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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-ANILINOMETHYL DERIVATIVES OF 5-HYDROXYINDOLE

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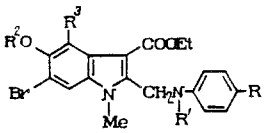
It was demonstrated earlier that 2-alkylaminomethyl derivatives of 5-acetoxy (hydroxy)indoles possessed antiviral activity [1, 2]. However, the literature holds not information on 2-arylaminomethyl derivatives of indole. In this connection it was of interest to study the antiviral activity of structures of compounds such as 2-anilinomethyl derivatives of 5-acetoxy (hydroxy)indole, the syntheses of which were brought about by alkylation of a substituted aniline with the bromomethyl derivative of 5-acetoxyindole (I), obtained earlier [2]. The condensation proceeded in benzene, both triethylamine and an excess of one of the reaction components, the corresponding aniline, may be used as acceptor of the HBr produced. The yields of the anilinomethyl derivatives of the substituted 5-acetoxyindoles (II-VI) were 60-76%. In the preparation of indole III, a 3.2% yield of N,N-bis(1-methyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole) (VII) also was isolated. The yield of compound VII could be increased to 10% if the reaction is carried out not with aniline but with excess aniline hydrochloride in aqueous dioxane with heating. Basic hydrolysis of the substituted 1-methyl-2-anilinomethyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindoles II-VI lead to the formation of the corresponding substituted 5-hydroxyindoles (VIII-XI). Aminomethylation of the latter have the 4-aminomethyl indole derivatives (XII-XV).



I-VI, VIII-XV

R=H(II, III, VIII, IX, XII, XIII), OMe(IV, X), Cl(V, XI, XIV, XV) NO_2(VI); R^1=H(III—VI, IX—XII, XIV, XV), Me(II, VIII, XIII); R^2=H(VIII—XV), Ac(II—VI); R^3=H(II—VI, VIII, XI), CH_2NMe_2(XII—XIV), CH_2-morpholino (XV)

The structures of all of the compounds were verified by mass spectroscopy and by IR spectroscopy, which showed valence oscillation absorption bands characteristic of the OAc, COOEt, OH, and NH groups (cf. Table 1). Further, compounds XII-XV showed absorption bands in the 3200-3400 cm^{-1} region, characteristic of the valence oscillation of the OH group, indicating the zwitter-ionic character of these compounds, which is connected with the presence in these molecules of the phenolic hydroxyl group in position 5 and the basic dialkylaminomethyl group in position 4.

EXPERIMENTAL

IR spectra were determined on a Perkin-Elmer 599 instrument (USA) in Vaseline oil. Mass spectra were obtained with a Varian MAT-112 spectrometer (FRG). Control of the purity of the materials was maintained over the

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TABLE 1. Characteristics of the Synthesized Compounds II-XV

Compound	Yield, %	M.p., °C[a]	IR Spectrum, ν_{max}, cm^{-1}	Empirical Formula
II	65,0	154—6	1775, 1680 (C=O),	$C_{22}H_{23}BrN_2O_4$
III	69,1	176—7	1720, 1680 (C=O), 3370 (NH)	$C_{21}H_{21}BrN_2O_4$
IV	71,1	172—4	1760, 1680 (C=O), 3330 (NH)	$C_{22}H_{23}BrN_2O_5$
V	76,8	198—200	1765, 1690 (C=O), 3370 (NH)	$C_{21}H_{20}BrClN_2O_4$
VI	60,1	232—4	1760, 1700 (C=O), 3300 (NH)	$C_{21}H_{20}BrN_3O_6$
VII	3,2	234—5	1720, 1680 (C=O)	$C_{36}H_{35}Br_2N_3O_6$
VIII	95,9	222—3	1640 (C=O), 3220 (OH)	$C_{20}H_{21}BrN_2O_3$
XI	91,6	208—10	1705 (C=O), 3250 (OH), 3330 (NH)	$C_{19}H_{19}BrN_2O_3$
X	78,2	195—6	1640 (C=O), 3200 (OH), 3380 (NH)	$C_{20}H_{21}BrN_2O_4$
XI	81,7	214—5 Dec.	1640 (C=O), 3200 (OH), 3370 (NH)	$C_{14}H_{18}BrClN_2O_4$
XII	89,4	166—8	1690 (C=O), 3330, 3360 (NH)	$C_{22}H_{26}BrN_3O_3$
XIII	73,6	180—82	1690 (C=O)	$C_{23}H_{28}BrN_3O_3$
XIV	100	188—90	1690 (C=O), 3380 (NH)	$C_{22}H_{25}BrClN_3O_3 \cdot HCl$
XV	83,3	207—8 Dec.	1690 (C=O), 3380 (NH)	$C_{24}H_{29}BrClN_3O_4$

[a]Recrystallization solvents: II-VI, VIII-XI, acetone; VII, alcohol—dioxane; XIII, XIV, XVI, acetonitrile; XV, acetone—methanol—ether; XII, i-PrOH-DMF.
[b]Isolated as the hydrochloride.

course of the reaction by chromatography on Silufol UV-254 sheets in $CHCl_3$, $CHCl_3$-MeOH (98:2), or benzene-acetone (9:1).

The characteristics of synthesized compounds II-XV are presented in Table 1.

The elemental analyses found corresponded with the calculated values.

Chemistry

Derivatives of 1-Methyl-2-anilinomethyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole (II-VI). A reaction mixture composed of 30 mmoles of the corresponding indole derivative (I), 30 mmoles of triethylamine, and 30 mmoles of aniline or its derivative in 250 ml of dry benzene was stirred at 20°C for 5-10 h. The precipitate was filtered off, washed with water and dried. The benzene solution was washed with water, dried with $MgSO_4$ and concentrated under vacuum. The residues were combined and recrystallized to give compounds II-VI.

A. The mother liquor after the crystallization of compound III gave **N,N-bis-(1-methyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole) (VII).**

B. A reaction mixture composed of 4.33 g (10 mmoles) of indole I, 2.5 g (20 mmoles) of aniline hydrochloride and 50 ml of water was heated on a water bath for 3 h, then dioxane was added to dissolve the precipitate and stirred for 2 h. The precipitate resulting after cooling was filtered off to give 0.850 g (10.6%) of compound VII.

Derivatives of 1-Methyl-2-anilinomethyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole (VIII). A. To a suspension of 18 mmoles of the corresponding acetoxyindole (II-VI) in 150 ml of absolute alcohol was added 40 mmoles of KOH in 50 ml of absolute alcohol, and the mixture was stirred for 4 h at room temperature. Then 25 ml of water was added and acidified with acetic acid to pH 4. The precipitate was filtered off, washed with water and dried to give VIII-XI.

Derivatives of 1-Methyl-2-anilinomethyl-3-ethoxycarbonyl-4-dialkylaminomethyl-5-hydroxy-6-bromoindole (XII-XV). A reaction mixture composed of 10 mmoles of indoles VII-XI and 20 mmoles of the corresponding bis-(dialkylamino)methane in 25 ml of dry dioxane was boiled for 3-10 h. The solvent and excess amine were removed under vacuum to give compounds XII-XVI. The hydrochloride of XV was obtained by acidification of an acetone solution of the base with ethereal HCl.

Biology

The antiviral activity of these materials was studied with the RNA-containing virus of the A_0/FPV (H7N7) group in cell culture of the first trypsinated fibroblast of chicken embryos (FCE). The cells were infected with 10

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

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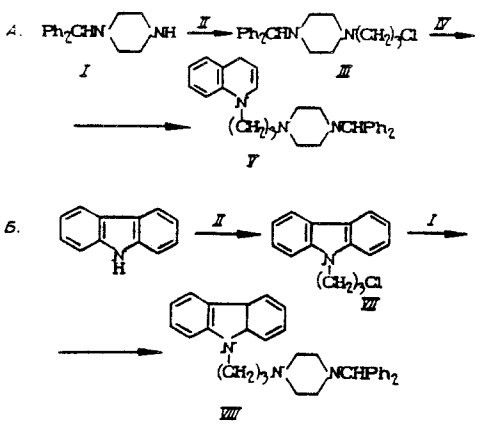
In the search for compounds with antiallergic activity, we synthesized compounds of the general formula $ArRN(CH_2CH_2)_2NCHPh_2$ (Table 1).

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.

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