SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NITROGEN-CONTAINING DERIVATIVES OF BENZO-1,4-DIOXANE

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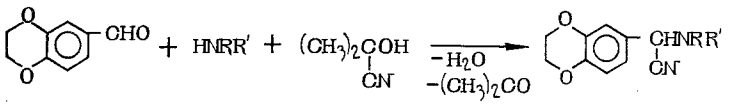
The biological activity of benzo-1,4-dioxane derivatives is known [1]; however, there is little information in the literature about their antimicrobial action. The object of the present work was to synthesize previously undescribed nitrogen-containing derivatives of benzo-1,4-dioxane and investigate their antimicrobial properties.

A series of aminonitriles and azomethines containing the benzo-1,4-dioxane ring has been synthesized. On reaction of 6-formylbenzo-1,4-dioxane with a series of aliphatic and aromatic amines and acetone cyanohydrin, which was used as a source of hydrogen cyanide [2], the 6-benzodioxanylaminoacetonitriles (I-XIII) were formed in good yield:



I: R=R′= C_2H_5; *II*: RR′=*N*-piperidyl; *III*: RR′=*N*-morpholyl

IV R = H, R′ = C_6H_5; V R = H, R′ = 4-CH_2-C_6H_4;

VI R = H, R′ = 4-CH_3O-C_6H_4; VII R = H, R′ = 4-Br-C_6H_4;

VIII R = H, R′ = 4-I-C_6H_4; IX R = H, R′ = 2,5-Cl_2-C_6H_3;

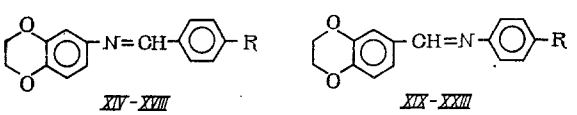
X R = H, R′ = 4-NO_2-C_6H_4; XI R = H, R′ = 4-SO_2NH_2-C_6H_4;

XII R = H, R′ = 2-naphthyl; XIII R = H, R′ = benzo-1,4 dioxanyl-6

A brief heating of the reagents (55-60°C) is required to carry out the reaction. When there are electron-donor substituents in the benzene ring of the aromatic amines, the reaction proceeds more easily with aniline derivatives which contain electron-acceptor substituents.

Analytical figures for aminonitriles I-XIII are given in Table 1. In their IR spectra there are intense absorption bands in the 1250 cm^{-1} region, which are characteristic of benzo-1,4-dioxane derivatives and corresponding stretching vibrations of the C−O−C group of the dioxane ring [3, 4], plus bands in the 2240-2255 cm^{-1} region which are assignable to the stretching vibrations of the CN group.

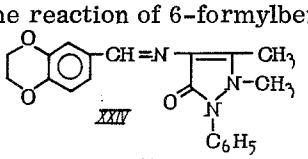
By reaction of 6-aminobenzo-1,4-dioxane with aromatic aldehydes and of 6-formylbenzo-1,4-dioxane with para-substituted anilines, a series of azomethines (XIV-XXIII) was obtained, containing the benzodioxane ring.



XIV-XVIII XIX-XXIII

R = OCH_3 (XIV), $N(CH_3)_2$ (XV), Cl (XVI), NO_2 (XVII), benzo-1,4-dioxanyl-6 (XVIII), CH_3 (XIX), OCH_3 (XX), Cl (XXI), I (XXII), NO_2 (XXIII)

Compound XXIV was obtained from the reaction of 6-formylbenzo-1,4-dioxane with 4-aminoantipyrine.



XXIV

The azomethines synthesized are colored crystalline substances with definite melting points, whose structures have been confirmed by elemental analyses, IR spectra, and some chemical transformations (Table 2).

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TABLE 1. Aminonitriles I-XIII

Compound	Yield, %	mp, °C	Found, %			Molcular formula	Calculated, %		
			C	H	N		C	H	N
I	62	64—5	68,54	7,11	11,68	$C_{14}H_{18}N_2O_2$	68,27	7,36	11,38
II	87	97—8	70,14	6,82	10,73	$C_{15}H_{18}N_2O_2$	69,75	7,02	10,86
III	74	131—2	64,83	6,25	10,76	$C_{14}H_{16}N_2O_3$	64,59	6,19	10,76
IV	61	94—5	72,18	5,42	10,58	$C_{16}H_{14}N_2O_2$	72,13	5,29	10,52
V	71	145—6	73,16	5,41	10,30	$C_{17}H_{16}N_2O_2$	72,77	5,75	10,00
VI	70	85—6	68,96	5,01	9,31	$C_{17}H_{16}N_2O_3$	68,91	5,44	9,44
VII	51	135	55,79	3,98	8,37	$C_{16}H_{13}BrN_2O_2$	55,64	3,79	8,11
VIII	92	128—9	49,41	3,12	7,41	$C_{16}H_{13}IN_2O_2$	49,00	3,34	7,14
IX	60	100—1	57,62	3,69	8,52	$C_{16}H_{12}Cl_2N_2O_2$	57,27	3,61	8,36
X	32	177—8	62,02	4,61	13,59	$C_{16}H_{13}N_3O_4$	61,73	4,20	13,50
XI	37	190—1	55,78	4,71	12,36	$C_{16}H_{15}N_3O_4S$	55,64	4,38	12,16
XII	69	129—30	76,28	5,45	8,97	$C_{20}H_{16}N_2O_2$	75,94	5,09	8,86
XIII	72	158—9	66,91	4,42	8,71	$C_{18}H_{15}N_2O_4$	66,87	4,67	8,66

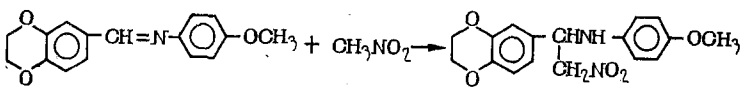
*Compounds I and II were crystallized from 50% alcohol; III-V, VII-IX, and XI-XIII from alcohol; VI from a mixture of hexane and benzene (3 : 1); and X from isopropyl alcohol.

TABLE 2. Azomethines XIV-XXIV

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
XIV	77	77	71,58	5,42	5,38	$C_{16}H_{15}NO_3$	71,33	5,60	5,20
XV	70	114—5	72,14	6,13	9,61	$C_{17}H_{18}N_2O_2$	72,33	6,42	9,93
XVI	66	67—8	65,43	4,14	5,38	$C_{15}H_{12}ClNO_2$	65,82	4,42	5,10
XVII	98	165—6	63,69	4,51	9,67	$C_{15}H_{12}N_2O_4$	63,36	4,25	9,85
XVIII	56	96	68,37	5,51	4,97	$C_{17}H_{15}NO_4$	68,68	5,08	4,71
XIX	58	59	75,59	5,42	5,82	$C_{16}H_{15}NO_2$	75,87	5,96	5,53
XX	82	101	71,48	5,96	5,57	$C_{16}H_{15}NO_3$	71,33	5,60	5,20
XXI	60	69	65,52	4,87	5,44	$C_{15}H_{12}ClNO_2$	65,82	4,42	5,10
XXII	88	70	49,60	3,58	4,11	$C_{15}H_{12}NO_2$	49,31	3,31	3,83
XXIII	58	178	63,52	4,60	9,99	$C_{15}H_{12}N_2O_4$	63,36	4,25	9,85
XXIV	90	208—9	68,92	5,97	12,30	$C_{20}H_{19}N_3O_3$	68,75	5,77	12,03

*Compounds XIV, XVI, and XIX-XXII were crystallized from hexane; XV, XVII, and XXIV. from alcohol; XVIII from propanol; and XXIII from methanol.

It is known that Schiff bases undergo addition reactions with compounds containing a mobile hydrogen. Knowing this, we prepared an addition product by the reaction of azomethine XX with nitromethane, in which the latter added across the C=N multiple bond of the azomethine:



XX XXV

On reaction of azomethine XIX with acetone cyanohydrin, an aminonitrile was obtained which was identical to the previously synthesized compound V. The comparatively mild reaction conditions and the ease of azomethine formation permit one to assume that in the synthesis of aminonitriles I-XIII, in the first stage of reaction, as a result of reaction of the amine and aldehyde a Schiff base is formed, and that this then adds hydrogen cyanide, which is regenerated by the acetone cyanohydrin in the presence of bases, and this leads to the formation of the aminonitriles.

In the IR spectra of azomethines XIV-XXIV there is an absorption band in the 1620-1630 cm^{-1} region which is characteristic of the C=N bond in Schiff bases. Moreover, absorption bands characteristic of benzo-1,4-dioxane are observed in the spectra of compounds XIV-XXV.

The antimicrobial activity of the aminonitriles and azomethines was determined by the serial dilution method in liquid growth medium [5] (Table 3). It was ascertained that the minimum bacteriostatic concentration of the compounds studied with respect to Staphylococcus aureus (strain 209) is in the range from 7.81 to 62.5 μg/ml; with respect to E. coli (strain 365), S. typhi (strain 495), or B. anthracoides (strain 297), from 15.62 to 125.0 μg/ml; with respect to Proteus vulgaris (strain 409) or Ps. aeruginoca (strain 128), from 31.25 to 250 μg/ml. The minimum fungistatic concentration of the aminonitriles and azomethines with respect to yeast-like fungi of the Candida type is in the range from 7.81 to 125 μg/ml.

TABLE 3. Antimicrobial Activity (in μg/ml) of Aminonitriles I-XIII and Azomethines XIV-XXV

Compound	Microorganisms						
	Staphyloc. aureus 209	E. coli 365	S. typhi 495	B. anthracoides 297	B. proteus vulgaris 409	Ps. aeruginosa 128	Candida albicans 688
I	31,25	62,5	62,5	31,25	62,5	62,5	31,25
II	15,62	31,25	62,5	31,25	125,0	62,5	15,62
III	31,25	62,5	62,5	31,25	125,0	62,5	15,62
IV	15,62	31,25	31,25	15,62	125,0	62,5	31,25
V	31,25	62,5	62,5	31,25	125,0	125,0	31,25
VI	31,25	125,0	125,0	250,0	250,0	125,0	62,5
VII	7,81	31,25	31,25	62,5	62,5	62,5	15,62
VIII	7,81	31,25	31,25	31,25	62,5	62,5	15,62
IX	62,5	125,0	62,5	31,25	62,5	62,5	62,5
X	31,25	62,5	62,5	31,25	62,5	62,5	31,25
XI	7,81	15,62	31,25	15,62	31,25	62,5	7,81
XII	31,25	62,5	31,25	62,5	31,25	62,5	31,25
XIII	31,25	31,25	62,5	31,25	62,5	62,5	31,25
XIV	62,5	62,5	125,0	62,5	62,5	62,5	62,5
XV	31,25	62,5	125,0	31,25	125,0	125,0	62,5
XVI	62,5	125,0	125,0	62,5	125,0	125,0	62,5
XVII	15,62	31,25	31,25	31,25	62,5	62,5	15,62
XVIII	31,25	62,5	62,5	31,25	62,5	125,0	125,0
XIX	31,25	62,5	62,5	31,25	62,5	125,0	62,5
XX	31,25	62,5	62,5	31,25	62,5	62,5	62,5
XXI	15,62	62,5	31,25	62,5	62,5	125,0	31,25
XXII	31,25	62,5	62,5	31,25	62,5	62,5	31,25
XXIII	7,81	31,25	31,25	15,62	125,0	62,5	15,62
XXIV	31,25	62,5	62,5	31,25	125,0	125,0	31,25
XXV	7,81	15,62	31,25	15,62	62,5	62,5	7,81

Some dependence of the antimicrobial activity of the compounds synthesized on their chemical structure was noted. Thus, the introduction of bromine or iodine atoms as substituents into the benzene ring of an aminonitrile molecule (compounds VII and VIII) leads to an increase in antimicrobial activity with respect to all the test-cultures investigated. Among the aminonitriles I-XIII, compound XI, which contains a sulfamide group and possesses high anti-Candida activity in identical degree also, displays the maximum activity toward gram-positive and also toward gram-negative bacteria.

Of the group of azomethines XIV-XXIV, the most active are the compounds which have electron-acceptor substituents in the benzene ring (compounds XVII, XXI, and XXIII).

On transition from the azomethines to the aminonitriles of analogous structure (compounds XIX, XX, XXII, and XXIII and the corresponding V, VI, VIII, and X), basically a certain decrease in antimicrobial activity is observed. Comparing the action of compounds XX, VI, and XXV, one may say that the addition of HCN to the unsaturated C = N bond leads to a reduction in antimicrobial activity, while addition of CH_3NO_2 leads to an increase in it.

EXPERIMENTAL

Aminonitriles (I-XIII). To a mixture of 10 mmoles of 6-formylbenzo-1,4-dioxane and 10 mmoles of the corresponding amine was added 1-3 ml of freshly distilled acetone cyanohydrin, until solution of the mixture occurred. The solution was heated for 3-6 h at 55-60°, and was allowed to stand overnight. In the case of preparation of compounds III, V, and VII-XIII, precipitates were formed. In the synthesis of compounds I, II, IV, and VI, the excess acetone cyanohydrin and the acetone and water formed in the reaction were distilled off under water-pump vacuum from a water bath. On cooling, the residues crystallized after a certain period. The solids formed were filtered off and crystallized from appropriate solvents.

Azomethines (XIV-XXIV). A mixture of 5 mmoles of 6-aminobenzo-1,4-dioxane (or 6-formylbenzo-1,4-dioxane) and 5 mmoles of the corresponding aldehyde (or amine) was dissolved in 5-10 ml of alcohol and the mixture was allowed to stand overnight at room temperature. The precipitates formed were filtered off and crystallized from appropriate solvents.

1-(p-Methoxyphenyl)amino-1-(benzo-1,4-dioxanyl-6)-2-nitroethane (XXV). A solution of 0.7 g (2.5 mmole) of azomethine XX and 0.3 g (5 mmole) of nitromethane in 15 ml of absolute alcohol was boiled for 6 h. The precipitate formed on cooling was filtered off and crystallized from alcohol. Compound XXV (0.51 g, 62%) was obtained, having a mp of 145-146°C. Found, %: N 8.66. $C_{17}H_{18}N_2O_5$. Calculated, %: N 8.48.

Aminonitrile (V). To a solution of 0.25 g (1 mmole) of azomethine XIX in 4 ml of acetone cyanohydrin was added three drops of piperidine and the mixture was heated for 1 h at 50-60°C. Then the reaction mixture was allowed to stand overnight. The precipitate, which had settled out, was filtered off, and 0.27 g (96%) of crystals was obtained, having mp 145-146° (from alcohol). A mixture mp test with the previously prepared aminonitrile V gave no mp depression.

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DERIVATIVES OF 1,5-NAPHTHYRIDINE-2-CARBOXYLIC ACID, THEIR N-OXIDES, AND REDOX REACTIONS OF 1,5-NAPHTHYRIDINE-2-ALDEHYDE N,N'-DIOXIDE

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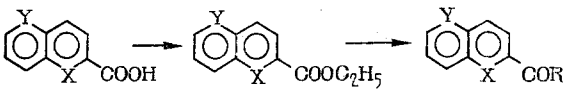
N-Oxides of amides and hydrazides of quinoxaline-2-carboxylic acids have exhibited high antibacterial activity [1]. In this connection, it was of interest to synthesize analogous derivatives of 1,5-naphthyridine-2-carboxylic acid and their N-oxides and to study the antibacterial activity of the obtained compounds. The compounds contemplated for study were obtained from the esters of the corresponding acids.

It has been shown previously that the methyl ester of 1,5-naphthyridine-2-carboxylic acid is formed via the reaction of the acid (I) with methanol in the presence of concentrated sulfuric acid [2]. Esters of the 1,5-di-N-oxides of 1,5-naphthyridine-2-carboxylic acid could not be obtained by this method; in the conditions mentioned, as well as on heating in alcohols in the presence of HCl, the main product was the starting 1,5-di-N-oxide of 1,5-naphthyridine-2-carboxylic acid (II).

The ethyl ester of 1,5-naphthyridine-2-carboxylic acid 1,5-di-N-oxide (III) was obtained in high yield on heating II with thionyl chloride in nonaqueous ethanol (see Table 1). This same method was used to obtain the ethyl ester V from 1,5-naphthyridine-2-carboxylic acid 5-N-oxide and the ethyl ester VI from I.



I, II, IV

I X=Y=N
II X=Y=N→O
III X=Y=N→O
IV X=N, Y=N→O

III, V, VI

V X=N, Y=N→O
VI X=Y=N

XIII-XVIII

XIII X=Y=N, R=NH_2
XIV X=Y=N, R=$NHNH_2$
XV X=N, Y=N→O, R=NH_2
XVI X=Y=N→O, R=NH_2
XVII X=Y=N→O, R=$NHCHCH_2C_6H_5$ (CH$_3$)
XVIII X=Y=N→O, R=$NHNH_2$

The acid IV was isolated while studying the redox reactions of 1,5-naphthyridine-2-carboxaldehyde 1,5-di-N-oxide (VII) in the presence of alkaline reagents.

It has been shown previously that pyrazine-2-carboxaldehyde 1,4-di-N-oxide (VIII), containing the aldehyde group as the hydrate, on attack by alkaline reagents behaves analogously to N-oxides of aromatic heterocycles substituted with α-hydroxyalkyl groups in positions ortho and para to the oxidized nitrogen of the ring [3, 4] and undergo oxidation of the α-dihydroxyalkyl group with simultaneous dioxidation of a heterocyclic

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