SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-ALKYLAMINOMETHYL DERIVATIVES OF 5-OXYINDOLE

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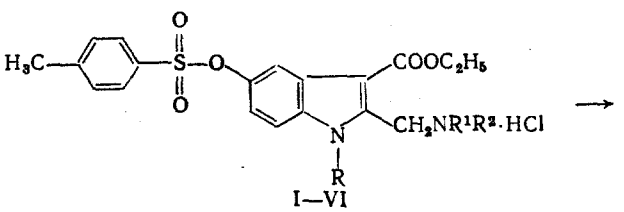
The 2- and 4-alkylaminomethyl derivatives of 5-oxyindole are known to have a broad spectrum of biological activity [1-5]. In that connection, we have continued studies on the synthesis of 2-alkylaminomethyl derivatives of 5-oxyindole and their biological activity. It has been shown earlier that 1-methyl-2-diethylaminomethyl-3-carbethoxy-5-tosyloxyindole causes a temporary reduction of arterial pressure and exhibits antiarrythmic, antifibrillatory, and anticonvulsant activity [4].

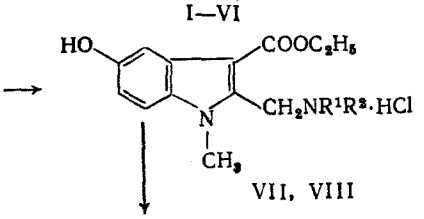
By reacting the previously described 2-bromomethyl derivatives of 5-tosyloxyindole [4] with primary and secondary amines, we obtained 2-alkylaminomethyl derivatives of 5-tosyloxyindole (I-VI). Alkaline hydrolysis of 1-methyl-2-diethylaminomethyl- and 1-methyl-2-morpholinomethyl-3-carbethoxy-5-tosyloxyindole [4] results in the formation of the corresponding 5-oxyindole derivatives (VII and VIII).

We also thought it would be of interest to obtain compounds that simultaneously have an alkylaminomethyl substituent in both position 2 and position 4 of the indole ring.

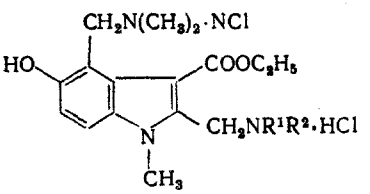
We obtained 2,4-bis(alkylaminomethyl)-5-oxyindoles (compounds IX and X) by the aminomethylation of compounds VII and VIII.



I—VI



VII, VIII



IX, X

R = CH_3 (II); C_6H_5 (I, III); p-BrC_6H_4 (IV—VI); R^1 = H (III, IV); CH_3 (I, II, V); C_2H_5 (VII, IX); $R^2 = CH_3$ (I, II, V); C_2H_5 (VII, IX); $CH_2C_6H_5$ (III, IV)
NR^1R^2 = morpholino (VI, VIII, X)

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The antiviral activity of the synthesized compounds was examined. The study demonstrated that they exhibit antiviral activity against RNA-containing influenza viruses (the orthomyxovirus group) and vesicular stomatitis viruses (the rabies virus group).

EXPERIMENTAL — CHEMICAL

1-Phenyl-2-dimethylaminomethyl-3-carbethoxy-5-tosyloxyindole Hydrochloride (I). A 25-ml benzene solution saturated with dimethylamine (0.9 g, 0.02 mole) was added to a solution of 5.3 g (0.01 mole) of 1-phenyl-2-bromomethyl-3-carbethoxy-5-tosyloxyindole [1] in 100 ml of abs. benzene. The reaction mixture was then left for 20-22 h at 20°C. The resultant dimethylamine bromohydrate precipitate was filtered off and the benzene was distilled off. The base (Ia) was recrystallized from methanol. Yield 4.7 g (95.9%), mp 140-141°C. Found, %: C 65.75; H 5.80; N 5.65; S 6.53. $C_{27}H_{28}N_2SO_5$. Calculated, % C 65.83; H 5.73; N 5.69; S 6.51.

Compound I was obtained by acidifying an acetone solution of the Ia base with an hydrochloric ester solution. Yield 87%, mp 186-187°C (from isopropyl alcohol). Found, %: Cl 6.84. $C_{27}H_{29}ClN_2SO_5$. Calculated, %: Cl 6.70.

Compounds II-VI were obtained in a similar fashion. Data are given in Table 1.

1-Methyl-2-diethylaminomethyl-3-carbethoxy-5-oxyindole Hydrochloride (VII). A 2.3-g (0.005 mole) portion of 1-methyl-2-diethylaminomethyl-3-carbethoxy-5-tosyloxyindole [1] was added to 1.4 g (0.025 mole) of KOH in 20 ml of ethyl alcohol and the mixture was boiled for 2 h. The reaction solution was poured into water, cooled, and acidified with HCl until the neutral point. The residue of the VIIa base was filtered off, washed with water, and dried. Yield 0.9 g (60%), mp 187-188°C (from isopropyl alcohol). Found, %: C 67.23; H 7.55; N 9.13. $C_{17}H_{24}N_2O_3$. Calculated, %: C 67.08, H 7.95; N 9.20.

Compound VII was obtained in the same way as I. mp 202-203°C (with decomposition from an acetone–methanol mixture). Found, %: Cl 10.42. $C_{17}H_{25}ClN_2O_3$. Calculated, %: Cl 10.40.

Compound VIII was obtained in the same way. Data are given in Table 1.

1-Methyl-2-diethylaminomethyl-3-carbethoxy-4-dimethylaminomethyl-5-oxyindole Dihydrochloride (IX). A 0.35-g (0.035 mole) portion of bis(dimethylamino)methane was added to a solution of 0.7 g (0.0023 mole) of 1-methyl-2-diethylaminomethyl-3-carbethoxy-5-oxyindole (VIIa) in 5 ml of abs. dioxane, and the reaction mixture was boiled for 2.5 h. The solvent was distilled off and the residue was dissolved in absolute ether and then acidified with a HCl solution. Yield of IX 0.6 g (60.6%), mp 205-206°C (with decomposition from an acetone–methanol mixture). Found, %: C 55.61, H 7.23; Cl 16.09; N 9.37. $C_{20}H_{33}Cl_2N_3O_3$. Calculated, %: C 55.30; H 7.66; Cl 16.32; N 9.67.

Compound X was obtained in the same way. Data are given in Table 1.e.

EXPERIMENTAI—BIOLOGICAL

The antiviral activity of the synthesized compounds (I-X) was studied in relation to three representatives of RNA-containing viruses: Influenza A virus strains A/PR-8/34 (H0N1), A/WSN (H0N1), A/FPV (H7N7), the vesicular stomatitis virus (VSV) "Indiana" strain, and the Venezuelan equine encephalomyelitis virus (VEE) strain No. 230. The virus-inhibiting activity of the substances was studied in a primary trypsinized culture of chick embryo fibroblasts (CEF) infected by 10-100 TCD_{50} of the virus. The maximum tolerable concentration (MTC) of the substances for the CEF cells was determined in preliminary experiments and did not exceed 20 μg/ml for all of the compounds under study. The antiviral activity of the compounds was studied by using concentrations that were 1/4 and 1/8 of the MTC. The compounds' virus-inhibiting activity was evaluated by the degree to which they prevented the virus's cytopathic effect on cells and by the reduction in the number of patches in the experimental flasks in comparison to the control.

DISCUSSION OF RESULTS

Virus-inhibiting action against influenza virus was exhibited by compounds I, III, IV, VI, and 1-(n-chlorophenyl)-2-bromomethyl-3-carbethoxy-5-tosyloxyindole which was obtained by the generally accepted method [1]. At a concentration of 1.25 - 5 μg/ml these compounds reduced the number of patches in the experimental flasks by 40-50% in comparison to the control

TABLE 1. 5-Oxyindole Aminoalkyl Derivatives

Compound	Yield, %	mp, °C, (solvent for crystallization)	Found, %						Empirical formula	Calculated, %					
			C	H	Br	Cl	N	S		C	H	Br	Cl	N	S
II	97,1	202—3 (Isopropyl alcohol)	56,15	6,10		7,36	5,62	6,52	$C_{22}H_{27}ClN_2SO_5$	56,58	5,83	—	7,59	6,00	6,87
IIIa	95,6	107—8 (Isopropyl alcohol)	69,5	5,91	—	—	4,76	5,87	$C_{32}H_{30}N_2SO_5$	69,29	5,45	—	—	5,05	5,78
III	87,3	212-3 (Acetone–ethanol)	—	—	—	5,92	—	—	$C_{32}H_{31}ClN_2SO_5$	—	—	—	6,00	—	—
IV	91,5	223—5 (Acetone–methanol	57,56	4,70	11,59	5,14	4,11	4,60	$C_{32}H_{30}BrClSO_5N_2$	57,36	4,51	11,93	5,29	4,18	4,78
Va	93,7	166—7 (Methanol–dioxane)	55,75	4,68	14,36	—	4,96	5,48	$C_{27}H_{27}BrN_2SO_5$	56,74	4,76	13,98	—	4,90	5,61
V	85	202—3 (Acetone–methanol)	—	—	—	5,89	—	—	$C_{27}H_{28}BrClN_2SO_5$	—	—	—	5,83	—	—
VIa	96,4	159-60 (Methanol–dioxane)	56,46	4,60	13,32	—	4,30	5,21	$C_{29}H_{29}BrN_2SO_6$	56,77	4,76	13,02	—	4,57	5,23
VI	89,3	203—4 (Acetone–methanol–ether)	—	—	—	5,45	—	—	$C_{29}H_{30}BrClN_2SO_6$	—	—	—	5,45	—	—
VIIIa	98	174—5 (Isopropyl alcohol)	64,12	6,90	—	—	8,66	—	$C_{17}H_{22}N_2O_4$	64,13	6,96	—	—	8,80	—
VIII	52,2	239—40 with decomposition, acetone–methanol)	—	—	—	9,78	—	—	$C_{17}H_{23}ClN_2O_4$	—	—	—	9,99	—	—
X	98	168—70 (Acetone–isopropyl alcohol–ether)	53,20	6,89	—	15,53	9,07	—	$C_{20}H_{31}Cl_2N_3O_4$	53,57	6,97	—	15,81	9,37	—

($P < 0.01$). Antiinfluenza virus activity was neither exhibited by compound II which was obtained by replacing the phenyl radical on the nitrogen of the indole ring with a methyl radical while retaining the same substituents in the remaining indole positions, nor by 1-methyl-2-benzylaminomethyl-3-carbethoxy-5-tosyloxyindole HCl [1].

However, we found that compound II, like compound I, inhibited the growth of another representative of the RNA-containing viruses, i.e., the VSV (the rabies virus group). These compounds (I and II) reduced the infectious titer of VSV by 1.0 log TCD_{50}. The remaining compounds under study did not exhibit any activity against this virus. None of the examined compounds inhibited the reproduction of the VEE virus (arbovirus group).

Thus, the results of our study has shown that compounds I, III, IV, and VI exhibit antiviral activity against RNA- containing influenza virus (orthomyxovirus group), and that compounds I and II also exhibit activity against the VSV viruses (the rabies virus group). The examined compounds did not exhibit any activity against the VEE virus (arbovirus group).

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