SYNTHESIS AND BIOLOGICAL ACTIVITY OF NITRO DERIVATIVES OF ARYLFURANS

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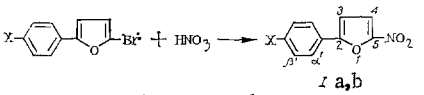
In a continuation of our research on the synthesis and study of the biological activity of arylfuran derivatives [1], we have synthesized and investigated the antimicrobial activity of nitro and bromo derivatives of arylfurans. The mono- and dibrominated arylfuran derivatives which we have previously synthesized served as starting materials in the synthesis of the nitro derivatives of arylfurans [1].

In the reaction of 2-aryl-5-bromofurans with nitric acid, replacement of bromine by a nitro group took place, and 2-aryl-5-nitrofurans were formed (Ia, b).

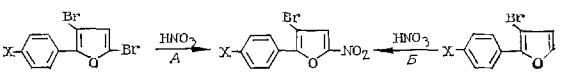


I a,b

Ia X = NO_2, Ib X = Cl

Data on the NMR spectra of compounds Ia and Ib are shown in Table 1. The magnitude of the spin–spin coupling constant for the protons of the furan ring (J = 3.4 Hz for Ia and 3.8 Hz for Ib) corresponds to the interaction of 3 and 4 ring protons. Hence it follows that the nitro group has entered into the 5-position of the furan ring.

On reaction with nitric acid the 2-aryl-3,5-dibromofurans exchanged the bromine in the 5-position for a nitro group and formed 2-aryl-3-bromo-5-nitrofurans (IIa-c) (method A). Nitrofuran IIc was also obtained by nitration of 2-(p-bromophenyl)-3-bromofuran (method B).



IIa,b

IIa) X = NO_2, IIb) X = Cl, IIc) X = Br

The structure of compounds IIa-c was confirmed by evidence from the NMR spectra (see Table 1). The narrow singlet at 7.33-7.38 ppm which is observable in the NMR spectra of IIa-c (signal width at half-height is equal to 0.30 Hz) was assigned to the H^4 proton of the furan ring. Assignment of the singlet to the H^4 proton in compounds IIa-c was done similarly to the way which was described for the 2-aryl-3,5-dibromofurans in [1].

TABLE 1. NMR Spectral Data for Compounds I and II

Compound	δH^3, ppm	δH^4, ppm	$\delta H^{\alpha'}$, ppm	$\delta H^{\beta'}$, ppm	JH^3H^4, Hz
Ia	7,06	7,46	8,04	8,34	3,4
Ib	6,82	7,40	7,74	7,44	3,8
IIa	—	7,49	8,28		—
IIb	—	7,34	7,99	7,44	—
IIc*	—	7,38	7,91	7,60	—
IIc†	—	7,33	7,85	7,55	—

* Compound obtained by method A.

† Compound obtained by method B.

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TABLE 2. Antimicrobial Activity of Nitro Derivatives of Arylfurans

Compound	Staph. aureus	Str. hemolyticus	Cl. diphtheriae	B. anthracoides	Sal. typhi	Sh. dysenteriae	E. coli	M. tuberculosis $H_{37}R_V$	Tr. vaginalis
	Minimum effective concentration, μg/ml								
Ia	31,2	31,2	31,2	31,2	7,8	7,8	2	<3,9	—
Ib	7,8	62,5	31,2	<2	7,8	15,6	3,9	—	8
IIa	>125	>125	>125	>125	>125	>125	>125	>1000	16
IIb	500	500	500	500	500	500	500	500	62
IIc	<3,9	<3,9	7,8	<3,9	>500	>500	>500	15,6	2

TABLE 3. Physicochemical Properties of Nitro and Bromonitro Derivatives of 2-Arylfurans

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Br, Cl	N		C	H	Br (Cl)	N
Ia	94	175.5—7.0*	51.2	3.0	—	12.0	$C_{10}H_6N_2O_5$	51.3	2.6	—	12.0
Ib	87	101.5—3.0	54.0	3.2	15.6	—	$C_{10}H_6ClNO_3$	53.7	2.7	15.9	
IIa	22	177—7.5†	38.0	1.6	25.3	8.8	$C_{10}H_5BrN_2O_5$	38.4	1.6	25.5	8.9
IIb	74	114—6†	39.7	2.0	—	4.5	$C_{10}H_5BrClNO_3$	39.7	1.7	—	4.6
IIc	83	127—8.5†	34.6	1.5	46.1	3.9	$C_{10}H_5Br_2NO_3$	34.6	1.5	46.1	4.0

* From chloroform.

† From ethanol.

The antimicrobial activity of the compounds synthesized was studied in experiments in vitro by the method of twofold serial dilutions in a liquid growth medium [2] with respect to four types of Gram-positive bacteria, five forms of Gram-negative bacteria, tuberculosis mycobacteria of strain $H_{37}R_V$, and five forms of pathogenic bacteria and trichomonads. It was ascertained that the compounds Ia and b have a definite bacteriostatic activity with respect to both Gram-negative and also Gram-positive bacteria (Table 2). On introduction of bromine into the 3-position of the furan ring, a sharp reduction in the antibacterial activity takes place (compounds IIa, b). Compound IIc is highly active only with respect to Gram-positive bacteria. The compounds studied essentially have no effect on pathogenic fungi or the Gram-negative bacteria B. pyocyaneum and Pr. vulgaris. The compounds investigated showed a definite activity with respect to Trichomonas vaginalis in vitro (see Table 2).

EXPERIMENTAL

NMR spectra were taken on Varian XL-100 (USA) or Jeol C-60 HL (Japan) spectrometers; the solvent was deuterochloroform; the internal standard was tetramethylsilane.

2-(p-Nitrophenyl)-5-nitrofuran (Ia). Method A. To 2.8 g of 2-(p-nitrophenyl)-5-bromofuran [1], over a period of 20 min, under a blanket of nitrogen was added, at room temperature, dropwise 13 ml of nitric acid (d 1.2); then the reaction mixture was heated at 50°C until the evolution of bromine vapor ceased. The reaction mixture, cooled to room temperature, was neutralized with a saturated sodium bicarbonate solution and was extracted with ether. The ether solution was washed with a sodium bicarbonate solution and with water, and was dried over sodium sulfate and evaporated. The residue was recrystallized from ethyl alcohol. Compounds Ib and IIa-c were prepared similarly (see Table 3).

2-(p-Bromophenyl)-3-bromo-5-nitrofuran (IIc). Method B. To a solution of 3.8 g of 2-(p-bromophenyl-3-bromofuran [1] in 25 ml of acetic anhydride. The mixture was stirred for 2 h at 0°C, then for 1.5 h at 12°C, after which the reaction mixture was poured into 300 ml of ice water, neutralized with a saturated sodium bicarbonate solution, and extracted with ether. The ether extract was washed with a saturated sodium bicarbonate solution and then with water to a neutral reaction, dried with sodium sulfate, and evaporated under vacuum.

The residue was recrystallized from alcohol. The yield of compound IIc obtained was 1.3 g; mp 127-128°C. A mixed melting point test of compound IIc obtained by method A with that obtained by method B gave no depression mp.

LITERATURE CITED

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SYNTHESIS AND PHARMACOLOGICAL STUDY OF N-(2-SUBSTITUTED-NICOTINOYL) AMINO ACIDS

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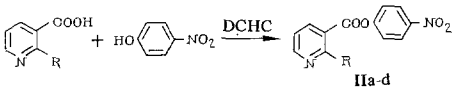
The therapeutic effect of nicotinic acid in the treatment of certain psychic ailments has served as the basis for a search for new psyochotropic substances based on nicotonic acid [1]. Thus, N-nicotinoyl-γ-aminobutyric acid (N-nicotinoyl-GABA) displays a high physiological activity [2]; and another nicotinic acid derivative—nicolite—exerts a tranquilizing action [3, 4]. One of the trends in the search for pharmacologically active substances among the derivatives of nicotinic acid is introduction of various substituents, particularly in the 2- or 4-positions of the pyridine ring, as a result of which it has been ascertained that the 2-anilino derivatives of nicotinic acid display a definite anticonvulsant and analgesic activity [5, 6]; some of them are reserpine antigonists and intensify the action of amphetamine [5], while amides of 4-methoxynicotinic acid are antagonists to amphetamine and apomorphine [7].

The objective of the present work was the synthesis of N-(2-substituted-nicotinoyl)-amino acids and the study of both the character of the substituents (chloro-, hydroxy-, methoxy-, benzyloxy-, and phenoxy groups) in the 2-position of the pyridine ring of these compounds, and also of the structure of the amino acid residues (γ-aminobutyric acid, glutamic acid, glycine, alanine, etc.) on neurotropic activity, since the amino acids themselves, as is well known, play a definite role in the transfer of nerve impulses.

Synthesis of the 2-substituted nicotinoylamino acids Ia-h was effected starting from the 2-substituted nitocinic acids using the activated ester method [8]. p-Nitrophenyl esters of the 2-substituted nicotonic acids (IIa-d) were prepared by esterification of the 2-substituted nicotinic acids with the aid of dicyclohexyldicarboimide (DCHC).

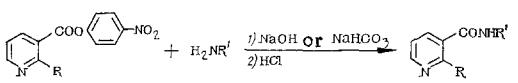


IIa-d

IIa: R = Cl IIc: R = $OCH_2C_6H_5$
IIb: R = OC_6H_5 IId: R = OCH_3

In the IR spectra of the p-nitrophenyl esters of the 2-substituted nicotinic acids so obtained, IIa-d, there are stretching vibrations for the ester group in the 1747—1723 cm^{-1} region and for the nitro group in the 1517-1527 and 1352—1347 cm^{-1} regions.

Compounds Ia-h were synthesized by aminolysis of the esters IIa-d with amino acids (GABA, glutamic acid, glycine, β-alanine, or the racemate of β-phenylalanine, brought into reaction in the form of the Na salt) in aqueous DMF.



IIa-c Ia-h

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