SYNTHESIS AND ANTIVIRAL ACTIVITY OF THE BISULFITE DERIVATIVE OF 1-PHENYL-2-METHYL-4-OXOINDENO [1,2-b]PYRROLYL-3-GLYOXAL*

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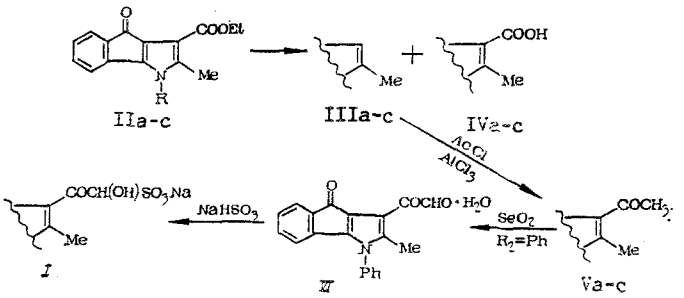
As a continuation of our search for substances with antiviral activity [1, 2], we synthesized a bisulfite derivative of 1-phenyl-2-methyl-4-oxoindeno [1,2-b]pyrrolyl-3-glyoxal (I) by oxidizing 3-acetyl-4-oxoindeno [1,2-b]pyrrole (V) with selenium dioxide.



R= Ph IIa-Va; CH_2Ph IIb-Vb C_6H_4Me-n IIc-Vc

Inasmuch as we were not successful in obtaining derivatives of indeno[1,2-b]pyrrole containing an acetyl group in position 3 of the pyrrole ring by method [2], our starting compounds were derivatives of 3-carbethoxyindeno [1,2-b]pyrroles (IIa-c) which were decarboethoxylated by the action of pyridine chlorohydrate. Along with the resultant derivatives of indeno[1, 2-b]pyrrole (IIIa-c) with an open position 3, we also obtained derivatives of carboxylic acids (IV) which we were able to decarboxylate by the use of a copper catalyst in quinoline.

In comparison to the spectra of the initial compounds IIa-c, the PMR spectra of compounds IIIa-c exhibit a proton signal in position 3 in the form of a quartet in the region 6.01-6.1 ppm whereas the region 2.00-2.1 ppm has proton signals of the methyl group in the form of a doublet which is due to the spin—spin interaction between the methyl group protons and the proton in position 3 of the pyrrole ring.

In comparison to the spectra of compounds IIIa-c, the IR-spectra of compounds IVa-c, in addition to the carbonyl group absorption band (1670 cm^{-1}), also have absorption bands that correspond to the vibrations of C=O and OH of carboxylic acid at 1710 and 2660 cm^{-1} respectively.

A Friedel—Crafts acylation of compounds IVa-c resulted in the 3-acetyl derivatives of indeno[1, 2-b]pyrrole (Va-c). Their IR-spectra exhibited absorption bands corresponding to the vibrations of groups $COCH_3$ and C=O in the regions of 1650-1660 cm^{-1} and 1690 cm^{-1} respectively.

Compound Va was oxidized by selenium dioxide to glyoxal (VI). In comparison to the spectrum of the initial compound Va, the IR spectrum of glyoxal, in addition to the absorption bands at 1660 ($COCH_3$) and 1700 (C=O), exhibited an absorption band (3200 cm^{-1}) which corresponded to the hydroxyl group. This confirmed the existence of glyoxal in the form of a hydrate.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	MP, °C[a]	Found, %			Empirical formula	Calculated, %			IR-spectrum cm^{-1}	
		C	H	N		C	H	N	C=O	OH
IIIa[b]	175—6	83,7	4,9	5,2	$C_{18}H_{13}NO$	83,4	5,1	5,4	1600	
IIIb	138—40	83,3	5,5	5,2	$C_{19}H_{15}NO$	83,5	5,5	5,1	1690	
IIIc	149—50	83,3	5,5	5,1	$C_{19}H_{15}NO$	83,5	5,5	5,1	1690	
IVa	268 (with decomposition)	75,7	4,8	4,7	$C_{19}H_{13}NO_3$	75,2	4,3	4,6	1670, 1700	2660
IVb	209—11	75,7	4,5	4,3	$C_{20}H_{15}NO_3$	75,7	4,7	4,4	—	—
IVc	254—5	75,6	4,5	4,2	$C_{20}H_{15}NO_3$	75,7	4,7	4,4	1670, 1710	2660
Va	223—4	79,7	5,2	4,8	$C_{20}H_{15}NO_2$	79,7	5,0	4,7	1660, 1700	
Vb	186—7	80,0	5,3	4,5	$C_{21}H_{17}NO_2$	80,0	5,4	4,4	1660, 1700	
Vc	222—4	80,2	5,7	4,4	$C_{21}H_{17}NO_2$	80,0	5,4	4,4	1660, 1700	
VI	222—4	72,1	4,5	4,0	$C_{21}H_{13}NO_3 \cdot H_2O$	72,1	4,5	4,2	1670, 1700	3400
Vc	—	57,0	3,4	3,4	$C_{20}H_{14}NSO_6Na$	57,2	3,4	3,3		

Note. [a]Compounds IIIa-c, Va, b were recrystallized from methanol; IVa from 50% methanol; IVb, c from 70% dioxane; Vc from a 7:3 methanol-dioxane mixture; and VI from 60% alcohol.

[b]Found, %: S 7.8. Calculated, %: S 7.6. [b]UV-spectrum, λ_{max}, nm: 205 (4.47), 230 (4.29), 257 (4.52).

[c]PMR spectrum ($CDCl_3$): compound IIIa — 2.10d (2-CH_3), J = 1 Hz, 6.1 q (3-H), 7.60 - 6.90 m (aromatic ring protons); compound IIIb — 2.10d (2-CH_3), J = 1 Hz, 6.01 q (3-H) 5.15 s (1-CH_2), 7 — 7.3 m (aromatic ring protons); compound IIIc — 2.0 d (2-CH_3), j = 1 Hz, 6.05 q (3-H), 2.46 q (4-CH_3), 6.90 — 7.03 (aromatic ring protons).

treating glyoxal VI with sodium bisulfite resulted in the formation of the bisulfite derivative I.

EXPERIMENTAL (CHEMICAL)

The IR spectra were read on a Perkin-Elmer 599 spectrophotometer (USA) in the form of suspensions in petroleum jelly. The UV spectra were recorded on a EPS-3 instrument (Japan) in alcohol. The PMR spectra were recorded on an XL-100 Varian spectrometer (USA). The internal standard was TMS. Reaction progress and compound purity was checked by TLC on Silufol UV-254 plates in benzene—acetone 1:1, chloroform, and ether systems.

The characteristics of the resultant compounds are given in the Table.

Derivatives of 2-methyl-3-carbethoxyindeno[1,2-b]pyrrole (IIa-c) were obtained by method [2].

1-Phenyl-2-methyl-4-oxoindeno[1,2-b]pyrrole (IIIa). A. The reaction mixture composed of 3.3 g (0.01 mole) of compound IIa and 3.3 g (0.03 mole) of pyridine chlorohydrate was stirred at 200-220°C in a nitrogen stream for 1 h. The reaction mass was then decanted into water and acidified with diluted HCl to pH 5.0, and the resultant oil was extractd with chloroform. The organic layer was washed with water, the solvent was vacuum distilled, and the residue was separated on a $CHCl_3$ column chromatograph. The yield of IIa was 1.1 g (33.2%) and that of IIIa was 0.6 g (23.2%). The silica gel core was then extruded and the rose-colored layer was then excised. A 10 ml portion of methanol was added and the silica gel was filtered off. The methanol solution was made alkaline to pH 9.0 with 8% NaOH after which 20 ml of water was added and followed by filtration. The filtrate was acified with diluted HCl. The resultant precipitate was filtered off, washed with water, and dried. The yield of IVa was 0.12 g (3.96%).

B. A mixture containing 0.3 g of compound IVa, 0.01 g of copper powder, and 1 ml of quinoline was heated for 5 min at 230°C. The reaction mixture was cooled, the copper powder was filtered off, and the mother liquor was acidified. A 5 ml portion of water was added and the resultant residue was filtered off and dried. The yield of IIIa was 0.07 g (25.6%).

1-Benzyl-2-methyl-4-oxoindeno[1,2-b]pyrrole (IIIb) was obtained in a similar manner as the previous compound from IIb at a temperature of 200°C at a yield of 0.25 g (27.5%). Compound IVb was obtained at a yield of 0.09 g (8.5%); IIb was recovered at a yield of 0.3 g.

1-n-Tolyl-2-methyl-4-oxoindeno[1,2-b]pyrrole (IIIc). In manner similar to IIIa, IIc was obtained from IIc (1 h at 200-220°C and 1 h at 220-230°C) at a yield of 0.25 g (9.15%). Compound IVc was obtained at yield of 0.5 g (15.8%). The amount of recovered IIc was 1 g.

Derivatives of 2-methyl-3-acetyl-4-oxoindeno[1,2-b]pyrrole (Va-c). A 1.9 g (0.015 mole) portion of $AlCl_3$ was added in portions while stirring to a solution of 0.05 mole of compounds IIIa-c in 20 ml of benzene at 20°C. The reaction mixture was kept for 20 min at 20°C after which 1 ml (0.012 mole) of AcCl was slowly added. The mixture was then kept at 20°C for 1.5 h and then at 50-55°C for 0.5 h. The reaction mixture was decanted into water and acidified to pH 5.0 with conc. HCl. The organic layer was separated and the aqueous layer was extracted with benzene (2 × 50 ml). The extracts were combined, washed with water, and the solvent was vacuum evaporated. The yields of Va, Vb, and Vc were 62, 55.6, and 47.5% respectively.

1-Phenyl-2-methyl-4-oxoindeno[1,2-b]pyrrolyl-3-glyoxal (VI). A solution of 1.5 g (0.005 mole) of compound Va in 35 ml of dioxane was added while stirring at 60-65°C to a solution of 0.6 g (0.005 mole) of SeO_2 in 5 ml of dioxane and 0.5 ml of water. The reaction mixture was boiled for 3.5 h, cooled, and filtered off from the selenium. The mother liquor was vacuum evaporated. The yield of VI was 0.7 g (43.7%).

Bisulfite Derivatives of 1-Phenyl-2-methyl-4-oxoindeno[1,2-b]pyrrolyl-3-glyoxal (I). A 1.75 ml portion of a 40% $NaHSO_3$ solution was added to a solution of 0.7 g of compound VI in 15 ml of 40% alcohol at 70°C. The reaction mixture was cooled to 20°C and kept at that temperature for 2 h. Then 30 ml of water was added, the mixture cooled, and the resultant precipitate was filtered off and dried. The yield of I was 0.81 g (91%).

EXPERIMENTAL (BIOLOGICAL)

The antiviral action of the bisulfite derivative of compound I was tested in a culture of chick embryo cells (CEC) against representatives of DNA viruses which included Herpes simplex Types I and II (strains 1-C, L_2, TRIC) as well as RNA viruses such as the A/FPV influenza (HavlN1) virus, vesicular stomatitis virus, and the Venezuelan equine encephalitis virus. The test substance was adminisstered at maximum tolerated (5 μg/ml) and minimum concentrations 1 h after the viral inoculation of a cell monolayer. The results were judged by the ability of compound I to prevent virus-induced cytopathology.

The therapeutic effect of compound I was studied on models of experimental mouse influenza pneumonia caused by virus A/Bethesda/63 (H_2N_2) and experimental rabbit herpes keratoconjunctivitis (Herpes simplex Type 1, strain Koptev) by the methods described earlier [3].

In addition, we studied the virus-inhibiting and virocidal action of compound I in experiments on 9-day old developing chick embryos inoculated with influenza A (PR-8)34 (HON1) and in in vitro contact experiments.

The results of our experiments indicated that compound I inhibits the reproduction of the Herpes simplex Types I and II viruses, although the compound is less active against the Type II virus. thus, at a concentration of 2.5 μg/ml compound I reduced the infectious titer of Type I Herpes by 1.5 to 2.0 log TCD_{50} and the titer of Type II by 0.75 log TCD_{50}.

Compound I in the form of a 0.5% ointment had a poor therapeutic effect in a model of experimental rabbit herpes keratoconjunctivitis in which case three daily applications of the ointment for 10 days somewhat reduced the gravity of the infectious process in the eye. Higher concentrations of the substance (1 and 2%) caused eye irritation, and a 0.25% ointment was inactive.

Compound I was found to have a pronounced virus-inhibiting and virocidal action against the influenza virus. In experiments on developing chick embryos (in ovo) the injection of compound I into the allantoic cavity at doses of from 0.25 to 1 mg 1 h before inoculation with 10 EID_{50} of the influenza virus prevented the infection of 80 to 100% of the chick embryos whereas 100% of the control group embryos became infected. In in vitro contact experiments a 10 μg/ml concentration of compound I reduced the virus titer by 2.0 log EID_{50}. However, compound I did not exhibit any therapeutic effect in a model of mouse influenza pneumonia when administered per os at maximum and minimum tolerated doses, nor did the compound inhibit influenza virus replication in a chick embryo culture.

With regard to the other RNA viruses we found that compound I at a concentration of 1.25 μg/ml suppressed vesicular stomatitis virus reproduction in a chick embryo culture. In comparison to the control it reduced its titer by 1.25-1.5 log TCD_{50}, and did not inhibit Venezuela equine encephalitis virus in that culture.

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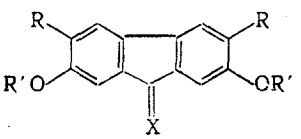
Interest in alkylated 2,7-dihydroxy-9-fluorenones has been aroused by their extremely wide spectrum of pharmacological activity, especially antiviral activity, resulting from the ability of these compounds to induce interferon in experimental animals [4, 6].

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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