The effect of the substances on diuresis was tested with white rats weighing 150-200 g. Observations of the animals were conducted over a period of 2 h after administration of the test preparations. Results were compared to the control preparation – a 45% NaCl solution.

Test results are given in Table 2. Compounds Ie and IIc displayed slight analgesic activity. Anti-inflammatory properties were detected in Id, Ie, and IIb, the other compounds showing no activity in this respect. The diuresis study revealed that none of the test compounds exhibit diuretic activity.

Compound Ie, which has a p-bromphenyl radical at position 1 and a methyl group at position 2, exhibits both analgesic and anti-inflammatory properties (see Table 2), while our data shows that biological activity is reduced in the analogous compound having a phenacyl group at position 2 (IIc).

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SYNTHESIS OF BIOLOGICALLY ACTIVE 4(3H)-QUINAZOLINONIUM PERCHLORATES

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In order to establish the influence of benzyl and substituted benzyl groups on the biological activity of quinazolinoium compounds, and in pursuance of earlier work [5], a method has been developed for the synthesis of arylamides of N-(2,4)- and -(3,4)-dimethoxybenzanthranilic acids.

TABLE 1. N-R^1-Benzylideneanthranilarylamides (IIIa-n)

Compound	Yield, %	Melting point, °C	Empirical formula
IIIa	63,0	105—6	$C_{20}H_{16}N_2O$
IIIb	65,0	140—2	$C_{21}H_{18}N_2O_2$
IIIc	90,0	118—20	$C_{22}H_{20}N_2O_2$
IIId	80,0	105—8	$C_{22}H_{20}N_2O_2$
IIIe	91,0	122—5	$C_{22}H_{20}N_2O_3$
IIIf	96,0	125—7	$C_{22}H_{20}N_2O_3$
IIIg	80,0	173—4	$C_{23}H_{22}N_2O_3$
IIIh	91,0	135—7	$C_{23}H_{22}N_2O_3$
IIIi	71,0	138—40	$C_{23}H_{22}N_2O_4$
IIIj	98,0	192—4	$C_{22}H_{19}ClN_2O_3$
IIIk	58,0	128—30	$C_{22}H_{20}N_2O_3$
IIIℓ	91,0	235—7	$C_{23}H_{22}N_2O_3$
IIIm	52,0	120—3	$C_{23}H_{22}N_2O_3$
IIIn	75,0	132—4	$C_{22}H_{19}ClN_2O_3$

*Here and in Tables 2-4, all the compounds were crystallized from ethanol.

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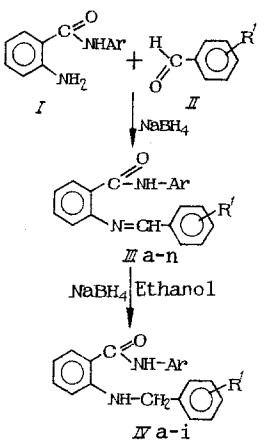
TABLE 2. N-R^1-Benzylanthranilarylamides (IVa-i)

Compound	Yield, %	mp, °C	Empirical formula
IVa	103—5	81,0	$C_{22}H_{22}N_2O_3$
IVb	123—6	60,0	$C_{23}H_{24}N_2O_3$
IVc	121—3	63,0	$C_{23}H_{24}N_2O_3$
IVd	105—8	44,0	$C_{23}H_{24}N_2O_4$
IVe	118—20	68,0	$C_{22}H_{21}ClN_2O_3$
IVf	120—3	48,0	$C_{22}H_{22}N_2O_3$
IVg	127—30	51,0	$C_{23}H_{24}N_2O_3$
IVh	128—31	50,0	$C_{23}H_{24}N_2O_3$
IVi	170—3	53,0	$C_{22}H_{21}ClN_2O_3$

For this purpose, the reaction of anthranilarylamides with 4-methoxy-, 2,4-dimethoxy, and 3,4-dimethoxybenzaldehyde followed by reduction of the products with sodium borohydride in ethanol was examined.



Ar=C_6H_5(IIIa,b,f,g IVa,f), 3=$CH_3C_6H_4$(IIIc,g,ℓ IVb,g), 4-$CH_3C_6H_4$(IIId,h,m IVc,h), 4-$CH_3O_6H_4$(IIIe,i IVd), 4-ClC_6H_4 (IIIℓ,n IVe,i); R'=H(IIIa), 4-CH_3O(IIIb-e), 2,4-$(CH_3O)_2$ (IIIf-ℓIVa-e), 3,4-$(CH_3O)_2$ (IIIk-n IVf-i)

N-Benzylideneanthranilarylamides (IIIa-b) were obtained by a facile method in 52-98% yields (Table 1).

The IR spectra of these compounds showed absorption for stretching vibrations at 1680-1670, 1640-1610, 1530-1510, 1480-1470, 1385-1374, 1334-1320, 1287-1280, and 1220-1165 cm^{-1}. Their alcoholic solutions were strongly luminescent.

It was found that the condensation of anthranilarylamides with aldehydes required the use of equimolar amounts of the reactants in a high state of purity, a polar solvent (96% ethanol), and reaction temperatures between 36 and 40°C, since temperatures outside these limits resulted in cyclization of the arylamides (III) to the corresponding 1,2,3,4-tetrahydro-4-quinazolines [8].

Reduction of N-benzylideneanthranilarylamides with sodium borohydride in ethanol was found to give the N-benzylanthranilamides (IVa-i) in 43-81% yields (Table 2). The reductions were carried out in ethanol which had been previously cooled to 0°C for 2 h at ambient temperature, followed by heating on the water bath for 15-20 min.

The arylamides (IVa-i) were obtained as colorless, crystalline solids which were insoluble in water, but readily soluble in ethanol, carbon tetrachloride, acetone, and dilute mineral acids.

The IR spectra of these compounds showed strong absorption at 3425-3200 cm^{-1} due to stretching vibrations of the NH group, and absorption for stretching vibrations at 1660-1640 cm^{-1}, 1620-1570 cm^{-1}, and 1330-1300 cm^{-1} which may be assigned to the characteristic amide I, II, and III bands.

TABLE 3. N-Acetyl-N-(2',4')- or -(3',4')-dimethoxybenzylanthranilarylamides (Va-i)

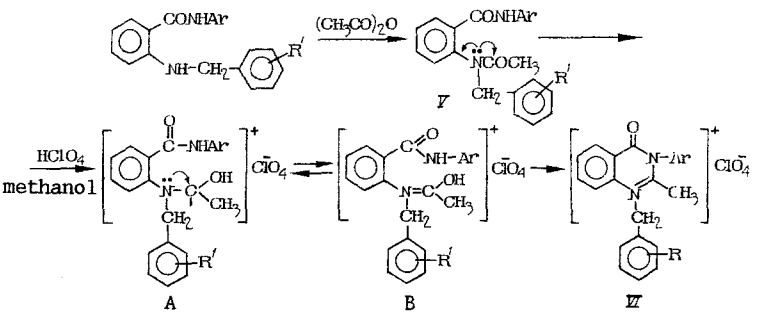
Compound	Yield, %	mp, °C	Empirical formula
Va	79,0	162—4	$C_{24}H_{24}N_2O_4$
Vb	68,0	184—6	$C_{25}H_{26}N_2O_4$
Vc	84,0	143—6	$C_{25}H_{26}N_2O_4$
Vd	64,0	145—7	$C_{25}H_{26}N_2O_5$
Ve	57,0	180—2	$C_{24}H_{23}ClN_2O_4$
Vf	59,0	128—30	$C_{24}H_{24}N_2O_4$
Vg	68,0	180—1	$C_{25}H_{26}N_2O_4$
Vh	73,0	128—31	$C_{25}H_{26}N_2O_4$
Vi	67,0	143—5	$C_{24}H_{23}ClN_2O_4$

The PMR spectra of (IVa-i), obtained in deuteroacetone or deuterochloroform, showed singlets for the three methyl protons at 2.20-2.30 ppm, signlets for the three methoxy protons in the p-position of the benzyl radical at 3.65-3.75 ppm or a singlet for the three protons of the methoxygroup in the orthoposition of the benzyl radical, a doublet (or quadruplet) for the two interacting protons of the methylene group of the benzyl radical at 4.25-4.30 ppm, multiplets for the aromatic protons of the benzene ring centered at 6.95-7.05 ppm, and a signal for the single proton on the NH group of the arylamide moiety at 9.00-9.25 ppm. A signal for the NH group of the benzylamino-group was not seen, since it lies in the region of the signals for the aromatic protons. It is noteworthy that in a less polar solvent (chloroform), the signal for the single proton of the NH group lies in the region of signals for the aromatic ring protons.

These N-(2',4')- or -(3',4')-dimethoxybenzylanthranilarylamides have found practical application for the synthesis of biologically active 1-[(2',4'- or -(3',4')-dimethoxybenzyl]-2-methyl-3-aryl-4(3H)-quinazolinonium perchlorates [1, 2].

It was found that N-acylation of these compounds followed by cyclization with 57% perchloric acid gave the perchlorates (Table 3).

Acylation of (IV) proceeded readily and in satisfactory yields (57-98%).



Ar=C_6H_5(Va,fVIa), 3-$CH_3C_6H_4$(Vb,gVIb,e), 4-$CH_3C_6H_4$(Vc,hVIc,f), 4-$CH_3OC_6H_4$(Vd), 4-ClC_6H_4(VeiVId,g); R'=2,4-$(CH_3O)_2$(Va-eVIa-d), 3,4-$(CH_3O)_2$(Vf-iVIe-g)

The acyl derivatives were obtained as colorless, crystalline solids which were insoluble in water and mineral acids, but readily soluble in organic solvents (alcohol, benzene, toluene, dioxane, acetone, and dimethyl sulfoxide).

The IR spectra of (Va-i) showed strong absorption at 3385-3240 cm^{-1} for stretching vibrations of the NH group, and the absorptions at 1698-1640, 1540-1500, 1488-1470, 1415-1400, and 1322-1300 cm^{-1} may be assigned to the characteristic amide bands I, II, and III.

The cyclization of (V) to the 4(3H)-quinazolinium perchlorates (VI) involves initial protonation of the oxygen of the carbonyl group in the acylamide grouping to give the carbonium-onium cation (A), which on shifting the lone pair from the adjacent nitrogen is converted into the carbonium-immonium cation B, the latter then undergoing stabilization by dehydration to give the 4(3H)-quinazolinonium perchlorate (VI) (Table 4).

The 4(3H)-quinazolinonium salts (VIa-g) were obtained as colorless or yellow crystalline solids which were insoluble in water, sparingly soluble in ethanol, acetone, and xylene, and moderately soluble in dimethyl sulfoxide.

TABLE 4. 1-(R-Benzyl)-2-methyl-3-aryl-4-(3H)-quinazolinonium Perchlorates (VIa-g)

Compound	Yield, %	mp, °C	Empirical formula
VIa	71,2	191—3	$C_{24}H_{21}ClN_2O_7$
VIb	67,1	212—5	$C_{25}H_{24}ClN_2O_7$
VIc	63,4	228—30	$C_{25}H_{24}ClN_2O_7$
VId	98,3	236—8	$C_{24}H_{22}Cl_2N_2O_7$
VIe	64,3	205—7	$C_{25}H_{24}ClN_2O_7$
VIf	68,5	221—3	$C_{25}H_{24}ClN_2O_7$
VIg	93,3	268—70	$C_{24}H_{22}Cl_2N_2O_7$

TABLE 5. Biological Activity of 4(3H)-Quinazolonium Perchlorates

Compound	Acute toxicity mg/kg (intraperitoneal, mice)	Antioonvulsant activity			Analgesic activity	Arbitaray pharmacological activity, LD_{50}/ED_{50}	
		maximum electroshock test		corazole convulsion test			
		peak of effect, min	ED_{50}, mg/kg	ED_{50} mg/kg	time of defensive reflex, sec, in a dose of 1/5 at peak of effect	maximum electroshock	corazole convulsions
VId	600 (531—696)	30	111 (91—135)	80 (74—86)	34,9±15,8	5,4	7,5
VIg	520 (430—624)	30	80 (63—124)	46 (35—60)	27,0±19,6	6,5	11,3
Hexamidine	340 (288—401)	240	90 (79—103)	—	—	3,7	—

The structures of these compounds were confirmed by their IR, UV, and PMR spectra.

The IR spectra of (VIa-g) showed characteristic absorption bands, namely strong absorption at 1742-1700 cm^{-1} due to stretching vibrations of the carbonyl group, quinazoline absorption at 1677-1641, 1630-1610, 1590-1560, and 1498-1460 cm^{-1}, and absorption at 1120-1100 cm^{-1} due to stretching vibrations of the chlorate anion.

The PMR spectra of (VIa-g), obtained in trifluoroacetic acid, show singlets for the three methyl protons at 2.25-2.45 ppm, doublets for the six protons of the two methoxy groups in the benzyl radical at 3.55-3.72 ppm, doublets for the two interacting protons of the methylene group in the benzyl moiety at 6.40-6.53 ppm, and multiplets for the eleven aromatic protons of the benzene rings of the quinazoline system centered on 7.32-7.64 ppm. Subsequent studies showed that 4(3H)-quinazolinonium perchlorates display anticonvulsant, analgesic, and antimicrobial activity [2, 5].

Compounds (VIa-g) are structurally reminiscent of the alkaloid papaverine, which contains a dimethoxybenzyl radical, while the introduction of a dimethoxybenzyl radical into 4(3H)-quinazolinonium salts results in enhancement of their biological activity.

EXPERIMENTAL (CHEMICAL)

N-2,4-Dimethoxybenzylideneanthranil-4-chloroanilide (IIIj). To a solution of 2.47 g (0.01 mole) of anthranil-4-chloroanilide, obtained by the magnesylamine method [8], in 10 ml of ethanol was added with stirring in two portions a solution of 1.66 g (0.01 mole) of 2,4-dimethoxybenzaldehyde in 7 ml of ethanol while maintaining the temperature at 36°C. The mixture was kept at ambient temperature for 30 min, then the solid which separated on cooling was filtered off, washed on the filter with 10 ml of cold ethanol, and dried at ambient temperature to give 98.0% of long yellow needles, $C_{22}H_{19}ClN_2O_3$, mp 192-194°C. IR spectrum (Vaseline grease): 1678, 1615, 1552, 1500, 1470, 1383, 1330, 1287, 1220.

N-2,4-Dimethoxybenzylanthranil-4-chloroanilide (IVe). N-2,4-Dimethoxybenzylideneanthranil-4-chloroanilide (IIIj) (1.95 g, 0.005 mole) and 0.2 g (0.0055 mole) of sodium borohydride were mixed in the dry state until homogeneous, then 25 ml of ethanol cooled to 0°C was added. The mixture was stirred at ambient temperature for 2 h, then heated on the water bath for 15 min, filtered, and the filtrate acidified with 10% acetic acid to pH 6. The solid which separated was filtered off and recrystallized from ethanol to give 68% of colorless needles, mp 118-120°C.

N-Acetyl-N-(2',4'-dimethoxybenzyl)anthranil-4-chloroanilide (Ve). A mixture of 3.96 g (0.01 mole) of (IVe) and 10 ml of acetic anhydride was heated on the water bath for 45 min, then cooled, 50 ml of water added, and the mixture neutralized with anhydrous sodium carbonate until alkaline to litmus. The solid which separated was filtered off, washed on the filter with 150 ml of water, and recrystallized from ethanol to give 57% of colorless crystals, $C_{24}H_{23}ClN_2O_4$. mp 180-182°C. IR spectrum, cm^{-1}: 3260, 1648, 1543, 1500, 1470, 1410, 1320.

1-(2',4'-Dimethoxybenzyl)-2-methyl-3-(4'-chlorophenyl)-4(3H)-quinazolinonium Perchlorate (VId). A solution of 4.38 g (0.01 mole) of N-acetyl-N-2,4-dimethoxybenzylanthranil-4-chloroanilide in 30 ml of methanol was treated with 1.76 g (0.01 mole) of 57% perchloric acid, and the mixutre kept on th water bath at 70-80°C for 30 min. Methanol (15 ml) was distilled off, and the solid which separated was filtered off, washed on the filter with 2 × 5 ml of methanol, and crystallized from dry methanol to give 90% of yellow prisms, mp 236-238°C. IR spectrum, cm^{-1} (Vaseline grease): 1722, 1660, 1590, 1498, 1470, 1305, 1100.

EXPERIMENTAL (BIOLOGICAL)

The 4-(3H)-quinazolonium perchlorates (VIIa-m)* were tested for analgesic, anticonvulsant, and antimicrobial activity. The most active compounds were tested for acute toxicity by the method of Pershin [6], involving intraperitoneal administration to white mice in 2% starch mucilage.

Antimicrobial activity was assessed by serial dilutions against reference strains of Staphylococcus aureus and Escherichia coli. The activity was expressed as the minimum inhibitory concentration (MIC, μg/ml) which retarded the growth of the bacterial cultures.

Analgesic activity was determined by the method of Eddy and Leimbach, and anticonvulsant activity by the maximum electroshock [7] and the corazole convulsion tests, in comparison with the widely used medicinal drug hexamidine [2, 3, 5, 7]. The results were treated statistically by the method of Lichfield and Wilcoxon for $p = 0.05$.

Pharmacological screening of the perchlorates showed them to possess analgesic, anticonvulsant, and antimicrobial activity.

The minimum ihibitory concentrations of the compounds lay in the range 500-1000 μg/ml.

The greatest anticonvulsant and analgesic activity was shown by those compounds in which a 4-chlorophenyl radical was present in the 3-position of the quinazolone ring. The screening results are shown in Table 5, from which it will be seen that the test compounds are superior in their activity, acute toxicity, and chemotherapeutic ratio to hexamidine [1, 2].

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*Translator's note: (VIIa-m) should presumably read (VIa-g).