Among the piperidin-4-ol derivatives studied, the benzoate ester V, which differs from other compounds by the presence of a benzoxyl group at the $C_{(4)}$ atom of the piperidine ring, has the highest pharmacological activity and the most acute toxicity (see Table 1).

All the data confirm expediency of further search for effective neurotropic preparations in the series of 4-substituted 1-methylpiperidin-4-ol derivatives.

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STUDY IN THE SERIES OF 4-QUINAZOLINONES.

XVII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2-DISUBSTITUTED 4-QUINAZOLINONES

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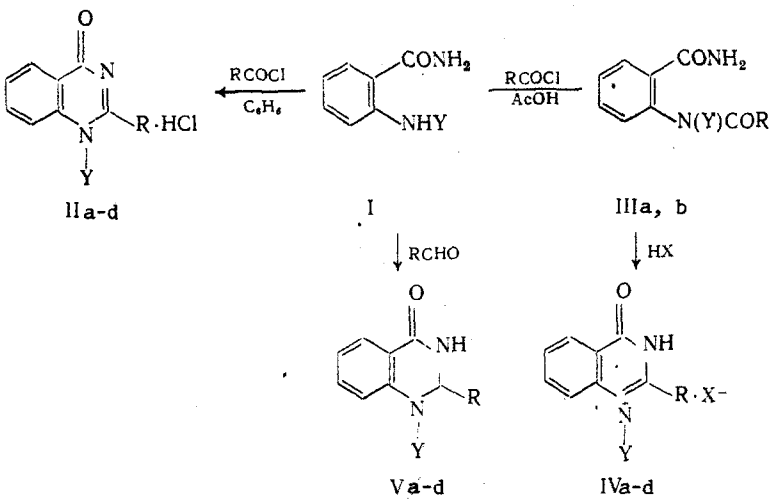
In order to search for biologically active compounds and to continue the studies in [8], derivatives of 4-quinazolinone substituted at the 1– and 2-positions of the quinazolinone ring were obtained from N-(2-methoxyphenyl) anthranylamide (I).



IIa: R = Me; IIb: R = Et; IIc: R = Ph; IId: R = CH_2Ph; IIIa: R = Me; IIIb: R = = Et; IVa, c: R = Me; IVb, d: R = Et; IVa, b: X = Br; IVc, d: X = ClO_4; Va: R = Pr; Vb: R = Ph; Vc; R = C_6H_4OMe-4; Vd: R = furyl-2; Y = 2-methoxyphenyl (IIa-d; I; IIIa, b; IVa-d; Va-d)

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TABLE 1. Pharmacological Activity and Acute Toxicity of 1,2-Disubstituted 4-Quinazolinones

Compound	Antispasmodic activity ED_{50} mg/kg, or protection, %	Analgesic action		Acute toxicity LD_{50}, mg/kg
		dose, mg/kg	time of defense reflex, sec	
Control	—	—	11,5±4,1	—
IIa	153 (120,5—194,3)	153	35,2±12,3	232 (198,2—271,4)
IIb	16,6	—	—	—
IIc	33,3	300	24,7±5,8	—
IId	No activity	—	—	—
IVa	170 (129,7—227)	170	29,8±7,2	355 (338,1—372,7)
IVb	168 (134,4—210,0)	168	31,4±6,6	325 (256,0—411,7)
IVc	16,6	—	—	467,5(380,1—475,0)
IVd	33,3	—	—	398 (306,2—517,4)
Va	No activity	—	—	—
Vb	33,3	—	—	—
Vc	No activity	—	—	—
Vd	230 (191,7—276,0)	230	26,3±2,6	463 (373,4—547,1)
Chloracon*	142 (115,4—172,5)	—	—	650 (586,0—722,0)
Amidopyrine**	—	100	27,6±2,6	249 (208,0—294,0)

* According to the data in [4]. ** According to data in [5].

When amide (I) was heated with acid halides in benzene, hydrochlorides of 1-(2-methoxyphenyl)-2-R-4(1H)-quinazolinones (IIa-d) were obtained in a 51-87% yield. N-Acetyl(propionyl-N-(2-methoxyphenyl) anthranylamides (IIIa, b) were obtained by the acylation of amide I under milder conditions. By the action of hydrobromic and perchloric acids in methanol, these amides were cyclized into 1-(2-methoxyphenyl)-2-methyl(ethyl)-4(3H)-quinazolinonium bromides (IVa, b) and perchlorates (IVc, d). 1-(2-Methoxyphenyl)-2-R-2,3-dihydro-4(1H)-quinazolinones (Va-d) were obtained by condensing amide I with aryl(heteryl)aldehydes.

1,2-Disubstituted 4-quinazolinones (II, IV, V) are colorless crystalline compounds, which are sparingly soluble in ethanol; compounds IIa, b are soluble in water and ethanol. The structure of the compounds was confirmed by IR and UV spectra and data of elemental analysis.

In the IR spectra of all the 4-quinazolinones, absorption bands are observed in the region of 1690-1730 (Ar—C=O), 1600-1635, 1510-1570, 1460-1500 cm^{-1} (the quinazolone ring). In the IR spectra of compounds IV, in contrast to those of compounds II, there is an absorption band at 3100-3300 cm^{-1}, caused by the vibrations of the NH group. In the IR spectra of perchlorates IVc,d, there is an intense absorption band at 1130-1135 cm^{-1} (the perchlorate anion In the spectra of compounds II there is an intense band in the 1890-1910 cm^{-1} region, which is absent in other 4-quinazolinones and can be assigned to the vibrations of the $-C(=O)-N=$ group.

EXPERIMENTAL (CHEMICAL SECTION)

The IR spectra were run on a UR-20 spectrophotometer (GDR) in the form of a suspension in a mineral oil. The UV spectra were recorded on a SF-16 spectrophotometer (USSR) for 10^{-5} M solutions of the compounds in ethanol.

1-(2-Methoxyphenyl)-2-methyl-4(1H)-quinazolinone Hydrochloride (IIa). A 1.2 ml portion (17 mmoles) of AcCl is added to a suspension of 3.5 g (14.5 mmoles) of I in 20 ml of dry benzene, and the mixture is boiled on a water bath for 4 h. When cool, the precipitate is filtered, washed with 20 ml of benzene, and crystallized from n-amyl alcohol. IR spectrum, ν_{max}, cm^{-1}: 1880 ($-C(=O)-N=$), 1707 (Ar—C=O), 1618, 1560, 1467 (the quinazolone ring), 1252 ($Ar-OCH_3$). UV spectrum, λ_{max}, nm (log ε): 274 (3.45), 304 (3.72). Compounds IIb-d are obtained in a similar way. Given are for IIa-d, mp, °C, yield, %, empirical formula, found (calculated), Cl, N, %; IIa: 239-241, 80.1, $C_{16}H_{15}ClN_2O_2$, 11.91 (11.71), 8.90 (9.25); IIb: 203-205, 87.9, $C_{17}H_{17}ClN_2O_2$, 11.20 (11.19), 8.71 (8.84); IIc: 275-278; 51.0, $C_{21}H_{17}ClN_2O_2$, 9.52 (9.72), 7.80 (7.68); IId: 233-235, 78.3, $C_{22}H_{19}ClN_2O_2$, 9.14 (9.36), 7.26 (7.39).

N-Acetyl-N-(2-methoxyphenyl)anthranylamide (IIIa). A 0.7 ml portion (10 mmoles) of AcCl is added dropwise to a suspension of 3 g (8 mmoles) of I in 15 ml of AcOH, and the mixture is heated on a water bath for 1 h. The reaction mixture is then poured into 50 ml of

cold water and neutralized by Na_2CO_3 to pH 7.0. The precipitate that separates is filtered, washed with water, and crystallized from methanol. Colorless prisms, mp 83-86°C. Yield, 85.5%. Found, %: C 67.25; H 5.82; N 9.66. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.59; H 5.67; N 9.85. IR spectrum, ν_{max}, cm^{-1}: 3410, 3515 (NH_2), 1635 (amide I), 1598 (amide II), 1250 (Ar–O–CH_3). Compound IIIb is obtained in a similar way. Colorless prisms, mp 141-143°C (ethanol). Yield 85.3%. Found, %: C 68.60; H 6.24; N 9.12. $C_{17}H_{18}N_2O_3$. Calculated, % C 68.44; H 6.08; N 9.39. IR spectrum, ν_{max}, cm^{-1}: 3390, 3540, 1635, 1598, 1256.

1-(2-Methoxyphenyl)-2-methyl-4(3H)-quinazolinonium bromide (IVa). A solution of 2 g (7 mmoles) of IIIa in 20 ml of methanol and 1.2 ml (7 mmoles) of 47% HBr is boiled on a water bath for 40 min. The precipitate that separates on cooling, is filtered and recrystallized from ethanol. IR spectrum, ν_{max}, cm^{-1}: 3103 (NH), 1716 (Ar–C=O), 1620, 1560, 1470 (the quinazolone ring), 1292 (Ar–O–CH_3). UV spectrum, λ_{max}, nm (log ε): 224 (4.35), 274 (3.91), 302 (3.95). Compound IVb is obtained in a similar way. Given are mp, °C; yield, %; empirical formula, found (calculated) Br, N, %: IVa 248-250, 69.7, $C_{16}H_{15}BrN_2O_2$, 23.36 (23.01), 7.75 (8.07); IVb: 241-243, 49.6, $C_{17}H_{17}BrN_2O_2$, 22.50 (22.12), 7.79 (7.76).

1-(2-Methoxyphenyl)-2-methyl-4(3H)-quinazolinonium Perchlorate (IVc). A solution of 2.3 g (8 mmoles) of IIIa in 20 ml of methanol and 1.4 ml (8 mmoles) of 57% $HClO_4$ is boiled on a water bath for 30 min. When cool, the precipitate that separates is filtered, and crystallized from ethanol. IR spectrum, ν_{max}, cm^{-1}: 3177, 1732, 1623, 1570, 1473, 1272, 1135 (ClO_4^-). Compound IVd is obtained in a similar way. Given are mp, °C, yield, %, empirical formula, found (calculated) Cl, N, %: IVc: 273-275; 57.4, $C_{16}H_{15}ClN_2O_6$, 9.72 (9.67), 7.30 (7.64); IVd: 256-259, 52.2 $C_{17}H_{17}ClN_2O_6$, 9.12 (9.31), 7.02 (7.36).

1-(2-Methoxyphenyl)-2-phenyl-2,3-dihydro-4(1H)-quinazolinone (Vb). A 1.2 ml portion (12 mm of benzaldehyde and a drop of concentrated HCl are added to a solution of 2.4 g (10 mmoles) o I in 30 ml of ethanol. The mixture is boiled on a water bath for 6 h, and then half of the solvent is distilled. After cooling, the precipitate that separates is filtered, dried, and crystallized from ethanol. IR spectrum, ν_{max}, cm^{-1}: 3176 (NH), 1664, 1610, 1478 (the quinazolone ring), 1256 (Ar–O–CH_3). Compounds Va, c, d are obtained in a similar way. Given are for Va-d mp, °C, yield, %, empirical formula, found (calculated), C, H, N, %: Va: 115-117, 81.7, $C_{18}H_{20}N_2O_2$, 72.66 (72.95), 6.72 (6.80), 9.87 (9.45); Vb: 166-168, 73.3, $C_{21}H_{18}N_2O_2$, 76.40 (76.32), 5.70 (5.49), 8.32 (8.48); Vc: 175-178, 71.8, $C_{22}H_{20}N_2O_3$, 73.12 (73.32), 5.75 (5.59), 7.72 (7.77); Vd: 153-156, 70.5, $C_{19}H_{16}N_2O_3$; 71.41 (71.24), 5.12 (5.03), 8.93 (8.74).

EXPERIMENTAL (PHARMACOLOGICAL SECTION)

The acute toxicity, the antispasmodic, and the analgesic action of 1,2-disubstituted 4-quinazolinones were studied. The investigations were carried out on 670 nonpedigree white mice of both sexes weighing 20-23 g each.

The acute toxicity (LD_{50}) of the compounds was determined by the G. N. Pershin method [6 The antispasmodic activity was studied by the maximal electrical shock method, in the K. S. Raevskii modification [7], and was compared with the activity of Chloracon. For the active compounds, the mean effective doses (ED_{50}) were calculated. The analgesic effect was determined by the Eddy and Leimbach thermal irritation method [1], and was compared with that for amidopyrine. The results were statistically treated by the method of Leachfield and Wilcoxon [2] with calculation of the mean arithmetic values at P = 0.05. The compounds studied were introduced intraperitoneally in the form of a suspension in a 2% starch mucilage half an hour before evaluation of activity. The antispasmodic action of the active compounds was tested in 10-13 different doses, and the remaining compounds in a dose of 300 mg/kg. The analgesic effect was studied in ED_{50} units found from the electrical shock test. The control group animals were injected with equivoluminar amounts of starch mucilage. The results of the investigation of the biological action and acute toxicity of 1,2-disubstituted 4-quinazolinones are given in Table 1.

The tests showed that, according to the K. K. Sidorov classification [3] in intraperitoneal administration to white mice, the compounds belong to the III rd class, i.e., to the class of slightly toxic compounds. The LD_{50} values show that all the compounds have similar toxicity values. Among 12 compounds, 9 have antispasmodic action. Compounds IIa, IVa, IVb have an activity equal to that of chloracon. Compound Vd is inferior by a factor of 1.6, and the antispasmodic activity of the remaining five compounds is much less than that of Chloracon. The antispasmodic effect develops in 0.5-1 h, as in the case of Chloracon. The anal-

gesic activity in 5 of the 12 compounds develops in the course of a similar period of time. All the compounds have an activity similar to that of amidopyrine.

The data obtained show that it is advisable to carry on with a search for antispasmodic and analgesic properties among the 4-quinazolinone derivatives.

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SYNTHESIS AND HYPOCHOLESTEREMIC ACTIVITY OF AMINOACETYLENYL LINOLEATES

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Aminoacetylenyl esters of unsaturated fatty acids have been shown [4] to possess high hypolipidemic activity. It was of interest to examine the hypocholesteremic activity of aminoacetylenyl linoleates. These compounds were obtained as follows:

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOCH_2C{\equiv}CH + CH_2O + HNR_2 \longrightarrow$$
$$\longrightarrow \underset{\text{I}}{CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOCH_2C{\equiv}CCH_2NR_2}$$
$$\text{II—V}$$

II: $NR_2 = N(C_2H_5)_2$; III: $NR_2 = \overline{|NCH_2CH_2CH_2CH_2CH_2|}$; IV: $NR_2 = \overline{|NCH_2CH_2OCH_2CH_2|}$;
V: $NR_2 = N(CH_2C_6H_5)_2$.

Propargyl linoleate (I) was obtained from linoleic acid and propargyl alcohol as described in [3]. The compounds synthesized (II-V) were high-boiling liquids of a dark brown color, soluble in most organic solvents but insoluble in water. The structures of (II-V) were confirmed by their elemental analyses and their IR and PMR spectra.

EXPERIMENTAL (CHEMICAL PART)

IR spectra were obtained on a UR-20 spectrometer (East Germany) in KBr pellets, and PMR spectra on a Hitachi instrument (Japan) (60 MHz, CCl_4 solution, internal standard hexamethyldisiloxane).

4-Diethylamino-2-butynyl Linoleate (II). In a round-bottomed flask, fitted with a reflux condenser with a calcium chloride tube, were heated at 100-105°C for 7 h 0.45 g of paraformaldehyde, 1.2 ml of diethylamine, 3.15 g (0.01 mole) of (I), 0.17 g of copper acetate, and 70 ml of dioxane. When the reaction was complete, 100 ml of water was added to the mixture, which was then acidified with 10% HCl to pH 2.0-3.0, and extracted with diethyl ether. The acidic aqueous layer was basified with ammonia solution to pH 8.0-9.0, then extracted

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