Thus, our experimental results indicate that compound I exhibits anti-herpes activity although it is not as effective as contemporary anti-herpes preparations (Bonafton, Acyclovir) [4]. Compound I also exhibited virus-inhibiting and virocidal action against certain RNA viruses (influenza and vesicular stomatitis viruses) in both in vitro and in ovo experiments.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2,7-BIS[AMINOETHOXY]-9-FLUORENONES AND THEIR PHENYLHYDRAZONES

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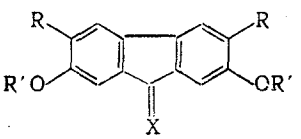
Interest in alkylated 2,7-dihydroxy-9-fluorenones has been aroused by their extremely wide spectrum of pharmacological activity, especially antiviral activity, resulting from the ability of these compounds to induce interferon in experimental animals [4, 6].

In addition to tylorone and some other 2,7-bis(dialkylaminoalkoxy)-9-fluorenones, antiviral activity is shown by 2,7-bis(piperidinoethoxy)- and 2,7-bis(morpholinoethoxy)-9-fluorenone (IV and VII) [5], obtained in yields of 28 and 43% respectively. As we have shown, under the conditions described previously [5], alkylation of 3,6-disubstituted 2,7-dihydroxy-9-fluorenones gives yields of the 2,7-dialkoxy-compounds no greater than 25% [Table 1, method A, compounds (V), (VI), (VIII), and (IX)].

The present investigation was undertaken to obtain new fluorenones for studies of the relationship of the structures of compounds of this type to their antiviral activity. Another aim was to increase the yields of 2,7-bis(aminoethoxy)-9-fluorenones.



I—XVIII

R = H (I, IV, VII, X, XIII, XVI); Br (II, V, VIII, XI, XIV, XVII); Cl (III, VI, IX, XII, XV, XVIII); R' = H (I—III, X—XII); $(CH_2)_2N(CH_2)_5$ (IV—VI, XIII—XV); $(CH_2)_2N(CH_2CH_2)_2O$ (VII—IX, XVI—XVIII); X = O (I—IX), NNHPh (X—XIII).

The starting materials used were 2,7-dihydroxy-9-fluorenone and its 3,6-dihalo-derivatives [3] (I-III), alkylation of which [5] (method A) gave (V), (VI), (VIII), and (IX) (Table 1).

In order to increase the yields of alkylated products, the reactions were carried out under conditions of phase-transfer catalysis (PTC). Reaction of (I-III) with piperidino- or morpholinoethyl chloride hydrochlorides in aqueous toluene in the presence of base, using dibenzo-18-crown-6 as catalyst gave 2,7-bis(aminoethoxy)-9-fluorenones (method B), which on treatment with ethereal hydrogen chloride gave the dihydrochlorides (Table 1).

The yields and duration of the preparation of 2,7-bis(aminoethoxy)-9-fluorenones by the Williamson reaction and under PTC conditions are given in Table 2. The advantages of method B over the method A are the increased yields of products, shortening of the reaction times by a factor of more than three, and the possibility of obtaining the dibasic ether as the

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TABLE 1. 2,7-Bis(aminoethoxy)-9-fluorenones and Their Phenylhydrazones

Compound	Yield, %	Method of preparation	mp, °C*	Found, %				Empirical formula	Calculated, %				Mass spectrum,** M^+
				C	H	Hal	N		C	H	Hal	N	
V	17 48	A B	238—40	48,96	5,31	34,57	4,40	$C_{27}H_{32}N_2Br_2O_3 \cdot 2HCl$	48,74	5,16	34,74	4,21	592
VI	21 70	A B	243—5	56,53	5,66	24,48	4,92	$C_{27}H_{32}N_2Cl_2O_3 \cdot 2HCl$	56,26	5,96	24,65	4,86	503
VIII	23 48	A B	226—8	44,66	4,54	34,67	4,82	$C_{25}H_{28}N_2Br_2O_5 \cdot 2HCl$	44,87	4,53	34,53	4,19	596
IX	15 36	A B	239—41	51,87	5,25	20,61	4,98	$C_{25}H_{28}N_2Cl_2O_5 \cdot 2HCl$	51,74	5,22	20,34	4,83	507
XIII	— 91	C D	238—40	66,48	7,02	12,05	9,57	$C_{33}H_{40}N_4O_2 \cdot 2HCl$	66,31	7,10	11,86	9,38	—
XIV	— 79	C D	219—21	52,65	5,21	30,74	7,31	$C_{33}H_{38}N_4Br_2O_2 \cdot 2HCl$	52,46	5,35	30,54	7,42	—
XV	— 82	C D	234—6	59,33	6,01	21,45	8,23	$C_{33}H_{38}N_4Cl_2O_2 \cdot 2HCl$	59,46	6,06	21,27	8,40	—
XVI	35 72	C D	233—5	62,05	6,16	12,01	9,17	$C_{31}H_{36}N_4O_4 \cdot 2HCl$	61,89	6,38	11,79	9,32	—
XVII	53 90	C D	220—2	49,08	4,65	30,38	7,46	$C_{31}H_{34}N_4Br_2O_4 \cdot 2HCl$	49,01	4,74	30,43	7,35	—
XVIII	46 84	C D	176—8	55,71	5,34	21,30	8,21	$C_{31}H_{34}N_4Cl_2O_4 \cdot 2HCl$	55,53	5,42	21,15	8,36	—

*Melting point determined on a plate

**The mass of the base molecular ion is given.

TABLE 2. Comparative Data for the Preparation of 2,7-Bis(aminoethoxy)-9-fluorenones by Different Methods

Compound	Williamson reaction (method A)		Under PTC conditions (method B)	
	time, h	yield, %	time h	yield, %
IV	20	28	6	86
V	20	17	6	48
VI	20	21	6	70
VII	20	43	6	58
VIII	20	23	6	48
IX	20	15	6	36

crystalline base, without the need for special techniques of isolation, thus facilitating the purification of the dihydrochloride.

Phenylhydrazones of 2,7-bis(aminoethoxy)-9-fluorenones were obtained by two methods (C and D). In method C, reaction of (I-III) with phenylhydrazine in ethanol with heating gave the phenylhydrazones (X-XII) [2], which were alkylated by method B to give (XIII-XVIII). In method D, compounds (XIII-XVIII) were obtained by reacting (IV-IX) with phenylhydrazone. Method D was to be preferred, since the products were obtained in higher yields, and did not require further purification.

The structures of the products were confirmed by IR spectroscopy and mass spectrometry. The IR spectra of the compounds showed the following absorptions (ν, cm^{-1}) [1]: 1700 (C=O), 1120–1100 (C–O–C), 1600 (C=N), 3380 (NH), 770 (C–Cl), and 780 (C–Br). The mass spectra of the dibasic ethers of showed peaks for the molecular ions of (IV)–(IX) (Table 1).

The antiviral activity of the 2,7-bis(aminoethoxy)-9-fluorenones and their phenylhydrazones was examined using standard methods in developing chick embryos against the A2/Leningrad strain of influenza virus, in dilutions of 10^{-5}. The protection factor for (IV-IX) and (XVIII) was 25-35%, for (XV) 50%, and for (XIII), (XIV), (XVI), and (XVII) 60-80%, the most active compound being (XVI).

These data show that replacement of the carbonyl group in 2,7-bis(aminoethoxy)-9-fluorenones by the phenylhydrazono-group increases antiviral activity. The phenylhydrazones merit further investigation.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer-457 spectrometer (West Germany) in KBr disks, and mass spectra on a Varian MAT-112 mass spectrometer (West Germany) with direct introduction into the source, ionizing voltage 100 eV. The purities of the compounds were checked on Silufol UV-254 plates (Czech SSR) in the system benzene–chloroform–ethanol (5:3.5:1.5).

2,7-Bis(aminoethoxy)-9-fluorenones (IV)-(IX). A. A mixture of 9.25 g (0.025 mole) of (II), 15.6 g (0.085 mole) of 2-piperidinoethyl chloride hydrochloride, and 9.52 g (0.17 mole) of KOH in 50 ml of toluene and 25 ml of water was heated for 20 h with vigorous stirring. When the reaction was complete, the mixture was cooled, and the solid filtered off, washed several times with water, and dried. The organic layer was separated from the filtrate, washed with 40% NaOH and several times with water, and the solvent removed under reduced pressure. The residue was combined with the main fraction, and recrystallized from benzene. The product was obtained as the base, which was dissolved in propan-2-ol and converted into the dihydrochloride by treatment with ethereal HCl to give 2.83 g (17%) of 3,6-dibromo-2,7-bis[2-piperidino)-ethoxy]-9-fluorenone dihydrochloride (V) as an orange-colored powder.

B. A mixture of 5.3 g (0.025 mole) of (I), 15.6 g (0.085 mole) of 2-piperidinoethyl chloride hydrochloride, and 9.52 g (0.17 mole) of KOH in 50 ml of toluene and 25 ml of water in the presence of 0.1 g of dibenzo-18-crown-6 was heated for 6 h with vigorous stirring. Workup and isolation of the product was carried out as in method A, to give 10.9 g (86%) of (IV).

The properties of the 2,7-bis(aminoethoxy)-9-fluorenones are given in Table 1.

2,7-Bis(aminoethoxy)-9-fluorenone Phenylhydrazones (XIII-XVIII). C. A mixture of 6 g (0.02 mole) of (X), 60 ml of toluene, 8 g (0.44 mole) of morpholinoethyl chloride hydrochloride, 7.4 g (0.12 mole) of KOH, 20 ml of water and 0.1 g of dibenzo-18-crown-6 was heated with vigorous stirring for 10 h. Workup and isolation of the product was carried out as in method A, to give 4.2 g (35%) of the phenylhydrazone (XVI).

2,7-Bis[2-(piperidino)ethoxy]-9-fluorenone Phenylhydrazone Dihydrochloride (XIII). 2.17 g (0.005 mole) of (IV) was dissolved in 150 ml of ethanol, and 1 ml (0.01 mole) of phenylhydrazine added followed by acetic acid to pH 3.5-4.0. The mixture was boiled for 2 h, cooled, and basified with aqueous ammonia. The solid phenylhdrazone (IV) which separated was recrystallized from benzene. The base was then dissolved in the minimum amount of benzene, propan-2-ol added, and acidified with ethereal HCl. The precipitate was filtered off and dried to give 2.7 g (91%) of (XIII) as yellow crystals.

Compounds (XIV-XVIII) were obtained similarly (Table 1).

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2,5-DIPHENYLPYRROLES AND 2-AMINO-3-CYANO-4,5-DIMETHYLPYRROLES*

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Pyrroles are known to display a wide spectrum of biological activity. Compounds are known which show antiviral [5], antiinflammatory [6], antitumor [4], and analgesic [8] activity. There have also been reports in the literature that heterocycles containing aldehyde or hydroxymethyl groups, together with their derivatives [hydrazones, carbazones (CH=NR), and ethylenes ($CH{=}CR_2$)] are biologically active [2, 7, 9]. It has been found that the occurrence of activity of a given type is governed not only by the nature of the substituents present in the ring, but also their positions with respect to the heteroatom [1]. For this reason, we have synthesized and examined the antiviral activity of some 2,5-diphenyl- and 2-amino-3-cyano-4,5-dimethylpyrroles containing the unbranched fragments C=O, C=C, and C=N in the 3(2)-position. The starting material used was 2,5-diphenylpyrrole, Vilsmeir formulation of which gives 2,5-diphenyl-3-formylpyrrole (I). The structure of (I) was confirmed by its IR and PMR spectra. Thus, the PMR spectrum showed a singlet for the CHO proton at 9.75 ppm, and a doublet for the 4-proton at 7.01 ppm, with J = 2.6 Hz, and the IR spectrum showed absorption for the NH and CHO groups at 3220 and 1660 cm^{-1} respectively.

Reduction of the 3-formylpyrrole (I) with sodium borohydride gave the hydroxymethyl derivative (II) in 93% yield. The presence of the hydroxyl group in (II) was confirmed by the

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