TCD_{50} (tissue cytopathic dose) of the virus. The viral inhibitory activity was indicated by suppression of the cytopathic effect and the lowering of the virus infection titer in FCE cells. The compounds were used at concentrations of 5.0 and 2.5 μg/ml, which is 1/2 and 1/4 of the maximum tolerated dose of the compounds for FCE cells.

High activity was not observed among the studied materials, but two of them (XII and XIII) showed activity at 0.75 log TCD_{50}. The remaining compounds II, III, VI, IX, XIV, and XV were practically inactive.

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SYNTHESIS OF 1-[ω-(BENZHYDRYLPIPERAZIN-1-YL)ALKYL]INDOLES, 9-[3-(4-BENZHYDRYLPIPERAZIN-1-YL)PROPYL)CARBAZOLE AND ITS DERIVATIVES AND THEIR ANTIALLERGIC ACTIVITY

N. A. Komissarenko, V. P. Gorbunova, V. B. Nikitin, M. E. Kaminka, and N. N. Suvorov

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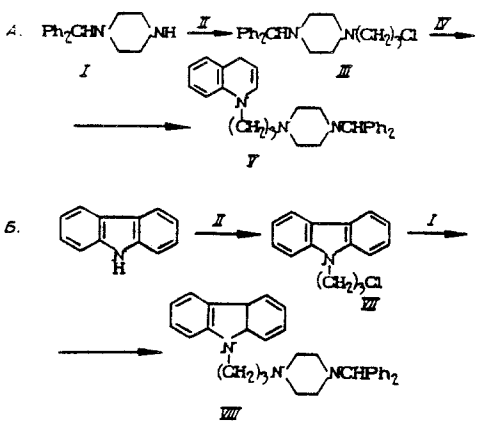
In the search for compounds with antiallergic activity, we synthesized compounds of the general formula $ArRN(CH_2CH_2)_2NCHPh_2$ (Table 1).

To prepare the desired compounds, two principal schemes of synthesis were used.



According to scheme A, 1-(3-chloropropyl)-4-benzhydrylpiperazine (III) was obtained by alkylation of 1-benzhydrylpiperazine [2, 3, 12] (I) by 1-bromo-3-chloropropane [5] (II). 1-[3-(4-Benzhydrylpiperazin-1-yl)propyl]indole (V) and 9-[3-(4-benzhydrylpiperazin-1-yl)propyl]-4-oxo-1,2,3,4-tetrahydrocarbazole (VI) were obtained by alkylation of indole (IV) and 4-oxo-1,2,3,4-tetrahydrocarbazole [9, 10, 11], respectively, by compound III, using the method of interphase catalysis in a medium or 50% NaOH on DMSO—50% NaOH. Triethylbenzylammonium chloride (TEBAC) was used as a catalyst for the interphase transfer.

D. I. Mendeleev Moscow Chemical-Engineering Institute. S. Ordzhonkidze All-Union Scientific-Research Chemical Pharmaceutical Institute, Moscow.

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TABLE 1. 1-Benzhydrylpiperazine Derivatives

Compound	Ar	R	Method
V	1-Indolyl	$-(CH_2)_3-$	A
VI	4-Oxo-1,2,3,4-tetrahydrocarbazol-9-yl	$-(CH_2)_3-$	A
VIII	9-Carbazolyl X	$-(CH_2)_3-$	B
X	1,2,3,4-tetrahydrocarbazol-9-yl	$-(CH_2)_3-$	B
XII	1-Oxo-1,2,3,4-tetrahydrocarbazol-9-yl	$-(CH_2)_3-$	B
XIV	1-Indolyl	$-(CH_2)_4-$	B
XVI	1-Indolyl	$-CH_2CH(OH)CH_2-$	

TABLE 2. Antihistaminic and Antianaphylactic Action of 1-Benzhydrylpiperazine Derivatives

Compound	Histaminic intoxication		Exudative effect of the 48-80 compound	
	dose mg/kg	survival,	dose mg/kg	inhibition
V	12±4,1*	50	40	26
VI	16	33	40	6
VIII	16	17	40	12
X	16	17	40	18
XII	2,1±0,9*	50	31±3,3*	50
XIV	3±1,8*	50	39±6,5*	50
XVI	16	33	40	−5
Oxatomide	0,6±0,7*	50	6±3,4*	50

*ED_{50} at $P = 0.05$.

According to scheme B, 9-(3-chloropropyl)carbazole (VII), 9-(3-chloropropyl)-1,2,3,4-tetrahydrocarbazole (IX) and 9-(3-chloropropyl)-1-oxo-1,2,3,4-tetrahydrocarbazole (XI) were obtained by alkylation of carbazole, 1,2,3,4-tetrahydrocarbazole [4] and 1-oxo-1,2,3,4-tetrahydrocarbazole [6, 7, 8], respectively, by compound II. Under the same conditions indole was introduced into the alkylation reactions with 1-bromo-4-chlorobutane and epichlorohydrin. As a result, 1-(4-chlorobutyl)indole (XIII) and 1-(2,3-epoxypropyl)indole (XV) were obtained. The reaction of compounds VII, IX, XI, XIII and XV with compound I gave 9-[3-(4-benzhydrylpiperazin-1-yl)propyl]carbazole (VIII), 9-[3-(4-benzhydrylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydrocarbazole (X), 9-[3-(4-benzhydrylpiperazin-1-yl)propyl]-1-oxo-1,2,3,4-tetrahydrocarbazole (XII), 1-[4-(4-benzhydrylpiperazin-1-yl)butyl]indole (XIV) and 1-[2-hydroxy-3-(4-benzhydrylpiperazin-1-yl)propyl]indole (XVI).

The structure of all the synthesized compounds was confirmed by IR, PMR spectra, mass spectrometry, and the data of elemental analysis.

EXPERIMENTAL (CHEMICAL)

The ^1H NMR spectra were recorded on a Bruker WP-200 spectrometer (200.13 MHz); the shifts were measured relative to tetramethylsilane, using $CDCl_3$ as the solvent.

The IR spectra were recorded on a UR-20 spectrophotometer with KBr prisms in mineral oil.

The mass spectra were run on a "Kratos" chromato-mass-spectrometer (England). The energy of the ionizing electrons was 70 eV; the cathode emission current was 1.5 mA; temperature of the ionization chamber from 60 to 300°C; direct introduction of the sample into the ionic source.

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates ("Kavalier," CSSR). The spots were detected upon irradiation by UV light and treatment with iodine vapor. Silica gel L 40/100 (CSR) was used for the column chromatography.

1-(3-Chloropropyl)-4-benzhydrylpiperazine (III). A 5.04 g portion (20 mmoles) of I was dissolved in 25 ml of acetone, 10 ml of 25% NaOH was added, and then 6.69 g (22 mmoles) of II was added with slow stirring. The reaction mixture was stirred for 20 h, the organic layer was separated, 25 ml of diethyl ether was added, and the solution was

washed with water, and dried. The solvent was evaporated off, and 5.9 g (90%) of III was obtained in the form of an oil, which was further used without additional purification.

1-[3-(4-Benzhydrylpiperazin-1-yl)propyl]indole (V). A 0.41 g portion (1.8 mmole) of TEBAC and 2.1 g (18 mmoles) of IV were added to 5.9 g (18 mmoles) of III. A 15 ml portion of 50% NaOH was added at 60°C with vigorous stirring. The reaction mixture was stirred for 4 h at 80°C, then poured into water, the precipitate that separated out was filtered off, washed with water, and dried. Yield, 2.25 g (31%) of V, mp 134-5°C (from ethanol). PMR spectrum, δ, ppm: 7.09 (1H) 6.46 (1H, J 3.17 and 0.98 Hz), 7.60 (1H), 4.18 (2H, J 6.84 Hz), 1.97 (2H, J, 6.84 Hz), 2.28 (2H, J 6.84 Hz), 2.43 (8H), 4.22 (1H), $C_{28}H_{31}N_3$.

9-[3-(4-Benzhydrylpiperazin-1-yl)propyl]-4-oxo-1,2,3,4-tetrahydrocarbazole (VI) was obtained in a similar way as compound V. The product was purified by column chromatography, using $CHCl_3$ as eluent. The yield of VI was 42%, mp 170-1°C (from ethanol). PMR spectrum, δ, ppm: 2.56 (2H, J, 6.50 Hz), 2.22 (2H), 2.97 (2H, J 6.40 Hz), 8.24 (1H), 4.17 (2H, J 7.08 Hz), 1.96 (2H, J 6.60 Hz), 2.30 (2H), 2.43 (8H), 4.22 (1H). $C_{32}H_{35}N_3O$. M^+ 478, M 477.65.

9-(3-Chloropropyl)carbazole (VII) was obtained in a similar way as compound V in a 95% yield in the form of an oil, and was used further without additional purification.

9-[3-(4-Benzhydrylpiperazin-1-yl)propyl]carbazole (VIII). An 8.33 g portion (33 mmoles) of I, 5.52 g (40 mmoles) of K_2CO_3 and 5.45 g (33 mmoles) of KI were added to a solution of 8 g (33 mmoles) of VII in isoamyl alcohol. The mixture was boiled for 6 h. A 100 ml portion of water was added, and the mixture was extracted with diethyl ether, the ether solution was dried, and ether was evaporated. Yield, 4.8 g (32%) of VIII, mp 129-131°C. PMR spectrum, δ, ppm: 8.08 (2H, J 7.82 Hz), 4.38 (2H), 2.02 (2H, J = 6.59 Hz), 2.31 (2H), 2.43 (8H), 4.27 (1H), $C_{32}H_{33}N_3$. M^+ 460, M 4.59, 640.

9-(3-Chloropropyl)-1,2,3,4-tetrahydrocarbazole (IX) was obtained in a similar way as compound V in a yield of 92%. The compound was used further without additional purification.

9-[3-(4-Benzhydrylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydrocarbazole (X) was obtained in a similar way as compound VIII. The product was purified by column chromatography, using $CHCl_3$ as eluent. The yield of X was 20%, mp 133-4°C (from a 1:2 mixture of diethyl ether and petroleum ether). PMR spectrum, δ, ppm: 2.70 (4H), 1.88 (4H), 4.05 (2H, J 7.08 Hz), 1.92 (2H), 2.32 (2H, J 7.08 Hz), 2.43 (8H), 4.21 (1H), $C_{32}H_{37}N_3$.

9-(3-Chloropropyl)-1-oxo-1,2,3,4-tetrahydrocarbazole (XI) was obtained in a similar way as compound V in DMSO. The product was purified by column chromatography, using $CHCl_3$ as eluent. The yield of XI was 66%.

9-[3-(4-Benzhydrylpiperazin-1-yl)propyl]-1-oxo-1,2,3,4-tetrahydrocarbazole (XII) was obtained in a similar way as compound VIII. The product was purified by column chromatography, using $CHCl_3$ as eluent. The yield of XII was 48%, mp 129-130°C (from a 1:2 mixture of diethyl ether and petroleum ether). PMR spectrum, δ, ppm: 3.01 (2H, J = 6.10 Hz), 2.20 (2H, J 6.10 Hz), 2.63 (2H, J 6.10 Hz), 4.56 (2H, J 7.08 Hz), 1.93 (2H, J 7.08 Hz), 2.33 (2H, J, 7.08 Hz), 2.42 (8H), 4.21 (1H), $C_{32}H_{37}N_3O$. M^+ 477, M 477.65.

1-(4-Chlorobutyl)indole (XIII) was obtained in a similar way as compound V and was purified by column chromatography, using a 1:10 mixture of diethyl ether and petroleum ether as eluent. The yield of XIII was 53%, oil. PMR spectrum, δ, ppm: 7.09 (1H), 6.50 (1H, J 3.46 and 0.8 Hz), 7.64 (1H), 7.10 (1H), 7.21 (1H), 7.34 (1H), 3.51 (2H, J, 6.40 Hz), 1.75 (2H), 2.01 (2H), 4.17 (2H, J 6.71 Hz).

1-[4-(4-Benzhydrylpiperazin-1-yl)butyl]indole (XIV). A mixture of 2.1 g (11 mmoles) of XIII, 2.53 g (11 mmoles) of I, and 4.6 g (33 mmoles) of K_2CO_3 was boiled in toluene for 15 h. A 100 ml portion of water was added and the mixture was extracted with diethyl ether. The ether layer was dried, the solvent was evaporated, and the residue was separated on a column, using diethyl ether as eluent. The yield of XIV was 0.9 g (22%), mp 72-3°C, PMR spectrum, δ, ppm: 7.08 (1H), 6.46 (1H, J 3.17 Hz), 4.12 (2H, J 6.84 Hz), 1.84 (2H), 1.49 (2H), 2.3-2.4 (10H), 4.19 (1H). $C_{29}H_{33}N_3$. M^+ 423, M 423.6.

1-(2,3-Epoxypropyl)indole (XV) was obtained in a similar way as compound V. The yield of XV was 70%, bp 135-7°C (1 mm Hg). PMR spectrum, δ, ppm): 7.14 (1H), 6.53 (1H, J 3.36 Hz and 0.8 Hz), 7.64 (1H), 7.13 (1H), 7.24 (1H), 7.39 (1H), 4.44 (1H), 4.20 (1H, J 15.26 Hz), 3.29 (1H, J 3.36 Hz and 5.09 Hz), 2.47 (1H), 2.81 (1H, 4.6 Hz, 2.44 Hz, 4.1 Hz). Found, %: epoxy group 25.0. $C_{11}H_{11}NO$. Calculated, %: epoxy group 24.9.

1-[2-Hydroxy-3-(4-benzhydrylpiperazin-1-yl)propyl]indole (XVI). A mixture of 1.26 g (5 mmoles) of I and 0.86 g (5 mmoles) of XV in ethanol was stirred at 50°C for 5 h. Ethanol was distilled off and the residue was separated by column chromatography, using $CHCl_3$ as eluent. Yield, 1 g (50%) of XVI, mp 105-6°C. IR spectrum, ν_{max} cm^{-1}: 3530 (OH). PMR spectrum, δ, ppm: 7.09 (1H), 6.48 (1H, J 3.42 Hz), 7.59 (1H, J, 7.8 Hz), 4.15 (2H), 4.04 (1H), 3.35 (1H), 2.59 (1H), 2.63 (1H, J 12.5 Hz), 2.3-2.4 (8H), 4.22 (1H). $C_{28}H_{31}N_3O$.

EXPERIMENTAL (PHARMACOLOGICAL)

The antihistaminic activity of the synthesized compounds was studied on guinea pigs of both sexes, each weighing 250-300 g, and was characterized by the rate of survival of the animals after inhalation of a 1% solution of histamine dihydrochloride for 5 min.

The antianaphylactic activity of the compounds was determined on male rats, each weighing 160-180 g, from the influence on the edema of the posterior extremity induced by the noncytoxic activator of fat cells — the 48/80 compound. The exudative reaction was recorded pletismometrically 30 min after a subplantary injection of the 48/80 compound (5 μg per 0.1 ml).

The compounds tested and oxatomide, serving as a reference preparation, were administered orally 2 h before the induction of the response to histamine and the 48/80 compound. The maximal doses of the compounds in the histamine intoxication and anaphylactic edema tests was 16 and 40 mg/kg, respectively. The methods of calculation of activity (ED_{50}) were adapted from [1].

The experimental results given in Table 2 show that all the compounds studied alleviate the intoxication of guinea pigs with a histamine aerosol. The antihistaminic effect was most pronounced in compounds V, XIV, XII, but the doses of these compounds giving to protection to 50% of the animals in a group from death (ED_{50}) were higher than in the case of oxatomide. Compared with the histamine antagonism, the ability to inhibit the edema of a paw in rats induced by compound 48/80 was found to be a less effective component of the antiallergic activity of the synthesized compounds and the reference preparation. Thus at the maximally used dose (40 mg/kg), the anti-edema action was not detected in compounds VI and XVI, while compounds XII and XIV, as well as compounds XII and XIV, and also oxatomide inhibited the development of the exudative reaction to the extent of 50% in doses (ED_{50}) 10-20 times higher than the equieffective antihistaminic doses.

On comparing the effectiveness of the compounds with the characteristic features of their chemical structures it can be deduced that in the series studied, oxatomide (1-[3-4-diphenylmethyl-1-piperazinyl)propyl]-1,3-dihydro-2H-benzimidazol-2-one has the most favorable structure for displaying antiallergic activity. Replacement of the benzimidazolone fragment by an indole or carbazole fragment resulted in reduction of the antiallergic effect by a factor of 3 or more. The activity of the synthesized oxatomide analogs decreased in the series XII, XIV > V > VI, VIII, X, XVI.

In conclusion, of the synthesized 1-benzhydrylpiperazine derivatives, the N-alkyl-substituted derivatives of indole (compounds XIV and V) and 1-oxo-1,2,3,4-tetrahydrocarbazole (compound (XII) had the most pronounced antiallergic activity.

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