SYNTHESIS OF SOME FURYLNITROOLEFINS WITH POTENTIAL BIOLOGICAL ACTIVITY

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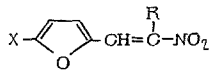
Many nitrovinylated derivatives in the aromatic and heterocyclic series have rather high physiological activity [1, 2, 4]. A number of β-(furyl-2)-nitroolefins have been prepared previously [3-10] with the general formula



I-XXIII

All of them have clearly pronounced physiological activity. Thus, (furyl-2)-nitroethylene (XV, X = R = H) and (furyl-2)-nitropropene (XVI, X = H, R = CH_3) irritate mucous membranes. This property decreases in the series X = H, CH_3, I, Br, Cl. Introduction of a thiocyano or nitro group in position 5 of the furane nucleus weakens the irritating effect and enhances bacteriostatic properties. 5-Thiocyanofurylnitroethylene (XVII, X = SCN, R = H) is capable of also inhibiting the growth of anthrax bacilli* in 1:10,000 dilution. (5-Nitrofuryl-2)-nitroethylene (XVIII, X = NO_2, R = H)† and (5-nitrofuryl-2)-nitropropene (XIX, X = NO_2, R = CH_3) possess not only great bactericidal effect but also a fungicidal one [11, 12].

Introduction of a methyl group in the side chain (R = CH_3) does not affect the nature of the physiological effect appreciably while the presence of a chlorine atom at the double bond of the side chain (R = Cl) markedly strengthens bactericidal properties and leads to the appearance of new valuable qualities. Thus, (5-nitrofuryl-2)-chloronitroethylene (XX, X = NO_2, R = Cl) revealed the ability to inhibit the growth of Bacillus pyocyaneus; however, it is somewhat toxic.

It was of interest to trace the effect of other substituents at the double bond of the side chain (R), for example, a bromine atom and a phenyl group, since the corresponding derivatives of nitrostyrene have high antimicrobial and insecticidal activity [13]. For this purpose we synthesized the following compounds, which have not yet been described in the literature: β-(5-nitrofuryl-2)-α-bromonitroethylene (VI, see Table 1) and β-(5-nitrofuryl-2)-α-phenylnitroethylene (XII), and also the corresponding furyl, 5-methylfuryl, and 5-halofuryl nitroolefins (I-III, V, VIII-XI).

For the synthesis of β-(furyl-2)-α-bromonitroethylenes (I-V) was utilized the condensation of the corresponding 5-substituted furfurals (X = H, CH_3, Cl, Br, I) with bromonitromethane in the presence of basic catalysts (potassium hydroxide, sodium hydroxide – method A). Methylamine (method B) is the best catalyst for the preparation of β-(furyl-2)-α-phenylnitroethylenes (VII-XII). Basic catalysts proved unsuitable in the case of phenylnitromethane because they lead to resinification of the reaction mixture. In the series of 5-substituted derivatives of furfural with X = H, CH_3, Cl, Br, I, NO_2 the reaction rate decreases. Thus, compound XII was obtained in a yield of 26% only after keeping the reaction mixture at 20°C for 14 days. When the temperature is raised, appreciable resin formation is observed. It did not prove possible to synthesize compound VI by condensation of 5-nitrofurfural with bromonitromethane under these conditions. It was obtained in high yield by nitration of I in analogy with XVIII [14] or by nitration of IV in analogy with XX [3].

*The tests were carried out in the Department of Microbiology of the Rostov Medical Institute under direction of Professor A. A. Kashaeva.

†The tests were carried out at the S. Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific Research Institute.

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TABLE 1. β-(Furyl-2)-nitroolefins

Compound	X	R	Preparation method	Yield (%)	mp (in deg)	Found (%)				Empirical formula	Calculated (%)				*λmax (nm)	lg ε
						C	H	halogen	N		C	H	halogen	N		
I	H	Br	A	70,5	57—8	33,55	2,04	36,72	6,67	$C_6H_4BrNO_3$	33,05	1,85	36,65	6,42	365	4,11
II	CH_3	Br	A	68	81—2	36,82	3,07	34,28	6,34	$C_7H_6BrNO_3$	36,23	2,61	34,43	6,03	387	4,26
III	Cl	Br	A	66,6	82—3	29,24	1,94	45,90	5,70	$C_6H_3ClBrNO_3$	28,54	1,20	45,69	5,54	369	4,24
IV	Br	Br	A (a)	76,8	88—9	24,86	1,35	53,46	4,92	$C_6H_3Br_2NO_3$	24,27	1,02	53,82	4,72	375	4,09
			A (b; from XV)	65												
V	I	Br	A (a)	52	92—3	—	—	60,56	4,27	$C_6H_3BrNO_3$	—	—	60,14	4,07	367	4,04
			A (b; from IV)	70,8												
VI	NO_2	Br	A (a; from I)	88,4	90—1	28,16	1,64	30,02	10,53	$C_6H_3BrN_2O_5$	27,40	1,15	30,38	10,65	359	4,29
			A (b; from IV)	38,5					10,49							
VII	H	C_6H_5	B	78	87—8	67,14	4,62	—	6,60	$C_{12}H_9NO_3$	66,98	4,22	—	6,51	353	4,18
VIII	CH_3	C_6H_5	B	68,5	58—9	68,65	4,90	—	6,17	$C_{13}H_{11}NO_3$	68,12	4,83	—	6,11	373	4,26
IX	Cl	C_6H_5	B	73,6	85—6	58,24	4,09	14,15	5,72	$C_{12}H_8ClNO_3$	57,73	3,23	14,20	5,63	360	4,28
X	Br	C_6H_5	B	75,2	92—3	50,42	3,15	26,91	4,80	$C_{12}H_8BrNO_3$	49,05	2,74	27,17	4,76	363	4,30
XI	I	C_6H_5	B	70,3	110—11	41,82	2,90	37,61	4,29	$C_{12}H_8BrNO_3$	42,26	2,36	37,21	4,10	369	4,19
XII	NO_2	C_6H_5	B	26,1	91—2	55,50	3,40	—	10,53	$C_{12}H_8N_2O_5$	55,39	3,10	—	10,77	359	4,22
XIII	4,5-Br_2	C_6H_5	B	45	95—6	39,68	2,20	43,01	3,59	$C_{12}H_7Br_2NO_3$	38,64	1,89	42,85	3,76	357	4,02
XIV	4-Br-5-I	C_6H_5	B	39	102—3	—	—	48,98	3,34	$C_{12}H_7BrINO_3$	—	—	49,24	3,37	368	4,28

*UV spectra were obtained on spectrophotometer SF-4A in methanol solution.

Compound IV may also be prepared by bromination of I in analogy with (5-bromofuryl-2)-chloronitroethylene (XXI, X=Br, R=Cl) [3] or by cleavage of hydrogen bromide from β-(5-bromofuryl-2)-α,β-dibromonitroethane which forms in quantitative yield in the bromination of (5-bromofuryl-2)-nitroethylene (XXII, X=Br, R=H) in chloroform in analogy with derivatives of ω-nitrostyrene [15]. In the bromination of XV under these conditions there takes place not only addition of bromine to the double bond of the side chain, but also substitution of a hydrogen in position 5 of the furane nucleus. β-(5-Iodofuryl-2)-α-bromonitroethylene (V) can be prepared in good yield from the corresponding bromo derivative (IV) by exchange with potassium iodide in glacial acetic acid in analogy with (5-iodofuryl-2)-nitroethylene (XXIII, X=I, R=H) [5].

EXPERIMENTAL

β-(Furyl-2)-α-bromonitroethylenes (Method A). To a solution of 0.01 mole of the appropriate 5-substituted furfural and 0.01 mole of bromonitromethane in 30 ml methanol a solution of 0.02 mole of potassium hydroxide in 3 ml water is added dropwise in the course of 30 min with stirring and cooling with an ice–salt mixture, and the reaction mixture is kept in the cooling bath for another 30 min. Then 30 ml water is added and the mixture poured gradually into a cooled mixture of 3.2 ml concentrated hydrochloric acid and 12 ml water. After 30 min the precipitate (or oil) is separated, washed with water to neutral reaction, purified by steam distillation, and then recrystallized from ethanol. Yield, mp, and analytical results are listed in Table 1.

β-(5-Bromofuryl-2)-bromonitroethylene (IV). To a solution of 0.015 mole XV in 50 ml chloroform is added a solution of 0.3 mole bromine in 20 ml chloroform in the course of 30 min with stirring at 0°. The solution is kept at 20-25° for 3-4 h. The solvent is then distilled off at room temperature. β-(5-Bromofuryl-2)-α,β-dibromonitroethane is obtained in the residue as a pale yellow oil which decomposes on storage or distillation. The same oil was obtained by bromination of XXII. The identity of the samples was demonstrated by comparison of thin-layer chromatograms on aluminum oxide (chloroform solvent, sulfuric acid developing agent).

The oil obtained, 5.3 g, is treated at 20-25° under vigorous stirring with a solution of 3.4 g potassium hydroxide in 50 ml water. The precipitate formed is separated, washed with water to neutral reaction, dried in a desiccator over phosphorus pentoxide, and recrystallized twice from hexane. Yield, 2.7 g (64%), yellow crystals, mp 94-95° (from hexane). A sample mixed with IV, obtained by method A, gave no melting point depression (mp 94-95°). The identity of the products was also demonstrated by comparison of their UV and IR spectra* and by comparison of thin-layer chromatograms on aluminum oxide (benzene solvent, sulfuric acid developer).

β-(5-Nitrofuryl-2)-α-bromonitroethylene (VI). a) To a mixture of 3.58 g nitric acid (d, 1.52), 6 ml acetic anhydride, and 0.5 g concentrated sulfuric acid cooled in ice–salt a solution of 3 g I in 8 ml acetic anhydride is added dropwise in the course of $\frac{1}{2}$ h. Stirring is continued for another 2 h at 0°. The mixture is then poured into 100 g of chopped ice. After 15 min the precipitate is separated, washed with water, and dried in a desiccator over phosphorus pentoxide. Yield, 3.2 g (88.4%), light yellow needles, mp 90-91° (from ethanol).

b) A mixture of 1.49 g IV and 3.5 ml nitric acid (d, 1.2) is heated until the start of an exothermic reaction which is accompanied by a vigorous bromine evolution. The mixture is then poured on ice, the precipitate formed is separated and washed with water to neutral reaction. Yield, 0.52 g (39.5%), mp 90-91° (from ethanol). A mixed sample with VI, obtained from I, did not give a melting-point depression (mp 90-91°).

β-(Furyl-2)-α-phenylnitroethylenes (Method B).† To a solution of 0.01 mole of the appropriate 5-substituted furfural in 10 ml ethanol is added 0.01 mole phenylnitromethane, 0.1 g methylamine hydrochloride, and an equivalent amount of sodium carbonate. The mixture is held from 3 to 7 days in the refrigerator. The crystals, which have precipitated, are separated and recrystallized from ethanol.

LITERATURE CITED

1. O. Schales and H. Graefe, J. Am. Chem. Soc., 74, 4486 (1962).
2. R. Dale, U. S. Patent No. 2,899,429 (1959); Ref. Zh. Khim., 1961, No. ZL102.

*λ_{max} 375 nm, log ε 4.14; $\nu_{C=C}$ of side chain 1610 cm^{-1}, $\nu^{as}_{NO_2}$ 1516 cm^{-1} and $\nu^{S}_{NO_2}$ 1302 cm^{-1}.
†With the participation of Yu. N. Il'ina.

3. I. P. Tsukervanik and G. F. Potemkin, Dokl. Akad. Nauk Uzb. SSR, No. 8, 26 (1951).
4. Z. N. Nazarova, Zh. Obshch. Khim., 24, 575 (1954).
5. Z. N. Nazarova and F. T. Pozharskii, ibid., 28, 1503 (1958).
6. Z. N. Nazarova, ibid., 25, 539 (1955).
7. Z. N. Nazarova and L. E. Nivorozhkin, ibid., 30, 3297 (1960).
8. Z. N. Nazarova and G. F. Potemkin, ibid., 34, 157 (1964).
9. Idem., Zh. Org. Khim., 1, 1705 (1965).
10. Z. N. Nazarova, G. F. Potemkin, and O. A. Pustovarova, Khim. Geterotsikl. Soedin., No. 6, 1128 (1967).
11. R. G. Owens and H. M. Novotny, Contrib. Boyce Thompson Inst., 20, No. 2, 151 (1952).
12. I. F. Urvantsev (editor), Drug Handbook [in Russian], Minsk (1968), p. 275.
13. K. Schumann and R. Kaltofen, East German Patent No. 7356 (1954).
14. S. A. Giller and M. Ya. Berklav, Izv. Akad. Nauk Latv. SSR, 5, 115 (1959).
15. K. S. Rumyantseva and L. D. Dorogoikina, Uch. Zap. Mosk. Gos. Univ., No. 66, Part 1, 45 (1967); Ref. Zh. Khim., 1968, No. 14Zh220, 8Zh19.