The most active amides, IIIc and IIId, were tested with respect to sarcoma 180. These compounds showed moderate antitumor activity by inhibiting its growth by 48-51% ($\alpha > 0.95$) and did not show toxic effects on the organism of the experimental rats.

Thus, the antitumor effect that we have found (compounds IIIc, d) shows promise for carrying out further search among amides of 2-oxo-1-oxaspiro[4,5]decane-4-carboxylic acid.

Investigation of the psychotropic properties of compounds I, IIId, and IIIf showed that they cause some oppression of the motor activity in mice. Given at a dose of 100 mg/kg, the compounds prolong the soporific effect of hexenal almost two times ($p < 0.05$) and essentially do not affect the toxicity of tryptamine.

In experiments in vitro the compounds under investigation have weak antimonoamine oxidase activity (20-25%).

During investigation of compounds IIIe-f with the experimental model of arrhythmia of the heart it was found that at doses of 3-5 mg/kg they possess antiarrhythmic activity and a noticeable effect on the arterial pressure and the frequency of heart contractions.

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SYNTHESIS AND PROPERTIES OF 1,4-BENZODIKETO- AND 1,4-BENZOMONO KETODICARBOXYLIC ACIDS AND THEIR DERIVATIVES

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Alkyl- and arylglyoxylic acids are important intermediates in the metabolism and biosynthesis of many natural amino acids, and, because of the presence of highly reactive groupings, they are also widely used in the syntheses of heterocyclic and other organic compounds. Data on the known methods of synthesis and properties of α-ketoacids are presented in reviews [2, 3].

One of the most promising methods of preparation of arylglyoxylic acid is based on the oxidation of ethyl-substituted benzenes by potassium permanganate solutions. It was previously shown that in the oxidation of 1,4-diethylbenzene by $KMnO_4$ in an alkaline medium, a mixture of 1,4-benzenediketodicarboxylic acid (I), 1,4-benzenemonodicarboxylic (II) and terephthalic (III) acids is formed [1].

However, these acids could not be separated into individual components, and their properties, except for III were practically not investigated. It was of interest to obtain them in a pure state and to study the chemical characteristics of the structurally similar compounds I and II.

We have now separated acids I and II from the mixture of oxidation products of p-diethylbenzene for the first time. The free acids were isolated by acidifying the partially evaporated aqueous solutions of potassium salts of the oxidation products with hydrochloric acid to pH 3.0-3.5 and separating the precipitated terephthalic acid III. A mixture of I and II was obtained by extraction from a strongly acidified filtrate with diethyl ether.

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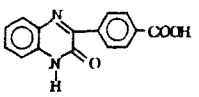
TABLE 1. Antimicrobial Activity of Derivatives of 1,4-Benzenemonoketodicarboxylic and 1,4-Benzenediketodicarboxylic ACids, Maximum Tolerated concentration (MTC) (in μg/ml)

Compound	H37Rv	M. kansasii	M. avium	AKC 607	Bac. subtilis 6633	E. coli ATCC 25922	Pr. vulgaris 6896	Ps. aeruginosa 27853	St. aureus 309—P	M. canis 3/84	Tr. gypseun 5/85	C. albicans 1755
VIII	153	1000	>1000	1000	>250	>250	>250	>250	>250	>250	>250	>250
VI	23	153	1000	1000	>250	>250	>250	>250	>250	125	125	>250
IX	>153	>153	1000	153	>250	>250	>250	>250	>250	>250	>250	>250
X	>153	>153	>1000	>1000	>250	>250	>250	>250	>250	>250	>250	>250
XI	153	153	1000	>1000	>250	>250	>250	>250	>250	>250	>250	>250
XV	>153	>1000	153	1000	>250	>250	>250	>250	>250	>250	>250	>250

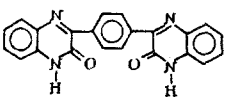
Compounds I and II were separated by fractional crystallization, taking advantage of their different solubilities in acetone and benzene. The purity of the separated compounds I and II was determined by gas liquid chromatography, preliminarily converting them into methyl esters.

Acids I and II readily form derivatives at the keto group: thiosemicarbazones (XIV and VII), semicarbazone (VIII), phenylhydrazones (XIII and VI); similarly from ketoester IV thiosemicarbazone XI, semicarbazone XII, phenylhydrazone X were obtained. It should be noted that while the reaction of the ketoacids with semicarbazides proceeds fairly completely in the presence of an acid catalyst, from the ketoester IV, the semicarbazone XII, and phenylhydrazone X are formed in lower yields.

Acids I and II react readily with o-phenylenediamine, giving quinoxalinone derivatives – 4-[2(3H)-oxoquinoxalinyl]benzoic acid IX and 3,3'-(1,4-phenylene)bis(quinoxalin-2(3H)-one) (XV), respectively. Derivatives of keto acids I and II and their methyl esters were characterized by the IR, ^{1}H NMR and mass spectral data.



IX



XV

The derivatives of 1,4-benzenemonoketodicarboxylic and 1,4-benzenediketodicarboxylic acids I-XV that were synthesized in the present work were tested for antubercular and antibacterial activity; the results are given in the experimental biological part and in Table 1.

EXPERIMENTAL (CHEMICAL)

The ^{1}H NMR spectra of the compounds were run on an XL-200 "Varian" spectrometer (Switzerland) with a 200 MHz working frequency for the ^{1}H nuclei, using $CDCl_3$ as a solvent and TMS as a standard. The IR spectra were determined on a "Perkin-Elmer-457" spectrophotometer (Sweden), and the mass spectra on a "Varian MAT-12" spectrometer, with energy of the ionizing electrons of 70 eV, and temperature of the ionization chamber 180°C. The results of the elemental analysis corresponded to the calculated values.

1,4-Benzenemonoketodicarboxylic Acid (II). 1,4-Diethylbenzene (2.5 g, 18.7 mmoles) and 25 ml of a 10% KOH (44.6 mmoles) were added in one portion to 800 ml of a 2.5% aqueous solution of $KMnO_4$ (12.7 mmoles) heated to 75°C. The mixture was stirred for 50 min at 75°C, and, after adding 2 ml of ethanol, was allowed to stand for 10 min. The MnO_2 precipitate was filtered off and washed with 15 ml of water. The combined filtrates were evaporated on a water bath to a volume of 200 ml, acidified with a concentrated HCl to pH 3.0-3.5, and the precipitate of III [0.62 g (21.4%)] was filtered off. By extraction with diethyl ether from a strongly acidified filtrate by HCl, a mixture of I, II and III (2.49 g) was separated with a composition of 28.5, 69.0 and 2.5%, respectively.

The mixture of the acids was dissolved in 100 ml of hot acetone; after cooling the solution, the precipitate of III [0.06 g (21%)] was filtered off. The filtrate was concentrated to 1/3 of the initial volume and an equal volume of hot benzene was added to the hot solution. The precipitate that separated out was filtered off and washed with benzene. The yield of II was 1.02 g (36%), mp 221-222°C. White powder, readily soluble in water and polar organic solvents. IR spectrum, ν_{max}, cm^{-1}: 1680, 1710 (C=O), 3515 (OH), 820 (1,4-substituted benzene ring). Mass spectrum: m/z M^+ 194 $[M-COOH]^+$ (149), $[M-CO]^+$ (121), $C_9H_6O_5$.

1,4-Benzenediketodicarboxylic Acid (I). After the separation of II, the filtrate was evaporated to 1/2 of the initial volume and cooled. The precipitate that separated out, containing a mixture of I and II, was filtered off. After the evaporation of filtrate, compound I was obtained, yield 0.25 g (6.03%), mp 218-219°C. White powder, which is readily soluble in water and polar organic solvents. IR spectrum, ν_{max}, cm^{-1}: 1680, 1710 (C=O), 3515 (OH), 1610, 820 (1,4-substituted benzene ring). Mass spectrum: M^+ 222, calculated M^+ 222. $C_{10}H_6O_6$.

Dimethyl Ester of 1,4-Benzenemonoketodicarboxylic Acid (IV). A 0.5 g portion of concentrated H_2SO_4 was added to 1.0 mole of 1,4-benzenemonoketodicarboxylic acid (II) and 5 g of absolute methanol, and the mixture was boiled for 5 h under a reflux condenser. A large part of the alcohol was then evaporated on a water bath. Ice water and a 15% sodium carbonate were added to the residue, and the mixture was extracted with ether. After the distillation of ether, 0.97 g (84.7%) of dimethyl ester IV was obtained in the form of white crystals; mp 98-99%, sparingly soluble in alcohols, soluble in chloroform and acetone. $C_{11}H_{10}O_5$. Mass spectrum: a low intensity peak of the molecular ion with m/z 222; the maximal peak belongs to the ion $[MCOOCH_3]^+$ (163), and to decomposing ion $[MCOCOOCH_3]^+$ (135), $[OCH_3]^+$ (104), $[CO]^+$ (76), M^+ 222.

Dimethyl Ester of 1,4-Benzenediketodicarboxylic Acid (V). In analogy to the preparation of IV, to 1 g (5.1 mmole) of I and 5 g of methanol, 0.5 g of concentrated sulfuric acid was added, and the mixture was boiled for 5 h under reflux condenser. Ice water and a 15% solution of sodium carbonate was added to the residue and the mixture was extracted with ether. The solvent was evaporated and 0.92 g (92%) of dimethyl ester of 1,4-benzenediketodicarboxylic acid V was obtained. White needle-like crystals, mp 129-130°C, which are sparingly soluble in polar organic solvents and soluble in chloroform and benzene. $C_{12}H_{10}O_6$.

Phenylhydrazone of 1,4-Benzenemonoketodicarboxylic Acid (VI). A solution of 0.38 g (2.6 mmoles) of phenylhydrazine hydrochloride in 5 ml of 50% ethanol was added to a solution of 0.5 g (2.6 mmoles) of 1,4-benzenemonoketodicarboxylic acid in 5 ml of ethanol. The mixture was allowed to stand for 4 h at 20°C, and the phenylhydrazone precipitate that separated out was filtered off and washed with water. The yield of VI was 0.69 g (94.6%). Yellow crystals, mp 197-198°C. The compound is sparingly soluble in alcohols, and insoluble in water and $CHCl_3$. IR spectrum, ν_{max}, cm^{-1}: 3410, 3260 (NH, OH), 1525, 1610 (C=N), (C=O), 860-880 (disubstituted benzene ring), M^+ 284.

Thiosemihydrazone of 1,4-Benzenemonoketodicarboxylic Acid (VII). A 0.24 g portion (2.64 mmoles) of thiosemicarbazide in 8 ml of water was added to a solution of 0.5 g (2.6 mmoles) of II in 5 ml of ethanol, and the mixture was allowed to stand for 24 h at 20°C. The light-yellow precipitate was filtered off and washed with water. Yield 0.64 g (93.5%) of VII, which was dissolved in 4.8 ml of 1 N KOH. The solution obtained was filtered and acidified with 4.8 ml of 1 N HCl. The precipitate that separated out was filtered off and washed with water. Yield, 0.59 g (86.1%). Light-yellow crystals, mp 273-274°C (dec). The compound is practically insoluble in water and organic solvents. IR spectrum, ν_{max}, cm^{-1}: 1535, 1605, 1710, (C=N, C=O), 3180, 3305 (OH, NH). M^+ 267. $C_{10}H_9O_4N_3S$.

Semihydrazone of 1,4-Benzenemonoketodicarboxylic Acid (VIII). A 0.28 g portion (2.6 mmoles) of semicarbazide hydrochloride in 7 ml of water was added to a solution of 0.5 g (2.6 mmoles) of 1,4-benzenemonoketodicarboxylic acid in 5 ml of ethanol, and the mixture was allowed to stand for 24 h at 20°C. The precipitate of VIII was filtered off and washed with water. Yield 0.49 g (77.4%) mp 219-220°C. A white colored compound, sparingly soluble in ethanol and insoluble in water. IR spectrum, ν_{max}, cm^{-1}: 3480, 3350 (NH_2), 1710 (COOH), 1690 (NHCO) (amide I), 1550 (amine II), 1310 (amide III), M^+ 251. $C_{10}H_3N_3O_5$.

4-[2(3H)-Oxoquinoxalinyl]benzoic Acid (IX). A 0.28 g portion (2.59 mmoles) of o-phenylenediamine in 3 ml of ethanol was added to a solution of 0.5 g (2.6 mmoles) of 1,4-benzenemonoketodicarboxylic acid in 5 ml of ethanol; after 20 h 0.67 g (97.0%) of IX was filtered off. Dark-yellow crystals, mp 356-357°C (from aqueous ethanol). $C_{15}H_{10}N_2O_3$.

Phenylhydrazone of Dimethyl Ester 1,4-Benzenemonoketodicarboxylic Acid (X). A solution of 0.33 g (2.25 mmoles) of phenylhydrazine hydrochloride in 5 ml of 50% methanol was added to a solution of 0.5 g (2.25 mmoles) of dimethyl ester of 1,4-benzenemonoketodicarboxylic acid in 5 ml of methanol. The precipitate of phenylhydrazone, which separated out after 5 h of standing at 20°C, was filtered off, and washed with water. The yield of X was 0.58 g (82.5%). Yellow crystals, mp 116-117°C. $C_{17}H_{16}O_2N_4$.

Thiosemicarbazone of Dimethyl Ester 1,4-Benzenemonoketodicarboxylic Acid (XI). A solution of 0.21 g (2.25 mmoles) of thiosemicarbazide in 5 ml of 50% methanol was added to a solution of 0.5 g (2.25 mmoles) of dimethyl ester of 1,4-benzenemonoketodicarboxylic acid in 5 ml of methanol and the mixture was allowed to stand for 10 h at 20°C. The light yellow precipitate was filtered off, and washed with water. The yield of XI was 0.54 g (81.8%), mp 227°C.

Semicarbazone of Dimethyl Ester 1,4-Benzenemonoketodicarboxylic Acid (XII). A solution of 0.25 g (2.3 mmoles) of semicarbazide hydrochloride in 5 ml of 50% methanol was added to a solution of 0.5 g (2.25 mmoles) of dimethyl ester of 1,4-benzenemonoketodicarboxylic acid in 5 ml of methanol and the mixture was allowed to stand for 20 h at 20°C. The precipitate of XII was filtered off and washed with water. Yield 0.43 g (67.7%), mp 148-149°C. A white substance, sparingly soluble in alcohols and insoluble in water.

Phenylhydrazone of 1,4-Benzenediketodicarboxylic Acid (XIII). A solution of 0.76 g (5.26 mmoles) of phenylhydrazine hydrochloride in 7 ml of 50% ethanol was added to a solution of 0.5 g (2.25 mmoles) of 1,4-benzenediketodicarboxylic acid in 5 ml of ethanol, and the mixture was allowed to stand for 6 h 20°C. The precipitate of phenylhydrazone that separated out was filtered off and washed with water. The yield of XIII was 0.80 g (88.5%). Yellow crystals mp 304-305°C. The compound is sparingly soluble in alcohols, and insoluble in water.

Thiosemihydrazone of 1,4-Benzenediketodicarboxylic Acid (XIV). A solution of 0.48 g (5.28 mmoles) of thiosemicarbazide in 12 ml of water was added to a solution of 0.5 g (2.25 mmoles) of I in 5 ml of ethanol, and the mixture was allowed to stand for 24 h at 20°C. The light-yellow precipitate was filtered off and washed with water. Yield 0.73 g (88.5%) of XIV, mp 305-306°C. The compound is sparingly soluble in alcohols and insoluble in water and $CHCl_3$.

3,3'-(1,4-Phenylene)bis(quinoxalin-2(3H)-one) (XV). A 0.56 g protion (5.18 mmoles) of o-phenylenediamine in 5 ml of ethanol was added to a solution of 0.5 g (2.25 mmoles) of I in 5 ml of ethanol; after 20 h 0.78 g (94.5%) of XV was filtered off. Dark-yellow crystals, mp 324-325°C (from aqueous ethanol).

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity was studied by the method of serial dilutions on a liquid culture medium.* In experiments with mycobacteria the Soton medium was used, and with bacteria, the Saburo bouillon. The tuberculosis mycobacteria (strains $H_{37}Rv$, M. kansasii, M. avium, M. intracellulare, M. fortuitum and ATCC 607) were used as the test cultures. The activity with respect to bacteria was tested on strains St. aureus 209P, E. coli, ATCC 25922, Pr. vulgaris, ATCC 6896, Ps. aeruginosa 165 and clinical strains of dermatophyte fungi M. canis 3/84 and Tr. gypseum 5/85 and the yeast-like fungi C. albicans 1755.

The optical density of one-day old agar suspension of the cultures was determined according to the 5-unit turbidity standard followed by dilution with a sterile physiological solution to the final concentration equal to $1 \cdot 10^5$ CFU (colony forming units)/ml for bacteria, and to $1 \cdot 10^6$ CFU/ml for fungi.

The time of cultivation of the mycobacteria at 37°C was from 5 to 14 days, and for fungi at 25°C for 1 day with C. albicans and 5 days in experiments with M. canis and Tr. gypseum. The starting concentration of the tested compounds in the series of dilutions was 1000 μg/ml for the mycobacteria and 250 μg/ml for bacteria and fungi.

Our investigation showed that compounds VIII, IX, X, XI, XV have no antibacterial and antifungal activity. Compound VI has weak activity with respect to dermatophytes and Gram-positive bacteria.

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*The antibacterial and antifungal activity of compounds I-XV was studied by colleagues from the Laboratory of Chemotherapy of Infectious Diseases of the All-Union Scientific Research Chemical Pharmaceutical Institute under the direction of Prof. E. N. Padeiskaya, to whom the authors wish to express their gratitude.

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SEARCH FOR NEW DRUGS AMONG PESTICIDES

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We established earlier [2] that derivatives of benzo-2,1,3-thiazole which regulate the growth and development of lower and higher plants, insects, and nematodes may be inhibitors and/or stimulators of viruses, and also possess radio-protective and/or radio-sensitizing activity, while their mechanism of action is connected with the disruption of cellular bioenergetics, capability of changing the permeability of the membrane, as well as with modification of enzymatic activity and inhibition of DNA synthesis [5, 7, 8, 15, 16, 18].

For example, 4-chloro-5-ethoxycarbonylmethoxybenzo-2,1,3-thiadiazole, an herbicide and a plant growth stimulant [15, 18] which protects mice from death upon exposure to γ-irradiation (750 R) in a dose of 300 mg/kg, manifests highly significant antiviral activity in ovo [4]. However, in vivo the indicated compound behaves as a stimulator of viruses and contributes to an increase in the death rate of animals from viral infections [4]. 4-Hydroxybenzo-2,1,3-thiadiazole stimulates the growth of plants, possesses fungicidal and nematocidal activity [9], and shows inhibition of viruses in vitro and in ovo [4, 5], as well as radioprotective activity [6].

It seemed expedient to follow up the discovery of the principle on known pesticides in order to study the antiviral activity of the fungicides, herbicides, and insecticides presented in Table 1, which we obtained from industrial technical products, isolated from the pesticide formulation, i.e., from wettable powders and concentrated emulsions [1], or synthesized by known methods [14].

The antiviral activity was determined in ovo by developing 10-day chicken embryos, inoculated with 2A/Victoria virus in dilutions of 10^{-5} and 10^{-3}. The pesticides were dissolved in pharmacopeial dimekside and introduced simultaneously with the virus into the chorioallantoic cavity in the concentration indicated in Table 1. The index of protection, the coefficient of protection, and the average geometrical titre were determined according to [3]. The results are presented in Table 1. Information on the toxicity of the pesticides and rimantadine are taken from literature sources [10, 13, 17].

It can be seen from Table 1 that all of the pesticides possess antiviral activity, which confirms the principles indicated above. The mechanism of their action was studied with different objectives and was considered in [12].

2,4-D,2M-4X,4,4'-DDE (metabolite of 4,4'-DDT) and chlorophos [13, 17] were not of interest for further study, since they showed moderate antiviral activity.

Akrex, 4,4'-DDT, hexachlorobenzene, lindane, metaphos, rogor, sevin, and phosalone [13, 17] showed themselves to be effective virus inhibitors, but they are toxic except for hexachlorobenzene (cf. Table 1), they possess carcinogenic activity [11] except for phosalone, and application of the indicated pesticides (except for rogor and phosalone) is sharply limited or prohibited [11], and consequently their examination for antiviral activity was conducted only on theoretical considerations.

The herbicides 2M-4XP, prometryne, propazine, and simazine [13, 17], are effective in large doses, but decreased doses, for example with prometryne, lead to a sharp decrease in antiviral activity.

Interest for further study was obtained with the herbicides basagran (II) and semeron (XV), and the fungicide triforin (XVIII), the structures for the active materials of which are given below:

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