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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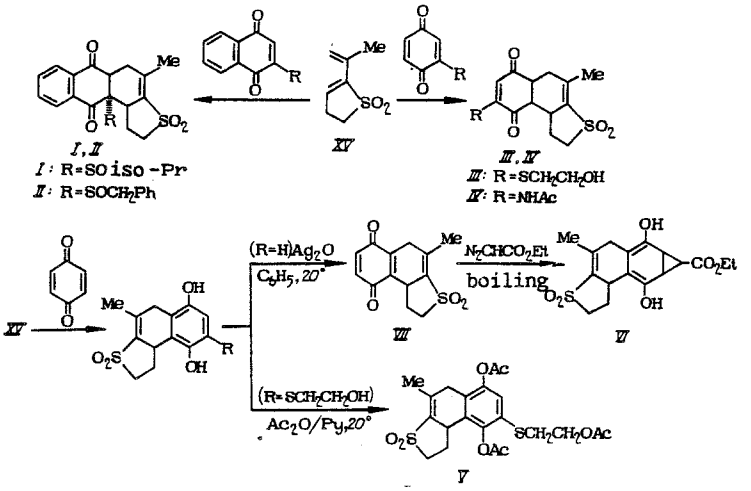
0091-150X/90/2407-0465$12.50

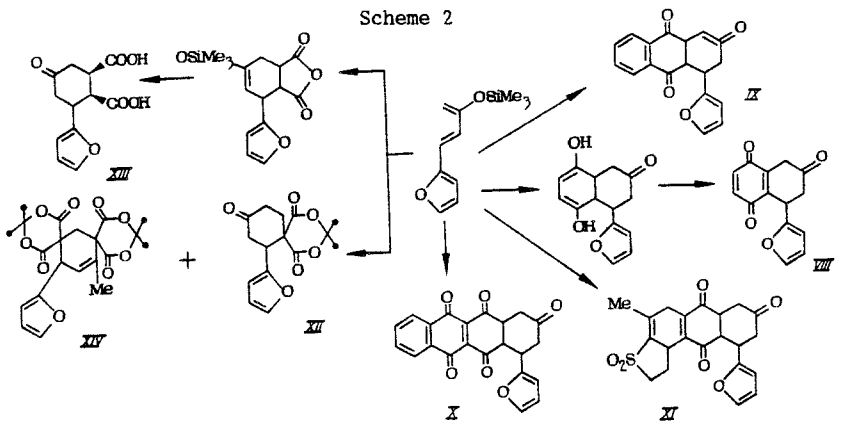
Scheme 1



EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a UR-20 (GDR) instrument in a fine layer. PMR spectra were recorded on a BS-567B spectrometer in $CDCl_3$, internal standard TMS. TLC was employed to analyze and control the purity of the synthesized compounds on Silufol UV-254 plates; eluents; benzene–ethyl acetate (10:3); benzene–ethyl acetate–acetone (10:2:1); chloroform–methanol (20:1). Elemental analysis data satisfied the calculated values.

Scheme 2



4-(2-Acetamido)-9-methyl-11,11-dioxo-11-thiatricyclo[8.3.0.$0^{2,7}$]trideca-4,9-diene-3,6-dione (IV). A solution of 0.94 g (0.059 mole) of diene XV in 40 ml of CH_2Cl_2 was added dropwise to a solution of 1.4 ml of $BF_3 \cdot Et_2O$ in 20 ml of anhydrous CH_2Cl_2 at 0°. Then a solution of 0.94 g (0.059 mole) of diene XV in 40 ml of CH_2Cl. The reaction mixture was stirred for 12 h at 0°, dissociated by the addition of 0.8 ml of 6 N HCl, then washed with water. After drying and evaporation of the organic layer from ethylacetate, the resultant yield was 1.85 g of a mixture of compound IV and the 5-(2-acetamido)substituted isomer. Recrystallization of the substance from isopropyl alcohol resulted in 1.65 g (87%) of pure compound IV, mp 218-220°C. $C_{15}H_{17}NO_5S$. IR-spectrum, ν, cm^{-1}: 875, 1135, 1155, 1280, 1300, 1570, 1610, 1680, 3280. PMR spectrum: δ, ppm: 2.35 s (CH_3), 2.28 d (CH_3, j = 2.5 Hz), 2.88 m (3H, $H^{1,13}$), 3.42 m (4H, $H^{8,12}$), 3.72 m (2H, $H^{2,7}$), 5.22 s (1H, NH), 6.48 s (1H, H^5).

3,7-Dihydroxy-10-methyl-5-ethoxycarbonyl-12,12-dioxo-12-thiatetracyclo[9.3.0.$0^{2,8}0^{4,6}$]-trideca-3,7,10-triene (VI). A solution of 0.15 g (0.0012 mole) of N_1CHCO_2Et was added dropwise to a solution of 0.3 g (0.0011 mole) of substance VII in 30 ml of benzene. The reaction mixture was boiled in a reflux condenser for 16 h. Upon cooling 0.12 g (34.5%) of the original VII was filtered off. Evaporation of the benzene and recrystallization of the residue from ethyl acetate resulted in a 0.06 g (17%) yield of compound VI, mp 160-165°C (from ethyl acetate). $C_{17}H_{20}O_6S$. IR-spectrum, cm^{-1}: 1135, 1310, 1590, 1680, 1725, 3460, 3570. PMR spectrum, δ, ppm: 1.47 t (CH_3), 2.05 m (2H, cyclopropyl), 2.76 s (CH_3), 3.30 d (1H, H^5), 3.60 m (5H, $H^{1,9,14}$), 3.90 m (2H, H^{13}), 4.53 q (2H, CH_2), 7.25 (2H, OH).

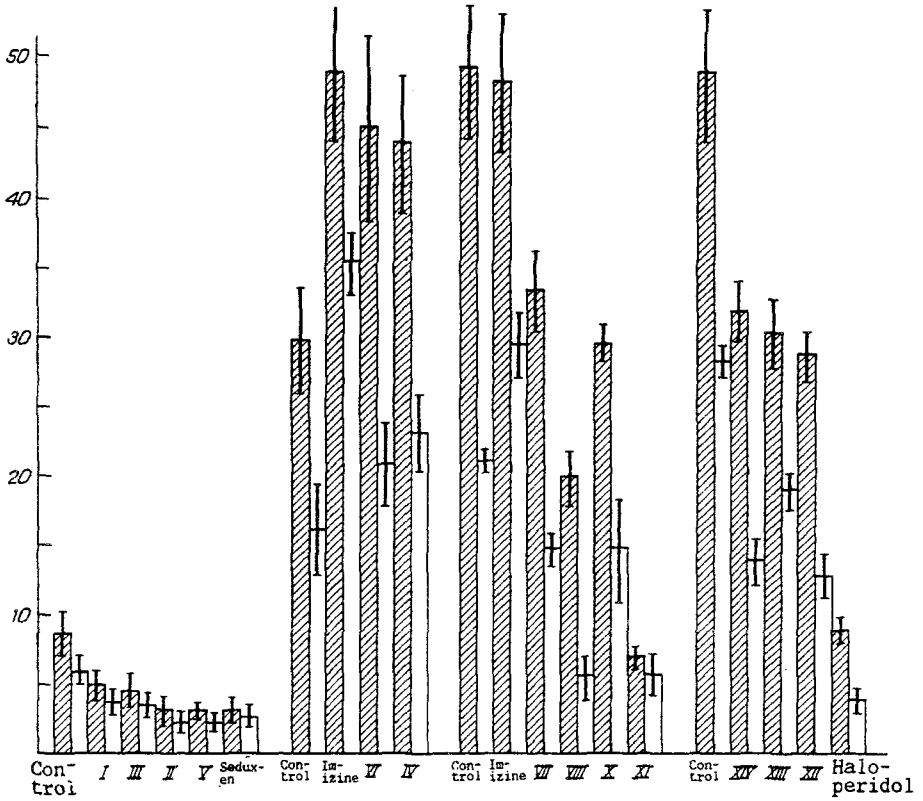


Fig. 1. Effect of compounds I-XIV on changes in orientational responses of animals (working dose 2.5 mg/kg). Clear columns – examined apertures, hatched columns – vertical stand-ups. Y-axis – number of orientational responses.

TABLE 1. Acute Toxicity and Psychotropic Action of New Quinone Derivatives

Compound	Toxicity LD_{50}, mg/kg	Potentiation of hypnotic action					Stereotypy duration		Hypothermia			
		hexenal, min	% of control	thiopental, min	% of control	chloral-hydrate, min	% of control	A – apomorphine, B – phenamine, min	% of control	dose, mg/kg	% of effect after 1 h	after 2 h	after 3 h
I	7000	196.3±58.0	196	336,5±4.9	494	85.0±9.7	173	B – 300±2.4	113	–	–	–	–
II	7000	158.3±39.0	158	329,4±4.7	483	111,0±1,8	226	B – 58,1±2.2	22	–	–	–	–
III	380	171.0±61.0	171	288,0±51,0	423	74,3±17	151	B – 264,0±18.8	99	–	–	–	–
IV	1800	96.0±6.7	259	–	–	–	–	A – 108,0±0.2	124	–	–	–	–
V	350	289.5±53.0	289	251,5±5.5	369	46.0±2.0	93	B – 290,0±6.1	109	–	–	–	–
VI	1800	69.2±5.3	186	–	–	–	–	A – 120,0±0.2	114	2.5+reserpine	30	50	100
VII	781	230.0±26.2	306	–	–	235,0±27,3	293	A – 83±5,9	95	2,5	30	50	100
VIII	3020	100.2±14.7	133	–	–	59.0±14.6	74	A – 100,2±2.2	95	2,5	30	35	60
IX	3000	185,0±2.8	247	–	–	182.2±42.6	228	A – 108,0±0.15	124	–	–	–	–
X	1400	56.0±4.5	154	–	–	244,7±18.2	281	A – 100,7±3.7	120	–	–	–	–
XI	3000	329.2±34.6	228	–	–	204,7±1,1	280	A – 100,0±0.16	118	–	–	–	–
XII	2710	78,0±4.2	104	–	–	132,0±8.2	165	A – 100,7±3.7	118	2,5	25	35	60
XIII	3125	72,0±2,5	96	–	–	93,5±12,3	116	A – 77,8±1,5	77	2,5	15	30	50
XIV	2810	136.6±9.3	181	–	–	101,1±0,6	126	A – 92,3±5,2	92	2,5	15	35	60
Seduxen	500	248,9±1,2	[illegible]	–	–	–	–	–	–	–	–	–	–
Imizine	455	155.8±11.8	184	–	–	–	–	–	–	1.0+reserpine	15	30	80
Haloperidol	80	138,4±5.4	206	–	–	–	–	–	–	1.0	25	50	95

4-Methyl-10-(α-furyl)-3,3,8-trioxo-1,2,5,6a,7,8,9,10,10a,11b-octahydrothieno[3,2-a]-anthraquinone (XI). A 0.62 g (0.27 mole) portion 1-(2-furyl)-3-trimethylsiloxybutadiene was added to a solution of 0.65 g (0.27 mole) of substance VII in 50 ml of benzene, and boiled for 15 h. The resultant solution was passed through a silica gel layer (15 g), then evaporated, and the residue was recrystallized from alcohol. The resultant yield was 0.76 g (76%) of compound XI, mp 159-161°C. $C_{21}H_{20}O_6S$. IR-spectrum, ν/, cm^{-1}: 1110, 1120, 1300, 1320, 1670, 1690. PMR spectrum, δ, ppm: 2.63 m, 2.88 m (2H, H^7), 2.66 s (CH_3), 2.99 m, 3.15 m (2H, H^9), 3.25 m, 3.52 m (6H, $H^{1,2,5}$), 3.82 dt (2H, $H^{6,12}$), 3.99 dd (1H, $H^{10}a$), 4.25 dt (1H, H^{10}), 5.81 d, 5.88 d (2H, H β-furyl), 0.61 dd (1H, Hα-furyl).

TABLE 2. Effect of Polycyclic Sulfones on Emotional Stress and Their Analgesic and Antiinflammatory Activity

Compound	Analgesic activity				Antiinflammatory activity			Emotional stress			Phenamine toxicity	
	dose, mg/kg	hot plate test	electric pain stimulation	chemical irritation	dose, mg/kg	carrageenin edema	formalin edema	dose, mg/kg	emotional responses, b	aggression b	individual	group
I	10,0	28,6±2,1	34,2±1.0	—	10,0	68,5±2,5	43,0±0,45	2,5	0,6±0.2	2,0±0,2	3/6	2/6
II	10,0	23,3±7,3	31,2±0,5	—	10,0	57,1±5,6	48,7±2,8	2,5	0,6±0.2	2,0±0,2	4/6	2/6
III	2,5	30,3±4,3	30,6±0,4	—	10,0	53,0±5,6	52,7±4,3	2,5	1,2±0.2	1,8±0,4	6/6	3/6
V	2,5	22,7±2,2	39,5±1.2	—	10,0	48,4±5,1	47,7±5,1	2,5	0,8±0.0	1,8±0,2	6/6	3/6
Control	—	47,3±0,75	33,8±0.8	—	—	71,5±7,1	60,9±1,1	—	2,8±0.2	3,0±0,4	6/6	6/6
Analgin	20	25,5±6,0	30,5±6,2									
Seduxen	—	—	—					2,5	0,4±0,0	2,0±0,2	..	-
IX	2,5	—	67,2±2,0	16,8±1,6								
	5,0	—	66,8±4,3	9,7±1,3								
Control			44,5±2,9	31,6±2,5								
Phentanyl	25 µg/kg		65,6±4,3	29,7±3,1								
Voltaren	8,0					52,0±1,36	45,7±2,25					

EXPERIMENTAL (BIOLOGICAL)

The biological activity of the compounds was tested on white non-pedigree mice weighing 18-22 g and rats weighing 180-200 g. The compounds' effect on the CNS was tested by orientation responses (vertical and horizontal tests), by the duration of phenamine stereotypy (10 mg/kg ip for rats), apomorphine stereotypy (20 mg/kg subcutaneous injection to mice), prolongation of hypnotic effect (hexenal – 75 mg/kg, chloralhydrate – 300 mg/kg, and sodium thiopental – 60 mg/kg ip), and by changes in rectal temperature. Phenamine toxicity (group and individual) was assayed for some of the compounds. Analgesic activity was tested on three generally recognized models – "hot plate," "acetate cramps" (0.75% solution), and electric pain stimulation of the paws.

The range of the compounds' acute toxicity was between 380 and 7000 mg/kg (Table 1). All of the examined compounds reduced animal motor activity (see Fig. 1). The compounds can be divided into three groups with respect to orientation response effects. The animals given compounds I-III, V, and XI exhibited the greatest reduction in motor activity. Characteristically, the potentiation effects of hypnotics in these compounds was on the average twice that of hexenal and chloral hydrate in the control group and six times that of sodium thiopental in the control group. We found that this group of compounds only slightly increased the duration of phenamine stereotypy. The compounds were capable of reducing the group toxicity of phenamine by 1.5-1.3 times, but did not alter individual (except I and II) toxicity. These results indicate that substances I-III, V, and XI can be classified as tranquilizers with respect to their range of psychotropic activity in accordance with the classification of [4, 5]. One should note, however, that when substance XI is administered in large doses (10 mg/kg) it can suppress phenamine stereotypy and somewhat increases the animals' motor activity, so that it might be classified as an atypical tranquilizer, i.e., tranquilizers with an activating component [2]. Thus, substances I-III, V, and XI are classified as tranquilizers whose activity is no less than that of seduxen. These compounds are significantly less toxic than seduxen (see Table 1).

Substances I-III, similar to seduxen, reduce animal aggression and emotional activity. In addition, these compounds exhibit significant antiinflammatory activity at doses of 1/1000 of the LD_{50} as demonstrated on carragheenin and formalin edema models. This action of the tested compounds is similar to the effect of voltaren when administered at a dose of 1/40 of the LD_{50}. Compounds tested in the "hot plate" test exhibited an analgesic action that was at least the equal of analgin. The indicated compounds did not induce destruction of the gastric mucous membrane (Table 2).

Compounds IV, VI, IX, and X restricted animal motor activity (mobility increased with greater dosage), potentiated the action of hexenal while doubling its side reaction, and amplified apomorphine stereotypy (see Fig. 1, Table 1). From the cited data the compounds of this group might be classified as antidepressants. Their activity is analogous to that

of imizine. The substances of this group did not influence the hypothermic effect of reserpine, but do not themselves exhibit the ability to lower body temperature. In view of the above, they might be classified as atypical antidepressants [4]. Compound IX exhibited analgesic activity which was not less than that of phentanyl (see Table 2).

When compounds VII, VIII, XII-XIV were administered orally at increased dosages they reduced orientational responses. This group of substances characteristically arrested apomorphine stereotypy, and the most active in this respect were substances VII and XIII. They exhibited the lowest potentiation of hexenal and chloral hydrate sleep. Compound VII exhibited a significant sedative effect, but substance VIII exhibited the ability to reduce the duration of chloral hydrate sleep considerably. All the substances of this group characteristically exhibited the ability to lower temperature by 4-7°C. The most pronounced hypothermic effect was exhibited by compound VII. In view of the cited data (see Table 1) compounds VII, VIII, XII-XIV can be classified as neuroleptics whose activity is analogous to that of haloperidol.

Our examination of the psychotropic action–chemical structure relationship in the series of synthesized quinone adducts demonstrates that the presence of a sulfolane ring results in increased sedative properties (substances I-VII, XI). A similar manifestation of the sedative component in biological activity is also characteristic of the alkylthio- and alkylsulfinyl substituted compounds (substances I-III, V). The introduction of a nitrogen-containing substituent as well as a cyclopropane grouping (substances IV, VI) as well as an enlargement of the non-saturated compound (substance VII) results in animal stimulation. The psychotropic action of these compounds is accompanied by an activating effect. The introduction of an α-furyl substituent (substances VIII-XIV) was seen to heighten animal activity. One should note that the neuroleptic activity that is characteristic of the α-furyl substituted quinone derivatives (substances VIII, X) is also retained in the α-furyl-substituted cyclohexanones (substances XII-XIV) that do not contain a quinone fragment.

Thus, we have presented a new group of moderately toxic compounds that exhibit pronounced psychotropic activity.

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