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Note

N-Methylation of 2-Furylbenzothiazoles. The Influence of Substituents on the Rate of Quaternization[a,b]

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Quaternization of several 2-furylbenzothiazoles with dimethylsulphate in dioxane has been studied. The noticeable substituent dependence of the rate of methylation has been observed. The substituents (CH_3, Br, Cl) have been located at position 5 of the furane nucleus and/or position 6 of the benzo-ring.

Recently we reported the preparation and properties of some 2-(2- or 3-furyl)benzothiazoles[1]. Like many other thiazoles[2], due to their weak basic character they can give quaternary salts. Comparing 2-(2-methyl-3-furyl)benzothiazoles with the 2-(5-methyl-2-furyl) analogue it was observed that the nucleophilicity (and basicity) of benzothiazole nitrogen is influenced by the position of the methyl group in the furane nucleus. The effect was illustrated by hydrochloride formation and with quaternization by methylation[1]. In the present paper we wish to discuss further the quaternization of several furyl--substituted benzothiazoles since noticeable substituent dependance of the rate during methylation with dimethylsulphate has been observed.

N-alkylation of organic bases is a very well known reaction, sometimes refered to as a Menshutkin's reaction[3]. Many nitrogen heterocycles, including thiazoles, have been investigated in this sense[4]. Simple bimolecular kinetics invariable were observed, and the reaction is usually regarded as a pure S_N2 process. Surprisingly, only a limited interest has been paid so far to benzothiazole *N*-alkylation. The observed difference in the rate of *N*-methylation could be related to the nucleophilicity of benzothiazole nitrogen and its substituent dependance. It was shown[5] that the benzothiazole system is very efficient in transmitting substituent effects from the benzo-ring to the group bonded at the thiazole nucleus. The effects are transmitted through the thiazole nucleus mainly by nitrogen[6]. Consequently the electron density of thiazole nitrogen should be greatly influenced by the substituent effects from the benzo-group. Regarding the position of substituents 5 and 6 they can be considered as »meta« and »para« respectively[6]. The substituents (CH_3, Br, Cl) of the compounds elaborated in present studies were located at position 5 of the furane nucleus and/or position 6 of the benzo-ring. Substituents at the benzo-ring can be regarded as »para« when explaining their effects on electron density of thiazole nitrogen.

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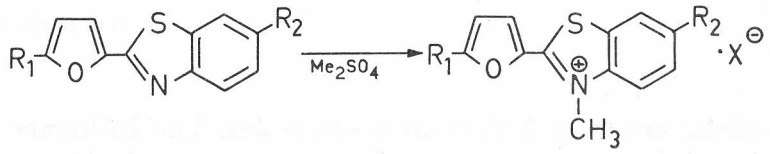
[a] Thioamides. XVI. for part XV see: loc. cit. 1.; Simultaneously XX. Part of the Studies in Furane Series.

[b] Taken in part from the PhD Thesis of L. Fišer-Jakić, University of Zagreb, 1977.

The methylation of 2-(furyl)benzothiazole was performed with dimethylsulphate in dry dioxane[c] to form the corresponding quaternary salt. (Figure 1)



R_1 = H, CH_3 Br; R_2 = H, CH_3, Br, Cl
X^- = $CH_3SO_4^-$

Figure 1.

The rate of reaction was followed by UV measurements since the absorbtion maxima of the starting benzothiazole and the corresponding *N*-methyl derivative were separated by 30—60 nm from each other (Table 1). The absorbance decrease in the 318—334 nm region was related to the concentration drop of the starting compound.

The optimal reaction conditions were found to be at 80 °C. At this temperature the rates of reaction were suitable to be followed either at an equimolar reactant ratio or with a tenfold excess of dimethylsulphate. The experiments with reactant ratio above 1 : 10 were rejected since the reproducibility of measurement was not good enough.

TABLE I

			Benzothiazole[a] (A)		Quatern. salt[a] (B)				
No.	R_1	R_2	m. p. (°C)	λ_{max} (log ε)	m. p. (°C)	λ_{max} (log ε)	$\delta^{b}_{N-CH_3}$ (ppm)	$10^5 \cdot k_1/s^{-1}$ (80 °C)	$t_{1/4}$ min
I	H	H	105[7]	318 (4.37)	165	351 (4.32)	4.60	2.89	165
II	H	CH_3	111—12[7]	321 (4.45)	180—2[c]	355 (4.35)	4.47	6.06	77
III	H	Br	142[8]	323 (4.38)	170[d] (decomp.)	358 (4.34)	4.60	2.88	190
IV	H	Cl	123—4[1]	322 (4.46)	198—200[e]	356 (4.28)	4.57	2.02	248
V	CH_3	H	101—2[1]	328 (4.41)	194[f]	368 (4.60)	4.50	6.69	70
VI	CH_3	CH_3	85—6[1]	334 (4.43)	216 (decomp.)	368 (4.53)	4.37	—[h]	—
VII	Br	H	128—9[1]	325 (4.42)	207—8[g]	367 (4.05)	4.53	2.34	180

[a] Prepared according to the reported procedure[1]; [b] In CF_3COOH with TMS as internal standard; [c] Iodide, m. p. 194—5 °C; [d] Iodide, m. p. 217—19 °C; [e] Iodide, m. p. 210 °C; [f] Iodide, m. p. 209 °C; [g] Iodide, m. p. 230 °C. [h] Exact measurements were prevented by instant appearance of microcrystaline methosulphate and due inhomogenity of the mixture.

[c] For preparative work xylene has proved to be better solvent[1].

All experiments were performed with a 5×10^{-2} molar solution of corresponding benzothiazole in dioxane. The experimental data for the reactions at an equimolar amount of dimethylsulphate fit the 2nd order rate equation while at tenfold excess the 1st order rate equation was satisfied. The data for calculation were mean value of three measurements disregarding points overshooting more than 2% of the mean value.

For the compound I the measurements were performed at different temperatures (70, 80 and 100°). The rate data, pseudo first-order rate constant, energy and entropy of activation calculated in the usual manner[9] are given: $k_1 \times 10^5 \times s = 1.52$ (70 °C), 2.89 (80 °C), 9.64 (100 °C); $E = 66.3$ kJ/mol; $\Delta S^{\ddagger} = -195.4$ J mol^{-1} K^{-1}.

Rate constants of other benzothiazole quaternization at a single temperature (80 °C) are tabulated in Table 1, and were obtained using the usual integrated form of the first order law. The rates were determined from measurements covering not more that the first 25% of the reaction. By limiting the measurements to this range, deviations from salt effects are minimized.

In a number of cases the repeated determination of the rate constant at widely separated intervals of time yielded results which agreed with a precision better than 5%.

The results are in good agreement with the prediction stating that electron donating groups (methyl group) in position 6 or at the furyl-substituent situated in position 2 of the benzothiazole system would increase the electron density of nitrogen and its nucleophilicity, speeding up the reaction with alkylating reagent. Halogens (Br, Cl) cause the opposite effect. Similarly as in the case of halogensubstituted benzimidazoles[10], this could be rationalized by supposing that chlorine and bromine show a smaller (+ M) mesomeric effect, and their inductive effect (—I) is more noticeable. The influence of the methyl substituent present both at the benzo-ring and at the furyl-substituent (comp. VI) seems to be additive.

EXPERIMENTAL SECTION

The melting points are uncorrected. The purity of the compounds was checked on a silica gel GF tlc plate. The UV spectra were recorded on a Hitachi-Perkin-Elmer Model 124 spectrophotometer.

The benzothiazoles (IA—VIIA) (Table I) were prepared from appropriately substituted thiofuranilide by the reported procedure[1]. The *N*-methyl-derivatives in form of methosulphate (IB—VIIB) (Table I) were prepared by heating a solution of the corresponding benzothiazole and dimethylsulphate (3 mole per mol of benzothiazole) in refluxing xylene (4—10 ml) for 0.5—3.0 h. Crystalline methosulphate was separated on cooling and recrystallized from ethanol. The structure of the investigated compounds were supported by ^{1}H NMR spectra and IR spectra. Previously unreported quaternary salts (Table I except VB) were confirmed by satisfactory elemental analyses.

The rate of reaction of the benzothiazole with dimethylsulphate was studied in dry dioxane at 70, 80 and 100 °C for comp. IA, and at 80 °C for all other benzothiazoles (IIA-VIIA), with temperature deviations less than ±0.1 °C. Pseudo-first-order kinetics were maintained during the course of the kinetic run where benzothiazole was 5×10^{-2} M and $(CH_3)_2SO_4$ was 5×10^{-1} M (10-fold excess). The concentrations of diluted aliquots in given periods were monitored by UV absorption at the appropriate wavelength. From the height of the band at λ_{max} the percentage of unreacted benzothiazole was calculated and ploted against time.

General procedure. — In a typical experiment a 0.5 mol (100—140 mg) sample of a substituted 2-furylbenzothiazole (IA-VIIA) was dissolved in a small portion of dry dioxane. To the solution freshly distilled dimethylsulphate (1—10 mole per mol

of a benzothiazole) was added. The mixture was diluted to 10.0 ml with dry dioxane. A small aliquot (0.02 ml) of such a 5×10^{-2} M solution (with respect to benzothiazole) was diluted to 5.00 ml with ethanol and the starting absorbance at an appropriate wavelength was immediately recorded. The main portion of the reaction mixture was thermostated at a given temperature (±0.1 °C). At chosen times 0.02 ml aliquots were taken out, diluted with ethanol as at starting time and the UV absorbance at the same wavelength was recorded.

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SAŽETAK

N-Metiliranje 2-furilbenztiazola. Utjecaj supstituenata na brzinu kvaternizacije

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Studirana je reakcija metiliranja nekoliko 2-furilbenztiazola koji u furanskoj jezgri i/ili benzo-prstenu sadrže supstituente pozitivnog i/ili negativnog elektronskog efekta (CH_3, Br, Cl). Kao sredstvo za metiliranje korišten je dimetilsulfat, a kao medij suhi dioksan. Brzina reakcije praćena je mjerenjem pada absorbancije kod λ_{max} odgovarajućeg polaznog benztiazola. U uvjetima reakcije pseudo-prvog reda (deseterostruki suvišak sredstva za metiliranje) određene su konstantne brzine reakcije, čiji odnos potvrđuje očekivani utjecaj supstituenata na bazičnost dušika i visoku djelotvornost prijenosa elektronskih efekata unutar 2-furilbenztiazolnog sustava.

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