4(3H)QUINAZOLONES.

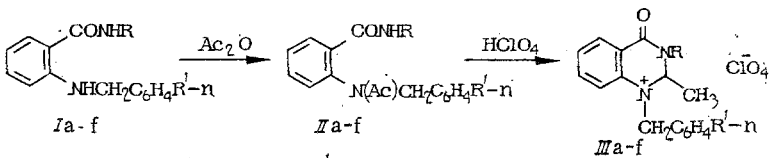
XII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-BENZYL(4'-NITROBENZYL)-2-METHYL-3-ALKYL(ARYL)-4(3H)QUINAZOLINONIUM PERCHLORATES

N. I. Chernobrovin, Yu. V. Kozhevnikov, V. S. Zalesov, and I. I. Gradel'

UDC 615.213.547.856.1.012.1

Continuing earlier investigations [3], we have synthesized some 1-benzyl(4'-nitrobenzyl)-2-methyl-3-alkyl(aryl)-4(3H)-quinazolinonium perchlorates (IIIa-f).

From methyl N-benzylanthranilate there were obtained the alkyl(aryl)amides of N-benzylanthranilic acid (Ia, b, e, and f) (Table 1). The arylamides of N-(4'-nitrobenzyl)anthranilic acid (Ic and d) were obtained by reaction of the anthranilic acid arylamides with 4-nitrobenzyl chloride [4] in pyridine. Treatment of (Ia-f) with acetic anhydride gave the N-acetyl-N-benzyl(4'-nitrobenzyl)anthranilic acid alkyl(aryl)amides (IIa-f) (Table 2), which cyclized in boiling methanol in the presence of 57% $HClO_4$ to the perchlorates (IIIa-f) (Table 3).



I-IIIa: R = $C_6H_3(CH_3)_2$-2,4; R' = H;
I-IIIb: R = C_6H_4OMe-4, R' = H;
I-IIIc: R = C_6H_4OMe-4, R' = NO_2;
I-IIId: R = C_6H_4OEt-4, R' = NO_2;
I-IIIe: R = Bu, R' = H
I-IIIf: R = Hex R' = H

The required products (IIIe) and (IIIf) were obtained without isolating the acyl derivatives (IIe) and (IIf), which were difficult to purify.

The perchlorates (IIIa-f) were colorless, crystalline solids which were sparingly soluble in ethanol, acetone, xylene, and dioxane, and moderately soluble in DMF and DMSO. The structures of the compounds were confirmed by their UV and IR spectra (see Fig. 1). The IR spectra of the perchlorates (IIIa-f) showed the following typical absorptions: 1700-1725 (Ar—C=O), 1610-1630, 1560-1580, and 1460-1470 (quinazoline ring), and 1100-1120 cm^{-1} (chlorate anion).

EXPERIMENTAL CHEMISTRY

IR spectra were recorded on a UR-20 instrument (East Germany) as suspensions in vaseline oil.

TABLE 1. Alkyl(aryl)amides of N-Benzyl(4'-nitrobenzyl)anthranilic Acid (Ia-f)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
Ia	83,4	103—11 (MeOH)	78 01	6,7	8,5	$C_{22}H_{22}N_2O$	77,97	6,71	8,48
Ib	78,3	111—2 (MeOH)	75,9	6,0	8,45	$C_{21}H_{20}N_2O_2$	75,88	6,06	8,42
Ic	74,66	113—6 (ethanol)	66,87	5,15	11,11	$C_{21}H_{19}N_3O_4$	66,83	5,07	11,13
Id	58,6	123—5 (ethanol)	67,63	5,37	10,85	$C_{22}H_{21}N_3O_4$	67,5	5,4	10,73
Ie	63,1	50—51 (MeOH)	76,61	7,91	9,83	$C_{18}H_{22}N_2O$	76,56	7,85	9,92
If	64,4	53—5 (MeOH)	77,91	7,78	9,28	$C_{20}H_{24}N_2O$	77,89	7,84	9,08

Note. IR spectrum of (Ia), ν_{max}, cm^{-1}: 3330, 1648, 1520 1482, 1410.

Perm Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 7, pp. 830-833, July, 1984. Original article submitted June 17, 1983.

0091-150X/84/1807-0485$08.50

TABLE 2. Arylamides of N-Benzyl(4'-nitrobenzyl)-N-acetyl-anthranilic Acid (IIa-d)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIa	75,25	147—9 (MeOH)	77,21	6,39	7,65	$C_{24}H_{24}N_2O_2$	77,39	6,49	7,52
IIb	98,1	132—3 (ethanol)	73,98	6,0	7,53	$C_{23}H_{22}N_2O_3$	73,78	5,92	7,48
IIc	61,3	177—9 (MeOH)	65,8	5,12	10,11	$C_{23}H_{21}N_3O_5$	65,86	5,05	10,02
IId	62,5	180—2 (MeOH)	66,43	5,48	9,72	$C_{24}H_{23}N_3O_5$	65,5	5,35	9,69

Note. IR spectrum of (IIa), ν_{max}, cm^{-1}: 3258, 1645, 1520, 1484, 1440, 1246.

TABLE 3. 1-Benzyl(4'-nitrobenzyl)-2-methyl-3-alkyl(aryl)-4(3H)-quinazolinonium Perchlorates (IIIa-f)

Compound	Yield, %	mp, °C (abs. alcohol)	Found, %		Empirical formula	Calculated, %	
			N	Cl		N	Cl
IIIa	96,3	205—7	6,05	7,93	$C_{24}H_{23}ClN_2O_5$	6,15	7,79
IIIb	98,1	248—50	6,07	7,87	$C_{23}H_{21}ClN_2O_5$	6,17	7,75
IIIc	63,2	218—20	8,45	7,22	$C_{23}H_{21}ClN_3O_8$	8,35	7,04
IIId	31,3	214—17	8,29	6,80	$C_{24}H_{23}ClN_3O_8$	8,12	6,86
IIIe	42,5	175—6	6,63	8,96	$C_{20}H_{23}ClN_2O_5$	6,88	8,71
IIIf	41,1	175—7	6,52	8,03	$C_{22}H_{25}ClN_2O_5$	6,47	8,18

Note. IR spectrum of (IIIb), ν_{max}, cm^{-1}: 1725, 1612, 1592, 1462, 1302, 1102.

N-Benzylanthranilic Acid Butylamide (Ie). To a solution of EtMgBr, obtained from 17.28 g (0.16 mole) of EtBr and 3.84 g (0.16 mole) of Mg in 50 ml of dry ether, was added 5.85 g (0.08 mole) of n-butylamine in 20 ml of dry ether, and the mixture was heated on the water bath for 30 min. A solution of 12 g (0.05 mole) of methyl N-benzylanthranilate [9] in 35 ml of dry ether was then added dropwise, and when the reaction was complete the organomagnesium compound was decomposed with 10% acetic acid. The aqueous layer was extracted with ether, steam distilled, and the solid which separated was filtered off and recrystallized from methanol to give 63.1% of needles, mp 50-51°C. Found, %: C 76.61; H 7.91; N 9.83. $C_{18}H_{22}N_2O$. Calculated, %: C 76.56; H 7.85; N 9.92. IR spectrum, ν_{max}, cm^{-1}: 3340, 1640, 1512, 1480, 1410.

Compounds (Ia), (Ib), and (If) (see Table 1) were obtained similarly. Amides (Ic) and (Id) were obtained from anthranilic acid 4-anisidide and 4-phenetidide [7].

N-(4'-Nitrobenzyl)anthranilic Acid 4-Anisidide (Ic). Anthranilic acid 4-anisidine (2.42 g; 0.01 mole) and 1.7 g (0.01 mole) of 4-nitrobenzyl chloride in 20 ml of pyridine were heated for 1.5 h, cooled, and 50 ml of water added. The solid which separated was filtered off, washed in the filter with water, and crystallized from ethanol. Yield 63.2%. Found, %: C 66.87; H 5.15; N 11.0. $C_{21}H_{19}N_3O_3$. Calculated, %: C 66.83; H 5.07; N 11.13. IR spectrum, ν_{max}, cm^{-1}: 3382, 1642, 1518, 1476, 1385.

N-(4'-Nitrobenzyl)anthranilic Acid 4-Phenetidide (Id). A mixture of 2.56 g (0.01 mole) of anthranilic acid 4-phenetidide and 1.7 g (0.01 mole) of 4-nitrobenzyl chloride in 25 ml of pyridine was heated for 1 h, cooled, and 50 ml of water added the solid which separated was filtered off, washed on the filter with 100 ml of water, and crystallized from ethanol to give 58.6% of colorless needles, mp 123-125°C. Found, %: C 67.63, H 5.37; N 10.85. $C_{22}H_{21}N_3O_4$. Calculated, %: C 67.5; H 5.4; N 10.73. IR spectrum, ν_{max}, cm^{-1}: 3390, 3282, 1675, 1642, 1516, 1484, 1242.

N-Acetyl-N-benzylanthranilic Acid 2,4-Xylidide (IIa). A solution of 3.3 g (0.01 mole) of (Ia) in 12 ml of acetic anhydride was kept at 80°C for 30 min, then kept for 0.5 h at ambient temperature, decomposed with 50 ml of water, and neutralized with sodium carbonate to pH 7.0. The solid which separated was filtered off, washed on the filter with 150 ml of water, dried, and crystallized from methanol to give 75.25% of prisms, mp 147-149°C. Found, %: C 77.21; H 6.39; N 7.65. $C_{24}H_{24}N_2O_2$. Calculated, %: C 77.39; H 6.49; N 7.52. IR spectrum, ν_{max}, cm^{-1}: 3258, 1645, 1520, 1484, 1440, 1246.

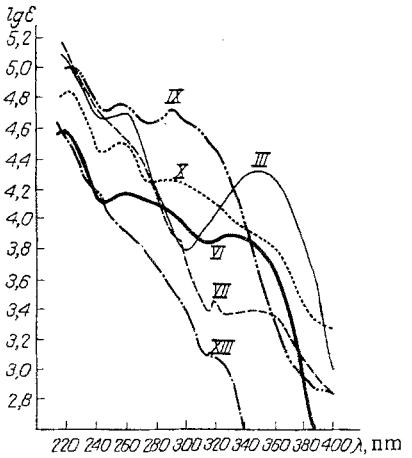


Fig. 1. UV spectra of $1 \cdot 10^{-5}$ M solutions of (III), (VI), (VII), (IX), (X), and (XIII). x axis) wavelength (λ, nm); y axis) log molar extinction coefficient (ε).

N-Acetyl-N-benzylanthranilic Acid 4-Anisidide (IIb). A solution of 3.32 g (0.01 mole) of N-benzylanthranilic acid 4-anisidide in 12 ml of acetic anhydride was kept at 80°C for 30 min, then cooled, 50 ml of water added, and neutralized with sodium carbonate until neutral to litmus. The solid which separated was filtered off, washed on the filter with 50 ml of water, dried and crystallized from ethanol to give 98.1% of needles, mp 132-133°C. Found, %: C 73.98; H 6.0; N 7.53. $C_{23}H_{22}N_2O_3$. Calculated, %: C 73.78; H 5.92; N 7.48. IR spectrum, ν_{max}, cm^{-1}: 3254, 1648, 1522, 1486, 1445, 1400, 1248.

(IIc) and (IId) were obtained similarly.

1-Benzyl-2-methyl-3-(2',4'-xylyl)-4(3H)-quinazolinonium Perchlorate (IIIa). A solution of 3.46 g (0.01 mole) of (IIa) in 30 ml of methanol and 1.76 ml of 57% $HClO_4$ was boiled for 30 min, 15 ml of methanol distilled off, and the solid which separated on cooling was filtered off, washed with 10 ml of methanol, and recrystallized from absolute ethanol to give 96.3% of needles, mp 205-207°C. Found, %: N 6.05; Cl 7.93. $C_{24}H_{23}ClN_2O_5$. Calculated, %: N 6.15; Cl 7.79. IR spectrum, ν_{max}, cm^{-1}: 1714, 1614, 1590, 1100.

1-Benzyl-2-methyl-3-(4'-anisyl)-4(3H)-quinazolinonium Perchlorate (IIIb). A solution of 3.74 g (0.01 mole) of (IIb) in 20 ml of methanol and 1.76 ml of 57% $HClO_4$ was boiled for 30 min, 10 ml of methanol distilled off, and the solid which separated on cooling was filtered off, washed on the filter with 10 ml of methanol, and recrystallized from absolute ethanol to give 98.1% of needles, mp 248-250°C. Found, %: N 6.07; Cl 7.87. $C_{23}H_{21}ClN_2O_5$. Calculated, %: N 6.17; Cl 7.75. IR spectrum, ν_{max}, cm^{-1}: 1725, 1612, 1592, 1462, 1302, 1102.

1-(4'-Nitrobenzyl)-2-methyl-3-(4'-anisyl)-4(3H)-quinazolinonium Perchlorate (IIIc). To 4.19 g (0.01 mole) of (IIc) was added a solution of 1.76 ml of 57% $HClO_4$ in 25 ml of methanol, and the mixture was heated on a boiling water bath for 33 min. Methanol (15 ml) was then distilled off, and the solid which separated on cooling was filtered off and recrystallized from absolute ethanol to give 63.2% of colorless needles, mp 218-220°C. Found, %: N 8.45; Cl 7.22. $C_{23}H_{21}ClN_3O_8$. Calculated, %: N 8.35; Cl 7.04. IR spectrum, ν_{max}, cm^{-1}: 1718, 1615, 1518, 1460, 1362, 1100.

1-(4'-Nitrobenzyl)-2-methyl-3-(4'-ethoxyphenyl)-4(3H)-quinazolinonium Perchlorate (IIId). A solution of 4.33 g (0.01 mole) of (IId) in 30 ml of dry methanol and 1.76 ml of 57% $HClO_4$ was boiled for 30 min, 20 ml of methanol distilled off, and the solid which separated on cooling was filtered off, washed with 5 ml of dry methanol, dried, and crystallized from absolute ethanol to give 31.3% of colorless prisms, mp 214-217°C. Found, %: N 8.29, Cl 6.80. $C_{24}H_{21}ClN_3O_8$. Calculated, %: N 8.12; Cl 6.86. IR spectrum, ν_{max}, cm^{-1}: 1709, 1617, 1518, 1462, 1360, 1100.

1-Benzyl-2-methyl-3-n-butyl-4(3H)-quinazolinonium Perchlorate (IIIe). A solution of 2.82 g (0.01 mole) of N-benzylanthranilic acid n-butylamide in 5 ml of acetic anhydride was

kept at 80°C for 30 min. After cooling, the resulting solution was treated with 20 ml of methanol and 1.76 ml of 57% $HClO_4$, and the mixture was boiled for 30 min. Methanol (10 ml) was distilled off, and the solid which separated was filtered off, washed on the filter with 10 ml of methanol, and recrystallized from absolute ethanol to give 42.5% of prisms, mp 175-176°C. Found, %: N 6.63; Cl 8.96. $C_{20}H_{23}ClN_2O_5$. Calculated, %: N 6.88; Cl 8.71. IR spectrum, γ_{max}, cm^{-1}: 1703, 1610, 1500, 1463, 1305, 1109.

1-Benzyl-2-methyl-3-n-hexyl-4(3H)quinazolinonium Perchlorate (IIIf). A solution of 3.08 g (0.01 mole) of (If) in 10 ml of acetic anhydride was kept at 80°C for 30 min, followed by 20 min at ambient temperature, and a solution of 1.76 ml of 57% $HClO_4$ was added. The mixture was kept on a boiling water bath for 35 min, 10 ml of methanol distilled off, and the solid which separated on cooling was filtered off, and recrystallized from absolute ethanol to give colorless prisms (41.1%), mp 175-177°C. Found, %: N 6.52; Cl 8.03. $C_{22}H_{25}ClN_2O_5$. Calculated, %: N 6.47; Cl 8.18. IR spectrum, γ_{max}, cm^{-1}: 1700, 1641, 1500, 1303, 1468, 1108.

EXPERIMENTAL PHARMACOLOGY

Pharmacological studies were carried out in white mice of both sexes, weighing 18-23 g. The compounds were administered intraperitoneally in 2% starch mucilage. The acute toxicities [5] and anticonvulsive activity by the maximum electroshock test (MET) [8] were determined for all the compounds prepared. The results were evaluated statistically (Litchfield and Wilcoxon) for P = 0.05 [1]. For active compounds, the nominal breadth of pharmacological activity (NBPA), equal to the LD_{50}/ED_{50}, was calculated. Anticonvulsive activity was compared with that of hexamidine.

The tests showed that of the perchlorates (IIIa-f), only (IIIc) displayed anticonvulsive activity in the MET (ED_{50} = 150 mg/kg). The LD_{50} of (IIIc) was 440 mg/kg, the NBPA being 2.9. This compound was inferior to the anticonvulsive drug hexamidine, and the toxicity could be the same, since the LD_{50} values were not statistically different at P = 0.05 (LD_{50} = 340 mg/kg). None of the other perchlorates showed any anticonvulsive activity in the MET at a dose of 300 mg/kg. In a dose of 1000 mg/kg, (IIIa), (IIIb), and (IIIf) were not lethal to animals over a period of 15 days, but at this dose (IIIe) was 100% lethal to the animals.

LITERATURE CITED

1. M. L. Belen'kii, Fundamentals of the Quantitative Measurement of Pharmacological Effects [in Russian], Riga (1959), p. 71.
2. A. M. Berkengeim, Laboratory Manual for Synthetic Drugs, Perfumes, and Photographic Reagents [in Russian], Moscow-Leningrad (1942), p. 164.
3. Yu. V. Kozhevnikov, N. N. Smirnova, V. S. Zelesov, et al., Khim.-farm. Zh., No. 6, 55-59 (1981).
4. Methods of Preparation of Chemical Reagents and Compounds [in Russian], Moscow (1964), No. 10, p. 65.
5. G. N. Pershin (ed.), Methods of Experimental Chemotherapy [in Russian], Moscow (1959), pp. 109-117, 456.
6. P. A. Petyunin and Yu. V. Kozhevnikov, Zh. Obshch. Khim., 30, No. 8, 2453 (1960).
7. P. A. Petyunin and Yu. V. Kozhevnikov, ibid., 2028.
8. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495-497 (1961).
9. L. Baiocchi, G. Gorki, and G. Palazzo, Ann. Chim., 55, 116-125 (1965).