UDC 547.724+543.39+542.953

SYNTHESIS IN THE FIELDS OF 5-NITROFURYL-2-POLYALKENALS AND 5-NITROFURYL-2-POLYALKENONES. VII*. SYNTHESIS AND INVESTIGATION OF THE ANTIBACTERIAL PROPERTIES OF DERIVATIVES OF α,β-UNSATURATED AND POLYENE ALDEHYDES AND KETONES OF THE 5-NITROFURAN SERIES

S. A. Giller, S. P. Zaeva, K. K. Venter, L. N. Alekseeva, L. V. Kruzmetra, and S. K. Germane

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2, pp. 187-194, 1965

Antibacterial properties and toxicities were determined for 66 compounds of the 5-nitrofuran type to ascertain the connection between structure and biological activity.

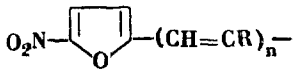
Unsaturated 5-nitrofuran aldehydes and some of their simplest derivatives (acetals, acylals) have high antibacterial activity and a broad spectrum. However, these compounds cannot be used in medicine because of their appreciable toxicities and low stabilities. One of the α,β-unsaturated ketones in this series, 5-nitrofurfurylideneacetone, has a broad antibacterial spectrum combined with lower toxicity. Low-toxicity derivatives of 1-aminohydantoin and 3-amino-2-oxazolid-2-one are among the imino derivatives of high antibacterial activity investigated.

The search for antibacterial substances which, unlike those already known, will act on strains of microorganisms resistant to antibiotics and chemotherapeutic agents of the sulfonamide type and prevent the build-up of resistance, is still a very real problem.

In this respect, the nitrofurans are a comparatively new and promising class of chemotherapeutic compounds, and several of practical importance have already appeared [1-11].

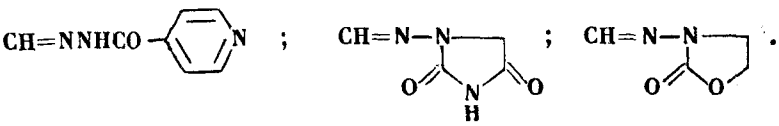
Recently it has been discovered that the introduction of vinylidene groups into the molecules of previously known compounds of this series considerably improves their antimicrobial action. 1-[β-(5'-nitrofuryl-2')acrylideneamino]-hydantoin or Furagin (F-35) is based on this principle and is recommended for medical use. It is the vinylene-olog of 1-(5'-nitrofurfurylideneamino)hydantoin (the known chemotherapeutic agent Furadonin or F-30) [10-14].

Continuing the search in this direction, a study has been made of the antibacterial properties and toxicities of 66 functional derivatives of aldehydes and ketones of the 5-nitrofuran series having different numbers (0-3) of vinylidene groups in the molecule and the general formula I.



I

n = 0-3, R = H, alkyl, alkoxy-methyl; X=CHO; $CH(OC_2H_5)_2$; $CH(OCOCH_3)_2$; $COCH_3$; $COC(CH_3)_3$; $CH=NNHCONH_2$; $CH=NNHCSNH_2$; $CH=NOH$; $CH=NNHCOCH_2CN$;



For the first screening the antibacterial activities of the compounds were determined in vitro for the following test bacteria: Staphylococcus aureus haemolyticus 209, Bac. mycoides No. 1; E. coli 675, Proteus vulgaris No. 1 (Table 1). The antibacterial activities of the compounds F-46, -140, -151, -145, -146, -117, -59, -115, and -124 were also determined for Staphylococcus 1, Staphylococcus NLA, Streptococcus 682, Streptococcus 284, Streptococcus 4879, Streptococcus viridans, Enterococcus (Table 2).

Investigation of unsubstituted 5-nitrofuran aldehydes showed that they definitely inhibit the multiplication of microorganisms. For example, 5-nitrofurfural (NFO), β-(5-nitrofuryl-2)acrolein (F-109), and 5-(5'-nitrofuryl-2')penta-2, 4-diene-1-al (F-116), in concentrations of 0.03-0.15 mg%, inhibit the growth of Staphylococcus aureus haemolyticus 209, Bac. mycoides, E. coli. One of these (F-116) proved quite active against Proteus vulgaris, stopping growth

* For Part VI see [1].

at a concentration of 0.07 mg%. However, these compounds are significantly toxic (e.g., for F-109 LD_{50} = 8.6 mg/kg, for F-116 LD_{50} = 16.5 mg/kg), so that it was not possible to recommend them for more detailed investigation.

TABLE 2

Antibacterial activities of some imino derivatives of unsaturated 5-nitrofuran aldehydes and ketones.

Compound number (name)	Minimum bacteriostatic concentration, mg%						
	Staphylococcus 1	Staphylococcus NLA	Streptococcus 682	Streptococcus 284	Streptococcus 4879	Streptococcus Viridans 1	Enterococcus
F-46 . .	0.1—0.3	0.1—0.2	0.04—0.2	0.7	0.1—0.7	0.3—1.4	0.2—1.4
F-140 .	0.1—0.3	0.1—0.6	0.1—0.6	0.3—0.6	0.3	0.3	0.3—1.1
F-151 . .	0.6	0.3—0.6	0.3—0.6	0.1—0.6	0.6	0.3—0.6	0.1—0.6
F-145 . .	0.9	0.9	0.1	0.2	0.03—0.2	0.1—0.9	0.1—0.2
F-146 . .	0.05	0.05—0.1	0.03—0.05	0.1—0.2	0.2—0.4	0.1—0.2	0.2—0.8
F-117 . .	0.3—0.6	0.6	0.3—0.6	0.3—0.6	0.3—0.6	0.3	0.3—0.6
F-59 . .	0.7	0.3—0.7	2.6	0.7—1.3	1.3—2.6	0.7—2.6	2.6
F-115 . .	0.8—1.6	0.4—0.8	0.8	0.8—3.2	0.8—1.6	1.6	1.6
F-124 . .	0.6	0.2—0.3	0.6—1.2	0.6—1.2	0.6—1.2	0.6—1.2	0.6—1.2

The simplest functional derivatives of the aldehydes, acetals and acylals, also have definite antibacterial activity, though in some cases less than the above compounds. The great disadvantage of these compounds, e.g., β-(5-nitrofuryl-2)acrolein diethylacetal (F-113), 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al diacetate (F-122), and β-(5-nitrofuryl-2)acrolein diacetate (F-114), is their comparatively poor storage stability.

Among the 5-nitrofuran α,β-unsaturated ketones, 5-nitrofurfurylideneacetone (F-105) has a broad antibacterial spectrum and is less toxic (LD_{50} = 174 mg/kg) than other similar compounds.

The derivatives of 1-aminohydantoin and 3-aminooxazolid-2-one are quite promising among the aldehyde and ketone imino derivatives listed in Table 1, and in almost all the series of compounds investigated they exhibit high antibacterial activity and low toxicity.

Among the most active of them are 3-[β-/5'-nitrofuryl-2')acrylideneamino]-oxazolid-2-one (F-46), 1-[α-methyl-β-(5'-nitrofuryl-2')acrylideneamino]-hydantoin (F-140), 1-[α-ethyl-β-(5'-nitrofuryl-2')acrylideneamino]-hydantoin (F-151), 1-[5"-(5'-nitrofuryl-2')penta-2",4"-dienealamino]-hydantoin (F-117), 1-[α-methoxymethyl-β-(5'-nitrofuryl-2')acrylideneamino]-hydantoin (F-145), and 3-[α-methoxymethyl-β-(5'nitrofuryl-2')acrylideneamino]-oxazolid-2-one. (F-146) (Table 2). At concentrations of 0.03-1.4 mg% they inhibit the development of staphylococci and streptococci. At concentrations of 0.3-3.2 mg% the oximes of β-(5-nitrofuryl-2)acrolein (F-59), 5-nitrofurfurylideneacetone (F-115), and 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al (F-124) are quite active in inhibiting growth of many microorganisms. They have a special significance as compared with other 5-nitrofuran derivatives thanks to their solubility in water, better than that of other imino derivatives of the series, and comparatively low toxicity (LD_{50} = 133-170 mg/kg).

Investigation of the effects of substituents in the 5-nitrofuran series of α,β-unsaturated aldehydes showed that introduction of an alkyl group at the α position in β-(5-nitrofuryl-2)acrolein has only an insignificant effect on the antibacterial activities of the derivatives prepared. However, the α-isopropyl derivatives (e.g., compounds F-133 and F-134) unexpectedly showed quite low activity. Introduction of methoxymethyl and ethoxymethyl groups in the α position evidently somewhat increases the antibacterial activity. F-145 and F-146 are evidently the most active of these compounds.

Investigated compounds containing a longer conjugated chain were: 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al and 7-(5'nitrofuryl-2')hepta-2,4,6-triene-1-al.

Almost all compounds of the series investigated possess high antibacterial activity, exhibited towards some forms of microorganisms even at concentrations of 0.1 mg%. But low solubilities in water (under 1:100 000) make the investigation and practical use of many of them difficult.

EXPERIMENTAL

α,β-unsaturated aldehydes and ketones of the 5-nitrofuran series were synthesized by methods previously described [15-18]. A somewhat modified form [19] of the method of preparing 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al and 7-(5'-nitrofuryl-2')hepta-2,4,6-triene-1-al by condensing β-(5-nitrofuryl-2)acrolein acetal and 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al acetal with vinylethyl ether was employed. Some of the derivatives of 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al and 7-(5'-nitrofuryl-2')hepta-2,4,6-triene-1-al are described here for the first time (Table 3).

The method of synthesizing the new compounds of Table 3 is given below.

5-(5'-nitrofuryl-2')penta-2,4-diene-1-al hydrazones. A solution of 1.95 g (0.01 mole) 5-(5'-nitrofuryl-2')penta-2,4-diene-1-al in 100 ml alcohol is heated to 50-60°, and a solution of the appropriate carbonyl reagent added, as fol-

TABLE 1

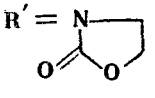
Antibacterial properties of type I derivatives of unsaturated aldehydes and ketones of the 5-nitrofuran series

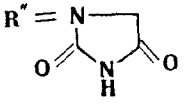
Compound number (name)	n	R	X	Minimum bacteriostatic concentration, mg%				Acute toxicity for white mice, i. p., LD_{50}, mg/kg
				Staphylococcus aureus haemolyticus 209	Bac. mycoides	E. Coli	Proteus vulgaris	
Streptomycin [20]	—	—	—	0.3—10.0				500
Chlortetracycline [20]	—	—	—	0.02—0.05				130
Chloromycetin [20]	—	—	—	0.2—1.0				250
NFO	0	—	CHO	0.05	0.03	0.15	0.8	43 (38—48)
F-111	0	—	$CH(OC_2H_5)_2$	3.3	2.0	3.3	>10.0	300 (273—330)
F-112	0	—	$CH(OCOCH_3)_2$	0.2	0.05	0.2	3.3	70 (40—112)
F-6 (Furacillin)	0	—	$CH=NNHCONH_2$	1.0	1.0	1.0	—	82 (77—88)
F-60 (Furazolidone)	0	—	CH=N—R′*	0.2	0.04	<0.007	0.7	1000 (874—1140)
F-30 (Furadonin)	0	—	CH=N—R″*	1.0—2.0	1.0—2.0	1.0—2.0	—	42 (23—76)
F-109	1	H	CHO	0.13	0.03	0.08	0.4	8.6 (6.1—12)
F-113	1	H	$CH(OC_2H_5)_2$	0.05	0.03	0.1	0.4	18.5 (15.6—21.3)
F-114	1	H	$CH(OCOCH_3)_2$	0.4	0.2	0.8	3.3	34 (26—43)
F-46	1	H	CH=N—R′*	0.3	0.3	0.01	0.1	4000 (3609—4440)
F-35 (Furagin)	1	H	CH=N—R″*	0.4	0.06	0.1	4.5	284 (263—300)
F-59	1	H	CH=NOH	1.05	0.3	0.05	4.1	133 (123—148)
F-105	1	H	$COCH_3$	0.2	0.05	0.1	0.8	174 (112—236)
F-110	1	H	$COC(CH_3)_3$	0.2	0.03	5.0	5.0	215 (176—262)
F-115	1	H	$C(CH_3)=NOH$	0.6	0.4	0.8	5.0	170 (145—199)
F-101	1	H	$C(CH_3)=NNHCONH_2$	>0.5	0.2	>0.5	>0.5	3050 (2618—3482)
F-102	1	H	$C(CH_3)=NNHCSNH_2$	0.2	0.15	1.4	>2.5	190 (155—224)
F-103	1	H	$C(CH_3)=NNHCOCH_2CN$	0.4	1.1	>1.6	>1.6	2750 (2318—3182)
F-107	1	H	$C(CH_3)=NNHCOC_5H_4N$*	0.2	0.08	0.5	>1.0	1000 (671—1329)
F-132	1	CH_3	CHO	1.7	3.3	0.31	1.7	
F-129	1	CH_3	$CH(OCOCH_3)_2$	2.2	1.1	1.1	3.3	
F-138	1	CH_3	$CH=NNHCONH_2$	0.8	0.2	>1.1	>1.1	
F-139	1	CH_3	$CH=NNHCSNH_2$	0.2	0.08	>0.5	>0.5	
F-136	1	CH_3	$CH=NNHCOCH_2CN$	0.2	0.05	0.6	0.6	11400 (10270—11654)
F-123	1	CH_3	$CH=NNHCOC_5H_4N$*	0.4	0.2	>0.6	>0.6	
F-125	1	CH_3	CH=N—R′*	0.1	0.01	0.1	0.1	
F-140	1	CH_3	CH=N—R″*	0.2	0.6	0.6	>1.7	
F-130	1	C_2H_5	$CH(OCOCH_3)_2$	2.2	1.1	2.5	>3.3	380 (314—460)
F-131	1	C_2H_5	$CH=NNHCONH_2$	0.7	0.4	>1.1	>1.1	
F-152	1	C_2H_5	$CH=NNHCSNH_2$	0.4	0.03	3.3	>5.0	

TABLE 1 (continued)

F-154	1	C_2H_5	CH=NNHCOCH$_2$CN	0.08	0.03	3.3	>5.0	
F-153	1	C_2H_5	CH=NNHCOC$_5$H$_4$N*	0.1	0.01	0.21	1.7	1170 (1083–1264)
F-155	1	C_2H_5	CH=N–R′*	0.05	0.03	5.0	>5.0	
F-151	1	C_2H_5	CH=N–R″*	0.28	0.2	8.3	>12.5	
F-133	1	i-C_3H_7	CH=NNHCONH$_2$	>0.2	0.2	>0.3	>0.3	
F-134	1	i-C_3H_7	CH=NNHCSNH$_2$	0.6	>0.6	>0.8	>0.8	
F-135	1	i-C_3H_7	CH=NNHCOCH$_2$CN	0.5	0.5	>0.7	>0.7	
F-137	1	i-C_3H_7	CH=N–R″*	0.3	0.4	>1.7	>1.7	
F-169	1	C_5H_{11}	CH=NNHCOCH$_2$CN	0.1	0.1	0.1	—	
F-108	1	CH_2OCH_3	CHO	3.3	1.7	0.8	3.3	
F-141	1	CH_2OCH_3	CH=NNHCONH$_2$	0.5	0.01	4.1	>6.2	
F-142	1	CH_2OCH_3	CH=NNHCSNH$_2$	0.1	0.01	3.9	>7.8	
F-164	1	CH_2OCH_3	CH=NOH	0.8	0.06	0.8	>5.0	290 (262–342)
F-144	1	CH_2OCH_3	CH=NNHCOCH$_2$CN	0.02	0.02	1.6	>6.3	
F-143	1	CH_2OCH_3	CH=NNHCOC$_5$H$_4$N*	0.05	0.03	1.7	>5.0	1250 (1213–1398)
F-146	1	CH_2OCH_3	CH=N–R′*	0.07	0.15	0.26	8.3	
F-145	1	CH_2OCH_3	CH=N–R″*	1.3	0.5	1.0	>6.3	
F-147	1	$CH_2OC_2H_5$	CH=NNHCONH$_2$	0.2	0.04	4.2	6.3	
F-148	1	$CH_2OC_2H_5$	CH=NNHCOCH$_2$CN	0.05	0.03	3.3	>5.0	
F-149	1	$CH_2OC_2H_5$	CH=N–R″*	0.1	0.1	1.7	>2.5	
F-116	2	H	CHO	0.07	0.07	0.03	0.07	16.5 (14–20)
F-122	2	H	CH(OCOCH$_3$)$_2$	3.3	3.3	0.02	0.05	49 (36–65)
F-119	2	H	CH=NNHCONH$_2$	0.1	0.03	0.3	>0.8	9200 (6345–13340)
F-120	2	H	CH=NNHCSNH$_2$	0.1	0.06	0.2	>0.8	535 (457–626)
F-124	2	H	CH=NOH (melts 194–195°)	0.5	0.1	0.5	>0.7	180 (90–360)
F-127	2	H	CH=NOH (melts 159–160°)	0.3	0.04	0.33	2.0	72 (55–94)
F-126	2	H	CH=NNHCOCH$_2$CN	0.07	0.03	0.07	0.55	6250 (4664–8375)
F-118	2	H	CH=NNHCOC$_5$H$_4$N*	0.2	0.2	0.2	>1.0	1850 (1360–2516)
F-121	2	H	CH=N–R′*	0.1	0.02	0.05	0.01	4600 (4107–5152)
F-117	2	H	CH=N–R″*	0.3–≥0.6	0.2	0.1	>0.5	14000 (12390–15820)
F-156	3	H	CH=NNHCONH$_2$	>1.3	0.03	>0.5	>0.5	
F-157	3	H	CH=NNHCSNH$_2$	0.2	0.03	3.3	>5.0	
F-159	3	H	CH=NNHCOCH$_2$CN	0.1	0.02	>0.5	>0.5	
F-158	3	H	CH=NNHCOC$_5$H$_4$N*	0.005	0.005	0.6	>5.0	
F-161	3	H	CH=N–R′*	0.8	0.13	>0.5	>0.5	
F-160	3	H	CH=N–R″*	0.3	0.08	0.7	>1.0	

* C_5H_4N=4-pyridyl;

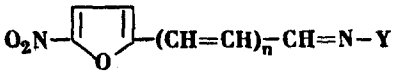


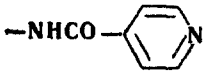
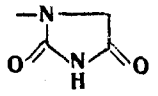
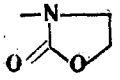
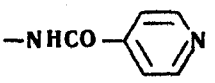
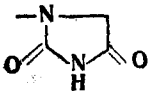
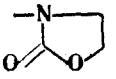


lows: A – 1.00 g (0.01 mole) cyanacetylhydrazide in 10 ml water; B – 1.4 g (0.01 mole) isonicotinoylhydrazide in 20 ml hot 50% alcohol; C – a solution of 1-aminohydantoin sulfate, prepared by cyclizing 1.5 g (0.0113 mole) 2-semicarbazidoacetic acid by heating with a mixture of 6 ml water and 1.8 g concentrated sulfuric acid for 3 hr.

TABLE 3

Imino derivatives of ω-(5-nitrofuryl-2)polyalkenals



n	y	bp, °C	Molecular formula	N, % Found	N, % Calculated	Yield, %
2	—NHCOCH$_2$CN	213—4	$C_{12}H_{10}N_4O_4$	20.71	20.43	98
2		237	$C_{15}H_{12}N_4O_4$	17.80	17.94	90
2		⩾260	$C_{12}H_{10}N_4O_4$	19.31	19.31	85
2		253—4	$C_{12}H_{11}N_3O_5$	14.91	15.16	80
3	—NHCOCH$_2$CN	214	$C_{14}H_{12}N_4O_4$	18.59	18.66	97
3		233	$C_{17}H_{14}N_4O_4$	16.80	16.56	80
3		⩾285	$C_{14}H_{12}N_4O_5$	17.54	17.72	82
3		247	$C_{14}H_{13}N_3O_5$	14.15	13.86	83

* All compounds melt with decomposition.

1-2 drops conc. HCl are also added, to accelerate formation of hydrazones with solution A. Using this method hydrazones are formed very readily and in almost quantitative yield. After holding at room temperature for 2 hr, the hydrazones are filtered off using suction, washed with 100 ml water, 30 ml alcohol, and dried at 100-105°.

3-[5"-(5'-nitrofuryl-2')penta-2", 4", diene-1"-alamino]-oxazolid-2-one (F-121). A mixture of 1.95 g (0.01 mole) 5-(5'-nitrofuryl-2')penta-2, 4-diene-1-al, 2.4 g (0.0126 mole) 3-benzylideneaminooxazoli-2-one, 25 ml water and 0.8 g conc. H_2SO_4 is steam-distilled to remove benzaldehyde. 100 ml alcohol are then added, the mixture heated to boiling under reflux, and then cooled to room temperature. After standing 2 hr, the crystals that have separated are filtered off with suction, washed with 100 ml water, then with 50 ml alcohol, and dried at 100-105°.

7-(5'-nitrofuryl-2')hepta-2, 4, 6-triene-1-al hydrazones are synthesized by methods analogous to those described for 5-(5'nitrofuryl-2')-penta-2, 4-diene-1-al hydrazones.

Antibacterial activity was determined in vitro by series culture in Khottinger's bouillon. Compounds of low solubility in water were first dissolved in dimethylformamide, and before carrying out the test, diluted with an amount of medium such that the resultant dimethyldormamide concentration did not inhibit the growth of the microorganisms.

Acute toxicity was determined by tests on white mice weighing 15-20 g, preparations being injected intraperitoneally. As the compounds studied had low solubilities, they were first wetted with a non-ionic detergent (6% solution of TVIN-80) and then suspended in an isotonic sodium chloride solution.

Preparation doses were reckoned per kg of mouse. Six to nine doses of each compound were tested, using 6 mice per dose. Experimental animals were observed for 72-120 hr from the moment of injecting the compound and the number of fatalities determined. The resultant experimental material was treated statistically by Litchfield's graphical test-analysis method with P = 0.05, and the LD_{50} values and their confidence limits were calculated.

REFERENCES

1. S. A. Giller, K. K. Medne, K. K. Venter, S. K. Germane, and A. Ya. Zile, DAN, 144, 108, 1962.
2. S. A. Giller, Collection: Furacillin and Experiments on its Applications [in Russian], Izd-vo AN Latv. SSR, Riga, 7, 1953.
3. S. A. Giller, Collection: Problems of Using Pentosan-Containing Raw Materials [in Russian], Izd-vo AN Latv. SSR, Riga, 451, 1958.
4. A. F. Blyuger, The Nitrofurans and Their Use in Medicine [in Russian], Izd-vo AN Latv. SSR, Riga, 1958.
5. R. L. Shub, The Significance of Vitamins and Nitrofurans in Midwifery and Gynecology [in Russian], Medgiz, Moscow, 1961.
6. F. Banci and E. Tubaro, Boll. Chim. Farm., 101, 539, 1962.
7. W. Weuffen, H. Starke, and B. Herrmann, Parmazie, 18, 490, 1963.
8. L. N. Alekseeva, Antibacterial Compounds – 5-Nitrofuran Derivatives [in Russian], Izd-vo AN Latv. SSR, Riga, 1963.
9. L. V. Kruzmetra, Nitrofurans for Combatting Staphylococcal Infections [in Russian], Izd-vo AN Latv. SSR, Riga, 1964.
10. S. A. Giller, K. K. Venter, and R. Yu. Kalnberg, Collection: Medical Science and Practice [in Russian], Izd-vo AN Latv. SSR, Riga, 63, 1957.
11. S. P. Zaeva, L. N. Alekseeva, N. S. Ratenberg, and M. N. Koptelova, Zh. mikrobiol., epidemiol., immunobiol., no. 7, 10, 1958.
12. S. A. Giller, Ya. P. Stradyn, and N. S. Ratenberg, Izv. AN Latv. SSR, no. 3, 107, 1959.
13. L. N. Alekseeva, Izv. AN Latv. SSR., no. 1, 145, 1960.
14. L. V. Kruzmetra, Izv. AN Latv. SSR., no. 12, 159, 1960.
15. S. A. Giller and K. K. Venter, Izv. AN Latv. SSR., no. 8, 99, 1959.
16. K. K. Venter, S. A. Giller, and N. O. Saldabol, Izv. AN Latv. SSR, no. 8, 99, 1959.
17. K. K. Venter and S. A. Giller, DAN, 137, 83, 1961.
18. K. K. Venter, S. A. Giller, A. A. Lazdyn'sh, Izv. AN Latv. SSR, no. 5, 87, 1961.
19. H. Saikachi and H. Ogawa, J. Am. Chem. Soc., 80, 3642, 1958.
20. F. Hauschild, Pharmakologie und Grundlagen der Toxikologie, Leipzig, 1956.

9 December 1964

Institute of Organic Synthesis AS Latvian SSR, Riga