SYNTHESES IN THE SERIES OF METHYL-2-FURYLKETONE

XII. (5-NITRO-2-FURYL)-SUBSTITUTED IMIDAZOHETEROCYCLIC COMPOUNDS WITH A COMMON NITROGEN ATOM

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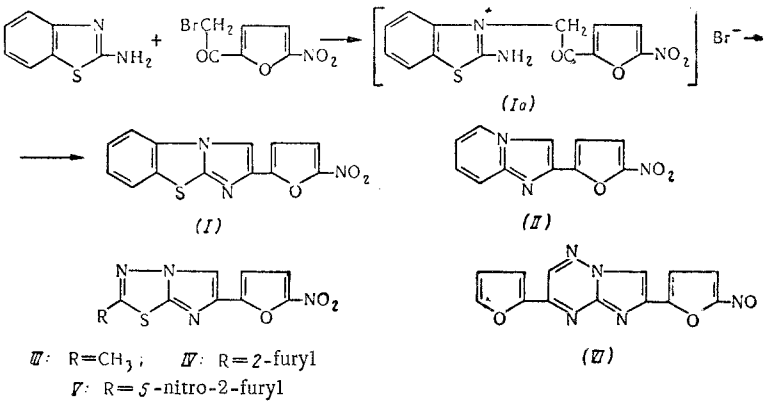
2-(5-Nitro-2-furyl)-substituted imidazo-[1,2-b]-benzothiazole and imidazo-[1,2-a]-pyridine, 6-(5-nitro-2-furyl)-substituted 3-(2-furyl)-imidazo-[1,2-b]-1,2,4-triazine, 2-methyl- and 2-(2-furyl)-imidazo-[2,1-b]-1,3,4-thiadiazoles and also 2,6-di-(5-nitro-2-furyl)-imidazo-[2,1-b]-1,3,4-thiadiazole were obtained from bromomethyl-5-nitro-2-furyl ketone and the corresponding heterocyclic amines with amidine structure. The greatest antimicrobial effect among the imidazo compounds is exhibited by 2-(5-nitro-2-furyl)-imidazo-[1,2-a]-pyridine but in most cases it has a weaker effect than furazolidone.

(5-Nitro-2-furyl)-substituted heterocyclic imidazo compounds with a common nitrogen atom (I-VI) were synthesized in the search for new highly effective chemotherapeutic agents, and their antimicrobial action was studied. These compounds were obtained by the Chichibabin method from bromomethyl-5-nitro-2-furyl ketone and heterocyclic amines with amidine structure,as shown in the example of 2-aminobenzothiazole. In addition to the latter, 2-aminopyridine, 3-amino-5-(2-furyl)-1,2,4-thiazine, 5-methyl-5-(2-furyl)-, and 5-(5-nitro-2-furyl)-substituted 2-amino-1,3,4-thiadiazoles were used in the reaction:



(Ia) (I) (II) (III) (IV) (V) (VI)

III: R=CH_3; IV: R=2-furyl; V: R=5-nitro-2-furyl

Depending on the properties of the amines and the reaction conditions, (5-nitro-2-furyl)-substituted heterocyclic imidazo compounds are formed either directly or the primary reaction products, 5-nitro-2-furacylammonium bromides, are obtained and then transformed into heterocyclic imidazo compounds under certain conditions. For example, from 2-aminobenzothiazole and 2-amino-5-methyl-1,3,4-thiadiazole, boiling with benzene, or a mixture of the latter with ethanol gives a large yield of 2-amino-3-(5-nitro-2-furacyl)-benzothiazolium (Ia) and 2-amino-3-(5-nitro-2-furacyl)-5-methyl-1,3,4-thiadiazoliumbromide (IIIa), respectively, which are stable compounds, which,like other analogous compounds [1, 2], are transformed into the imidazo compounds I and III only by boiling in water or dioxane. At the same time, Ia and IIIa behave differently in acetic acid: Ia is cyclized,by boiling in acetic acid,to I, and IIIa is decomposed, and one of the decomposition products is the initial 2-amino-5-methyl-1,3,4-thiadiazole. With 2-aminopyridine, bromomethyl-5-nitro-2-furyl ketone in dry low-polar solvents (ether, benzene) during cooling forms 2-amino-1-(5-nitro-2-furacyl)-pyridinium bromide (IIa) which even at room temperature and upon

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prolonged standing in these solvents is partly transformed to 2-(5-nitro-2-furyl)-imidazo-[1,2-a]-pyridine (II). The latter is formed from IIa upon boiling with water or ethanol and also in contact with aqueous sodium acetate, the yield in the two last cases being much greater (up to 87% calculated for the bromoketone) than in the synthesis of II from the amine and bromoketone, by boiling in a mixture of ethanol and dimethylformamide (63% calculated for bromoketone) [3-7]. In this case, as in the synthesis of II, III, and V, the conclusions of [8] to the effect that dimethylformamide has a specific weakening effect on the C–Br bond is not confirmed and thus it can be used as a medium for alkylation (i.e., also for the subsequent cyclization to imidazo compounds), with greater effect than the other solvents, for example, ethanol.

The product of the reaction of 3-amino-5-(2-furyl)-1,2,4-triazine with bromomethyl-5-nitro-2-furyl ketone, in accordance with the literature data of [9] may be a derivative either of imidazo-[1,2-b]-1,2,4-triazine (VI) or of imidazo-[2,3-c]-1,2,4-triazine, but we believe the structure VI to be more probable on the basis of the works [10, 11] which have demonstrated the greater reactivity of the N^2 compared with the N^4 triazine ring.

In contradistinction to the 5-methyl derivative, the 5-(2-furyl)- and the 5-(5-nitro-2-furyl)-substituted 2-amino-1,3,4-thiadiazoles, when boiled in ethanol or in a mixture of ethanol and dimethylformamide, form directly the imidazo compounds IV and V. We prepared the 2-amino-5-(2-furyl)-1,3,4-thiadiazole used in the synthesis by oxidation of the thiosemicarbazone of furfurol with potassium ferricyanide (identical with the preparation obtained by reaction of furoylchloride with thiosemicarbazide [12]).

The imidazo compounds I-V are high-melting yellow, shiny laminas; VI is a brownish powder. They are readily soluble in dimethylformamide, sparingly soluble in dioxane and ether, insoluble in water and ethanol. In presence of the furyl group (IV and VI) or a second nitrofuryl group (V), the compounds are sparingly soluble in a mixture of dimethylformamide and water. This circumstance caused difficulties in ascertaining their antimicrobial effect.

As it is shown in Table 1, the greatest antimicrobial effect, close to the effect of furazolidone [13], is exerted by 2-(nitro-2-furyl)-imidazo-[1,2-a]-pyridine (II), hence it was studied in greater detail (Table 2). Imidazothiadiazole V, despite the presence of two nitrofuryl groups, proved to have little activity, not only compared with furazolidone but also with the orginal 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole, which is known as a relatively powerful bacteriostatic agent [14]. The antimicrobial effect was determined by the previously described method [14].

EXPERIMENTAL

2-Amino-3-(5-nitro-2-furacyl)-benzothiazolium Bromide (Ia). To a solution of 2.34 g (10 millimoles) of bromomethyl-5-nitro-2-furylketone in 15 ml of dry benzene, a solution of 1.5 g (10 millimoles) of 2-aminobenzothiazole in 15 ml of the same solvent was added. Two days later, the yellow needles were filtered off, washed with dry ether, and dried over sulfuric acid. Yield 2.74 g (71%), mp 213-214°C. Found %: C 40.94; H 2.83; N 10.70. $C_{13}H_{10}BrN_3O_4S$. Calculated %: C 40.62; H 2.62; N 10.93.

2-Amino-1-(5-nitro-2-furacyl)-pyridinium Bromide (IIa) was prepared in dry ether with ice cooling in analogy to Ia, and filtered after 4 h. Yield 92%, mp 164-165°. Found %: C 40.70; H 3.45; Br 24.49. $C_{11}H_{10}BrN_3O_4$. Calculated %: C 40.26; H 3.07; Br 24.01.

TABLE 1. Antimicrobial Activity of the Nitrofurylimidazo Compounds

Microorganism	Number of strain	Min. conc. of prep. suppressing growth of microbes (μg/ml)			
		I	II	III	V
St. aureus	209	33	17	33	—
Bac. mycoides	537	1	0,5	0,5	—
E. coli	675	>100	12,5	60	>100
Sh. sonnei	5 063	>100	2	100	—
Salm. paratyphi A	290	>100	2	100	—
» » B	493	66	0,7	100	—
» typhi	4 446	100	2	100	>100

2-Amino-5-methyl-3-(5-nitro-2-furacyl)-1,3,4-thiadiazolium Bromide (IIIa). 1.15 g (10 millimoles) of 2-amino-5-methyl-1,3,4-thiadiazole, 2.34 g (10 millimoles) of bromomethyl-5-nitro-2-furylketone, 60 ml benzene and 30 ml ethanol were boiled for 2 h, and the precipitate filtered and washed with ether. Yield 3./5 g (96%), mp 232-233°. Found %: C 31.17; H 2.79; N 16.00. $C_9H_9BrN_4O_4S$. Calculated %: C 30.91; H 2.59; N 16.07.

2-(5-Nitro-2-furyl)-imidazo-[1,2-c])benzothiazole (I). A. 1 g of Ia and 700 ml ethanol are boiled for 30 min, cooled, and the yellow needles filtered off. Mp 249-250° (with decomposition).

TABLE 2. Antimicrobial Effect of 2-(5-nitro-2-furyl)-imidazo-[1,2-a]-pyridine (II) and Furazolidone

Microorganism	Number of strain	Min. conc. of prep., which depresses growth of microbes (μg/ml)		Microorganism	Number of strain	Min. conc. of prep., which depresses growth of microbes (μg/ml)	
		II	Furazolidone			II	Furazolidone
Shigella flexneri, т. 2-a	170	2	—	Salm. newport	5 761	4,1	—
» т. 2-a	337	2	—	» thomson	2 988	0,52	—
» »Sergeev	с/№	0,52	—	» enteritidis v. dublin	с/№	2	—
Shigella sonnei	714	4,1	0,41	» typhimurium . . .	с/№	0,52	—
» Stuzeri—Schmitzii	128	2	—	» »	4 867	1,04	—
» Boydii, т. I . . .	196	2	—	» »	5 591	66,6	—
» sonnei	5 063	2	0,2	Escherichia coli . . .	675	12,5	2
Salm. paratyphi A	290	2	0,83	» »	M-17	0,52	3,1
» » B	493	0,7	0,83	» »	3 535	16,6	12,5
» typhi	1 203	1,04	0,41	Bacilus aerogenes . .	3 545	0,26	8,3
» »	16 103	0,26	0,83	Proteus vulgaris . . .	1	100	33,3
» »	4 446	2	8,3	» »	5	66,6	33,3
» abortus equi . . .	с/№	2	—	» »	с/№	66,6	50
» anatum	378	2	—	» mirabilis	56/10	66,6	33,3
» enteritidis gartneri	с/№	3,1	—	» rettgeri	37/1	2	6,2
» london	9 005	2	—	» morgannii	723	50	25

B. 1 g of Ia is dissolved in 250 ml of boiling acetic acid. Following treatment of the solution with charcoal and cooling, 0.55 g (75%) of I is filtered off. Mp 250-251° (decomp.). Found %: C 54.83; H 2.49; S 10.93. $C_{13}H_7N_3O_3S$. Calculated %: C 54.72; H 2.47; S 11.24.

2-(5-Nitro-2-furyl)-imidazo-[1,2-a]-pyridine (II). A. 0.98 g of IIa is boiled 20 min in 5 ml water and the precipitate filtered. Yield 0.45 g (66%), mp 242°. After recrystallization from ethanol, mp 255°. Found %: C 57.34; H 3.28; N 18.24. $C_{11}H_7N_3O_3$. Calculated %: C 57.64; H 3.08; N 18.34. UV spectrum (in ethanol), λ_{max}, mμ (log ε): 233 (4.38); 280 (3.81); 370 (4.16).

B. 2.34 g (10 millimoles) of bromomethyl-5-nitro-2-furylketone, 0.94 g (10 millimoles) of 2-aminopyridine in 50 ml dry ether are left standing for 24 h, the ether is decanted and the residue boiled with 500 ml of ethanol, the solution treated with charcoal, cooled, and II filtered off. Yield 70-80%, mp 254.5-255°.

C. The precipitate of technical IIa, obtained as described in the experiment (A), is mixed for 30 min with a solution of 5 g crystalline sodium acetate in 20 ml water and II filtered off. Yield 2 g (87% calculated for bromoketone), mp 242-245°. After recrystallization from ethanol or acetic acid, mp 255°.

2-Methyl-6-(5-nitro-2-furyl)-imidazo-[2,1-c]-1,3,4-thiadiazole (III). 1 g IIIa and 30 ml water are boiled for an hour and III filtered off. Yield 0.6 g (83%), mp 262-263° (decomp.). After recrystallization from dioxane mp 262-264° (decomp.). Found %: C 43.20; H 2.50; S 12.90. $C_9H_6N_4O_3S$. Calculated %: C 43.20; H 2.42; S 12.81. UV spectrum (in ethanol) λ_{max}, mμ (log ε): 369 (3.88).

2-Amino-5-(2-furyl)-1,3,4-thiadiazole. 29 g (0.088 mole) of potassium ferricyanide, 25 g (0.18 mole) of crystalline sodium acetate, 200 ml water and 6.76 g (0.04 mole) of the furfurol thiosemicarbazone are mixed 6 h at 60-80°, the precipitate filtered off and washed with water. Yield 6.65 g (~100%), mp 230°. Following precipitation from dimethylformamide solution with water, mp 238-240° (238-239°) [12].

6-(5-Nitro-2-furyl)-2-(2-furyl)-imidazo-[2,1-c]-1,3,4-thiadiazole (IV). A. To a solution of 0.98 g (5.9 millimoles) of 2-amino-5-(2-furyl)-1,3,4-thiadiazole in 7 ml dimethylformamide, add a solution of 1.38 g (5.9 millimoles) of bromomethyl-5-nitro-2-furylketone in 7 ml ethanol, heat the mixture 2 h on the water bath, dilute with 50 ml water and filter off 0.54 g (28%) of IV. Mp 275-276° (decomp., from dioxane). Found %: C 47.83; H 2.16; S 10.42. $C_{12}H_6N_4O_4S$. Calculated %: C 47.68; H 2.00; S 10.61.

B. If the same quantities of the same reagents are boiled 2 h in 70 ml ethanol, the yield of IV is 34%, mp 276-278° (decomp.).

2,6-Di(5-nitro-2-furyl)-imidazo-[2,1-c]-1,3,4-thiadiazole (V). Mix solutions of 2.12 g (10 millimoles) of 2-amino-5-(5-nitro-2-furyl)-1,3,4- thiadiazole in 20 ml dimethylformamide and 2.57 g (11 millimoles)

of bromomethyl-5-nitro-2-furylketone in 15 ml ethanol, boil 5 h, let stand overnight, filter off the precipitate and wash with ethanol. Yield 1.3 g (40%), mp 283° (decomp.). By dilution of the filtrate with water precipitate 1.74 g of the reaction product with mp 140-160° (decomp.), from which an additional quantity of V with mp 283-286° (decomp., from dimethylformamide) is obtained by boiling with 50 ml water and crystallization from dimethylformamide. Found %: C 41.79; H 1.63; S 8.96. $C_{12}H_5N_5O_6S$. Calculated %: C 41.50; H 1.45; S 9.23.

6-(5-Nitro-2-furyl)-3-(2-furyl)-imidazo-[1,2-c]-1,2,4-triazine (VI). 0.81 g (5 millimoles) of 3-amino-5-(2-furyl)-1,2,4-triazine, 1.28 g (5.5 millimoles) of bromomethyl-5-nitro-2-furylketone, 5 ml dimethylformamide and 5 ml ethanol are heated 4 h on the water bath, the precipitate is filtered off and washed with boiling ethanol. Mp > 300°. Found %: C 52.62; H 2.51. $C_{13}H_7N_5O_4$. Calculated %: C 52.53; H 2.37.

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