SYNTHESIS AND ANTITUBERCULOSIS ACTIVITY OF SOME 2-(5-NITRO-2-FURYL)VINYL DERIVATIVES OF PYRIDAZINE AND s-TRIAZOLO[4,3-b]PYRIDAZINE

I. B. Lundina, N. N. Frolova,
I. Ya. Postovskii, A. V. Bedrin,
and N. N. Vereshchagina

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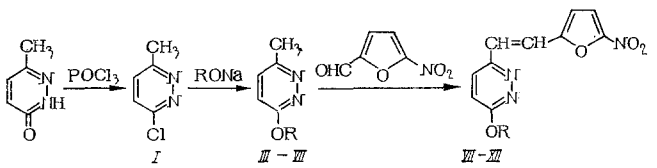
Many nitrofurylidene derivatives display antimicrobial action [1-3]. It was of interest to us to synthesize a number of 2-(5-nitro-2-furyl)vinyl derivatives of pyridazine and check their antituberculosis activity. The choice of heterocycle was brought about by the presence of physiological activity, including antituberculosis activity, in a number of derivatives [4, 5] and by the possibility of obtaining pyridazine compounds with various substituents. For example, the introduction of a homologous series of OR groups as substituents, where R = CH_3, C_2H_5, C_3H_7, C_4H_9, or C_5H_{11}, would make it possible to follow the change in physiological activity as a function of the length of R.

The synthesis of the 3-alkoxy-6-[2-(5-nitro-2-furyl)vinyl]pyridazines (VIII-XII) was carried out by the scheme



The compounds VIII-XII were obtained upon boiling the 3-alkoxy-6-methylpyridazines (III-VII) with 5-nitro-2-furfural in acetic anhydride. 3-Chloro-6-methylpyridazine (I) was synthesized by the procedure of [6], using a refined method. The products III-VII were obtained by boiling I with the appropriate alkoxides in the corresponding alcohols (Tables 1 and 2).

It seemed of interest also to synthesize compounds in which the 2-(5-nitro-2-furyl)vinyl group was removed from the OR substituent in the pyridazine ring. This could be done by preparing appropriate derivatives of biheterocyclic compounds in which the pyridazine ring was condensed with another heterocycle. In the 6-alkoxy-1-methyl-s-triazolo[4,3-b]pyridazines (XIV-XVIII), the methyl group at which the condensation with nitrofurfural is performed is remote from the limits of the pyridazine ring, and is thereby moved away from the OR group. Moreover, the triazole ring which is annelated with the pyridazine ring causes changes in the electronic structure of the pyridazine, breaking up its aromatic character.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Sverdlovsk Tuberculosis Scientific Research Institute, Ministry of Public Health, RSFSR. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 4, pp. 13-17, April, 1972. Original article submitted November 16, 1970.

TABLE 1. 3-Alkoxy-6-methylpyridazines

Compound	R	Yield (in %)	bp (in deg)	Found (in %)			Empirical formula	Calc. (in %)		
				C	H	N		C	H	N
III	CH_3	59	209—12 212—5 [8]	—	—	—	$C_6H_8N_2O$	—	—	—
IV	C_2H_5	60	224—6 229—31 [8]	—	—	—	$C_7H_{10}N_2O$	—	—	—
V	iso-C_3H_7	43	125—6(32mm)	—	—	—	$C_8H_{12}N_2O$	—	—	—
Picrate		—	153—4[1] (from alcohol)	44,52	4,21	18,71	$C_8H_{12}N_2O \cdot C_6H_3N_3O_7$	44,09	3,94	18,37
VI	C_4H_9	68	244—6	—	—	—	$C_9H_{14}N_2O$	—	—	—
Picrate		—	136—8[1] (from alcohol)	46,04	4,20	17,98	$C_9H_{14}N_2O \cdot C_6H_3N_3O_7$	45,57	4,30	17,72
VII	iso-C_5H_{11}	60	140—2(15mm)	—	—	—	$C_{10}H_{16}N_2O$	—	—	—
Picrate		—	137—9[1] (from alcohol)	47,29	4,29	17,16	$C_{10}H_{16}N_2O \cdot C_6H_3N_3O_7$	46,94	4,65	17,12

[1] mp (in deg.)

TABLE 2. 3-Alkoxy-6-[2-(5-nitro-2-furyl)vinyl]pyridazines and Their Tuberculostatic Activity (in μg/ml)

Compound	R	Yield (in %)	mp (in deg)	Found (in %)			Empirical formula	Calc. (in %)			Bacteriostatic titer in Soton medium (K_1 strain)	
				C	H	N		C	H	N	without serum†	with serum
VIII	CH_3	70	196—7 (from alcohol)	53,34	3,88	17,02	$C_{11}H_9N_3O_4$	53,44	3,64	17,00	0,25	2,0
IX	C_2H_5	65	157—8 (from alcohol)	55,43	4,47	16,75	$C_{12}H_{11}N_3O_4$	55,17	4,21	16,92	0,25	2,0
X	iso-C_3H_7	76	175—7 (from alcohol)	57,01	4,90	15,02	$C_{13}H_{13}N_3O_4$	56,73	4,73	15,27	2,00	4,0
XI	C_4H_9	54	117—9 (from alcohol)	58,21	5,61	14,54	$C_{14}H_{15}N_3O_4$	58,13	5,19	14,88	0,25	4,0
XII	iso-C_5H_{11}	60	121—3 (from aqueous alcohol)	59,40	5,68	14,13	$C_{15}H_{17}N_3O_4$	59,41	5,61	13,86	2,00	2,0
XIII[1]*	C_2H_5	50	187—8 (from alcohol)	62,33	4,81	15,93	$C_{14}H_{13}N_3O_3$	62,00	4,80	15,50	H Inactive	H Inactive

* Instead of the 5-nitro-2-furyl residue, compound XIII contains a p-nitrophenyl residue (see structural formula for VIII-XII).

†In the investigation of activity in Soton medium without serum, the activity at low concentrations of materials was not determined.

TABLE 3. 6-Alkoxy-1-methyl-s-triazolo[4,3-b]pyridazines

Compound	R	Yield (in %)	mp (in deg)	Found (in %)			Empirical formula	Calc. (in %)		
				C	H	N		C	H	N
XIV	CH_3	86	166—8 (166[7])	—	—	—	$C_7H_8N_4O$	—	—	—
XV	C_2H_5	70	135—7 (from water)	54,41	5,79	31,88	$C_8H_{10}N_4O$	53,93	5,61	31,46
XVI	iso-C_3H_7	51	108—10 (from petroleum ether)	56,48	6,32	29,10	$C_9H_{12}N_4O$	56,25	6,25	29,17
XVII	C_4H_9	66	70—2 (from butyl alcohol)	57,93	6,62	—	$C_{10}H_{14}N_4O$	58,25	6,79	—
XVIII	iso-C_5H_{11}	50	77—9 (from ether)	59,64	7,49	25,57	$C_{11}H_{16}N_4O$	60,00	7,27	25,45

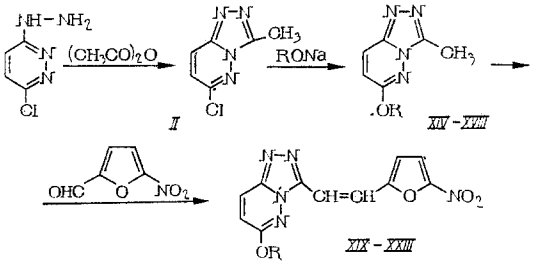
TABLE 4. 6-Alkoxy-1-[2-(5-nitro-2-furyl)vinyl]-s-triazolo[4,3-b]pyridazines and Their Tuberculostatic Activity (in μg/ml)

Compound	R	Yield (in %)	mp (in deg)	Found (in %)			Empirical formula	Calc. (in %)			Bacteriostatic titer in Soton medium (K_1 strain)	
				C	H	N		C	H	N	without serum	with serum
XIX	CH_3	49	255—7 (from alcohol)	50,58	3,45	24,46	$C_{12}H_9N_5O_4$	50,17	3,14	24,39	2,0†	2,0
XX	C_2H_5	55	229—31 (from acetone)	51,85	3,80	23,84	$C_{13}H_{11}N_5O_4$	51,82	3,65	23,25	2,0†	2,0
XXI	iso-C_3H_7	28	228—9 (from alcohol)	52,89	4,37	22,02	$C_{14}H_{13}N_5O_4$	53,33	4,13	22,22	62,0	250,0
XXII	C_4H_9	25	164—6 (from alcohol, from water)	54,50	4,24	21,74	$C_{15}H_{15}N_5O_4$	54,71	4,56	21,28	10,0	31,0
XXIII	iso-C_5H_{11}	24	138—40 (from alcohol, from water)	56,22	5,14	20,02	$C_{16}H_{17}N_5O_4$	55,98	4,94	20,41	2,0†	2,0
XXIV *	C_2H_5	70	243—4 (from dimethyl-formamide)	57,77	4,22	22,61	$C_{15}H_{13}N_5O_3$	57,88	4,21	22,51	500,0	Inactive

*Instead of the 5-nitro-2-furyl residue, compound XXIV contains a p-nitrophenyl residue (see structural formula for XIX-XXIII).

†In the study of activity in Soton medium without serum, activity for these compounds at low concentrations of material was not determined.

The 6-alkoxy-1-[2-(5-nitro-2-furyl)vinyl]-s-triazolo[4,3-b]pyridazines (XIX-XXIII) were prepared similarly to compounds VIII-XII (Tables 3 and 4). Their synthesis was effected by the scheme:



6-Chloro-1-methyl-s-triazolo[4,3-b]pyridazine (II) was synthesized by the procedure of [7]. For comparison, condensation products of compounds IV and XV with p-nitrobenzaldehyde were prepared (XIII and XXIV).

Investigation of the tuberculostatic activity of the synthesized materials in vitro was conducted in synthetic Soton medium and concurrently in the same medium with addition of 10% normal native serum. Human type H_1 strain of the tuberculosis mycobacterium was used. For certain compounds, a study was also conducted using the Academia-type strain of tuberculosis mycobacterium.

As a result of the studies, it was shown (see Tables 2 and 4) that all the synthesized compounds which contain the 5-nitrofuryl residue possess definite antitubercular activity, both in the medium without serum and also in the presence of serum. When the 5-nitrofuryl residue is replaced by a p-nitrophenyl group, (XIII or XXIV), the antitubercular activity disappears. The structure of the alkoxy group in the pyridazine ring does not exert a strong effect on the antitubercular activity of the compounds studied, although the tuberculostatic activity is somewhat higher in the compounds where R = CH_3, C_2H_5, or iso-C_5H_{11} (VIII, IX, XII, XIX, XX, or XXIII).

For compounds IX and XX, which showed the greatest activity in experiments in vitro, we determined the toxicity to white mice. These studies showed that 100 mg of preparation XX is tolerable in acute exposure, and daily injection of this preparation in a dose of 30 mg over a two-week period causes no changes in the organs of the animals. The minimum lethal dose of preparation IX is 25 mg for a white mouse weighing 20-21 g.

In treatment of white mice or guinea pigs infected with the H_1 strain of human tuberculosis mycobacterium started on the next day after inoculation and continued for one month, preparations IX and XX showed only a weak therapeutic action.

EXPERIMENTAL*

3-Chloro-6-methylpyridazine (I). This compound was prepared according to [6]. It was obtained in a yield of 90%, having a mp of 60-62° (lit. [6]: 58°), by heating 6-methyl-3-pyridazone with phosphorus oxychloride for 1 h at 70°. If, however, the reaction mixture is heated at 100°, as indicated in [6], the yield of I is reduced, and a substance of mp 207-208° (yellow needles from aqueous alcohol) is formed as a second reaction product; its elemental analysis corresponds to the empirical formula $C_{10}H_9ClN_4$.

3-Alkoxy-6-methylpyridazines (III-VII) and 6-Alkoxy-1-methyl-s-triazolo [4,3-b]pyridazines (XIV-XVIII). A solution of equimolecular amounts of I or II and the appropriate sodium alkoxide in the corresponding alcohol was boiled for 1 h, after which the precipitate of sodium chloride was filtered off, the alcohol was stripped, and the remaining material was distilled and identified in the form of the picrate (V-VII) or was recrystallized (XIV-XVIII). Compounds III and IV were prepared according to [8].

Analyses and mp of the compounds prepared are given in Tables 1 and 3.

3-Alkoxy-6-[2-(5-nitro-2-furyl)vinyl]pyridazines (VIII-XII) and 6-Alkoxy-1-[2-(5-nitro-2-furyl)vinyl]-s-triazolo[4,3-b]pyridazines (XIX-XXIII). A solution of equimolecular amounts of the starting methyl derivative (III-VII) or (XIV-XVIII) and 5-nitro-2-furfural in acetic anhydride was boiled for 4 h. The product which separated on cooling was filtered off and recrystallized.

* D. V. Kiryaeva participated in conducting the experimental part of the work.

Products XIII and XXIV were prepared similarly by condensation of IV or XV with p-nitrobenzaldehyde.

Analyses, mp, and results of testing for antitubercular properties are given in Tables 2 and 4.

LITERATURE CITED

1. S. A. Giller, K. K. Medne, K. K. Venter, et al., Dokl. Akad. Nauk SSSR, 144, No. 1, 108 (1962).
2. N. O. Saldabol, A. Ya. Medne, and S. A. Giller, Zh. Obshch. Khim., 34, 1598 (1964).
3. S. A. Giller, N. O. Saldabol, and A. Ya. Medne, Ibid., 33, 317 (1963).
4. N. B. Galstukhova, G. G. Predvoditeleva, I. M. Berzina, et al., Khim.-Farm. Zh., No. 4, 7 (1969).
5. Japanese Patent No. 1303 (1967); Chem. Abstracts, 66, 76,018 (1967).
6. W. G. Overend and L. J. Wiggins, J. Chem. Soc., 239 (1947).
7. Jakahayashi Naboru, Chem. Abstracts, 50, 8655 (1956).
8. O. Poppenberg, Ber., 34, 3623 (1901).