piration. Compound XIII does not influence the neuromuscular transmission; 3-5 min after its introduction in doses of 1-2 mg/kg, the heart stops and the animal dies.

Compounds IX-XI, in small doses equal to 1-2 mg/kg, cause a short-term increase of 40-80 mm Hg in the arterial pressure and excitation of respiration. These effects are prevented by ganglio-blocking preparation hexonium (0.3-0.5 mg/kg) or temequine (0.2 mg/kg). Hence, the arterial hypertension and intensification of respiration are caused by excitation of ganglia and formations related to them, i.e., nicotinelike properties of the compounds. In contrast, compound XII decreases the arterial pressure and after its administration, the nicotinelike preparation, cytisine (15 μg/kg), does not lead to increase in pressure and respiration excitation. Hence, compound XII exhibits ganglio-blocking action.

The results of our investigation presented in the present article and in earlier papers [1, 2] show that among the bisquaternary ammonium derivatives of indole there are compounds with moderately pronounced curarelike, ganglio-blocking, and nicotinelike properties.

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SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF α-ACYL DERIVATIVES OF β-N-R-OXAMOYLPHENYLHYDRAZINES

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In a search for biologically active compounds, we synthesized a series of new α-acyl-β-N-R-oxamoyl derivatives of phenylhydrazine [1].

The synthesis was carried out by acylation of β-N-R-oxamolyphenylhydrazines [1] by carboxylic acid chlorides in dry chloroform in the presence of triethylamine:

II, a: R = CH_3, R^1 = butyryl; b: R = C_3H_7, R^1 = butyryl; c: R = iso-C_3H_7, R^1 = butyryl; d: R = C_4H_9, R^1 = butyryl; e: R = iso-C_4H_9, R^1 = butyryl; f: R = cyclohexyl, R^1 = butyryl; g: R = CH_3, R^1 = valeryl; h: R = iso-C_3H_7, R^1 = valeryl; i: R = C_4H_9, R^1 = valeryl; j: R = iso-C_4H_9, R^1 = valeryl; k: R = $C_6H_5CH_2$, R^1 = valeryl; *l*: R = cyclohexyl, R^1 = valeryl; m = R = CH_3, R^1 = cinnamoyl; n: R = C_3H_7, R^1 = cinnamoyl; o: R = iso-C_3H_7, R^1 = cinnamoyl; p: R = C_4H_9, R^1 = cinnamoyl; q: R = iso-C_4H_9, R^1 = cinnamoyl; r: R = cyclohexyl, R^1 = cinnamoyl.

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TABLE 1. α-Acyl-β-N-R-oxamoylphenylhydrazines IIa-r

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %	IR spectra, $\tilde{\nu}$, cm^{-1}		
						CO (amide I)	NH (amide II)	NH
IIa	49	159—161	15,83	$C_{13}H_{17}O_3N_3$	15,95	1678	1498	3308,3242
IIb	64	100—102	14,34	$C_{15}H_{21}O_3N_3$	14,42	1670	1510	3300,3240
IIc	51	150—152	14,47	$C_{15}H_{21}O_3N_3$	14,42	1660	1500	3288, 3238
IId	53	136—137	13,81	$C_{16}H_{23}O_3N_3$	13,76	1666	1495	3321, 3270
IIe	53	140—142	13,68	$C_{16}H_{23}O_3N_3$	13,76	1665	1494	3310, 3265
IIf	71	180—182	12,89	$C_{18}H_{25}O_3N_3$	12,68	1663	1510	3296, 3265
IIg	67	139—141	15,04	$C_{14}H_{19}O_3N_3$	15,15	1672	1505	3310, 3245
IIh	67	118—120	13,84	$C_{16}H_{23}O_3N_3$	13,76	16,68	1505	3310, 3254
IIi	64	117—119	13,02	$C_{17}H_{25}O_3N_3$	13,15	16,62	1505	3296, 3236
IIj	59	125	13,25	$C_{17}H_{25}O_3N_3$	13,15	1670	1496	3220, 3270
IIk	49	153—155	12,02	$C_{20}H_{23}O_3N_3$	11,89	1667	1502	3300, 3245
IIl	50	117—119	11,98	$C_{19}H_{27}O_3N_3$	12,16	1660	1510	3292, 3260
IIm	75	210—212	13,15	$C_{18}H_{17}O_3N_3$	13,00	1670	1497	3310, 3245
IIn	56	127—129	11,79	$C_{20}H_{21}O_3N_3$	11,96	1665	1505	3305, 3260
IIo	63	204—205	11,96	$C_{20}H_{21}O_3N_3$	11,96	1660	1493	3347, 3330
IIp	50	167—169	11,34	$C_{21}H_{23}O_3N_3$	11,50	1666	1496	3305, 3255
IIq	57	133—134	11,64	$C_{21}H_{23}O_3N_3$	11,50	1670	1500	3370, 3247
IIr	82	193—195	10,83	$C_{23}H_{25}O_3N_3$	10,73	1665	1510	3288, 3248

Compounds IIa-r (Table 1) are white fine crystalline compounds. They crystallize from aqueous ethanol. Their structure was confirmed by the data of elemental analysis and IR spectroscopy.

The IR spectra of compounds IIa-r were compared with the spectra of the corresponding compounds I. In the spectra of the initial β-N-R-oxamoylphenylhydrazines, the bands in the 1684-1668 and 1545-1540 cm^{-1} regions have the highest intensity. The first of these corresponds to the stretching vibrations of the carbonyl group ($\nu_{C=O}$) (I amide band) and the second to deformational vibrations of the NH group (δ_{NH}) (II amide band) [2]. Besides the high intensity, due to the presence of two carbimide groups in the molecule, these bands have a resonance structure as the result of the formation of hydrogen bonds with the participation of proton-donor(>NH) and proton-acceptor (>C=O) centers in the molecule [3], and this, in turn, causes a different degree of shift of the $\nu_{C=O}$ and δ_{NH} bands. In the 1718-1721 cm^{-1} region there is a medium intensity band corresponding to the stretching vibrations of α-carbonyls present in the S-trans-conformation [4], especially as this conformation is stabilized by the presence of hydrogen bonds. This conclusion is also confirmed by the stretching vibration bands of the NH groups, whose maxima are shifted to the region of lower frequencies (3350-3230 cm^{-1}) and the contours are greatly broadened.

For α-butyryl, α-valeryl-, α-cinnamoyl-β-N-R-oxamoylphenyhydrazines IIa-r, the character of the spectra and all the above regularities remain unchanged, so that the above conclusions can be applied to this series of compounds.

In the spectra we found and identified other bands confirming the structure of the compounds synthesized.

We studied the antipyretic and antiinflammatory activity of the compounds synthesized (Table 2).

In the study of the antiinflammatory activity it was found that α-butyryl-, α-valeryl-, α-cinnamoyl derivatives of β-N-R-oxamoylphenylhydrazines containing R = CH_3, C_3H_7 groups in the oxamoyl residue decrease the inflammation by 23-13%, while with increase in the alkyl chain up to C_4 or the introduction of branched radicals, the antiinflammatory activity decreases or disappears, and in certain cases even an increase in edema is observed.

The highest antipyretic activity, similar to the activity of amidopyrine, was shown by α-valeryl-β-N-isobutyloxamoylphenylhydrazine (IIj).

From our study on α-substituted β-N-R-oxamoylphenylhydrazines, the structure of these compounds could be confirmed, the conformational structure and presence of hydrogen bridges could be suggested, and certain regular dependences of the antiinflammatory activity on the structure could be established.

TABLE 2. Antiinflammatory and Antipyretic Activity of α-Acyl-β-N-R-oxamoylphenylhydrazines IIa-r

Compound	% of inflammation depression	Decrease in temperature after introduction, °C		
		after 1 h	after 2 h	after 3 h
II a	20,8	—	—	—
II b	22,8	—	—	—
II c	Increase in edema	—	—	—
II d	Increase in edema	—	—	—
II e	Increase in edema	—	—	—
II f	13,0	1,0	0,8	0,9
II g	13,3	0,5	0,5	0,9
II h	9,6	0,9	0,9	0,7
II i	12,4	0,8	0,6	0,6
II j	5,3	1,1	0,8	1,0
II k	6,0	—	—	—
II l	7,7	—	—	—
II m	3,6	—	—	—
II n	1,6	—	—	—
II o	0	—	—	—
II p	Increase in edema	—	—	—
II q	Increase in edema	—	—	—
II r	16,4	0,6	0,8	0,8
Butadione	24,0	—	—	—
Amidopyrine	—	1,2	1,2	1,1

EXPERIMENTAL CHEMISTRY

α-Butyryl-β-N-methyloxamoylphenylhydrazine (IIa). β-N-Methyloxamoylphenylhydrazine, 1.93 g (0.01 mole), is dissolved in 20 ml of dry chloroform, and 1.5 g (0.015 mole) of triethylamine are added. Then, 1.06 g (0.01 mole) of butyryl chloride are added in portions, with cooling and stirring, to this mixture. The reaction mixture is washed with acidified water. The organic layer is separated, chloroform is evaporated, and the residue is crystallized from 70% ethanol. Yield, 1.1 g (49%) of IIa, mp 159-161°C. Compounds IIb-r are obtained in the same way.

The spectra were recorded on the UR-20 spectrophotometer (GDR) in the region of 3600-650 cm^{-1} with a scanning velocity of 64 $cm^{-1} \cdot min^{-1}$, recording scale of 10 mm/100 cm^{-1}, constant time 2 [sic] and slit-width 4 [sic]. The compounds were studied in the form of tablets with KBr.

EXPERIMENTAL BIOLOGY

The antiinflammatory activity was determined by the method of E. Yu. Strel'nikov [5] on white mice, weighing 18-20 g each, with reference to butadione. The compounds studied and butadione were administered in a dose calculated as 100 mg per kg body weight of the animal. Control experiments were set up at the same time. The antiinflammatory effect was judged from the ratio of the difference in weight between the edematous and nonedematous paws of the main experiments, and the data obtained from mice in the control group.

The antipyretic action of compounds IIf-j, r was studied on white rats by the method described in [6] with reference to amidopyrine. The body temperature was measured rectally by means of type TP ÉM-1 electrothermometer. To produce a milk-induced fever, skim boiled milk was administered intramuscularly to the animals in a dose of 1 ml per 100 g body weight of the animals. The compounds studied and amidopyrine were administered intragastrically in a dose of 1/10 LD_{50} after the temperature peak had been attained (5 h after the introduction of milk). The antipyretic effect was determined dynamically 1, 2, and 3 h after administration of the compounds studied. The results are listed in Table 2.

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SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF SUBSTITUTED 3-p-CHLOROPHENOXY-ACETYLAMINOQUINUCLIDINES

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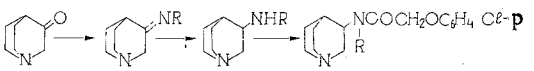
In continuation of the investigations previously carried out by us on the search for new antiarrhythmic agents among 3-amino and 2-aminomethylquinuclidines [1] we have synthesized and studied the antiarrhythmic action of new derivatives of 3-aminoquinuclidine containing a p-chlorophenoxyacetyl group as an acyl residue.

The synthesis of the substituted 3-p-chlorophenoxyacetylaminoquinuclidines (IVa-d) was effected according to the following scheme:



I IIa-d IIIa-d IVa-d

II — IV a: R = C_6H_5, b: R = p — ClC_6H_4, c: R = o-ClC_6H_4, d: R = $C_6H_5CH_2$.

According to the procedure described in the previous paper [1] quinuclid-3-one (I) was condensed with primary aromatic or aliphatic—aromatic amines and the resulting imino compounds (II) reduced to the secondary amine (III). Acylation of compounds (III) was effected with the acid chloride of p-chlorophenoxyacetic acid in a medium of boiling chloroform checking for the end of the reaction by the disappearance of the initial amine (III) by TLC. The process occurred fairly slowly (from 30 to 60 h) which is evidently linked with the steric hindrance of the substituted amino group in the quinuclidine nucleus.

On using sterically hindered aromatic amines (2,6-dichloroaniline, mesidine, etc.) difficulty was encountered even at the stage of obtaining the imino derivatives (II). Various procedures for condensation were studied, in boiling toluene or xylene in the presence of toluene-p-sulfonic acid with azeotropic distillation of water [1], melting in the presence of the same catalyst at 200°C, the use of molecular sieve type 3A as a water removing agent [2], phosphorus oxychloride [3], phosphorus pentoxide [4], etc., which did not lead to the appropriate imino compound (II).

The synthesized compounds (IVa-d) in the form of hydrochlorides displayed marked but short-term antiarrhythmic activity in experiments in animals. In addition these same compounds, as shown by the investigations of G. N. Pershin and L. M. Polukhina in the Laboratory of Chemotherapy of the All-Union Scientific-Research Institute of Pharmaceutical Chemistry (VNIKhFI), possessed marked activity in in vitro experiments in relation to gram positive bacteria (MTC 31.2-125 mg/ml) and acid-sensitive mycobacteria (MTC 15.6-62.5 μg/ml) but were weakly active in relation to gram negative bacteria and pathogenic fungi.

EXPERIMENTAL CHEMISTRY

3-[N-Phenyl-N-(p-chlorophenoxyacetyl)]aminoquinuclidine (IVa). p-Chlorophenoxyacetyl chloride (2.11 g:10 mmole) was added dropwise with stirring and water cooling to a solution of (IIIa) (1.8 g: 8.9 mmole) in dry chloroform (30 ml). The mixture was boiled for 57 h, checking the course of the reaction by TLC (system CH_3OH—$CHCl_3$—NH_4OH 20:20:1, R_f IVa 0.55, R_f IIIa 0.32). The reaction mixture was cooled, water (20 ml) added, then concentrated hy-

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