being 12.5-25 μg/ml and against some of the Gram-negative microorganisms 12.5-50 μg/ml, including S. typhosa, which is resistant to many chemotherapeutants.

Introduction of a methyl group into the 2-position has little effect on the antimicrobial activity of these compounds, except for those compounds which contain a carbazole moiety (IIf and IIo), and (IIc) and (IIℓ), in which the presence of a methyl group in the imidazole ring increases their activity. For instance, although the MIC of (IIf) is greater than 200 μg/ml, that of (IIo) is 25-100 μg/ml against both Gram-positive and Gram-negative bacteria; the MIC of (IIc) is greater than 200 μg/ml against all the Gram-negative test cultures, while that of (IIℓ) was 50-100 μg/ml, except for Proteus.

Compounds with the carboline structure (IIg) and (IIo) were inactive against these test organisms.

This investigation has thus shown that a search for antimicrobial compounds amongst these types of indole derivatives could be fruitful.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 3H-[1,4]DIAZEPINO-[2,3-g]INDOLES

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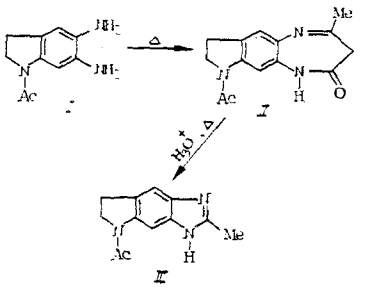
Hypotensives, antispasmodics, tranquilizers, and antitumor agents have been found among the pyrrolo- and indolobenzdiazepines [5, 7-9]. The diazepine ring in these compounds is directly coupled to the pyrrole ring. In an earlier studies [1, 6] we reacted 1-acetyl-5,6-diaminoindoline (I) with acetoacetic ester to obtain tetrahydrodiazepino[2,3-f] indole (II) which appeared to be a potential pharmacologically active substance within whose structure the 1,5-diazepine and indole rings are ortho-condensed along the benzene ring.



As a continuation of our search for biologically active compounds among condensed heterocyclic systems [2, 3] we obtained derivatives of a new heterocyclic system, 3H-[1,4]diazepino [2,3-g]indole (VI), and examined their pharmacological properties.

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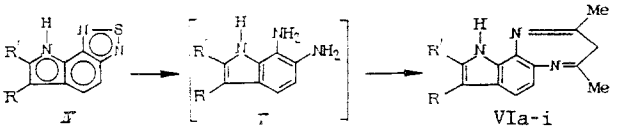
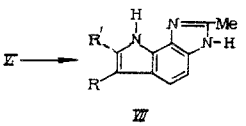


Everywhere a: R = H, R′ = Me; b: R = R′ = Me; c: R = Et, R′ = Me; d: R = H, R′ = Ph; e: R = Me, R′ = Ph; f: R + R¹ = $(CH_2)_3$; g: R + R′ = $(CH_2)_4$; h: R + R′ = $CH_2NMe_3CH_2CH_2$; i: R = H, R′ = COOEt

The starting compounds [1,2,5]thiadiazolo[3,4-g]indoles (IV) were obtained by the previously described method [3] from derivatives of 4-hydrazino-2,1,3-benzothiadiazole employing the Fischer indole synthesis.

The target compounds VIa-i were obtained by intermittently heating the IV thiadiazole indoles with zinc and HCl in an organic solvent followed by treating the resultant unstable 6,7-diaminoindoles (V) with acetyl acetone without removing them from the reaction mixture. The 2,4-disubstituted 1,5-benzdiazepines are known to be comparatively stable compounds. However, when exposed to aqueous acid solutions, the seven-membered ring is split and upon heating, recyclization takes place with subsequent aromatization and the formation of benzimidazole derivatives [10]. In a similar fashion, the corresponding 2-methylimidazo[2,3-f]-indole (III) is formed [1, 6] when diazepine indole II is subjected to acid hydrolysis. The TLC analysis of the diazepine indole VI synthesis also indicated the formation of the previously described [2] 2-methyl-1(3)H-imidazo[4,5-g]indoles (VII) which were probably formed as a result of the acid hydrolysis of compounds VI during the indicated reaction.



Actually, by heating the diazepine indoles VIb, e, and f with 10% H_2SO_4 we obtained a 11-30% yield of the known compounds 2,6,7-trimethyl-2,6-dimethyl-7-phenyl- and 2-methyl-6,7-cyclopenteno-1(3)H-imidazo[4,5-g]indoles VIIb, e, f. On the one hand this confirmed our hypothesis about the formation of benzimidazole derivatives as secondary products of the reaction between the V diaminoindoles and acetyl acetone, and on the other hand served as additional proof of the structure of compounds VIb, e, and f.

In solutions the synthesized 3H-[1,4]diazepino[2,3-g]indoles VIa-i exist in the form of diimines. Their structure was confirmed by element analysis and spectral characteristics. Thus, the IR spectra (KBr, $CHCl_3$) of all the VI compounds had intensive absorption bands for the NH-group of the indole fragment in the 3200-3500 cm^{-1} region. The PMR spectra (DMSO-D_6) in the 6.7-7.9 ppm region exhibited ortho-interacting aromatic proton signals for H_6 and H_7 in the form of doublets (SSSC 8-9 Hz), methylene group singlets in position 3 at 2.7-2.8 ppm, and broadened singlets at 10.6-11.5 ppm (NH). The UV spectra (C_2H_5OH) of the VI compounds were similar in nature to the spectrum of 2,4-dimethyl-1,5-benzodiazepine which also exists in the form of a diimine [11].

The derivatives of 3H-[1,4]diazepino[2,3-g]indole VIa-i are crystalline substances with a mp over 150°C, only very slightly soluble in water and hexane, soluble in chloroform (in the cold), acetone, and alcohols. They are stable when stored in the solid state. In solutions in the presence of moisture and atmospheric oxygen they decompose into the corresponding imidazo indoles VII and the oxidation products of diaminoindoles V.

Table 1 presents the physico-chemical characteristics of the synthesized compounds VIa-i. The pharmacological test results are given below.

EXPERIMENTAL (CHEMICAL)

UV-spectra were recorded on a Specord M-40 (GDR) spectrophotometer. IR-spectra were recorded on a UR-20 (GDR) spectrophotometer, and the PMR spectra were recorded on a Tesla BS-497 (Czechoslovakia) spectrometer, working frequency 100 MHz; internal standard was HMDS. Reaction progress and resultant compound purity controlled by TLC (Silufol UV-254, 2:1 acetone-benzene).

TABLE 1. Characteristics of 2,4-Dimethyl-3H-[1,4]diazepino[2,3-g]indoles VIa-i

Compound	mp, °C (aq. acetone)	Found, %			Empirical formula	Calculated, %			Yield, %	IR spectrum, ν_{max} cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm ($I_{(6,7)}$ 8-9 Hz)					
		C	H	N		C	H	N		NH		$H_{(3)}$	$H_{(6)}$	$H_{(7)}$	$H_{(8)}$	$H_{(9)}$	$H_{(10)}$
VIa	172—(Benzene)	74,6	6,5	18,7	$C_{11}H_{11}N_3$	74,6	6,7	18,7	82,8	3440	222 (4,32), 2,84 (4,23)	2,77 s (2H, CH_2)	6,80 d (H)	7,15 d (H)	6,06 s (H)	2,21 s (3H, Me)	10,87 s (NH)
VIb	205 (flash point)	75,2	6,8	17,7	$C_{12}H_{13}N_3$	75,3	7,2	17,6	81,5	3440	222 (4,41), 289 (4,33)	2,74 s (2H, CH_2)	6,79 d (H)	7,13 d (H)	2,07 s (3H, Me)	2,19 s (3H, Me)	10,60 s (NH)
VIc	212 (flash point)	76,2	8,1	17,0	$C_{16}H_{19}N_3$	75,8	7,6	16,6	78,9	3445	222 (4,41), 289 (4,32)	2,75 s (2H, CH_2)	6,81 d (H)	7,19 d (H)	1,10 t (3H, Me) 2,52 q (2H, CH_2)	2,22 s (3H, Me)	10,60 s (NH)
VId	248 (flash point)	79,8	6,2	15,1	$C_{16}H_{17}N_3$	79,4	6,0	14,6	59,2	3460	222 (4,26), 246 (4,20) 300 (4,41), 329 (4,41)	2,81 s (2H, CH_2)	6,88 d (H)	7,91 d (H)	6,81 s (H)	7,30 m (5H, Ph)	11,28 s (NH)
VIe	207—208	79,2	6,1	13,9	$C_{20}H_{19}N_3$	79,7	6,4	13,9	64,4	3470	222 (4,32), 248 (4,20) 299 (4,42), 325 (4,32)	2,79 s (2H, CH_2)	6,91 d (H)	7,80 d (H)	2,24 s (3H, Me)	7,45 m (5H, Ph)	11,0 s (NH)
VIf	225 (flash point)	76,3	7,3	16,7	$C_{13}H_{13}N_3$	76,5	6,8	16,7	71,7	3480	222 (4,38), 289 (4,31)	2,74 s (2H, CH_2)	6,78 d (H)	7,08 d (H)	2,52—2,86 m (2H, CH_2)	(2H, CH_2)	
VIg	236 (flash point)	76,9	7,7	15,7	$C_{17}H_{15}N_3$	77,0	7,2	15,8	81,1	3450	222 (4,39), 289 (4,30)	2,76 s (2H, CH_2)	6,80 d (H)	7,12 d (H)	2,60 s (2H, CH_2)	1,74 (2H, CH_2)	s (2H, CH_2)
VIh	195—8	72,6	7,4	19,5	$C_{17}H_{20}N_4$	72,8	7,2	20,0	78,6	3200	222 (4,35), 281 (4,32)	2,75 s (2H, CH_2)	6,82 d (H)	7,08 d (H)	3,42 s (2H, CH_2)	2,18 s (3H, Me)	2,70 s (2H, CH_2)
VIi	(Benzene-hexane) 153—6	67,7	6,1	14,9	$C_{16}H_{17}N_3O_2$	67,8	6,1	14,8	61,8	3140 1719 (CO)	233 (4,25), 260 (4,10) 291 (4,40), 313 (4,32)	2,80 s (2H, CH_2)	6,96 d (H)	7,40 d (H)	7,13 s (H)	1,21 t (3H, Me) 4,22 q (2H, CH_2)	11,50 s (NH)

Note. IR spectra of VIe, f recorded in chloroform. The PMR spectra of compounds VIa-i have methyl group proton singlets on atoms $C_{(2)}$ and $C_{(4)}$ in the 2.25-2.33 ppm region as well as the following proton signals: 10.74 s (11-NH) in the spectrum of compound VIf; 2.60 s (2H, 11-CH_2), 10.58 s (12-NH) in the spectrum of VIg; 2.66 s (2H, 11-CH_2), 10.76 s (12-NH) in the spectrum of VIh.

2,4,8,9-Tetramethyl-3H-[1,4]diazepino[2,3-g]indole (VIb). A 13 g (0.2 mole) portion of zinc powder and 20 ml of conc. HCl (in 2-3 ml portions) were added to a boiling solution of 4.07 g (0.02 mole) of 6,7-dimethyl[1,2,5]thiadiazolo[3,4-g]indole IVb [3] in 150 ml of isopropanol. The mixture was boiled in a reflux condenser for 10 min and then filtered. A 2 ml (0.02 mole) portion of acetyl acetone was then added to the resultant solution after it was cooled to room temperature, allowed to stand for 30 min, and then left overnight. The resultant precipitate was filtered off, suspended in 100 ml of water, and brought up to pH 9.0-10.0 with an aq. ammonia solution. The mixture was then stirred for 30 min and filtered. The precipitate was washed with water and air dried. The yield of compound VIb was 3.9 g (81.5%). The same procedure was used to obtain 2,4-dimethyl-9-phenyl-3H-[1,4]diazepino-[2,3-g]indole (VId) and 2,4,8-trimethyl-9-phenyl-3H-[1,4]diazepino[2,3-g]indole (VIe).

2,4-Dimethyl-8,9-cyclopentene-3H-[1,4]diazepine[2,3-g]indole (VIf). A 6.5 g (0.1 mole) portion of zinc powder and 20 ml of diluted (1:1) HCl (in 2-3 ml portions) were added to a boiling solution of 2.15 g (0.01 mole) of 6,7-cyclopentenel[1,2,5]thiadiazole[3,4-g]indole IV [3] in 85 ml of alcohol. The reaction mixture was boiled with a reflux condenser for 10 min and filtered. A 1 ml (0.01 mole) portion of acetyl acetone was then added to the mother liquor after it was cooled to room temperature. The solution was allowed to stand for 30 min and placed in a refrigerator for 2 to 3 h. The cooled reaction mass was decanted into a mixture of 500 ml of water and 50 ml of conc. aq. ammonia, stirred for 20 min, and filtered. The precipitate was washed with water and air dried. The yield of compound VIf was 1.8 g (71.7%). A similar procedure was used to obtain 2,4,9-trimethyl-3H-[1,4]diazepine[2,3-g]indole (VIa), 2,4,9-trimethyl-8-ethyl-3H-[1,4]diazepine[2,3-g]indole (VIc), 2,4-dimethyl-8,9,10,11-tetrahydro-3H-[1,4]diazepine[2,3-a]carbazole (VIg), and ethyl 2,4-dimethyl-3H-[1,4]diazepine[2,3-g]indole-9-carbonate (VIi).

2,4,9-Trimethyl-8,9,10,11-tetrahydro-3H-pyrido-[4,3-b][1,4] Diazepine [2,3-g]Indole (VIh). A 20 g (0.3 mole) portion of zinc powder was added in 1-2 g portions to a boiling solution of 4.89 g (0.02 mole) of 7-methyl-6,7,8,9-tetrahydropyrido[4,3-b][1,2,5]thiadiazole[3,4-g]indole IVh [3] in a mixture of 300 ml of water, 100 ml of alcohol, and 25 ml of conc. HCl. The mixture was boiled for 10-15 min and filtered. A 2 ml (0.02 mole) portion of acetyl acetone was added to the hot filtrate which was then air cooled for 30 min after which it was placed in a refrigerator for 2-3 h. The cooled reaction mixture was brought up to pH 9-10 (75-100 ml) with a 25% aq. ammonia solution. The resultant solution was extracted with 150 ml (3 × 50 ml) of chloroform and the organic phase was washed with water. The solvent was distilled off leaving a compound VIh yield of 4.4 g (78.6%).

2,6-Trimethyl-1(3)H-imidazo[4,5-g]indole (VIIb). A 2.39 g portion of diazepine indole VIb and 40 ml of 10% H_2SO_4 was boiled with a reflux condenser for 2 h, then cooled to 0-5°C, and neutralized with ammonia. The resultant precipitate was washed with water and air dried. The resultant 1.7 g of a dark brown substance was extracted with 60 ml of boiling acetone. The acetone extract was treated with 0.1 g of activated charcoal and filtered through an aluminum oxide (3 × 3 cm) layer (2nd degree activity). The mother liquor was evaporated to dryness, and the residue was crystallized from 80% ethanol. The yield of compound VIIIb was 0.55 g or 27.6%, flash point was 230°C [2]. A similar procedure was used to obtain compound VIIe at a yield of 11.5%, mp 256-258°C (with decomposition from alcohol), and compound VIIf at a yield of 31.1%, mp 260-263°C (from alcohol).

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological activity of compounds VIa-i was tested on white mice weighing 18-21 g and rats weighing 150-200 g with the aid of tests employed to evaluate psychotropic agents. The effect on rectal temperature of the mice was measured by comparing the test temperature to the initial body temperature for which purpose an electric TPEM-1 thermometer was used. The sedative effect of the compounds was assayed by the compounds' ability to prolong sleep induced by chloral hydrate (300 mg/kg ip). Muscle coordination effects were measured by the "rotating rod" test [14]. Corazole [15] and electric shock tremor [17] models were used to evaluate the antispasmodic activity. The analgesic activity of the compound was assayed by measuring the pain sensitivity threshold upon electrical stimulation [12]. In addition, compound VIc was tested for its ability to induce catalepsy, the ability to block the defensive reflex [13], as well as its antagonism against the effects of apomorphine [16].

Acute toxicity was measured in the mice upon the compounds' ip injection. The LD_{50} was computed by the method in [4].

The experimental results showed that compounds VIa-c, f, and g, at 1/5 of the LD_{50} dose exhibited hypothermal activity. That effect was manifested to the highest degree by compound VIc, f, and g which maintained that effect even when the dose was lowered to 50 mg/kg ($^1/_{20}$ LD_{50}). Compounds VId, e, and h were less active, but compound VIi did not have any effect on the mice body temperature.

All of the examined compounds, with the exception of VId, h, and i, prolonged the duration of chloral hydrate sleep. That ability was retained in compounds VIb, c, f, and g when the dose was lowered to 50-100 mg/kg ($^1/_{20}$-$^1/_{10}$ LD_{50}).

Muscular coordination was disrupted by compounds VIa-c, f, and g. The greatest myorelaxant effect was exhibited by compounds VIc and f which at a dose of 50 mg/kg impaired the animals' ability to hold on to the rotating piston.

Compound VIe at a dose of 200 mg/kg exhibited antispasmodic action in the corazole spasm test.

None of the examined compounds exhibited any analgesic effect. Cataleptic action was manifested by compound VIc (50 mg/kg). That effect increased gradually and reached a maximum in 2 h. Compound VIf exhibited a weaker cataleptic action. Both compounds lost their cataleptic action when the dose was reduced. Neither compound exhibited any significant effect on the conditional defensive reflex when administered at a dose of 10 mg/kg.

The study of the influence that compounds VIc and f had on apomorphine effects showed that at a dose of 50 mg/kg they did not affect apomorphine-induced stereotyping and hypothermia.

Compounds VIa-i were shown to be of low toxicity. Their LD_{50} was 400-1,000 mg/kg.

Thus, our pharmacological examination of the compounds in the 3H-[1,4]diazepine[2,3-g]-indole group has demonstrated that in certain pharmacological tests compounds VIc and f exhibited elements of neuroleptic activity. However, in contrast to the neuroleptics, the examined compounds did not affect the conditional defensive reflex or pharmacogenic stereotype.

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