"antimorphine" activity of the compound (the analgesic effect of 3.0 mg/kg of morphine was lowered 1.5-2 times from a dose of 30 mg/kg of the compound and 1.1-1.5 times from a dose of 100 mg/kg) and its antagonism to naloxone (at a dose of 100 mg/kg of the compound the latent period of removal of the tail was lowered from 180 to 127% under the action of 2 mg/kg of naloxone). The antiinflammatory activity of the compound in the "formaline edema of rat paws" test [2] was comparatively low: the edema was decreased by 27% ($p = 0.05$) at a dose of 75 mg/kg.

Thus, the compound may be classified with the group of analgesics with mixed activity: narcotic and nonnarcotic.

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1,2-POLYMETHYLENE-4-QUINOLONE-3-CARBOXYLIC ACIDS

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Among derivatives of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid, which have high antibacterial activity against Gram-positive and Gram-negative bacteria, are found highly active condensed tricyclic quinolines, in which the third ring is formed by a polymethylene or oxapolymethylene chain linked to the 1,8 positions of the quinoline system. Among similar compounds is the medicine ofloxacin, a derivative of 1,4-oxazinoquinoline [2, 4]. Therefore we decided on synthesizing tricyclic derivatives of 4-quinolone-3-carboxylic acids in which the polymethylene chain is condensed at positions 1 and 2 of the quinoline ring system. Convenient as starting compounds for the building of such structures could be derivatives of benzoylacetic acid and lactim ethers.

It is known that lactim ethers can react with compounds containing active methylene groups with formation of enamines of type (IV) [1]. When we started our work there were no data on the possibility of using such enamines for the synthesis of quinoline derivatives because it is known that the halogen atom in the benzene ring shows low reactivity towards nucleophilic reagents.

From o-halobenzoic acids (I) we prepared by known methods [3] aroylacetic esters and aroylacetonitriles (IIa-e), from which by reaction with O-methylbutyro-, valero-, and caprolactims (III) enamines IV were prepared. It should be noted that aroylacetic ester IIc, which contains such a strong electron-accepting group as NO_2, is very much inclined to enolization and the reaction of it with lactim ethers (III, $n = 1, 3$) could only be carried out successfully in DMSO, in which the keto-enol equilibrium of dicarbonyl compounds is shifted to the side of the ketone form. We were not able to isolate some enamines IV in a pure state.

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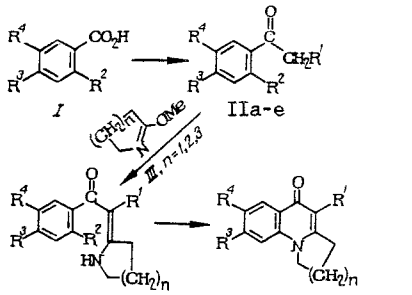

IVa-g Va-g, VIa-f, VII

R^1=CN(IVa-c, Va,**b**), CO_2Et(IV**d-g** V**c-g** VI**d**), COOH(VI**a-c, e**), $CONH_2$(VI**f**), H(VII);

R^2=Cl(IVa-**c, e-g**), **Br(IVd):**

R^3=H(IVa-d, Va-c, VIf), Cl(IVe-g, Vd-g, VIa, b), 4-Me-**piperazinyl**(VI**c, d,** VII);

R^4=H(IVa-**f**, Va-**e**, VIa,**b,f**), NO_2(IV**g**, V**f,g**, VI**c, d** VII)

R^3+R^4=—OCH_2O— (VI**e**).

The conclusion that these intermediates were formed was drawn from TLC data: from the disappearance of the spot of the starting benzoylacetic ester and the appearance of a new spot corresponding with the enamine. It was shown that enamines IV under the influence of reagents such as NaH, sodium alcoholate, and Et_3N undergo intramolecular cyclization to 1,2-polymethylenequinolones-4 (Va-g).

The nature of the substituent at the benzene ring of enamines IV has considerable influence on the ease of closure of the pyridine fragment of the quinoline. While cyclization of enamine IVf already proceeds under the action of Et_3N on heating a solution of the enamine in DMF and while enamines IVa, c, d cyclize in a refluxing ethanolic EtONa solution, we did not even succeed in carrying out the cyclization of enamine IVb in the presence of NaH in DMF at 90°C. The enamine with n = 2 is cyclized most easily, then follows the derivative with n = 3, and the pyrrolidine enamine is cyclized most difficultly.

We have studied some reactions of quinolines V. Hydrolysis of nitrile Va with 48% HBr proceeds with formation of amide VIf, and hydrolysis of esters Vd, e under acid or basic conditions with formation of corresponding acids VIa, b. The chlorine atom of quinolines Vf, g is relatively lightly substituted for a 4-methylpiperazino group. In that case the ester group of compound Vf is hydrolyzed at the same time. Heating of quinolone VId in concentrated HCl results in hydrolysis of the ester group, decarboxylation of the intermediate acid, and formation of quinolone VII.

EXPERIMENTAL (CHEMICAL)

General Method for the Preparation of Enamines (IVa-e). A mixture of benzoylacetonitrile or benzoylacetic ester II and lactim ether III in a molar ratio of 1:5 is heated at 130-140°C for 1-3 h and the presence of starting compound is monitored with TLC. After completion of the reaction (judged by disappearance of the spot of the benzoylacetic acid derivative on the chromatogram) the excess of lactim ether is distilled off under vacuum, the residual oil is triturated with ether or petroleum ether, and stored in the refrigerator till crystallization of the enamines. The prepared enamines are isolated and recrystallized from the proper solvents (Table 1).

Ethyl Ester of 2-(2-Pyrrolidinylene-3-oxo-3-(2,4-dichloro-5-nitrophenyl)propanoic Acid (IVf). A mixture of 30.6 g (0.1 mole) of 2,4-dichloro-5-nitrobenzoylacetic ester, 30 ml (0.3 mole) of O-methylbutyrolactim, and 100 ml of DMF was stored at room temperature for 72 h and the presence of the starting benzoylacetic ester was monitored. After completion of the reaction the mixture was poured out in 500 ml of water and the precipitated oil was triturated with fresh portions of water. The precipitate was filtered off, washed with 10 ml of isopropanol, and dried. Yield 18 g (50%) of compound IVf.

General Method for the Preparation of Quinolones (Va-c, e). To a solution of 2 mole of EtONa in ethanol is added 1 mole of the starting enamine. The mixture is refluxed for

TABLE 1. Enamines IVa-g and Quinolones Va-g, VIa-f, and VII

Compound	n	Yield, %	mp, °C
IVa	3	92	143—145[a]
IVb	1	83	138—140[b]
IVc	2	87	152—153[b]
IVd	3	27	91—93[c]
IVe	1	66	122—123[a]
IVf	3	46	52—53[d]
IVg	1	50	139—141[e]
Va	3	85	210—212[e]
Vb	2	86	258—259,5[e]
Vc	3	45	143—144[e]
Vd	1	66	169—171[b]
Ve	3	69	138—141[e]
Vf	1	90	224—225[f]
Vg	3	47	156—157[e]
VIa	1	55	>300[f]
VIb	3	76	225—225,5[f]
VIc	1	67	>300[f]
VId	3	88	212—212,5[e]
VIe	3	30	280—281[f]
VIf	2	35	290—292[f]
VII	3	85	>280[e]

[a]Ethyl acetate.
[b]Isopropanol.
[c]Heptane.
[d]Petroleum ether.
[e]Alcohol.
[f]DMF.

0.5-3 h while the presence of starting enamine is monitored with TLC. After completion of the reaction the mixture is poured out in water and the corresponding enamine is isolated (see Table 1).

Ethyl Ester of 1,2-Trimethylene-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylic Acid (Vd). A mixture of 3.5 g (107 mmole) of enamine IVe, 50 ml of dry toluene, and 0.5 g of NaH is stirred at room temperature for 1 h and then at 90°C for 1 h. To the reaction mixture is added 5 ml of MeOH and then 20 ml of water. The organic layer is separated off, the aqueous layer is extracted with toluene, and the combined extracts are dried over $MgSO_4$. Yield 1.9 g of quinolone Vd (see Table 1).

Ethyl Ester of 1,2-Trimethylene-4-oxo-6-nitro-7-chloro-1,4-dihydroquinoline-3-carboxylic Acid (Vf). A mixture of 12.3 g (32.7 mmole) of enamine IVg, 10 ml of Et_3N, and 20 ml of DMF is refluxed for 5 h and cooled in the refrigerator for 1 day. The precipitate is filtered off, washed with 2 × 20 ml of water and 20 ml of absolute ethanol, and dried. Yield 10 g of quinolone Vf (see Table 1).

Ethyl Ester of 1,2-Pentamethylene-4-oxo-6-nitro-7-chloro-1,4-dihydroquinoline-3-carboxylic Acid (Vg). A mixture of 10 g of 2,4-dichloro-5-nitrobenzoylacetic ester, 10 ml of O-methylcaprolactim, and 50 ml of absolute MeOH is refluxed for 10 h. To the reaction mixture is added 10 ml of O-methylcaprolactim and refluxing is continued for 15 h. The methanol is evaporated under vacuum, to the residue is added 100 ml of dry benzene, and with cooling and stirring 0.9 g of NaH is added in portions. The mixture is stirred at room temperature for 2 h, 50 ml of 0.5% AcOH is added, the benzene layer is separated off, the benzene is evaporated, and the oily residue is triturated with ethanol. Yield 5.6 g of quinolone Vg (see Table 1).

1,2-Trimethylene-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylic Acid (VIa). A mixture of 2 g of ethyl 1,2-trimethylene-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylate and 20 ml of 1 N NaOH is refluxed till complete solution of the starting compound. The reaction mixture is treated with activated carbon, filtered, and acidified with concentrated HCl to pH 1-2. The precipitate is filtered off, washed with water and with 10 ml of ethanol, and dried. Yield 1 g of compound VIa (see Table 1).

1,2-Pentamethylene-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylic acid (VIb) was prepared in the same way (see Table 1).

TABLE 2. Relative Activity of Compound VIc, Oxolinic Acid, and Pefloxacin According to Septicemia of Mice Evoked by Typhoid Bacilli (strain Ty_2 4446, intraperitoneal infection, treatment once, 30 min after the infection)

Compound (preparation), method of administration	Dose, mg/kg	Number of mice per group	Surviving on the 10th day		Total life span on the 10th day	
			abs.	%	abs.*	%**
VIc, per os	400	20	13	65	154/200	77
	200	20	0	0	24/200	12
Oxolinic acid (dioxacin, VNIKhFI), per os	200	30	30	100	300/300	100
	100	30	27	90	285/300	95
	50	30	19	63	207/300	69
	25	30	7	23	73/300	24
Pefloxacin (VNIKhFI), HCl, subcutaneously	100	20	20	100	100/200	100
	50	20	14	70	186/200	93
	25	20	14	70	182/200	91
	12,5	20	12	60	168/200	84
	6,25	20	11	55	159/200	79
	3,12	20	6	30	134/200	67
	1,57	20	5	25	50/200	25
Control	—	70	0	0	14/700	2

*In the numerator: total number of living mice-days in the group under consideration, in the denominator: the maximally possible value under the given conditions of the experiment.
**Percentage of the maximally possible life span in the case of observation for 10 days.

Hydrochloride of 1,2-Trimethylene-4-oxo-6-nitro-(4-methyl-piperazino)-1,4-dihydroquinoline-3-carboxylic Acid (VIc). A mixture of 2.5 g of compound Vf, 3 ml of 30% aqueous N-methyl-piperazine solution, and 30 ml of DMF is refluxed for 3 h. The reaction mixture is cooled for 16 h in the refrigerator, the precipitate is filtered off, washed with methanol, and dried. Yield 2 g of compound VIc (see Table 1).

Ethyl Ester of 1,2-Pentamethylene-4-oxo-6-nitro-7-(4-methylpiperazino)quinoline-3-carboxylic Acid (VId). A mixture of 1.2 g of quinolone Vg and 9 ml of a 30% aqueous N-methylpiperazine solution is refluxed for 20 h. The reaction mixture is cooled in the refrigerator for 11 h, the precipitate is filtered off, and dried. Yield 1.35 g of compound VId (see Table 1).

1,2-Pentamethylene-4-oxo-6,7-methylenedioxy-1,4-dihydroquinoline-3-carboxylic Acid (VIe). A mixture of 3 g of 2-chloro-4,5-methylenedioxybenzoylacetic ester and 6 ml of O-methylcaprolactim is heated at 160°C for 3 h. The excess of lactim ether is distilled off under vacuum and the residue is added to a solution of EtONa, prepared from 0.4 g of Na and 5 ml of absolute ethanol. The mixture obtained is refluxed for 2 h. The ethanol is evaporated, the residue is treated with a mixture of water and $CHCl_3$, and extracted. The combined extracts are dried over Na_2SO_4 and evaporated. The residue is triturated with ether, filtered, and dried. Yield 0.9 g of acid VIg (see Table 1).

Amide of 1,2-Tetramethylene-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (VIf). A mixture of 1 g of compound Vb and 25 ml of 48% HBr is refluxed for 2 h. The reaction mixture is poured out in 250 ml of cold water, the precipitate is filtered off, washed with water, and dried. Yield 0.4 g of compound VIf (see Table 1).

1,2-Pentamethylene-6-nitro-7-(4-methylpiperazino)quinolone-4 (VII). A mixture of 1 g of compound VId and 18 ml of 10% HCl is refluxed for 2.5 h. The hydrochloric acid is evaporated under vacuum, the residue is triturated with ethanol, filtered, and dried. Yield 0.7 g of compound VII (see Table 1).

The structures of the prepared compounds were confirmed by mass, PMR, and IR spectral data.

EXPERIMENTAL (BIOLOGICAL)

We studied the antimicrobial activity of 12 of the compounds synthesized (Va-d, f, VIa-f, and VII) in experiments in vitro with regard to eight species of bacteria and two species of pathogenic fungi. We used 13 strains of bacteria, viz.: S. aureus 209-P, 178, 191, and "Zhaev", E. coli M-17 and ATCC 25922, S. typhi Ty_2 4446, Sh. dysenteriae 644, Kl. pneumoniae 444, Proteus vulgaris No. 1 and ATCC 6896, Ps. aeruginosa 165, and B. subtilis ATCC 6633, and two clinical strains of fungi, viz.: Microsporum canis 7/84 and Candida albicans 1755.

We determined the minimal inhibitory concentration (MIC, μg/ml) by the generally accepted method of twofold serial dilutions in liquid culture media: 1) in experiments with bacteria in Hottinger's broth (120 mg% amino nitrogen) or in beef-extract broth at inoculum numbers of $2 \cdot 10^5$ and $1 \cdot 10^6$ pfu/ml and an incubation time of 20 h at 37°C; 2) in experiments with fungi in Sabouraud's broth at an inoculum number of $(2\text{-}4) \cdot 10^5$ pfu/ml and incubation at 28°C for 24 h for C. albicans and 5 days for M. canis.

Four compounds were selected for in vivo studies: Va (with a CN group at position 3), VIe (an analog of oxolinic acid), and two compounds with an NO_2 group at position 6 (Vf and VIc), whereby VIc may be considered as the 6-nitroanalog of the fluoroquinolone pefloxacin or the tricyclic quinolone ofloxacin. In vivo experiments were carried out with three models of acute bacterial infections caused by the highly virulent strains S. typhi Ty_2 4446, Ps. aeruginosa 165, and S. aureus 178 (polyresistant strain). We used infectious doses which in case of intraperitoneal infection in the form of suspensions in 0.4% aqueous agar caused the death of 80-100% of the nontreated control animals.

As preparations for comparison in the in vitro experiments we used oxolinic acid and pefloxacin, prepared at the All-Union Scientific Research Institute of the Chemical and Pharmaceutical Industry (VNIKhFI), and ofloxacin (tarivid of the firm Hoechst). In experiments in vivo the comparison preparations were oxolinic acid and pefloxacin. The animals were observed for 10 days. The activity was judged by the survival rate (absolute and in % of the number of animals in each group) and by the total increase in lifespan of the animals in experimental groups with observing them also for ten days. The experiments were carried out with 600 white non-inbred mice.

Compounds Va, Vf, VIc, VIe, and oxolinic acid were administered per os as suspensions in 1% starch gels at single doses to 400 mg/kg, 30 min after the infection; pefloxacin (as the hydrochloride) was administered subcutaneously as solutions in isotonic NaCl solutions. The dose under investigation was given in a volume of 0.5 ml.

In vitro experiments have shown that of the 12 compounds investigated only compound VIc has significant activity against bacteria. The highest activity, as compared with the activity of the reference preparations, was found against the Gram-positive bacteria E. coli, S. typhi, Sh. dysenteriae, and Kl. pneumoniae (MIC in the region from 1.95 to 15.6 μg/ml).

In experiments with the strains Ps. aeruginosa, Proteus, and S. aureus, the activity of compound VIc is substantially superior to that of pefloxacin and tarivid: MID 62.5-500 μg/ml and 0.5-15.6 μg/ml, respectively (at an inoculation number of $1 \cdot 10^6$-$1 \cdot 10^8$ pfu/ml). The other eleven compounds studied in experiments with bacteria were less active or inactive in vitro (MIC ≥ 250-500 μg/ml). The 12 compounds were inactive in vitro against the two strains of pathogenic fungi.

In vivo experiments have shown that compound VIc, which is the most active one in vitro, possesses chemotherapeutic activity in the model of septicemia in mice evoked by typhoid bacilli and effects survival of 65% of the treated animals when the maximal therapeutic dose is used. The data of Table 2 show that substitution of the quinoline ring at positions 1 and 2 with introduction of a polymethylene chain in the presence of an NO_2 group at position 6 considerably lowers the chemotherapeutic activity of the compound in vivo in experiments with typhoid infection relative to oxolinic acid and pefloxacin (ED_{50} > 200, 41.2, and 12.5, respectively).

In experiments with infections caused by S. aureus 178 and Ps. aeruginosa 165, compound VIc does not show activity in case of a single treatment, while under similar experimental conditions pefloxacin is highly active at doses of 100-200 mg/kg (survival rate of treated mice ≥80%) and shows a positive therapeutic effect at doses to 6.25-12.5 mg/kg. In the case of infections caused by S. aureus and Ps. aeruginosa, oxolinic acid is weakly active or inactive in the case of single administration at doses to 400 mg/kg.

Thus, the investigations that we have carried out show that introduction of a polymethylene chain that is condensed at positions 1 and 2 of the quinoline ring, either considerably lowers the antibacterial activity of derivatives of 4-quinolone-3-carboxylic acid or leads to complete removal of the activity, both in vivo and in vitro. It should be emphasized that also compounds containing a CN or $CONH_2$ group at position 3 of the quinoline ring are inactive in vitro.

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SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF DIHYDRO-, TETRAHYDRONAPHTHO-, AND ANTHRAQUINONES, CONTAINING A HETEROCYCLIC FRAGMENT

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The sulfonyl derivatives exhibit a broad spectrum of biological activity and a low level of toxicity so that the search for new physiologically active substances as potential drugs from among those derivatives seems quite promising [1, 6]. The sulfolanoquinones are of special interest with respect to biological activity. They contain a sulfonalane ring and are at the same time analogs of the natural naphtho- and anthraquinones [3, 12] that have come to be used in medicine in connection with various types of antibiotic activity. There have been recent reports about analgesic and antidepressant activity in a number of naphthoquinones [10, 11] and emodine [9].

We synthesized new quinone derivatives (I-XIV) and studied their psychotropic properties. Substances I-IV were obtained by employing a diene synthesis of 2-isopropenyl-2-thiolene-1,1-dioxide (XV) with substituted naphtho- and benzoxyquinones. Substance VI was obtained by boiling quinone VII with ethyl diazoacetate in benzene. The synthesis of compound I-VII is outlined in Fig. 1.

Substances VIII-XIV were obtained by employing a diene synthesis of 1-(2-furyl)-3-trimethylsiloxy-1,3-butadiene with various quinones, 3,3-dimethyl-5-methylene-2,4-dioxanedione, and maleic anhydride (Fig. 2).

The properties and spectral characteristics of compound I-III, V, VII are cited in [7], and those of VIII-X, XII-XIV are given in [8].

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