SYNTHESIS AND BIOLOGICAL ACTIVITY OF THIENO[3,2-b]INDOLE DERIVATIVES

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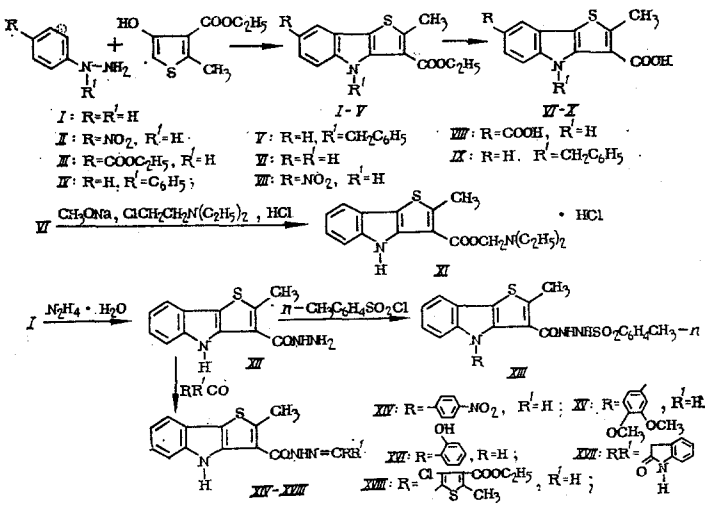
The search for antiviral agents extends to various classes of heterocyclic compounds, among derivatives of thiophene [1], carbazole [2-4], and pyrido- and pyrimidoindoles [5, 6]. Derivatives of thienoindoles are therefore interesting as condensed heterocycles including the thiophene ring, and as isoesters of carbazoles.

We synthesized and studied the antiviral activity of thieno[3,2-b]indole derivatives (I-V). The first derivative of this series, 2-methyl-3-carbethoxythieno[3,2-b]indole (I), was previously obtained by condensation of 2-methyl-3-carbethoxy-4-hydroxythiophene with phenylhydrazine by the Fischer method [7]. We extended the field of application of this reaction and synthesized thieno[3,2-b]indoles (II-V) by the reaction of phenylhydrazine derivatives with 2-methyl-3-carbethoxy-4-hydroxythiophene. The corresponding carboxylic acids (VI-X) were obtained from compounds (I-V), and the diethylaminoethyl ester (XI) from (VI). By the action of hydrazine hydrate on compound I, the hydrazide (XII) is formed, which with p-toluenesulfonyl chloride gives tosylhydrazide (XIII), and with ketones, hydrazones (XIV-XVIII). Hydrazides XII-XVIII are interesting since their analogs have antitubercular and antimicrobial activity [8-10].

The structure of the compounds obtained was confirmed by IR spectra. In the IR spectra of I-V, stretching vibration bands of the carbonyl group are observed in the 1670-1690 cm^{-1} region, as well as a band at 3400 cm^{-1} which is characteristic of the NH group and disappears in N-substituted derivatives, and absorption bands in the 790-810 cm^{-1} region characteristic of the thiophene ring. In the IR spectrum of compound X, the stretching vibration band of the carbonyl group is shifted to 1660 cm^{-1}.



EXPERIMENTAL CHEMICAL SECTION

The IR spectra of the compounds obtained were run on the UR-10 spectrophotometer (GDR) in a paste with mineral oil. Data on the compounds obtained are listed in Table 1.

2-Methyl-3-carbethoxy-7-nitrothieno[3,2-b]indole (II). The reaction mixture, consisting of 0.05 mole of 2-methyl-3-carbethoxy-4-hydroxythiophene, 0.05 mole of p-nitrophenylhydrazine,

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TABLE 1. Compounds Studied and Their Properties*

Compound	Yield, %	mp, deg C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
II	37	229—9,5	55,13	3,84	9,16	10,30	$C_{14}H_{12}N_2O_4S$	55,25	3,97	9,21	10,54
III	60	164—5	61,88	5,34	4,16	9,87	$C_{17}H_{17}NO_4S$	61,61	5,17	4,22	9,68
IV	51	114—5	71,17	4,84	4,04	10,03	$C_{20}H_{17}NO_2S$	71,62	5,11	4,18	9,56
V	19	82—3	72,63	5,40	3,94	9,19	$C_{21}H_{19}NO_2S$	72,18	5,48	4,01	9,18
VI	95	280	62,12	3,75	6,24	13,75	$C_{12}H_9NO_2S$	62,62	3,92	6,06	13,86
VII	80	308—10	52,16	3,25	9,99	11,08	$C_{12}H_8N_2O_4S$	52,16	2,92	10,14	11,61
VIII	90	314—6	56,30	3,40	5,11	11,32	$C_{13}H_{19}NO_4S$	56,72	3,29	5,09	11,65
IX	95	261—3	71,06	4,63	4,20	9,88	$C_{19}H_{15}NO_2S$	71,00	4,70	4,36	9,98
X	85	218—20	69,97	4,34	4,45	10,13	$C_{18}H_{13}NO_2S$	70,34	4,26	4,56	10,43
XI	58	213—4	59,27	6,42	8,04	8,47	$C_{18}H_{23}N_2O_2SCl$	58,92	6,32	7,63	8,74
XII	84	249—51	59,15	4,71	16,98	13,25	$C_{12}H_{11}N_3OS$	58,76	4,52	17,13	13,07
XIII	76	244—5	57,43	4,12	10,86	15,94	$C_{19}H_{17}N_3O_3S_2$	57,12	4,29	10,52	16,05
XIV	87	272—4	60,79	3,91	14,83	8,64	$C_{19}H_{14}N_4O_2S$	60,31	3,73	14,81	8,47
XV	43	261—3	63,99	5,27	10,27	8,07	$C_{21}H_{19}N_3O_3S$	64,10	4,87	10,68	8,15
XVI	80	256—8	64,40	4,88	10,92	8,40	$C_{19}H_{15}N_3O_2S$	64,10	4,87	10,68	8,15
XVII	80	297—9	64,11	3,93	15,01	8,27	$C_{20}H_{14}N_4O_2S$	64,16	3,77	14,99	8,56
XVIII	94	258—60	55,25	4,02	9,12	13,83	$C_{21}H_{18}N_3O_3S_2Cl$	54,83	3,94	9,14	13,94

*Compounds II-VI, XVIII were recyrstallized from a methanol–dioxane (1:1) mixture; VII, VIII from dimethylformamide; IX, X, XII-XIV, XVI from dioxane (XVI was crystallized from 0.5 mole of dioxane); XV, XVII from a dioxane–dimethylformamide (1:1) mixture; XI from a methanol–acetone (1:1) mixture. For XI, Cl, %: Found 9.81, calculated 9.66; for XVIII, Cl, %: Found 7.74, calculated 7.71.

0.05 mole of concentrated hydrochloric acid, and 120 ml of acetic acid, is heated on a water bath for 2 h and then cooled and poured onto ice. The precipitate is filtered.

2-Methyl-3,7-dicarbethoxythieno[3,2-b]indole (III). The reaction mixture, consisting of 0.01 mole of 2-methyl-3-carbethoxy-4-hydroxythiophene, 0.01 mole of p-carbethoxyphenylhydrazine, and 30 ml of a 50% aqueous solution of acetic acid, is heated on a water bath for 1 h, then cooled, and the precipitate filtered. Compounds VI, V are obtained similarly.

2-Methyl-3-carbethoxythieno[3,2-b]indole (VI). A solution of 0.08 mole of sodium hydroxide in 100 ml of 96% alcohol is added to a solution of 0.04 mole of I in 200 ml of dioxane. The reaction mixture is boiled for 3 h, cooled, poured into water, and acidified with dilute (1:1) hydrochloric acid. The precipitate is filtered. Compounds VII-X are obtained similarly.

Diethylaminoethyl Ester of 2-methyl-3-carbethoxythieno[3,2-b]indole Hydrochloride (XI). A 9.7-ml portion of a solution of sodium methoxide (prepared from 92 g of sodium in 920 ml of alcohol) is added to a suspension of 0.042 mole of acid VI in dioxane. The solvent is removed, 0.05 mole of diethylaminoethyl chloride is added to the residue, and the mixture is heated at 140°C for 1 h. The reaction mixture is poured into water and extracted with ether, and the extract is dried over calcined magnesium sulfate. Hydrochloride XI is separated by the action of an ethereal solution of hydrogen chloride.

Hydrazide of 2-methyl-3-carbethoxythieno[3,2-b]indole (XII). The reaction mixture, consisting of 0.03 mole of I and 50 ml of hydrazine hydrate, is heated for 1.5 h, then cooled, and the precipitate filtered.

Tosylhydrazide of 2-methyl-3-carbethoxythieno[3,2-b]indole (XIII). A 0.025-mole portion of p-toluenesulfonyl chloride is added to a solution of 0.02 mole of hydrazide XII in 50 ml of pyridine, and the mixture is heated at 100°C for 2 h, then cooled and poured into water containing hydrochloric acid.

(2-Methylthieno[3,2-b]-3-indolyl)-hdrazone of p-nitrobenzaldehyde (XIV). A 0.016-mole portion of p-nitrobenzaldehyde is added to a solution of 0.016 mole of hydrazide XII in 100 ml of a dioxane–ethanol (1:1) mixture. The reaction mixture is boiled for 2 h, cooled, and the precipitate filtered. Compounds XV-XVIII are obtained similarly.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The antiviral activity of the synthesized compounds II-XVIII towards the influenza virus A strain A/PR8/34(HON1) was studied. The antiviral action of the compounds on the influenza virus was determined by mixing given volumes of their solutions or suspensions of different concentrations with different amounts (1-100) of embryonic infection doses (EID_{100}) of the virus. The mixtures were held for 1 h at 14°C, and then 0.2-ml portions of the mixture were introduced into the allantoid pouch of 9-day old chicken embryos. After 48 h of incubation at 37°C in a thermostat, the titer of the influenza virus was determined in the allantoid fluid by means of a hemagglutination reaction. The activity of the compounds was expressed as the amount of neutralized EID_{100} of the influenza virus. Of the compounds studied, compound XI had the most pronounced antiviral action: In a concentration of 1000 μg/ml it inactivated 10 EID_{100}, and at a concentration of 100 μg/ml, 1 EID_{100} of the influenza virus.

The antimicrobial activity of compounds II-XVIII was studied *in vitro* by the method of double serial dilutions in a liquid culture medium [11] with respect to four types of Gram-positive, five types of Gram-negative microorganisms, and five types of pathogenic fungi. Only compound XI exhibited a slight activity towards Gram-positive bacteria.

The tuberculostatic activity of compounds II-XVIII was studied *in vitro* by the method of serial dilutions on Sutton's medium, starting from a 1:1000 dilution. The human type mycobacteria (*M. tuberculosis* H37RV) and the conditionally pathogenic mycobacteria (*M. fortuitum* ATCC-607) were used as the test cultures. Compound IX had a medium activity towards *M. tuberculosis* H37RV (minimal tuberculostatic concentration was 8 μg/ml).

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PYRROLOINDOLE AND BISINDOLE QUATERNARY AMMONIUM SALTS

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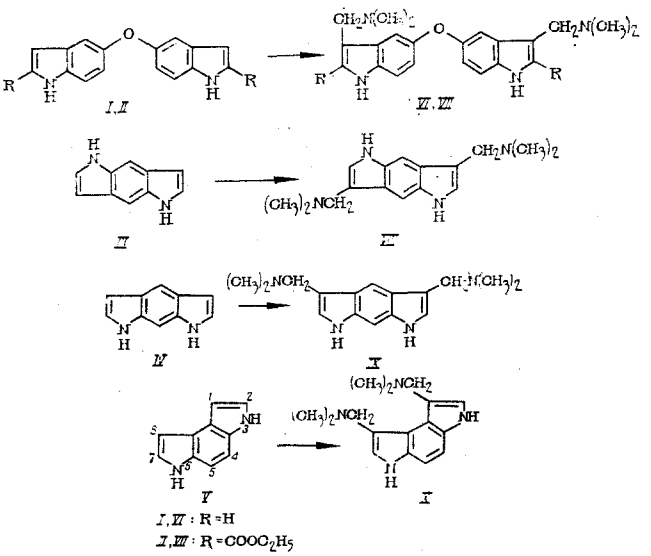
We have shown in a previous communication [1] that certain bisindole quaternary ammonium salts possess curariform activity. In continuation of these studies, we have synthesized the bisgramines (VI-X) by reacting the bis-(5-indolyl) oxide (I), its 2,2'-diethoxycarbonyl derivative (II)[2], and the pyrroloindoles (III-V) [3] with the Mannich reagent.

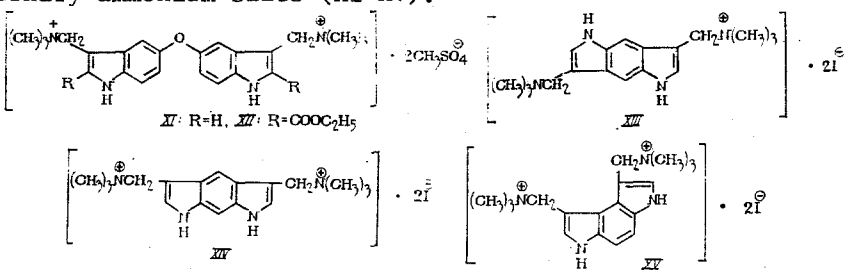


I, II: R = H
I, III: R = $COOC_2H_5$

3,3'-Di(dimethylaminomethyl)-bis-(5-indolyl) oxide (VI) was found to be unstable, and it was therefore converted without isolation into the dimethosulfate (XI).

The structures of the compounds obtained were confirmed by IR, UV, PMR (Table 1), and mass spectroscopy.

In order to study their curariform activities, compounds (VI-X) were converted into their water-soluble quaternary ammonium salts (XI-XV).



XI: R = H, XII: R = $COOC_2H_5$

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