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).

LITERATURE CITED

1. L. Bellamy, The Infra-Red Spectra of Complex Molecules [Russian translation], Mir (1963), p. 190.
2. L. A. Kitvinova, O. G. Yasinsksya, S. A. Andronati, et al., Khim.-farm. Zh., No. 9, 1058-1059 (1982).
3. L. A. Litvinova, S. A. Andronati, G. V. Lempart, et al., ibid., No. 10, 1177-1180 (1983).
4. N. P. Chizhov and V. I. Stroganov, Physiologically Active Compounds [in Russian], No. 13, Kiev (1981), pp. 3-9.
5. E. R. Andrews, R. W. Fleming, J. M. Grisar, et al., J. Med. Chem., 17, No. 18, 382-386 (1974).
6. R. H. Levin, Aldrichim. Acta, 12, No. 4, 77-82 (1979).

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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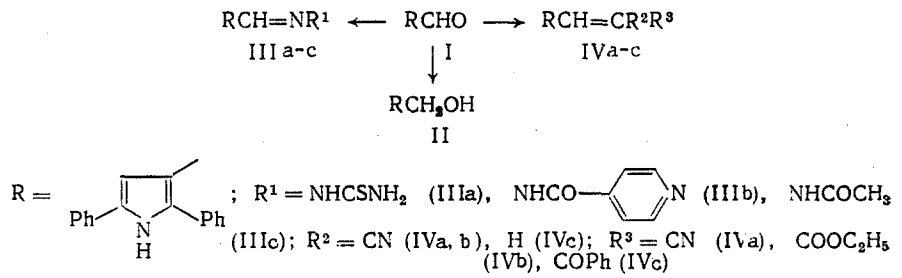
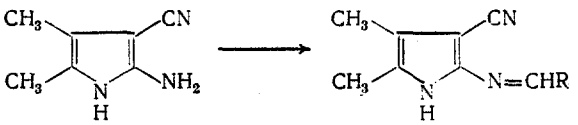


absorption at 3540 cm^{-1} in its IR spectrum.

Reaction of the aldehyde (I) with thiosemicarbazone, isonicotinic acid hydrazide, and acetylhydrazine gave the corresponding derivatives (IIIa-c).

The aldehyde (I) also reacts readily with ethyl cyanoacetate and malonodinitrile to give high yields of the vinylpyrroles (IVa, b), although the analogous condensation with acetophenone gave the vinylpyrrole (IVc) in only 39% yield.

In order to examine the biological activity of 2-amino-3-cyano-4,5-dimethyl-pyrroles, we prepared the Schiff bases (VIa-e)



V VIa-c

VIa R = C_6H_5; VIb: R = p-$OCH_3C_6H_4$; VIc: R = o-OHC_6H_4; VId: R = p-$NO_2C_6H_4$; VIe: R = C(=N—NHPh)COC_3H_7.

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a Perkin-Elmer 599 instrument (USA) in vaseline oil, and UV spectra on a Perkin-Elmer 575 spectrometer in alcohol. The PMR spectrum was recorded on a Jeol JNM-4H-100 spectrometer (Japan), internal standard TMS. The mass spectrum was obtained on a Varian MAT-112 mass spectrometer (West Germany). The purity of the products was checked and the progress of the reactions followed by chromatography on Silufol UV-254 plates in the system benzene—ethyl acetate (4:1).

The properties of the compounds obtained (I-IV) are given in Table 1, and those of (VIa-e) in Table 2.

2-Amino-3-cyano-4,5-dimethylpyrrole was obtained as described in [3].

2,5-Diphenyl-3-formylpyrrole (I). To a solution of 6.35 g (29 mmole) of 2,5-diphenylpyrrole in 30 ml of dry toluene and 3.2 g (30 mmole) of dimethylformamide was added dropwise with stirring 5.4 g (24 mmole) of phosphoryl chloride. The mixture was heated on a boiling water bath for 6 h. A saturated aqueous solution of sodium acetate (30 ml) was then added, and the mixture stirred for 30 min, cooled, the solid filtered off, washed with water, and dried.

2,5-Diphenyl-3-hydroxymethylpyrrole (II). To a suspension of 3 g (12 mmole) of (I) in 50 ml of methanol was added all at once with stirring 3 g (8 mmole) of sodium borohydride in 40 ml of methanol. After 1 h, the solid was filtered off, washed with water, and dried.

2,5-Diphenyl-3-formylpyrrole Thiosemicarbazone (IIIa). A suspension of 1.5 g (6 mmole) of (I), 0.8 g (6 mmole) of thiosemicarbazide hydrochloride, and 0.6 g (6 mmole of anhydrous sodium acetate in a mixture of 10 ml of alcohol, 10 ml of dioxane, and 3 ml of water was boiled for 2 h. The hot reaction mixture was then treated with 15 ml of water, boiled for 5 min, cooled, and the solid which separated was filtered off and chromatographed on a silica gel column (ether).

2,5-Diphenyl-3-formyl Isonicotinoylhydrazone (IIIb). A solution of 1.5 g (6 mmole) of (I) and 0.8 g (6 mmole) of isonicotinic acid hydrazide in 8 ml of alcohol and 16 ml of dioxane was boiled for 2 h. The yellow solid was filtered off and washed with methanol.

TABLE 1. Properties of Products (I)-(IV)

Compound	Yield, %	mp[a], °C	Found, %			Empirical formula	Calculated, %			UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}
			C	H	N		C	H	N		
I[b]	84,5	262—3 (decomp.)	82,7	5,5	5,4	$C_{17}H_{13}NO$	85,6	5,3	5,7	205, 230 shoulder, 255, 295 (4,36; 4,21; 4,31; 4,39)	3220 (NH), 1660 (C=O)
II	92,9	195—6	82,1	6,0	5,9	$C_{17}H_{15}NO$	81,9	6,1	5,6	208, 212 shoulder, 312 (4,24; 4,04; 4,42)	3200(NH), 3540 (OH)
IIIa[c]	47,9	203—5 (decomp.)	67,3	5,2	17,3	$C_{18}H_{16}N_4$	67,5	5,0	17,5	205, 230 shoulder, 340 (4,49; 4,12; 4,67; 4,54)	3500 (NH_2), 3400, 3240, 3140 (NH), 1590, 1610 (C=N, C=C)
IIIb	90	268—70 (decomp.)	75,5	5,1	15,2	$C_{23}H_{18}N_4O$	75,4	4,9	15,3	206, 230 shoulder, , 360 (4,53; 4,26; 4,57; 4,28)	3200, 3050 (NH), 1645 (C=O), 1580, 1610 (C=N, C=C)
IIIc[d]	72,4	185—7	75,2	6,0	13,9	$C_{19}H_{17}N_3O$	75,2	5,7	13,8	—	—
IVa	92,8	280 (decomp.)	81,2	4,5	13,9	$C_{20}H_{13}N_3$	81,3	4,4	14,2	205, 212 shoulder, 225 shoulder, 302, 405 (4,17; 4,12; 4,03; 4,42; 4,19)	3300 (NH), 2230 (C=N)
IVb	90	270—71 (decomp.)	77,5	5,5	8,2	$C_{22}H_{18}N_2O_2$	77,2	5,4	8,2		
IVc	39	221—3 (decomp.)	85,8	5,6	—	$C_{25}H_{19}NO$	85,9	5,5	—	205, 230, 260 shoulder, 310, 410 (4,55; 4,39; 4,43; 4,62; 4,52)	3280 (NH), 1630 (C=O), 1550, 1600 (C=C)

[a]Compounds recrystallized from: (I), (II), (IVb), methanol—dioxane, (IIIa), dioxane, (IIIb), acetic acid, (IIIIc), (IVa), (IVb), methanol.
[b]PMR spectrum (DMSO-D_6): 9.75 s (CHO); 7.95-7.91 (arom.); 7.01 d (4 = CH, J = 2.6 Hz).
[c]Found: S 10%; Calculated, S 10.1%.
[d]Mass spectrum, m/z (0): M 303 (68.7), 260 (81.5), 244 (62.5), 229 (100).

TABLE 2. Properties of Products (VIa-e)

Compound	Yield, %	mp*, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
VI	90	216—7	75,3	5,8	19,1	$C_{14}H_{13}N_3$	75,3	5,9	18,8
VI	98	179—80	71,0	6,1	16,8	$C_{15}H_{15}N_3O$	71,1	6,0	16,6
VI	63,5	273—4 (decomp.)	70,0	5,7	17,7	$C_{14}H_{13}N_3O$	70,2	5,5	17,6
VI	92	240—2 (decomp.)	62,5	4,6	20,6	$C_{14}H_{12}N_4O_2$	62,7	4,5	20,9
VI	50	223—4	68,2	6,2	20,8	$C_{19}H_{21}N_5O$	68,0	6,3	20,9

*(VIa-e) were recrystallized from methanol.

2,5-Diphenyl-3-formylpyrrole Acetylhydrazone (IIIc). To a suspension of 1.8 g (7 mmole) of (I) in 20 ml of alcohol and 20 ml of dioxane was added 0.62 g (8 mmole) of acetylhydrazine. The solvent was removed under vacuum, the residue treated with water, and the solid filtered off.

2,5-Diphenyl-3-(2,2-dicyanovinyl)pyrrole (IVa). A mixture of 1.2 g (5 mmole) of (I), 0.6 g (10 mmole) of malonodinitrile, and 10 ml of pyridine was heated on a water bath for 1 h. The mixture was cooled, and the solid filtered off and washed with methanol.

2,5-Diphenyl-3-(2-cyano-2-ethoxycarbonylvinyl)pyrrole (IVb). A mixture of 1.5 g (6 mmole) of (I), 6.4 g (6.5 mmole) of cyanoacetic ester, and 0.5 ml of piperidine in 20 ml of alcohol was boiled for 2 h. The mixture was cooled, and the solid which separated was filtered off.

2,5-Diphenyl-3-(2-benzoylvinyl)pyrrole (IVc). A. A mixture of 1.5 g (6 mmole of (I), 0.72 g (6 mmole) of acetophenone, and 0.5 g of ammonium acetate in 60 ml of acetic acid was boiled for 3 h. The solid was filtered off to give 0.72 g (48%) of (I). The mother liquors were poured into water, and the solid which separated was filtered off to give 0.21 g (19.8%) of (IVc).

B. A mixture of 0.3 g (1.2 mmole) of (I), 0.15 g (1.2 mmole) of acetophenone, 25 ml of abs. alcohol, and five drops of 5 N caustic alkali was boiled for 5 h. The alcohol was removed under reduced pressure to give 0.042 g (39%) of (IVc).

2-Amino-3-cyano-4,5-dimethylaminopyrroles (VIa-e). A mixture of 10 mmole of the amine (V) and 10 mmole of the appropriate aldehyde in 30 ml of benzene was boiled in a Dean and Stark apparatus for 1 h. The solid was filtered off the dried. 1-Formylpentane-1,2-dione 1-phenylhydrazone was obtained from methyl propyl ketone, as described in [2].

EXPERIMENTAL (BIOLOGICAL)

The antiviral activity of the compounds was examined against influenza A virus [strains A/PR-8/34 (*H0N1*), A/FPV (*H7N7*), and A/Bethesda/63 (H_2N_2)].

The virus-inhibitory and virucidal activity of the compounds was determined in vitro, using a primarily trypsinized culture of chick embryo fibroblasts (CEF) and nine-day developing chick embryos for viral reproduction.

The therapeutic activity of the compounds was examined in model influenzal pneumonia in mice, induced by intranasal infection with influenza virus.

The compounds were administered in the maximum tolerated and lower doses per os one day before infection, then daily for four days thereafter.

The results were assessed by the reduction in mortality (%) in the treated mice as compared with the control animals.

The antiviral activity of 11 novel 2,5-diphenylpyrroles and 2-amino-3-cyano-4,5-dimethylpyrroles was examined.

It was found that 2,5-diphenylpyrrole and some of its derivatives containing the three unbranched fragments C=O, C=C, and C=N in the 3-position [compounds (I), (IIIb, c),(IVa,b)] had viral inhibitory activity at concentrations from 5 to 10 μg/ml, against replication of the

influenza virus in cell culture, and reduced the infective titer of the virus by 1.0 log TID_{50} as compared with the controls. In concentrations of 1000 μg/ml, these compounds had a virucidal effect on influenza virus, reducing the infectivity of the latter by a factor of ten. No therapeutic activity in influenzal pneumonia was observed.

It is noteworthy that 2,5-diphenyl-3-formylpyrrole thiosemicarbazone (IIIa), unlike 2,5-diphenyl-3-formylpyrrole (II) itself, had no viral inhibitory or virucidal activity against influenza virus.

The 2-amino-3-cyano-4,5-dimethylpyrroles (VIa, d, e) were likewise devoid of activity.

These studies have therefore demonstrated antiviral activity in 2,5-diphenylpyrrole and some of its derivatives.

LITERATURE CITED

1. A. M. Kofman, V. E. Golender, L. Ya. Leitis, et al., Khim. Geterotsikl. Soedin., No. 1, 109-113 (1985).
2. M. D. Mashkovskii, Medicinals [in Russian], 10th edition, Moscow (1985), Parts 1-2.
3. V. I. Shvedov, M. V. Mezentseva, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 9, 1217-1224 (1975).
4. W. K. Anderson, M. J. Halat, and A. C. Rick, J. Med. Chem., 23, 87 (1980).
5. F. Arcamone, S. Penco, and V. Nicolella, French Pat. No. 90,359 (1967); Ref. Zhur. Khim., No. 15095P (1975).
6. M. Artico, F. Corelli, S. Massa, and G. Stefancich, J. Heterocycl. Chem., 19, 1493-1495 (1982).
7. F. A. French, E. J. Blanz, and J. P. Brocman, J. Med. Chem., 17, 172-181 (1970).
8. N. W. Gabel, ibid., 11, 403 (1968).
9. E. Hoggarth, A. R. Martin, N. S. Storey, and E. H. P. Young, Br. J. Pharmacol., 4, 248-253 (1949).
10. C. G. Overberger, M. Valentine, and J. P. Anselme, J. Am. Chem. Soc., 91, 687-694 (1969).