N-(3-Carboxyphenyl)nicotinamide 1-Oxide Picrate (IIIb). To a solution of amide (Ib) (0.5 g, 0.002 mole) in DMF (20 ml) was added a solution of picric acid (0.25 g, 0.025 mole) in DMF (10 ml). The mixture was cooled and the resulting precipitate was separated.

Picrates (IIIc), (IVb), and (IVc) were prepared in the same way.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF BIS(DIETHYLAMINOETHYL) ESTERS OF 2-METHYL-3-CARBOXYBENZINDOL-5-YLOXYACETIC ACIDS

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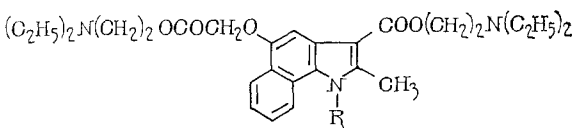
In conjunction with the interest in the preparation tilorone and its analogs, which have antiviral properties [1], we have synthesized and examined the antiviral activity of the hitherto unknown bis(diethylaminoethyl) esters of 2-methyl-3-carboxybenzindol-5-yloxyacetic acids (Ia)-(Ic).



Ia-c

R = a) CH_3, b) C_6H_5, c) o-$CH_3C_6H_4$

The starting compounds for the synthesis were 2-methyl-3-(ethoxycarbonyl)benzindol-5-yloxyacetic acids (IIa)-(IIc) [2], prepared from the 2-methyl-3-(ethoxycarbonyl)-5-hydroxybenzindoles [3]. Hydrolysis with alcoholic alkali converted (IIa)-(IIc) to the 2-methyl-3-carboxybenzindol-5-yloxyacetic acids (IIIa)-(IIIc).

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TABLE 1. 1-Substituted 1-Methyl-3-carboxybenzindol-5-yloxyacetic Acids (III), Their Bis(diethylaminoethyl) Esters (I), and the Ester Dicitrates (IV)

Compound	Yield, %	Melting point, °C	Found, %			Formula	Calculated, %			IR spectrum, cm⁻¹
			C	H	N		C	H	N	
Ia	57	—	67,71 67,88	8,35 8,17	8,38 8,59	$C_{29}H_{41}N_3O_5$	68,07 —	8,08 —	8,21 —	1750 (—CH_2CO—) 1690 (—CO—)
Ib	71	—	— —	— —	7,30 7,24	$C_{34}H_{43}N_3O_5$	— —	— —	7,32 —	1768 (—CH_2CO—) 1700 (—CO—)
Ic	70	—	70,64	7,84	—	$C_{35}H_{45}N_3O_5$	71,52	7,71	—	1760 (—CH_2CO—) 1690 (—CO—)
IIIa	92	253—4	64,88	5,10	4,53	$C_{17}H_{15}NO_5$	65,17	4,83	4,47	1730 (—CH_2CO—) 1635 (—CO—)
IIIb	78	241—242	70,34 70,42	4,59 4,85	3,60 3,68	$C_{22}H_{17}NO_5$	70,39 —	4,56 —	3,73 —	1715 (—CH_2CO—) 1625 (—CO—)
IIIc	88	207,5—208,5	70,73 70,46	5,25 4,93	3,86 —	$C_{23}H_{19}NO_5$	70,94 —	4,92 —	3,60 —	1699 (—CH_2CO—) 1625 (—CO—)
IVa	65	63—5	53,00 52,82	6,28 6,35	4,34 4,26	$C_{29}H_{41}N_3O_5 \cdot 2C_6H_8O_7 \cdot 2H_2O$	52,84	6,60	4,51	—
IVb	94	75—7	57,39 57,00	6,70 6,52	4,59 4,76	$C_{34}H_{43}N_3O_5 \cdot 2C_6H_8O_7 \cdot {}^1/_2H_2O$	57,14	6,25	4,35	—
IVc	85	68—70	55,76	6,70	5,04	$C_{35}H_{45}N_3O_5 \cdot 2C_6H_8O_7 \cdot 2H_2O$	56,00	6,50	4,16	—

Note. Compounds (Ia)-(Ic) are oils; (IIIa)-(IIIc) melt with decomposition; (IIIa) was crystallized from alcohol, (IIIb) and (IIIc) from methanol with added DMF, and (IVa)-(IVc) from a mixture of isopropanol, acetone, and diethyl ether.

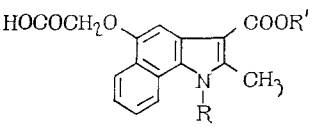
TABLE 2. Virucidal Effect of Compounds (IVa)-(IVc)

Compound	Concentration of the compound that completely neutralizes the infective dose of the virus, g/ml		
	100 ID_{100}	10 ID_{100}	1 ID_{100}
IVa	1000	1000	1000
IVb	1000	1000-1000	1000-100
	inactive		
IVc	1000	1000	100

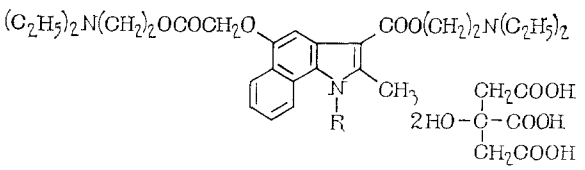
TABLE 3

Compound	Dose showing weak inhibition of growth of the virus after infection by 1 ID_{100}, mg per embryo
IVa	0.5 and 0.25
IVb	2 and 1
IVc	no detectable inhibitory effect

II a: $R = CH_3$, $R' = C_2H_5$;
b: $R = C_6H_5$, $R' = C_2H_5$;
c: $R = 2\text{-}CH_3C_6H_4$, $R' = C_2H_5$.
III a: $R = CH_3$, $R' = H$;
b: $R = C_6H_5$, $R' = H$;
c: $R = 2\text{-}CH_3C_6H_4$, $R' = H$



II, III



Reaction with sodium ethanolate gave the disodium salts, which were converted to the bis(dialkylaminoalkyl) esters (Ia)-(Ic) by reaction with β-chloroethyldiethylamine [4]. We used the water-soluble dicitrates (IVa)-(IVc) in the biological studies.

Compounds (Ia)-(Ic), (IIa)-(IIc), and (IIIa)-(IIIc) have typical IR spectra with characteristic carbonyl bands. The 3-carbonyl group of indole appears at lower frequency than the unconjugated carbonyl group.

EXPERIMENTAL CHEMISTRY*

The IR spectra of the synthetic compounds were recorded on Perkin-Elmer and UR-10 instruments. Melting points, yields, and IR spectra are summarized in Tables 1 and 2.

1,2-Dimethyl-3-carboxybenzindol-5-yloxyacetic acid (IIIa). Compound (IIa) (0.5 g, 1.4646 mmole) was refluxed with 23.5% potassium hydroxide solution (16.0 ml) in 95% ethyl alcohol for 40 min with stirring. The reaction mixture was left at room temperature for 1 h to cool. The precipitated dipotassium salt (1.3 g) was then filtered off and dissolved in water (16 ml). The solution was acidified with 2N hydrochloric acid until acid to Congo Red. The resulting precipitate of acid (IIIa) was filtered off, washed on the filter with a small amount of cold water, and dried.

*R. A. Zinov'eva assisted with the experimental work.

Compounds (IIIb) and (IIIc) were prepared in the same way (Table 1).

Bis(diethylaminoethyl) Ester of 1,2-Dimethyl-3-carboxybenzindol-5-yloxyacetic Acid (Ia). To an alcoholic solution of sodium ethanolate, prepared from sodium metal (0.28 g, 12.2 mmole) and absolute ethyl alcohol (4.8 ml, 3.81 g, 82.6 mmole), was added compound (IIIa) (2.00 g, 6.5 mmole). The reaction mixture was refluxed with vigorous stirring. The solvent was then stripped off under vacuum, benzene (15-20 ml) was added to the residue, and the solvent was again stripped under vacuum. To the resulting powdery solid, the disodium salt of compound (IIIa), was added β-chloroethyldiethylamine (2.24 g, 16.5 mmole) and the mixture was heated at 130°C for 1 h under reflux with vigorous stirring. The reaction mixture was cooled and treated with hot water (12-13 ml). After removal of the aqueous layer the residual oil was extracted with ether. The ethereal extract was dried over magnesium sulfate and the ether was stripped off. The residue was evaporated at 40°C under vacuum and then, to remove traces of the solvent, at 40°C under 1-2 mm Hg for 30 min. The yield of compound (Ia) was 1.85 g (3.6 mmole).

Compounds (Ib) and (Ic) were prepared in the same way (Table 1).

Dicitrate Dihydrate of the Bis(diethylaminoethyl) Ester of 1,2-Dimethyl-3-carboxybenzindol-5-yloxyacetic Acid (IVa). Base (Ia) (1.40 g, 2.7 mmole) was dissolved in isopropyl alcohol (13 ml) and acetone (13 ml). Anhydrous citric acid (1.38 g, 6.6 mmole) was dissolved in the minimum quantity of isopropyl alcohol. The two solutions were then mixed. The mixture was cooled and absolute diethyl ether (13 ml) was added. Rubbing with a glass rod initiated the formation of a crystalline precipitate, which was filtered off, washed on the filter with absolute diethyl ether, and dried. The yield of compound (IVa) was 1.65 g (1.8 mmole).

Compounds (IVb) and (IVc) were prepared in the same way (Table 1).

EXPERIMENTAL BIOLOGY

We examined the antiviral activity of compounds (IIa)-(IIc), (IIIa)-(IIIc), and (IVa)-(IVc) against two influenza viruses, A[PR]8(HON1) and A[Bethesda]63($H2N_2$).

The virucidal activity was assayed by mixing specific volumes of solutions or suspensions of the compuonds of various concentrations with various quantities of the infective doses (ID_{100}) of the virus. The mixtures were kept at 14°C for 1 h and then 0.2 ml was injected into the allantoic cavity of nine-day old chick embryos (Table 2).

The potency was assessed from the hemagglutination reaction. The absence of a positive reaction corresponded to virucidal activity. To evaluate the virustatic activity the compounds were injected in the maximum tolerable and lower doses into the allantoic sac of chick embryos 1 h before infection. The virustatic activity was evaluated from comparison of the hemagglutination titers of the influenza virus in the embryos into which the test compounds had been injected with those in the control embryos (physiological solution only).

We also assayed the chemotherapeutic activity of the compounds against influenzal pneumonia in mice. The mice were injected with the test compound in the maximum tolerable and lower doses 1 h before intranasal infection with influenza virus. The animals also received the same dose of the compound once a day for the next four days. The chemotherapeutic activity was evaluated from comparison of the survival rates in the experimental and control groups. A detailed description of our methods has appeared earlier [5].

We found that only compounds (IVa)-(IVc) have antiviral activity.

Table 3 summarizes the inhibitory effects of compounds (IVa)-(IVc) on the growth of influenza virus A[PR]8(HON1) in chick embryos.

Compounds (IVa)-(IVc) gave no therapeutic effect when administered to mice with influenzal pneumonia caused by A[Bethesda]63($H2N_2$) virus once a day for five days in the maximum tolerable and lower doses.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SULFONYL DERIVATIVES OF 1,2-DIHYDROISOQUINOLINES AND 1,2-DIHYDROQUINOLINES

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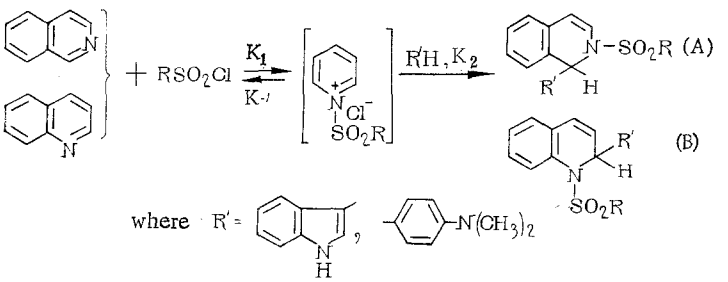
Though sulfonyl derivatives of various heterocycles are used as chemotherapeutic agents [1], such preparations are unknown in the quinoline, isoquinoline, and indole series. Nonetheless certain isoquinoline, quinoline, and indole derivatives have physiological, including antibacterial, activity [1].

We decided to synthesize and examine the properties of some new sulfonyl heteroaryl derivatives incorporating these heterocyclic fragments. We prepared these derivatives of (3-indolyl)-1,2-dihydroisoquinoline (A) and -quinoline (B) by direct heteroarylation of indole and dimethylaniline, by simultaneous reaction with the N-heteroaromatic compound (isoquinoline, quinoline) and a sulfonyl chloride [2]. The reaction apparently involves the intermediacy of the N-heteroaromatic arylsulfonyl salts:



Like the heteroarylation reactions using carboxylic acid chlorides [3] and phosphorus acid chlorides [4], we carried out the reaction of the sulfonyl chloride, isoquinoline (quinoline), and indole (dimethylaniline) in the ratio 1:2:1 in absolute benzene at room temperature over a period of 6-12 h.

N-Sulfonylisoquinolinium salts are most reactive in this reaction; at 18-20°C they easily heteroarylate indoles and dimethylanilene to form compounds of types A and B in high yield. Quinoline is less reactive, even on increase in temperature to 50-80°C; in this case side oxidation reactions develop and the heteroarylation products are accompanied by oxidation products of indole and dimethylaniline. We isolated a dye, Crystal Violet, from the reaction with dimethylaniline at higher temperature.

Aliphatic sulfonyl chlorides in the presence of reasonably strong bases are known to react by the elimination—addition mechanism via sulfene intermediates:

$$RCH_2SO_2Cl + NH(D) \xrightarrow[-B\cdot HCl]{B,\ K_1} [RCH{=}SO_2] + NH(D) \xrightarrow{K_2} \underset{(RCHDSO_2N),}{RCH_2SO_2N}$$

which initiate various side reactions [5].

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