3-(4-aminobenzenesulfonamido)-6-methoxypyridazine, and 6-(4-aminobenzenesulfonamido)-2,4-dimethoxypyrimidine with 15-crown-5 and 18-crown-6 ethers in solvents that ensure the dissolution of the starting materials. In the literature, spectral data are given on the complexation of 18-crown-6 ethers with SFAP, including 3-(4-aminobenzenesulfonamido)-6-methoxypyradizine and 6-(4-aminobenzenesulfononamido)-2,4-dimethoxypyrimidine [3], but preparatively, we succeeded only

*Deceased.


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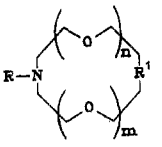
TABLE 1. Characteristics of Compounds Synthesized

| Compound | mp,* °C | $R_f$ | IR spectrum, $cm^{-1}$ | | | Found N, % | Empirical formula | Calculated N, % | $M^+$ | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | NH | $SO_2$ | COC | | | | | |
| Ia | 140—141 | 0,39† | 3380 | 1310, 1155 | 1110 | 9,1 | $C_{24}H_{40}N_4O_{10}S_2$ | 9,2 | | 95 |
| Ib | 226—227 | 0,27† | 3430 | 1150 | 1130 | 16,0 | $C_{28}H_{44}N_8O_{10}S_2$ | 16,2 | | 90 |
| IIa | 167—168 | 0,34 | 3380 | 1310, 1150 | 1095 | 7,6 | $C_{16}H_{28}N_2O_6S$ | 7,5 | 374 | 64 |
| IIb | 107—108 | 0,29 | 3370 | 1310, 1150 | 1090 | 6,9 | $C_{18}H_{30}N_2O_7S$ | 6,7 | 418 | 66 |
| II c | 150—151 | 0,39 | 3360 | 1300, 1130 | 1080 | 10,0 | $C_{24}H_{36}N_4O_8S_2$ | 9,8 | | 50 |

*Compound Ia was crystallized from dioxane, Ib and IIa, from water, IIb from benzene, IIc from ethanol.
†The value of $R_f$ is given for SFAP, since during the TLC the complexes decompose and 18-crown-6 forms a loop.

in isolating the 18-crown-6—SFAP complexes with 1:2 composition only when 4-aminobenzenesulfanomide (Ia) and 4-aminobenzenesulfoguanidine (Ib) were used. Complexes of 15-crown-5-ethers with SFAP could not be preparatively isolated. For the same purpose, compounds IIa-c were obtained from 4-aminobeenzenesulfonyl chloride and azacrown ethers.



IIa-c

II $R=SO_2C_6H_4NH_2$; a $R^1=O$, $n=1$, $m=2$; b $R^1=O$, $n=2$, $m=2$; c $R^1=NSO_2C_6H_4NH_2$. $n=2$, $m=2$

The reaction of compounds IIa-c with 18-crown-6 ethers does not lead to the preparative isolation of the complexes. This shows that for complexation with a crown ether it is apparently essential that a sterically unhindered, weakly basic (sulfamide and or sulfoguanidine) $H_2N$ groups be present in the molecule of SFAP.

## EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer in potassium bromide tablets, and the PMR spectra were run on a Tesla BS-407 spectrometer. The mass spectra were measured on a MAT-112 mass spectrometer at an ionizing voltage of 70 eV with a direct introduction of the sample into the source. The TLC was carried out on Silufol UV-254 plates, for compounds I in a 1:3 methanol—chloroform system, and for compounds II in a 1:2 acetone—benzene system, with development in UV light (extinction) and ninhydrine (red spots).

Complexes of 18-Crown-6 Ethers with SFAP (I) (Table 1). A 10-mmole portion of 18-crown-6 ether is added to a solution of 10 mmoles of 4-aminobenzenesulfamide in 20 ml of diozane or 4-aminobenzenesulfoguanidine in 200 ml of water at 100°C. After cooling and evaporation of the solutions, 1:2 complexes of 18-crown-6 with 4-aminobenzenesulfamide (Ia) and 18-crown-6 with 4-aminobenzenesulfoguanidine (Ib) crystallized. In the PMR spectra ($CF_3COOH$) of compounds I, the chemical shifts of the phenyl protons are 7.70-8.30 and of the oxymethylene protons 3.75-3.80 ppm.

Sulfanilyl-Containing Crown Ethers II (Table 1). A solution of 10 mmoles of monoaza-15-crown-5 or monoaza-18-crown-6 or 5 mmoles of diaza-18-crown-6 and 20 mmoles of triethylamine in 30 ml of dioxane is added to a solution of 10 mmoles of 4-acetylaminobenzenesulfonyl chloride dissolved in 50 ml of dioxane. The mixture is allowed to stand for 1 h, then filtered, and the filtrate is evaporated. The oil obtained is boiled for 5 min with 10 ml of 10% HCl, and the solution is then neutralized with 30 mmoles of sodium carbonate, and the oily products IIa-c are crystallized to yield 1,4,7,10-tetraoxa-13-(sulfanil)azacyclopentadecane (IIa), 1,4,7,10,13-pentaoxa-16-(sulfanil)azacyclooctadecane (IIb) and 1,4,10,13-tetraoxa-7,16-(disulfanil)diazacyclooctadecane (IIc). In the PMR spectra of compounds IIa, b (in $CDCl_3$) and IIc (in $CF_3COOH$), the chemical shifts of the phenyl group protons lie in the region of 6.47-7.53 and 7.70-0.17 ppm, respectively, of the $H_2N$ groups at 4.12 (IIa) and 4.17 (IIb) ppm, of $CH_2O$ groups at 3.60 (IIa, b) and 3.93 (IIc) ppm, of the $CH_2N$ at 3.17-3.33 (IIa, b) and 3.57 (IIc) ppm. The integral intensities of the groups of protons correspond to the formulas given.

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# 2-HYDROXYMETHYLAMINO-4-THIAZOLINONE. CONFIRMATION AND CHELATE FORMATION

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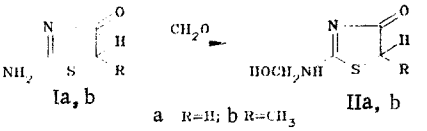
In DMSO-$d_6$ solution 2-hydroxymethylamino-4-thiazolinone, as well as its 5-methyl-congener, exists in the form of E- and Z-conformers relative to the exocyclic nitrogen-carbon bond; for each of these conformers, furthermore, both a transoid and cisoid orientation of the hydrogen and oxygen atoms, relative to the N–$CH_2$ bond, are possible. The transoid form is able to form a chelate derivative with intramolecular hydrogen bond formation. Both acids and bases catalyze transitions among the "open" forms, although chelate formation is only acid-catalyzed.

Heating 37% aqueous formaldehyde with 2-amino-4-thiazolinone (Ia) in ethanol at 70°C results in the formation of an adduct, namely, a monohydroxymethyl derivative. Tertiary amines accelerate the reaction, and hydroxymethylation occurs at room temperature in their presence. The adduct does not melt, even upon heating to 250°C, although its derivatograph (thermal gravimetric analysis) indicates that it loses one molecule of formaldehyde in the 140-160°C temperature range. The adduct gives only one spot with thiazolinone Ia on TLC, and its UV spectrum is identical [to that of thiazolinone Ia]. Because of its thermal lability, the adduct does not exhibit a molecular ion ($M^+$) peak in its mass spectrum, but does exhibit $M^+$ peaks due to compound Ia and formaldehyde.

We have previously demonstrated [1] that, for the hydroxymethylation of mesomeric anions, kinetic and thermodynamic regioselectivity overlap, as a result of which hydroxymethylation occurs on the "harder" site of an ambident anion, which, in this case, is the exocyclic nitrogen atom [2]. Hydroxymethylation of the neutral molecule takes place only at elevated temperatures, where addition to the carbonyl group carbon atom is reversible, and as a result, thermodynamic control of the product mixture leads to formation of the most stable hydroxymethylation derivative, whose structure in this case would correspond to the most stable tautomer of Ia, the aminotautomer [2]. Thus, the adduct should exhibit the structure of the 2-hydroxymethyl derivative IIa, regardless of whether it is the anionic form or neutral Ia which reacts. This expected hydroxymethylation pathway has been verified by NMR analysis of compound IIa.




PMR Spectra. The PMR spectrum of compound IIa in DMSO-$d_6$ at an operating frequency of 270 MHz (Fig. 1a) is totally unexpected. It contains four signals due to the NH proton, one of which, the most downfield, broadened one at about 10 ppm, cannot always be discerned; there are also four triplets due to the hydroxyl proton, four multiplet signals arising from the methylene protons of the hydroxymethyl group, and three signals due to the methylene protons attached to the heterocycle, $C_{(5)}H_2$. This type of PMR spectrum can be rationalized on

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