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Thioamides. XV.[a] Some New Substituted 2-(2- or 3-Furyl)-benzothiazoles. The Preparation and Properties[b]

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A number of 2-substituted benzothiazoles with 2-furyl- (Figure 1.) or 3-furyl- (Figure 2.) group as a substituent were prepared by the oxidative cyclization of corresponding thioanilides. Some of the prepared benzothiazoles were converted to *N*-methyl derivatives with dimethylsulphate. The compounds were isolated as quarternary salts. The influence of substituents on the basicity of the benzothiazole nucleus and on the rate of quarternization was established.

In our earlier papers[1] we had reported on the preparation of several 2-(2--furyl)benzothiazoles by intramolecular oxidative cyclization of corresponding *N*-aryl-2-thiofuramides. These studies ilustrate the usefulness of Jacobson's reaction[2] as a general method for preparation of furylsubstituted benzothiazoles, which like some other benzothiazoles posess bacteriostatic[3] or fungicidal[4] properties, and could be of some other chemotherapeutic or technical use.

Benzothiazoles are the class of heterocycles possesing a weak basic character[5], which is influenced by substituents according to their electronic effect. After alkylation benzothiazoles can give quarternary salts[6] which are of interest in the industrial syntheses of some colours. Surprisingly, there are only a few examples of (2-furyl)[6a] and none of (3-furyl) substituted benzothiazole quarternary salt described so far. Regarding furylbenzothiazoles one can find mostly 2-furyl derivatives described in literature, and to the best of our knowledge there are just a few examples in which 3-furyl substituent have appeared[7].

Our interest in the chemistry of benzothiazoles[1] especially those with furyl substituents has prompted us to investigate 2-(3-furyl)benzothiazoles regarding their basicity and reactivity in comparison with those having 2-furyl group as a substituent. The attention in this paper has been payed to the preparation of several 2-substituted benzothiazoles with a substituted or unsubstituted 2- or 3-furyl group as a substituent. (Figures 1. and 2.)

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[a] Part XIV.: D. Petrova and K. Jakopčić, *Croat. Chem. Acta* **48** (1976) 319. Simultaneously XIX. Part of the Studies in Furan Series. For Part XVIII. see: G. Karminski-Zamola and K. Jakopčić, *Glasnik hem. i tehnol. B i H* 25 (1978) 19.

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

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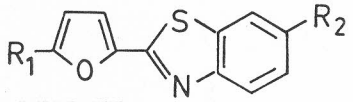
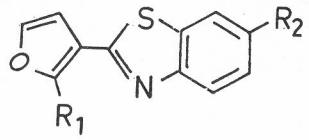


$R_1 = CH_3$, Br
$R_2 = H$, CH_3, Br, Cl

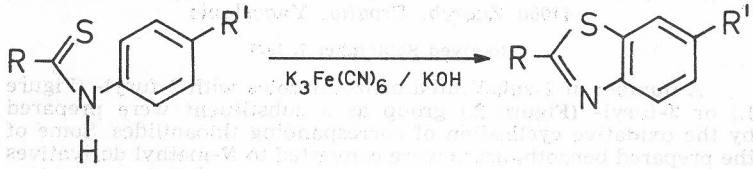
Figure 1.



$R_1 = H$, CH_3
$R_2 = H$, CH_3, Cl

Figure 2.

All benzothiazoles (Figure 1. and Figure 2., Table V. and VI.) were prepared using corresponding *N*-arylthioamides as a starting material according to scheme 1.:



R = 5-Methyl-2-furyl-; 5-Bromo-2-furyl-; 3-Furyl-; 2-Methyl-3-furyl-.
R′ = H, CH_3, Br, Cl.

Scheme 1.

Unlike relatively numerous examples of thioamides derived from 2-furancarboxylic acid[8] only a limited number of corresponding compounds derived from isomeric 3-furancarboxylic acid have been described so far[9], although one could assume that some specific characteristics existed. A report about the fungicidal and insecticidal activity of several 3-furancarboxylic acid derivatives[9,10] gave us an additional reason for the preparation of some new *N*-aryl--3-furanthiocarboxamides (Table IV.) not only as a starting material for benzothiazole synthesis, but as potentially biologically active compounds as well.

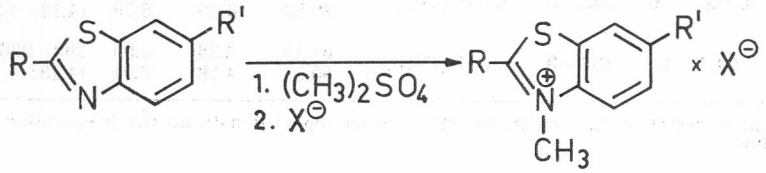
All 2- and 3-furanthiocarboxamides (Table III. and IV.) were synthetized by thionation of corresponding, mostly unknown, amides[a] (Table I. and II.) with phosphorus pentasulphide[13] according to the reported procedure[14]. The structure of the prepared thiofuramides was confirmed by ^{1}H NMR spectra. Apart from the broad signal at 8.40—9.20 ppm (*N—H* proton of monosubstituted thioamide group), signals of the CH_3 group located as singlets at 2.33—2.36 ppm for 5-methyl-2-furyl group and 2.53—2.66 ppm for 2-methyl-3-furyl group respectively were most useful.

Prepared *N*-aryl-thiofuramides were heterocyclized to corresponding 2-furylbenzothiazole (Table V. and VI.) by alkaline ferricyanide[2]. The structure of synthetized 2-furylbenzothiazoles was confirmed by ^{1}H NMR spectra. Signals of CH_3 groups located as singlets at 2.40—2.50 ppm for 2-(5-methyl-2-furyl) or 2.44—2.73 ppm for 2-(2-methyl-3-furyl) group, and 2.50—2.70 ppm for 6-methyl group respectively proved to be most useful.

[a] Prepared from corresponding acid cloride and amine by Schotten-Baumann or some other known[11,12], but modified procedure.

It turns out that some of the prepared benzothiazoles, i. e. 2-(2-methyl-3--furyl)benzothiazole (XXX) and 6-methyl-2-(2-methyl-3-furyl)benzothiazole (XXXI) gave stable hydrochlorides[a]. Comparing this fact with the impossibility of isomeric 5-methyl-2-furylbenzothiazole doing the same, we concluded that the positive electronic effect of the methyl group close to the thiazole nucleus in these compounds substantially increase electronic density on thiazole nitrogen. This assumption was in agreement with the fact that we were not able to prepare stabile hydrochlorides from similar benzothiazoles with the methyl group apart from nitrogen, or having a substituent with a negative electronic effect.

In the reaction with dimethylsulphate, the investigated 2-furylbenzothiazoles gave quarternary salts (Scheme 2.):



R = 5-Methyl-2-furyl-; 5-Bromo-2-furyl-; 3-Furyl-; 2-Methyl-3-furyl-.
R′ = H; CH_3; Br; Cl.
X^- = $CH_3SO_4^-$; J^-; ClO_4^-.

Scheme 2.

Quaternary salts prepared by the modified procedure of Kiprianov and Schulezhko[6a] were identified as methosulphate, iodide or perchlorate (Table VII.) The ^1H NMR spectra of methosulphates exhibit a sharp singlet at 4.35—4.50 ppm due to the N—CH_3 group.

In the early stage of these experiments we observed a substantial difference in the rate of quarternization depending not only on temperature and concentration of dimethylsulphate, but also on the nature and position of the substituent. This was in an agreement with the mentioned fact that basicity of the benzothiazole nucleus is greatly influenced by the substituent on the thiazole nucleus.

Our studies of the influence of substituents on the rate of benzothiazole quarternization will be the subject of an other paper in this series.

EXPERIMENTAL

The melting and boiling points are uncorrected. The UV spectra were recorded on a Perkin-Elmer 124 spectrophotometer using ethanolic solutions. The ^1H NMR spectra were recorded on a Varian T 60 spectrometer. Chemical shifts are given in ppm. with TMS as internal standard.

General Procedures

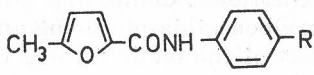
The Preparation of Furamides. (I—VII)

The furamides (Table I. and II.) were prepared by dropwise addition of corresponding acid chloride (in some instances as etheral solution) with stirring and cooling into a slight excess of an amine in 10% aqueous sodium hydroxide. The crude products were purified by crystallization from diluted ethanol.

[a] To the best of our knowledge there are no reports in literature on benzothiazole hydrochlorides.

TABLE I

2-Furamides

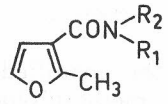


No.	R	Yield %	M. p. °C	Formula	Calc'd / Found Anal. C/%	Calc'd / Found H/%	N/%	UV spectrum λ_{max} (log ε)
I[a]	H	93	95	$C_{12}H_{11}NO_2$	71.63 71.59	5.51 5.35	6.96 7.02	192; 285 (4.22; 4.26)
II	CH_3	90	132—3	$C_{13}H_{13}NO_2$	72.54 72.83	6.09 6.29	6.57 6.76	202; 286 (4.12; 4.33)
III[b]	Cl	89	138—9	$C_{12}H_{10}ClNO_2$	61.15 60.84	4.28 4.18	5.95 6.01	203; 286 (4.18; 4.42)

[a] The comp. is tested as fungicide[9], but there is no reported data on the preparation.
[b] In pyridine.

TABLE II

3-Furamides



No.	R_1	R_2	Yield %	M. p. °C	Formula	Calc'd / Found Anal. C/%	Calc'd / Found H/%	N/%	UV spectrum λ_{max} (log ε)
IV[a]	H	CH_3	43	37—8	$C_7H_3NO_2$	60.40 60.40	6.52 6.46	10.07 10.33	213; 237 (sh) (3.88; 3.68)
V[b]	H	CH_2—C_6H_5	79	96—7	$C_{13}H_{13}NO_2$	72.54 72.80	6.09 6.13	6.51 6.72	210; 237 (sh) (4.22; 3.85)
VI[c]	C_2H_5	C_2H_5	83	32[d]	$C_{10}H_{15}NO_2$	66.28 66.22	8.34 8.19	7.73 7.82	212; 237 (sh) (3.93; 3.55)
VII[e]	CH_3	C_6H_5	90	67—8	$C_{13}H_{13}NO_2$	72.54 72.63	6.09 6.33	6.51 6.52	202; 244 (4.12; 3.83)

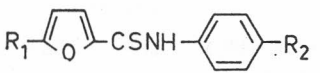
[a] In 1,2-dichloroethane.
[b] The comp. is tested as fungicide[9], but there is no reported data on the preparation.
[c] In dry benzene with substantial excess of diethylamine.
[d] B. p. 114—115/5 mm.
[e] In pyridine.

The Preparation of Thiofuramides. (VIII—XXI)

To a solution of an appropriate 2- or 3-furamide (3—20 mmol) in dry pyridine or dry dioxane (comp. XI and XII), phosphorus pentasulphide (0.7—1.0 mol pro mol of an amide) was added. The reaction mixture was heated 20—120 minutes near boiling point and poured into 5—10 ml of warm water. If there was no crystallization even after cooling, the oil was taken into ether, the organic layer separated and after drying with anhydrous magnesium sulphate the solvent evaporated. After such procedures all thiofuramides (Table III. and IV.) except VIII and XIV which

TABLE III

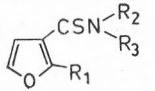
2-Thiofuramides



No.	R_1	R_2	React. time / min	Yield / %	M. p. / °C	Formula	Anal. C/%	Calc'd Found H/%	N/%	UV spectrum λ_{max} (log ε)
VIII	CH_3	H	45	81	70	$C_{12}H_{11}NOS$	66.32 66.61	5.10 5.38	6.45 6.08	203; 228(sh); 322 (4.15; 3.95; 4.34)
IX	CH_3	CH_3	120	87	84—5	$C_{13}H_{13}NOS$	67.55 67.71	5.66 5.71	6.05 6.01	199; 228(sh); 322 (4.24; 3.93; 4.32)
X	CH_3	Cl	120	100	98—9	$C_{12}H_{10}ClNOS$	61.15 60.84	4.28 4.18	5.95 6.01	199; 231; 323 (4.18; 3.94; 4.31)
XI	Br	Br	20	67	95	$C_{11}H_7Br_2NOS$	36.60 36.88	1.95 1.78	3.90 3.61	204; 233; 318 (4.16; 4.04; 4.33)
XII	Br	Cl	20	35	84—5	$C_{11}H_7BrClNOS \times 2H_2O$	40.57 40.62	2.79 2.81		199; 231(sh); 304 (4.29; 3.87; 4.18)

TABLE IV

3-Thiofuramides

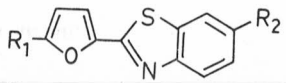


No.	R_1	R_2	R_3	React. time min.	Yield %	M. p. °C	Formula	Anal. C/%	Found Calc'd H/%	N/%	UV spectrum λ_{max} (log ε)
XIII	H	C_6H_5	H	60	79	89—90	$C_{11}H_9NOS$	64.99 64.70	4.46 4.71	6.89 6.63	207; 253 (4.35; 4.09)
XIV[a]	CH_3	H	H	60	82	100—101	C_6H_7NOS	51.04 50.79	4.99 5.24		208; 269; 299 (4.14; 3.87; 3.88)
XV	CH_3	CH_3	H	40	100	oil[b]	C_7H_9NOS	54.17 53.88	5.84 5.57		210; 226(sh); 270 (3.94; 3.69; 3.90)
XVI	CH_3	$CH_2C_6H_5$	H	120	55	70—71	$C_{13}H_{13}NOS$	67.51 67.34	5.66 5.52	6.05 5.85	207; 275 (4.31; 2.97)
XVII[b]	CH_3	C_6H_5	H	90	81	69—72	$C_{12}H_{11}NOS$	66.32 66.03	5.10 5.26	6.45 6,61	203; 213(sh); 296 (4.34; 4.30; 4.05)
XVIII	CH_3	*p*-$CH_3C_6H_4$	H	60	77	69—70	$C_{13}H_{13}NOS$	67.50 67.69	5.66 5.89	6.05 5.95	206; 293 (4.31; 4.05)
XIX	CH_3	*p*-Cl—C_6H_4	H	90	80	120—121	$C_{12}H_{10}ClNOS$	57.26 57.49	4.01 4.15	5.56 5.51	203; 305 (4.30; 4.11)
XX	CH_3	C_2H_5	C_2H_5	40	73	oil[d]	$C_{10}H_5NOS$	60.85 61.07	7.67 7.80		209; 227(sh); 283 (3.84; 3.53; 3.93)
XXI	CH_3	C_6H_5	CH_3	60	87	75—76	$C_{13}H_{13}NOS$	67.51 67.24	5.66 5.66	6.05 5.97	202; 294 (4.27; 4.17)

[a] Prepared also via nitrile.
[b] B. p. 150—155 °C/6 mmHg.
[c] The comp. is tested as fungicide[9], but there is no reported data on the preparation.
[d] B. p. 134—136 °C/5 mmHg.

TABLE V

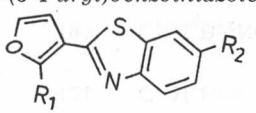
2-(2-Furyl)benzothiazoles



No.	R_1	R_2	Start. Comp.	Yield %	M. p. °C	Formula	Anal. Calc'd / Found C/%	Anal. Calc'd / Found H/%	Anal. Calc'd / Found N/%	UV spectrum λ_{max} (log ε)
XXII	CH_3	H	VIII	90	101—2	$C_{12}H_9NOS$	66.94 66.77	4.22 4.52	6.51 6.25	210; 225; 328 (4.17; 3.40; 4.41)
XXIII	CH_3	CH_3	IX	89	85—6	$C_{13}H_{11}NOS$	68.06 67.78	4.84 4.87	6.11 5.79	213; 231(sh); 334 (4.22; 4.06; 4.43)
XXIV	CH_3	Cl	X	67	148	$C_{12}H_8ClNOS$	57.72 57.74	3.28 3.00		202; 216; 332 (4.45; 4.40; 4.36)
XXV	Br	H	ref. 14.	75	128—9	$C_{11}H_6BrNOS$	47.16 47.25	2.16 2.14	5.00 4.85	209; 223(sh); 325 (4.36; 4.10; 4.42)
XXVI	Br	CH_3	ref. 14.	80	124	$C_{12}H_8BrNOS$	48.99 48.77	2.74 2.64	4.76 4.56	213; 228(sh); 331 (4.26; 4.02; 4.42)
XXVII	Br	Br	XI	80	190	$C_{11}H_5Br_2NOS$	36.79 36.95	1.40 1.49	3.90 3.93	215; 330 (4.12; 4.24)
XXVIII	Br	Cl	XII	90	177—8	$C_{11}H_5BrClNOS$	42.00 43.20	1.60 1.80		201; 216; 331 (4.67; 4.54; 4.50)

TABLE VI

2-(3-Furyl)benzothiazoles

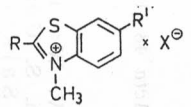


No.	R_1	R_2	Start. Comp.	Yield %	M. p. °C	Formula	Anal. / Calc'd / Found	C/%	H/%	N/%	UV spectrum λ_{max} (log ε)
XXIX	H	H	XIII	86	94—5[a]	$C_{11}H_7NOS$	Calc'd	65.66	3.51	—	217; 289
							Found	65.60	3.31	—	(4.44; 4.16)
XXX[b]	CH_3	H	XVII	62	176—8[c]	$C_{12}H_9NOS \times HCl$	Calc'd	57.26	4.01	—	201; 220; 295(sh); 303; 315(sh)
							Found	57.31	4.28	—	(4.26; 4.43; 4.19; 4.21; 4.14)
XXXI	CH_3	CH_3	XVIII	90	59—60[d]	$C_{13}H_{11}NOS$	Calc'd	68.06	4.84	—	201; 219; 295(sh); 303; 314
							Found	67.67	5.28	—	(4.20; 4.38; 4.18; 4.20; 4.12)
XXXII	CH_3	Cl	XIX	82	95—6	$C_{12}H_8ClNOS$	Calc'd	57.72	3.23	5.61	202; 222; 296(sh); 304; 316
							Found	57.85	3.46	5.35	(4.28; 4.42; 4.20; 4.21; 4.18)

[a] Picrate (XXIXa), m. p. 154 °C
[b] Hydrochloride (XXXa). The benzothiazole (XXX) is an oil.
[c] Picrate (XXXb), m. p. 165—6 °C.
[d] Hydrochloride (XXXIa), m. p. 182°C.

TABLE VII

N-Methyl-2-furylbenzothiazole Salts



No.	Benzothiazole (Table V and VI)	X	Yield %	M. p. °C	Anal. C/%	Calc'd Found H/%	N/%	UV spectrum λ_{max} (log ε)
XXXIII	(XXII)	CH_3SO_4	67	194				
		I		209				213; 368; (4.53; 4.60)
XXXIV	(XXIII)	CH_3SO_4	65	216	50.68 50.40	4.82 5.09	3.95 3.68	212; 368; (4.24; 4.53)
		I		195—7				200; 214; 369; (4.30; 4.50; 4.54)
XXXV	(XXV)	CH_3SO_4		207—8				
		I	70	230				199; 218; 367; (4.00; 4.11; 4.05)
XXXVI	(XXX)	I	89	203—4	43.71 43.16	3.39 3.50		200; 218; 247(sh); 285; 330 (4.45; 4.45; 3.81; 3.69; 4.16)
XXXVII	(XXXI)	I	78	220				199; 217; 243(sh); 284(sh); 325 (4.44; 4.47; 3.82; 3.72; 3.93)

are oily substances, crystallized and were purified by recrystallization from ethanol.

The Preparation of 2-(2-Furyl- or 3-Furyl)benzothiazoles. (XXII—XXXII)

The warm solution (40—50 °C) of a thioanilide (0.8—8.0 mmol) in aqueous sodium hydroxide (15—200 ml of 10% solution) was added to 20% aqueous potassium ferricyanide at 40—50 °C. After cooling mostly crystalline crude furylbenzothiazole was separated. The compounds were purified by repeated recrystallization from ethanol. In several instances a crude product reprecipitation by dilution of solution in conc. hydrochloric acid preceeded recrystallization.

The Preparation of Quarternary Salts. (XXXIII—XXXVII)

The solution of corresponding benzothiazole (0.5—7.5 mmol) and dimethylsulphate (3 mol per mol of benzothiazole) in xylene (4—10 ml) was refluxed for 0.5—3.0 hr. After cooling crystalline methosulphate of *N*-methylbenzothiazole was separated and recrystallized from ethanol.

For preparation of iodide the obtained methosulphate was treated with saturated solution of potassium iodide, and was recrystallized from ethanol.

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REFERENCES

1. D. Petrova and K. Jakopčić, *Croat. Chem. Acta* **48** (1976) 319 and preceeding papers of this seria.
2. P. Jacobson, *Chem. Ber.* **19** (1886) 1067.
3. See e. g.: P. J. Palmer, R. B. Trogg, and J. V. Warington, *J. Med. Chem.* **14** (1971) 248; T. Suzuki, H. Miyamatsu, S. Ueno, M. Shimizu, and J. Wada, *Yakugaku Zasshi* **94** (1974) 891; H. Saikachi, T. Hisano, and S. Yoshina, *J. Pharm. Soc. Japan* **74** (1954) 1318.
4. Gh. Miron and Gh. Ripeanu, *Comun. acad. rep. populare Romine* **11** (1961) 241.
5. See e. g.: R. M. Acheson, *An Introduction to the Chemistry of Heterocyclic Compounds,* Interscience Publ. Inc., New York (1960), p. 278; A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.* (1948) 2240.
6. a. A. I. Kiprianov and A. A. Schulezhko, *Zh. Obsch. Khim.* **34** (1964) 3932.
   b. H. Quast and E. Schmidt, *Chem. Ber.* **101** (1968) 4012.
   c. E. Balta, *Stud. Cercet. Chim.* **20** (1972) 957.
7. See e. g.: G. E. Ficken and J. D. Kendal, Brit. Patent 899.916, June 27. 1962; cf. *C. A.* **57** (1962) 12497h.
8. See. e. g.: a. Preceeding papers of this seria.
   b. W. Walter and J. Voss in J. Zabicky (Ed) *The Chemistry of Amides,* Interscience Publ., London 1970., p. 383—475.
9. G. A. White and D. G. Thorn, *Pestic. Biochem. Physiol.* **5** (1975) 380.
10. See e. g.: R. A. Davis, B. von Schmelling, E. E. Felauer, and M. Kulka, German Patent 2,006.471, Aug. 27. 1970.; cf. *C. A.* **73** (1970) 108740n; E. H. Pommer and B. Zech, *Pestic. Sci.* **8** (1977) 320.
11. W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.* **69** (1947) 515.
12. N. N. Maxim, *Bull. Soc. Chim. Romania* **12** (1930) 33.
13. E. Klingsberg and D. Papa, *J. Amer. Chem. Soc.* **73** (1951) 4988.
14. V. Hahn, Š. Zupanc, and K. Jakopčić, *Croat. Chem. Acta* **42** (1970) 585.

SAŽETAK

Tioamidi. XV. Novi supstituirani 2-(2- ili 3-furil)benztiazoli. Priprava i svojstva

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Više novih supstituiranih benztiazola s 2-furil- ili 3-furil-skupinama kao supstituentom u položaju 2 (slika 1. odnosno slika 2.) pripravljeno je oksidativnom ciklizacijom odgovarajućih tioanilida. Neki od pripravljenih benztiazola prevedeni su metiliranjem dimetilsulfatom u *N*-metil-derivate koji su izolirani kao kvarterne soli. U radu je istraživan utjecaj supstituenata na bazičnost benztiazola i na brzinu kvaternizacije.

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