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SYNTHESIS AND ANTIVIRAL ACTIVITY OF N-2-HYDROXYPHENYLBENZALDIMINE AND N-PHENYLSALICYLALDIMINE DERIVATIVES AND THEIR Mn^{2+}-CHELATES

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UDC 615.281.8.012.1

In order to obtain compounds which are active against animal viruses, we have synthesized derivatives of N-2-hydroxyphenylbenzaldimine (IIIa-e), N-phenylsalicylaldimine (VIa-c), and their Mn^{2+}-complexes, starting from the aldehydes (Ia-e, Va-c) and the amines (II, IVa-c).

The azomethine derivatives IIIa-e and VIa-c were obtained by the condensation of the appropriate aldehyde (Ia-e, Va-c) with the aniline derivative II or IVa-c in methanol solution.

$$\underset{\text{Ia-e}}{RC_6H_4CHO} + \underset{\text{II}}{H_2NC_6H_3OH\text{-}2\text{-}NO_2\text{-}5} \longrightarrow \underset{\text{IIIa-e}}{RC_6H_4CH{=}NC_6H_3OH\text{-}2\text{-}NO_2\text{-}5} + H_2O$$

Ia, IIIa: R = H; Ib, IIIb: R = OCH_3-4; Ic, IIIc: R = $N(CH_3)_2$-4; Id, IIId: R = NO_2-3; Ie, IIIe: R = Br-2.

$$\underset{\text{IVa-c}}{RC_6H_4NH_2} + \underset{\text{Va-c}}{CHOC_6H_3OH\text{-}2\text{-}R'} \longrightarrow \underset{\text{VIa-c}}{RC_6H_4N{=}CHC_6H_3OH\text{-}2\text{-}R'} + H_2O$$

IVa, VIa: R = NO_2-4; IVb, VIb: R = NO_2-3; IVc, VIc: R = $(OCH_3)_2$-2,5; Va, VIa: R′ = H; Vb, VIb: R′ = Cl-5; Vc, VIc: R′ = NO_2-5.

Chelates of Mn^{2+} with N-2-hydroxyphenylbenzaldimine derivatives (VIIa-e) were synthesized both by the method of ligand formation and by the direct reaction of a Schiff's base in aqueous methanol [1] (see scheme on next page).

Attempts to synthesize complexes of Mn^{2+} with N-phenylsalicylaldimine derivatives (VIIIa-c) both by the method of ligand formation and by the direct reaction of a Schiff's base with the metal salt proved to be unsuccessful. Apparently, the reaction is hindered by the presence of a more stable hydrogen bond than in the isomeric N-2-hydroxyphenylbenzaldimine, and

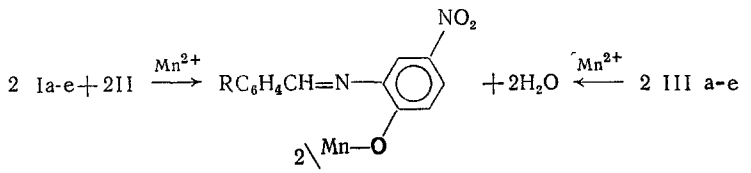
Moscow Physico-Technical Institute, All-Union Scientific-Research Institute of Veterinary Virology and Microbiology, Pokrov. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 2, pp. 178-181, February, 1984. Original article submitted March 16, 1983.

0091-150X/84/1802-0113$08.50

TABLE 1. Elemental Analysis of Derivatives of N-2-hydroxyphenylbenzaldimine (IIIa-e) and N-phenylsalycylamidine (VIa-c)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
IIIa	188—9	64,21	4,09	11,34	$C_{13}H_{10}N_2O_3$	64,46	4,13	11,57
IIIb	156—7	61,64	4,39	10,19	$C_{14}H_{12}N_2O_4$	61,76	4,41	10,29
IIIc	171—2	62,75	5,33	14,85	$C_{15}H_{15}N_3O_3$	63,16	5,26	14,74
IIId	203—4	54,44	3,09	14,58	$C_{13}H_9N_3O_5$	54,36	3,17	14,63
IIIe	164—5	48,49	2,88	8,64	$C_{13}H_9BrN_2O_3$	48,60	2,80	8,72
VIa	152—3	64,49	3,84	11,29	$C_{13}H_{10}N_2O_3$	64,46	4,13	11,57
VIb	174—5	56,61	3,14	9,84	$C_{13}H_9ClN_2O_3$	56,42	3,25	10,13
VIc	175—6	60,10	5,02	9,45	$C_{15}H_{14}N_2O_5$	59,6	4,64	9,27

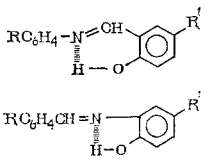
Note. IIIe: Found, %: Br 24.86; calculated, %: Br 24.92. VIb: Found, %: Cl 12.45; calculated, %: Cl 12.84.



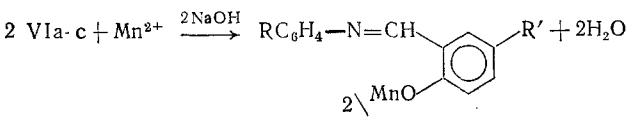
VIIa-e

VIIa: R = H; VIIb: R = OCH_3-4; VIIc: R = $N(CH_3)_2$-4; VIId: R = NO_2-3; VIIe: R = Br-2.

this gives rise to the formation of a six-membered pseudoaromatic ring:



The hydrogen bond was broken by methanolic sodium hydroxide, in which compounds VIa-c dissolved, although they are usually insoluble in weakly polar solvents [2]:



VIIIa-c

VIIIa: R = NO_2-4, R′ = H; VIIIb: R = NO_2-3, R′ = Cl-5; VIIIc: R = $(OCH_3)_2$-2,5, R = NO_2-5.

EXPERIMENTAL CHEMISTRY

Synthesis of N-2-hydroxy-5-nitrophenylbenzaldimine (IIIa). To 10.6 g (0.1 moles) of freshly prepared benzaldehyde in methanol was added a methanolic solution of 1.54 g (0.1 moles) of 2-hydroxy-5-nitroaniline (II). The reaction mixture was heated to boiling, whereupon a yellow crystalline precipitate separated. The Schiff's base was filtered off, washed with methanol, and dried in a vacuum dessicator. Compounds IIIb-e and VIc (Table 1) were obtained by the same method.

Synthesis of Bis(N-2-hydroxy-5-nitrophenylbenzaldeiminato)Mn^{2+} (VIIa). 1. A solution of 1.23 g (0.008 moles) of II in methanol was added to an aqueous methanolic solution of 0.86 g (0.008 moles) of freshly prepared benzaldehyde and 1.0 g (0.004 moles) of $Mn(CH_3COO)_2 \cdot 4H_2O$ or 0.8 g (0.004 moles) of $MnCl_2 \cdot 4H_2O$. After brief heating of the reaction mixture, the yellow precipitate obtained was filtered off, washed with methanol, and dried in a vacuum desiccator.

2. An aqueous solution of 0.5 g (0.002 moles) of $Mn(CH_3COO)_2 \cdot 4H_2O$ or 0.4 g (0.002 moles) of $MnCl_2 \cdot 4H_2O$ was added to a methanolic solution of 0.99 g (0.004 moles) of N-2-hydroxy-5-nitrophenylbenzaldimine (IIIa) and the mixture heated. A yellow precipitate separated and was filtered off, washed with methanol, and dried in a vacuum desiccator. The same method

TABLE 2. Elemental Analysis of Complexes of Mn^{2+} with Derivatives of N-2-Hydroxyphenylbenzaldimine VIIa-e and N-Phenylsalicylaldimine VIIIa-c

Compound	Found, %				Empirical formula	Calculated, %			
	C	H	Mn	N		C	H	Mn	N
VIIa	58,12	3,48	10,68	10,32	$C_{26}H_{18}MnN_4O_6$	58,10	3,35	10,24	10,43
VIIb	55,96	3,69	9,24	9,67	$C_{28}H_{22}MnN_4O_8$	56,30	3,68	9,20	9,40
VIIc	57,41	4,54	8,68	13,25	$C_{30}H_{28}MnN_6O_6$	57,28	4,49	8,83	13,43
VIId	49,61	2,72	8,35	13,21	$C_{26}H_{16}MnN_6O_{10}$	49,70	2,55	8,78	13,40
VIIe	44,63	2,19	8,03	7,96	$C_{26}H_{16}Br_2MnN_4O_6$	44,89	2,30	7,91	8,06
VIIIa	57,98	3,24	10,45	10,32	$C_{26}H_{18}MnN_4O_6$	58,10	3,35	10,24	10,43
VIIIb	51,65	2,89	8,86	9,04	$C_{26}H_{16}Cl_2MnN_4O_6$	51,48	2,64	9,07	9,24
VIIIc	54,85	4,15	8,54	8,94	$C_{30}H_{26}MnN_4O_{10}$	54,79	3,96	8,37	8,52

Note. VIIe: Found, %: Br 23.3; calculated, %: Br 23.02. VIIb: Found, %: Cl 11.59; calculated, %: Cl 11.72.

TABLE 3. Action of Compound on Chick Embryos Infected with Avian Influenza A Virus and Newcastle Disease Virus

Compound	Avian influenza A virus			Newcastle disease virus		
	dose, μg/chick embryo	quantity of chick embryo	% survival	dose, μg/chick embryo	quantity of chick embryo	% survival
IIIA	250	20	10,0	—	—	—
IIIb	500	20	10,0	—	—	—
IIIc	250	30	17,0	250	20	20,0
IIId	—	—	—	250	20	20,0
IIIe	—	—	—	125	30	17,0
VIa	250	30	10,0	—	—	—
VIb	250	30	23,3	—	—	—
VIc	250	20	0	—	—	—
VIIa	250	20	10,0	—	—	—
VIIb	125	20	10,0	—	—	—
VIIc	—	—	—	125	20	15,0
VIId	125	20	15,0	—	—	—
VIIe	—	—	—	250	20	10,0
VIIIa	250	30	10,0	250	20	15,0
VIIIb	250	30	23,3	250	30	17,0
VIIIc	250	20	10,0	250	20	20,0
Control: placebo	250	30	0	250	30	0
virus	250	30	100,0	250	30	100,0

was used to prepare compounds VIIb-e (Table 2).

Synthesis of Bis(N-4-nitrophenylsalicylaldiminato)Mn^{2+} (VIIIa). To a solution of 2.19 g (0.008 moles) of N-4-nitrophenylsalicylaldimine (VIa) – a slight (0.1 g) excess – in 25 ml of methanol, containing 0.32 g (0.008 moles) of sodium hydroxide, was added a solution of 1 g (0.004 moles) of $Mn(CH_3COO)_2 \cdot 4H_2O$ in methanol. The claret-colored precipitate was filtered off, washed with methanol, and dried in a vacuum desiccator. Compounds VIIIb-c were prepared in the same way (Table 2).

EXPERIMENTAL BIOLOGY

The biological activity of 16 compounds was studied. Data on the antiviral activity is given in Table 3. Compounds VIb and VIIIb gave the best protection: They prevented the destruction of developing chick enbryos, infected with avian influenza A virus in 23.3% of cases compared with 15-17% for compounds IIIc and VIId (100% destruction the control). The remaining compounds had very little effect.

On developing chick embryos, infected with Newcastle disease, the most active compounds were IIIc, IIId, and VIIIc, protecting the embryos from destruction in 20% of cases. However, because some of the compounds were poorly water-soluble, the full effect of their biological properties was not obtained.

It is interesting to note that compounds IIIc and VIIIb possess a similar activity on both reference-viruses: Their chemical structures might be modified to give more effective compounds.

Virulent strains of avian influenza A virus and Newcastle disease virus in the lyophilized dried state with infection titer of 8.5-9.5 ELD_{50}/ml and ten-day-old developing chick embryos were used. The maximum tolerable dose of compounds, reduced by twice the test interval, was injected into the allantoic cavity of the developing chick embryos, 1-1.5 h after inoculation with doses of 36 ELD_{50} (0.1 ml) avian influenza A virus and 10-15 ELD_{50} (0.1 ml) of Newcastle disease virus. For each dose of compound no less than 10 embryos were used. After introduction of the compounds the chick embryos were incubated in a thermostat at 37.5°C for 7 days and were flamed every 24 h, in order to determine the time at which the embryos were destroyed. The effectiveness of the compounds was evaluated by the percent survival rate. The maximum tolerable dose and the toxicity of the compounds was determined on intact and infected chick embryos by the method developed at the institute [3].

Because of the poor solubility of the test compounds in water, a weighed amount was dissolved in dimethylsulfoxide, and sterile physiological solution was added to give the desired volume. Infected developing chick embryos and chick embryos served as controls, into which the solvent of the test substances were introduced (placebo).

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