ANTIMICROBIAL ACTIVITY OF SOME ACYL HALIDE ARYLHYDRAZONES AND CARBOXYLIC ACID ARYLHYDRAZIDES

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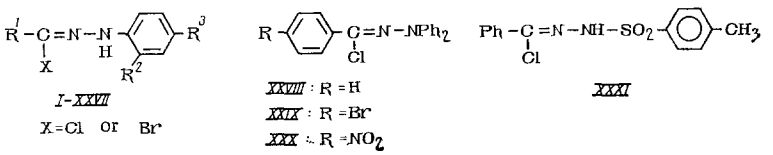
The search for new antifungal agents remains a current concern as a result of the widespread incidence of fungal diseases of humans, animals, and plants and the acquistition of resistance to the available preparations by the pathogens. The frequent complications of fungal diseases by bacterial infection necessitate the development of preparations that combine antifungal and antibacterial activity.

Among the groups with potential for the search for compounds with antimicrobial activity must be numered the acyl halide arylhydrazones, which have high chemical and biological activity [1]. They include compounds with anthelmintic [2, 3], insecticidal [4, 5], acaricidal [5], herbicidal [6], and insect-chemosterilant [7] activity. Antimicrobial properties have also been detected in chloroglyoxylic acid [8] and nitrobromoformaldehyde [9] arylhydrazones.

Here we report a study of the antimicrobial activity and the toxicity for warm-blooded animals of aryl- and diarylhydrazones of carboxylic acid chlorides and bromides (I-XXX) (Table 1) and carboxylic acid arylhydrazides (XXXII-LVI) (Table 2).



These complex studies contribute to the clarification of the effect of electronic and structural factors in these series of compounds on the magnitude of the gap between the toxic dose for warm-blooded animals and microorganisms, which can be expressed by the index of selective toxicity (IST), given by the ratio LD_{50}/fungicidal (bactericidal) concentration.

Table 1 shows that I, which can be considered as the key compound, has moderate antifungal activity and is not toxic to bacteria. Introduction of bromine or chlorine into the para position of the phenyl ring of the hydrazine fragment considerably enhances the fungicidal activity (I and II, I and III) and causes the appearance of the bactericidal properties (I and II), while the toxicity for warm-blooded animals diminishes, resulting in an increases in the IST.

Introduction of a nitro group into the same position reduces the fungicidal activity (I and IV), and hydrazone IV has only fungistatic properties.

The introduction of the same substituents into the para position of the benzene ring attached to the carbon atom of the hydrazone group (or the ylidene fragment) is less effective, although the relative order of the substituent effect remains the same (I-IV with VII, VIII, and X). For example, VII is only slightly more active than I toward Microsporum canis and is less active toward Trichophyton rubrum and T. mentagrophytes, whereas its isomer II is much more active toward dermatophytes. Both compounds (II, VII) are more active than their respective chloro analogs III and VIII.

The position of the substituent in the benzene rings of the hydrazone and the ylidene fragments has a considerable effect on the fungistatic and fungicidal concentrations and the toxicity for warmblooded animals. The p-substituted compounds are most active toward the test microorganisms and are more toxic; and o-and m-substituted compounds are two to three times less toxic (IV and V, XIII and XIV, XVI and XVII—NO_2 in the

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TABLE 1. Fungicidal (first figure), Fungistatic (second figure), and Bactericidal Concentrations of Acyl Halide Arylhydrazones I-XXVII

Compound	R^1	X	R^2	R^3	mp, °C	Trichophyton rubrum	Trichophyton mentagraphytes	Microsporum canis	Escherichia coli	Staphylococcus aureus 209-P	LD_{50}^{*}, mg/kg	IST†
I	C_6H_5	Cl	H	H	129—30	0,15/0,008	0,15/0,1	0,05/0,03	>0,5	>0,5	90 (70—106)	600—1 800
II	C_6H_5	Cl	H	Br	120—1	0,01/0,008	0,01/0,008	0,01/0,008	0,1	0,5	300 (250—360)	700—3 500
III	C_6H_5	Cl	H	Cl	107—8	0,05/0,005	0,1/0,007	0,05/0,003	>0,5	>0,5	300 (250—360)	3 000—6 000
IV	C_6H_5	Cl	H	NO_2	189—90	>0,1/0,05	>0,1/0,05	>0,1/0,05	>0,5	>0,5	250 (202—310)	—
V	C_6H_5	Cl	NO_2	H	162—4	>0,1/0,1	>0,1/—	>0,1/0,1	—	—	>1000	—
VI	C_6H_5	Cl	Br	Br	108—9	>0,1/0,5	>0,1/—	>0,1/—	—	—	1500 (1250—1800)	—
VII	4-BrC_6H_4	Cl	H	H	153—4	>0,1/0,01	>0,2/—	0,01/—	>0,5	>0,5	290 (226—371)	29 000
VIII	4-ClC_6H_4	Cl	H	H	148—9	>0,1/0,05	>0,1/0,1	0,05/0,01	>0,5	>0,5	290 (226—371)	5 800
IX	4-FC_6H_4	Cl	H	H	118—9	0,1/0,05	>0,1/0,03	0,05/0,03	—	—	250 (202—310)	2 500—5 000
X	4-$NO_2C_6H_4$	Cl	H	H	157—8	>0,1/0,1	>0,1/0,1	>0,1/01	>0,5	>0,5	123 (111—135)	—
XI	3-$NO_2C_6H_4$	Cl	H	H	132—3	>0,2/—	>0,2/—	0,05/—	—	—	300 (242—372)	6 000
XII	CH_3	Cl	H	Br	110—12	0,015/0,008	0,015/0,01	0,01/0,005	0,025	0,062	300 (250—360)	4 800—300 000
XIII	CH_3	Cl	H	NO_2	137—8	0,01/—	0,15/0,01	>0,1/0,1	0,5	0,5	310 (260—372)	620—31 000
XIV	CH_3	Cl	NO_2	H	76—7	>0,1/—	>0,1/—	>0,1/—	—	—	650 (520—816)	—
XV	CH_3	Cl	NO_2	NO_2	152—4	>0,1/—	>0,1/—	>0,1/0,1	—	—	1600 (1460—1760)	—
XVI	C_2H_5	Cl	H	NO_2	110—11	0,01/—	>0,1/—	>0,1/—	—	—	300 (242—372)	300 000
XVII	C_2H_5	Cl	NO_2	H	47—8	>0,1/—	>0,1/—	>0,1/—	—	—	1250 (1136—1375)	—
XVIII	n-C_3H_7	Cl	H	NO_2	80—81	0,01/—	>0,1/—	>0,1/—	>0,5	>0,5	220 (187—264)	22 000
XIX	C_6H_5	Br	H	NO_2	190—1	0,15/0,01	0,2/—	0,1/0,05	>0,5	>0,5	220 (180—272)	1 100—2 200
XX	C_6H_5	Br	Br	NO_2	172—3	>0,1/0,1	>0,2/—	0,05/0,01	—	—	>1500	—
XXI	C_6H_5	Br	Br	Br	115—6	>0,2/0,1	>0,2/0,1	>0,2/0,15	—	—	1700 (1452—2108)	—
XXII	3-C_5H_4	Br	H	NO_2	>350	>0,1/0,05	>0,1/0,05	>0,1/—	0,5	>0,5	800 (730—880)	4 000
XXIII	4-C_5H_4	Br	H	NO_2	>350	>0,1/0,05	>0,1/0,05	>0,1/0,05	0,025	0,025	>1000	—
XXIV	CH_3CO	Br	H	NO_2	231—3	>0,1/0,01	>0,1/0,01	>0,1/0,1	—	—	1100 (917—1320)	—
XXV	CH_3CO	Br	H	SO_2NH_2	201—2	>0,1/—	>0,1/—	>0,1/—	0,1	>0,5	—	—
XXVI	CH_3	Br	NO_2	NO_2	149—50	>0,1/—	>0,1/—	>0,01/0,1	>0,5	>0,5	3500 (3180—3850)	—
XXVII	n-C_3H_7	Br	NO_2	NO_2	122—4	>0,1/—	>0,1/—	>0,1/—	0,125	0,5	>3000	—

*White mice perorally.

†IST of the particular compound toward the microorganism. Brackets indicate the limits of variation.

TABLE 2. Fungicidal (first figure), Fungistatic (second figure), and Bactericidal Concentrations of Carboxylic Acid Arylhydrazides XXXII-LVI

Compound	R^1	R^2	mp, °C	Trichophyton rubrum	Trichophyton mentagraphytes	Microsporum canis	Alternaria sp.	Escherichia coli.	Staphylococcus aureus 209-P	LD_{50}*, mg/kg	IST†
XXXII	C_6H_5	H	168	0,01 / 0,0075	0,05 / 0,03	0,0075 / 0,0038	—	0,0062	>0,5	750 (680—825)	15 000—120 000
XXXIII	C_6H_5	4-Br	156	0,005 / 0,002	0,008 / 0,002	0,003 / 0,002	0,1 / 0,05	0,05	0,0062	300	3 000—100 000
XXXIV	C_6H_5	4-Cl	153—154	<0,01 / —	0,05 / 0,01	<0,01 / —	—	—	—	—	—
XXXV	C_6H_5	4-NO_2	193—194	>0,2 / 0,05	>0,2 / 0,05	>0,2 / 0,05	—	>0,5	>0,5	450 (409—495)	—
XXXVI	4-BrC_6H_4	H	198—199	>0,1 / 0,01	>0,1 / 0,01	>0,1 / 0,01	—	0,5	>0,5	600 (500—720)	1 200
XXXVII	4-ClC_6H_4	H	193—195	0,1 / 0,05	— / >0,1	0,05 / 0,01	—	>0,5	0,25	550 (500—605)	2 000—10 000
XXXVIII	4-FC_6H_4	H	177—179	0,1 / 0,05	— / >0,1	0,05 / 0,01	—	0,125	0,0312	350 (290—420)	2 800—11 200
XXXIX	3-IC_6H_4	H	142—144	0,1 / 0,05	— / >0,1	0,05 / 0,01	—	>0,5	>0,5	550 (450—660)	5 500—11 000
XL	4-CH_3O	H	177—178	>0,1 / —	>0,1 / —	>0,1 / —	—	>0,5	>0,5	1600 (1500—1760)	—
XLI	4-NO_2	H	200—201	>0,1 / 0,01	>0,1 / 0,01	>0,1 / 0,01	—	>0,5	>0,5	1200 (1090—1320)	—
XLII	H	2-NO_2	177	>0,2 / 0,1	>0,2 / 0,1	>0,2 / 0,05	—	0,5	>0,5	550 (500—605)	1 100
XLIII	H	4-NO_2	182	0,1 / 0,01	0,1 / 0,01	0,1 / 0,01	—	0,5	>0,5	500 (400÷650)	900—4 500
XLIV	CH_3	H	129	0,1 / 0,01	>0,1 / 0,1	0,05 / 0,01	—	0,0125	>0,5	270 (225—324)	2 700—21 600

XLV	CH_3	4-Br	167	0,005 / 0,003	0,02 / 0,01	0,008 / 0,003	0,01	0,05	0,062	320 (266—384)	5 160—64 00
XLVI	CH_3	2-NO_2	140—141	— / >0,1	— / >0,1	>0,1 / 0,1	—	>0,5	>0,5	800 (730—880)	—
XLVII	CH_3	4-NO_2	205	0,05 / 0,01	0,05 / 0,01	0,05 / 0,01	—	0,5	>0,5	400 (363—440)	800—8 000
XLVIII	CH_3	2,4-$(NO_2)_2$	202—203	>0,1 / —	>0,1 / —	>0,1 / —	—	—	—	750 (682—825)	—
XLIX	C_2H_5	4-Br	178—179	0,01 / 0,003	0,01 / 0,003	0,01 / 0,003	0,007 / 0,003	0,0625	>0,5	410 (348—483)	6 560—58 570
L	C_2H_5	4-NO_2	208—209	>0,2 / 0,05	>0,2 / 0,05	0,1 / 0,05	—	0,5	>0,5	325 (296—360)	650—3 250
LI	n-C_3H_7	4-Br	129—130	0,01 / 0,003	0,01 / 0,003	0,01 / 0,003	0,005 / 0,003	>0,5	>0,5	500 (455—550)	50 000—100 000
LII	n-C_3H_7	4-NO_2	199—200	>0,2 / 0,05	>0,2 / 0,05	>0,2 / 0,05	—	0,125	>0,25	250 (230—275)	1 000—2 000
LIII	n-C_4H_9	4-Br	119—121	0,01 / 0,003	0,01 / 0,003	0,007 / 0,003	0,005 / 0,003	>0,5	>0,5	550 (458—660)	55 000—110 00
LIV	n-C_4H_9	4-NO_2	149—150	>0,2 / 0,05	>0,2 / 0,05	>0 2 / 0,05	—	0,25	>0,5	500 (390—650)	2 000
LV	iso-C_4H_9	4-Br	148—149	0,01 / 0,003	0,01 / 0,003	0,007 / 0,003	0,005 / —	>0,5	>0,5	600 (500—720)	60 000—120 000
LVI	F_3C	H	127	0,05 / 0,01	0,05 / 0,01	0,01 / 0,003	0,05 ‡ / 0,015	0,00156	>0,5	270 (245—297)	5 400—180 000

*White mice perorally.

†Index of selective toxicity for the microorganisms most and least sensitive to this compound.

‡Candida albicans. Brackets enclose the limits of variation.

phenylhydrazone fragment, X and XI – NO_2 in the benzylidene fragment, XXII and XXIII – isomeric pyridyl radicals). The substituents in the monosubstituted derivatives of hydrazone I can be ranked in terms of the reduction in antifungal activity as 4-Br ≥ 4-Cl > H > 4-NO_2 ≥ 2-NO_2 in the hydrazine fragment and H ≥ 4-Br ≥ 4-F ≥ 4-Cl ≥ 4-NO_2 > 3-NO_2 in the ylidene fragment or in terms of the reduction in toxicity for warm-blooded animals as H > 4-NO_2 > 4-Cl > 4-Br > 2-NO_2 and H > 4-NO_2 > 4-F > 4-Cl > 4-Br > 3-NO_2 respectively.

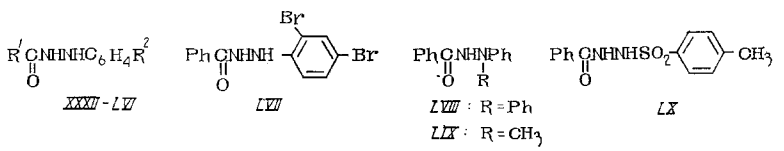
The introduction of a second substituent into the benzene ring of the hydrazine fragment in general reduces the antifungal activity (II and VI, XIX and XX, XIII and XV; see also XXI, XXVI, XXVII) and sharply reduces the toxicity for warm-blooded animals. The reduction in the toxicity prevails in both VI and XXI and in XX and XV, XXVI, and XXVII.

Replacement of phenyl by pyridyl (XXII, XXIII) or acetyl (XXIV) in the ylidene fragment slightly enhances the antifungal and antibacterial activity (IV). The aliphatic acyl halide arylhydrazones show some increase in the fungicidal properties and a higher inhibitory activity toward bacteria (II and XII, IV and XIII). Lengthening of the alkyl chain in the alkanoyl chloride 4-nitrophenylhydrazones reduces the width of the antimicrobial effect and slightly affects their toxicity (XIII, XVI, XVIII), whereas in the case of XIV and XVII lengthening of the chain by only one CH_2 group halves the toxicity for warm-blooded animals.

Compounds XXVIII (LD_{50} = 1100 mg/kg), XXIX, and XXX are inactive toward the test fungi and bacteria, pointing to the importance of the nitrogen hydrogen atom. A sulfonyl group located between the aryl residue and the hydrazone fragment (as exemplified by XXXI) also causes a loss of activity.

Thus, we can conclude that the antifungal activity of the acyl halide arylhydrazones is controlled by the substituents in both the ylidene and the hydrazine fragments. An important factor here is the presence of a halogen atom in the hydrazine fragment. For example the 2,4-dinitrophenylhydrazones of acetaldehyde (LD_{50} 1500 mg/kg), butyraldehyde, isobutyraldehyde (LD_{50} > 3000 mg/kg for both), and acetone (LD_{50} 3000 mg/kg) are inactive toward the test microorganisms.

Acyl halide arylhydrazones are known to be susceptible to hydrolysis to the corresponding carboxylic acid arylhydrazides [1], which include representatives with fungicidal activity [10-15]. Since they could be metabolites of and thereby responsible for the observed activity of the acylhalide arylhydrazones, we examined the properties of carboxylic acid arylhydrazides XXXII-LX in the same tests.



The fungicidal activity of the arylhydrazides is of the same order as that of the acyl halide arylhydrazones with the same substituents in the hydrazone and hydrazide groups. In some cases the arylhydrazides are more active than the equivalent acyl halide arylhydrazones toward all the fungi (for example, XXXII and I, XXXII and II, XLV and XII, XLVI and XIII) while in others the acyl halide arylhydrazones are more active toward individual fungi (VII-IX and XXXVI-XXXVIII, XVI and L, XVIII and LII). A comparative analysis of the figures of Tables 1 and 2 suggests that the antimicrobial properties of the acyl halide arylhydrazones have no connection with their susceptibility to conversion to carboxylic acid arylhydrazides and that both groups of compounds display these properties independently of each other, although their activities are similar.

We verified this conclusion in a separate series of tests on compounds II and XXXIII using thin-layer chromatography. We found that II can be detected unchanged in the growth medium and in the mass of the fungus. We did not detect its conversion to XXXIII under the conditions of the experiment.

The nature and position of the substituents in the hydrazine and carboxyl fragments of the arylhydrazides have the same type of effect on the fungicidal properties as in the acyl halide arylhydrazones (Tables 1 and 2). Introduction of bromine into the para position of the phenyl ring produces higher activity than does that of the NO_2 group into the same position (cf. XXXIII, XLV, XLIX, LI, LIII, LV with XXXV, XLVII, L, LII, LIV). Removal of the NO_2 group from the para to the ortho position almost destroys the antimicrobial properties and reduces the toxicity for warm-blooded animals (XLIII, XLVII with XLII, XLVI). In the aliphatic acid arylhydrazides as compared to the aromatic acid arylhydrazides the activity toward the must-causing agents Alternaria species is much higher (cf. XXXIII with XLV, XLIX, LI, LIII, and LV). Lengthening of the alkyl chain in the acyl fragment has no marked effect on the antifungal activity, but destroys the antibacterial prop-

erties (cf. XLV with XLIX, LI, LIII, and LV). Replacement of the methyl group in XLIV by trifluoromethyl (compound LVI) considerably enhances the antifungal activity; in addition LVI in a concentration of 0.05% also has fungicidal activity toward a representative yeast, Candida albicans.

The introduction of a second bromine atom, i.e., LVII (LD_{50} > 1000 mg/kg) relative to XXXIII, the attachment of a second phenyl (LVIII) or methyl (LIX, LD_{50} 500 mg/kg) to the nitrogen atom, and the replacement of the nitrogen phenyl by tosyl (LX) destroy the antifungal activity. This indicates the importance of the proton on the nitrogen atom bonded to the aryl group in both the acyl halide arylhydrazones and the carboxylic acid arylhydrazides in the development of antimicrobial activity by these compounds.

The antibacterial activity of the arylhydrazides in general is slightly higher than that of the acyl halide arylhydrazones, although the correlation with structure is not always the same. Thus Escherichia coli is more sensitive to benzoic and trifluoroacetic acid phenylhydrazides (XXXII and LVI), whereas Staphylococcus aureus is more sensitive to benzoic acid 4-bromophenylhydrazode (XXXIII).

The substituents in the carboxylic acid arylhydrazides and acyl halide arylhydrazones effect the toxicity for warm-blooded animals in different ways. For example the introduction of halogen into any phenyl ring of the key compound XXXII increases the toxicity, while the effect of introducing a nitro group is extremely selective (cf. XXXII with XXXV and XLI). In the 4-nitrophenylhydrazides XXXV, XLIII, XLVII, and LIV as compared to the phenylhydrazides XXXII, XXXVI-XLI, and XLIV, the effect of the carboxylic acid residue on the toxic properties of the arylhydrazides is lower.

Our results reveal the potential relevance of work on acyl halide arylhydrazones and carboxylic acid arylhydrazides to the search for new antimicrobial agents.

EXPERIMENTAL BIOLOGICAL PART

Antifungal activity was assayed by the method described in [16]. The fungistatic activity (the lowest concentration inhibiting the growth of the fungus) was assayed in terms of the effect on the growth of the fungus after inoculation in pure selective medium and the fungicidal activity (the lowest concentration preventing growth of the fungus) from the absence of growth after inoculation over a period of 30 days.

Bactericidal properties were examined by the serial dilution technique following the conventional procedure [17]. The bacterial load in the test was 500,000 microbial bodies per milliliter.

Toxicity was evaluated in white mice per peroral administration in acetone–oil solution; LD_{50} was calculated by Litchfield and Wilcoxon's method [18].

Hydrolytic Stability of Benzoyl Chloride 4-Bromophenylhydrazone (II). The fungus T. mentagrophytes was inoculated into Sabouraud's selective broth containing compound II in the fungicidal concentration and compound XXXIII for comparison. Each day for 10 days the growth medium in the control, kept separate from the fungus, and the mass of the fungus were treated with chloroform. The chloroform extracts were dried over calcium chloride and the products contained therein were identified chromatographically on Silufol UV-254 plates against standards (elution with ether–petroleum ether in various ratios). Compound II could be detected in the medium and in the mass of the fungus after 10 days; no transformations or conversion to the corresponding hydrazide XXXIII could be detected.

EXPERIMENTAL CHEMICAL PART

Acyl halide arylhydrazones (I-XI, XIII, XVI, XVIII-XXI, XXIV-XXX) and carboxylic acid arylhydrazides (XXXII-XLVIII, L, LII, LIV, LVI) were prepared by published procedure [1-15].

Acetyl Chloride 4-Bromophenylhydrazone (XII). To a suspension of XLV (6.9 g, 0.03 mole) and triphenylphosphine (9.8 g, 0.0375 mole) in freshly distilled acetonitrile (60 ml) was added with stirring carbon tetrachloride (3 ml, 0.03 mole). The mixture was stirred at 20-25°C for 6-8 h. The solvent was removed under vacuum. The thick residue was stirred with chloroform and after 12 h standing the precipitate of XII was filtered off. The yield was 38%, mp 110-112°C (from benzene–acetone). IR spectrum in Vaseline oil, ν, cm^{-1}: 3132 (NH), 1600 (aromatic ring C= C). UV spectrum in ethanol, λ_{max} (log ε), nm: 273 (4.34), 308 (3.78). Found, %: C 38.99; H 3.48; Br 32.51; Cl 14.08; N 11.19. $C_8H_8BrClN_2$. Calculated, %: C 38.79; H 3.23; Br 32.32; Cl 14.34; N 11.31.

Acetyl Chloride 2,4-Dinitrophenylhydrazone (XV). To phosphorus oxychloride (9 ml, 0.1 mole) at 13-15°C with stirring were added pyridine (1.8 ml, 0.02 mole) and then in small portions acetic acid 2,4-dinitrophenylhydrazide (4.8 g, 0.02 mole). The mixture was slowly heated to 75-80°C. After 1 h it was cooled and the pre-

cipitate was filtered off, washed with phosphorus oxychloride, dried, and recrystallized from ethanol and then from chloroform to give yellow crystals of XV (5.0 g, 98%) with mp 152-154°C (decomposition). IR spectrum in Vaseline oil (ν, cm^{-1}): 3186 (NH), 1626 (C = N), 1590 (aromatic ring C = C). UV spectrum in ethanol, λ_{max} (log ε), nm: 228 (4.18), 265 (4.06), 350 (4.28). Found, %: C 37.29; H 2.81; Cl 13.52; N 21.40. $C_8H_7ClN_4O_4$. Calculated, %: C 37.13; H 2.70; Cl 13.73; N 21.66.

Propionyl Chloride 2-Nitrophenylhydrazone (XVII). To phosphorus oxychloride (2.7 ml, 0.03 mole) was added at 15-20°C with stirring pyridine (0.8 ml, 0.01 mole). Propionic acid 2-nitrophenylhydrazide (2.1 g, 0.01 mole) was then added to this mixture in small portions. The mixture was heated on a water bath to 70-75°C and kept at this temperature for 1 h. After cooling it was poured into ice water. The precipitate was washed free of chloride ion with water. The yield was 75%, mp 47-48°C (from ethanol). IR spectrum in Vaseline oil, ν, cm^{-1}: 3303 (NH), 1620 (C = N). UV spectrum in methanol, λ_{max} (log ε), nm: 263 (4.28), 282 (4.17), 415 (3.78). Found, %: C 47.46; H 4.60; Cl 18.63; N 15.81. $C_9H_{10}ClN_3O_2$. Calculated, %: C 47.53; H 4.39; CL 18.46; N 15.60.

Nicotinoyl Bromide 4-Nitrophenylhydrazone (XXII) and Isonicotinoyl Bromide 4-Nitrophenylhydrazone (XXIII). To a suspension of 3- or 4-pyridinealdehyde 4-nitrophenylhydrazone (2.4 g, 0.01 mole) in acetic acid (80 ml) and potassium acetate (5 g) was added with stirring bromine (0.52 ml, 0.01 mole) over 3 min. After 30 min the yellow precipitate was separated and washed with acetic acid and then with ether. The yield was 92%, mp > 350°C (decomposition). IR spectrum in Vaseline oil, ν, cm^{-1}: XXII: 3122 (NH), 1598 (C = N and aromatic ring C = C); XXIII: 3111 (NH), 1603 (C = N and aromatic ring C = C). Found, %: XXII: C 44.92; H 3.02; Br 24.70; N 17.28; XXIII: C 44.66; H 2.98; Br 24.92; N 17.44. $C_{12}H_9BrN_4O_2$. Calculated, %: C 44.86; H 2.80; Br 24.92; N 17.44.

Pyruvoyl Bromide 4-Sulfamoylphenylhydrazone (XXV). To a suspension of methylglyoxal 4-sulfamoylphenylhydrazone (4.82 g, 0.02 mole) [19] in acetic acid (60 ml) was added, with stirring, bromine (1 ml, 0.02 mole) in acetic acid (10 ml) over 30-40 min. After 30 min the brownish yellow precipitate of XXV was separated and washed with acetic acid. The yield was 50%, mp 201-202°C (from acetic acid). IR spectrum in Vaseline oil, ν, cm^{-1}: 3320, 3236 (NH), 1690 (C = O). UV spectrum in methanol, λ_{max} (log ε), nm: 254 (4.0), 294 (3.77), 350 (4.39). Found, %: C 33.63; H 3.07; Br 24.81; N 13.31. $C_9H_{10}BrN_3O_3S$. Calculated, %: C 33.74; H 3.12; Br 25.00; N 13.12.

Butyryl Bromide 2,4-Dinitrophenylhydrazone (XXVII). To a suspension of butyraldehyde 2,4-dinitrophenylhydrazone (5.04 g, 0.02 mole) in acetic acid (20 ml) and acetic anhydride (0.2 ml) was added dropwise, with sitrring, a solution of bromine (6.1 ml, 0.1 mole) in acetic acid (5 ml) over 10 min. After another 10 min the precipitate was filtered off and washed with acetic acid and petroleum ether. Recrystallization from acetic acid gave yellow crystals of XXVII (2.7 g, 41%) with mp 122-124°C. IR spectrum in Vaseline oil, ν, cm^{-1}: 3256 (NH), 3106 (CH), 1626 (C = N), 1595 (aromatic ring C = N). UV spectrum in ethanol, λ_{max} (log ε), nm: 238 (4.15), 270 (4.00), 363 (4.20). Found, %: C 36.03; H 3.29; Br 24.52; N 17.06. $C_{10}H_{11}BrN_4O_4$. Calculated, %: C 36.25; H 3.32; Br 24.17; N 16.92.

4-Bromophenylhydrazides of Propionic (XLIX), Butyric (LI), Valeric (LIII), and Isovaleric (LV) Acids. 4-Bromophenylhydrazine (9.3 g, 0.05 mole) was refluxed for 1.5-2 h in propionic acid (13-15 ml) (or butyric, valeric, or isovaleric acids respectively) and the mixture was cooled. The precipitate was filtered off, washed with ether, and recrystallized from ethanol. Compound XLIX formed white crystals, yield 70-75%, mp 178-179°C. IR spectrum in Vaseline, ν, cm^{-1}: 3293, 3264 (NH), 1671, 1643, (amide), 1592 (aromatic ring). UV spectrum in ethanol λ_{max} (log ε), nm: 246 (4.22), 298 (3.22). Found, %: C 44.29; H 4.68; Br 33.14; N 11.73. $C_9H_{11}BrN_2O$. Calculated, %: C 44.44; H 4.52; Br 32.92; N 11.52. Compound LI formed light yellow crystals, yield 60-65%, mp 129-130°C. IR spectrum in Vaseline oil, ν, cm^{-1}: 3288, 3272 (NH), 1663, 1641 (amide), 1600 (aromatic ring). UV spectrum in ethanol, λ_{max} (log ε), nm: 246 (4.26), 295 (3.20). Found, %: C 46.81; H 5.17; Br 31.27; N 10.60. $C_{10}H_{13}BrN_2O$. Calculated, %: C 46.69; H 5.05; Br 31.12; N 10.89. Compound LIII formed white crystals, yield 50-55%, mp 119-121°C. IR spectrum in Vaseline oil, ν, cm^{-1}: 3290, 3220, 3190, 3150 (NH), 1666, 1641 (amide), 1602 (aromatic ring). UV spectrum in ethanol, λ_{max} (log ε), nm: 247 (4.23), 298 (3.18). Found, %: C 48.31; H 5.49; Br 29.14; N 10.48. $C_{11}B_{15}BrN_2O$. Calculated, %: C 48.70; H 5.53; Br 29.52; N 10.33. Compound LV formed white crystals, yield 47-50%, mp 148-149°C. IR spectrum in Vaseline oil, ν, cm^{-1}: 3307 (NH), 1647 (amide), 1594 (aromatic ring). UV spectrum in ethanol, λ_{max} (log ε), nm: 245 (4.23), 296 (3.16). Found, %: C 48.53; H 5.62; Br 29.66; N 10.72. $C_{11}H_{15}BrN_2O$. Calculated, %: C 48.70; H 5.53; Br 29.52; N 10.33.

LITERATURE CITED

1. Yu. P. Kitaev and B. I. Buzykin, Hydrazones [in Russian], Moscow (1974), pp. 151-218.
2. S. D. Folz, U. S. Patent No. 3721740; Ref. Zh. Khim., No. 3, N266 (1974).
3. Zh. V. Molodykh, A. N. Lisenkova, B. I. Buzykin, et al., Khim.-Farm. Zh., No. 1, 81 (1977).
4. J. E. Moore, U. S. Patent No. 3867449; Ref. Zh. Khim., 240512 (1975).
5. G. Kaugars and E. G. H. Gemrich, U. S. Patent No. 3879543; Ref. Zh. Khim., 50396 (1976).
6. T. Noguchi, T. Hosotsuji, H. Ishikawa, et al., Japanese Patent No. 43111; Ref. Zh. Khim., 18N497 (1972).
7. M. O. Lozinskii, M. N. Rotmistrov, S. N. Kukota, et al., in: Physiologically Active Substances [in Russian], Vol. 2, Kiev (1969), pp. 195-198.
8. A. I. Dychenko, E. F. Granin, L. P. Charuiskaya, et al., in: Physiologically Active Substances [in Russian], Vol. 9, Kiev (1977), pp. 54-56.
9. A. E. Smith, G. E. O'Brien, and A. Bernmann, U. S. Patent No. 2758051; Chem. Abstr., 51, 1524b (1957).
10. Y. Usui and Ch. Matsumura, Yakugaku Zasshi, 87, 38 (1967); Chem. Abstr., 67, 11452 (1967).
11. Y. Usui and Ch. Matsumura, Yakugaku Zasshi, 87, 43 (1967); Chem. Abstr., 67, 32382a (1967).
12. P. E. Frohberger, E. Urbschat, D. Mayer, et al., German Patent No. 2223936; Chem. Abstr., 80, 70557 (1974).
13. T. Taniguchi, Y. Yasuda, A. Nakada, et al., Japanese Patent No. 4911061; Ref. Zh. Khim., 23N628 (1974).
14. Dutch Patent No. 145435; Ref. Zh. Khim., 90354 (1976).
15. S. N. Milovanova and Z. G. Stepanishcheva, in: G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1971), 2nd edn., pp. 318-320.
16. S. N. Milovanova, in: G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1971), 2nd edn., pp. 104-106.
17. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effect [in Russian], Leningrad (1963), 2nd edn.
18.*
19. Yu. P. Kitaev, B. I. Buzykin, and L. P. Sysoeva, Zh. Org. Khim., 8, 515 (1972).

*Reference 18 omitted in Russian original – Publisher.

SYNTHESIS AND STUDY OF THE PHARMACOLOGICAL PROPERTIES OF 2-AMINOMETHYL AND 2,4-, 2,5-, AND 2,6-DIAMINOMETHYL DERIVATIVES OF 3-ARYLBENZOFURANS

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Continuing a search for cardiovascular agents in the benzofuran series, we have carried out the synthesis and have studied the pharmacological properties of 2-aminomethyl and 2,4-, 2,5-, and 2,6-diaminomethyl derivatives of 3-arylbenzofurans.

Using a published method, from α-phenoxypropiophenones (I-VI) we obtained 2-methyl-3-arylbenzofurans with substituents in position 5 (VII-X) or position 6 (XI-XIII) [1]. 2-Methyl-5-nitro-3-phenylbenzofuran (XIV) was obtained by nitrating the known 2-methyl-3-phenylbenzofuran [2].

As reported previously, 2-methylbenzofuran derivatives are brominated by N-bromosuccinimide in the methyl group [2]. In the present work we obtained a series of 2-bromomethyl derivatives of benzofuran which, without isolation, were converted into the 2-aminomethyl derivatives (XV-XXXII) under the action of secondary amines – diethylamine, piperidine, morpholine, and N-phenylpiperazine.

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