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ANTITUMOR AGENTS AMONG INDOLE SULFONAMIDE DERIVATIVES

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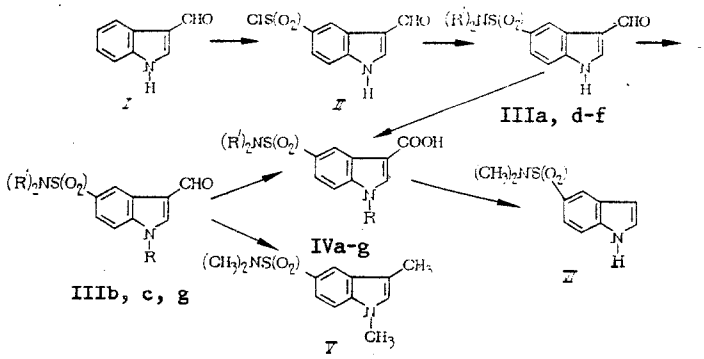
The literature contains limited information about the antitumor properties of indole derivatives [5, 6]. The present study presents results of a study of antitumor substances among new derivatives of indole, particularly the 5-sulfonamide derivatives of indole-3-carboxylic acids (IVa-g).

In order to synthesize these compounds, 3-formylindole chlorosulfonate was sulfochlorinated for the first time. The principal reaction product was 5-chlorosulfonyl-3-formylindole (II). The 5-dialkylaminosulfonyl-3-formylindoles (IIIa, d-f) were obtained by reacting II with dialkylamines and morpholine. Compounds IIIa and IIId were then alkylated with dimethylsulfate, and IIIa was alkylated with ethyl iodide by methods similar to [4, 8], with the resultant formation of 1-alkylsulfonamides (IIIb, c, g). The synthesized sulfonamides IIIa-g were further oxidized by potassium permanganate to the corresponding acids IVa-g. It is interesting to note that compound IVa decarboxylates at 2-3°C higher than its mp with the formation of 5-dimethylaminosulfonylindole (VI).

We proved the position of the introduced sulfoxychloride group by comparing the PMR-spectra of the synthesized acids IVa-g to the PMR-spectrum of ethyl 5-sulfo-2-ethoxycarbonylindole-3-carboxylate obtained by the Fischer reaction and methods [3], as well as by establishing the PMR-spectra and mp of compound VI and 5-dimethylaminosulfonamide indole which was synthesized by the indolin-indole method as described in [2].

We also synthesized compound V by reducing the aldehyde group by the Wolf-Kishner Reaction [7] in order to clarify the role the carboxyl group in the synthesized derivatives played in the manifestation of antitumor activity.



R = H(a, d-f), CH_3 (b, g), C_2H_5(c); $R^1 = CH_3$(a, c), C_2H_5 (d, g), CH_2CH_2Cl(e); $R^1 + R^1 = -(CH_2)_2O(CH_2)_2-$(f).

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TABLE 1. 1-R-3-Formyl-5-(Dialkylaminosulfonyl)Indoles

Compound	Yield, %	mp, °C (methanol)	Empirical formula	R_f
IIIa	64,2	230—231	$C_{11}H_{12}N_2O_3S$	0,40
IIIb	51,2	185—188	$C_{12}H_{14}N_2O_3S$	0,44
IIIc	54,3	124—126	$C_{13}H_{16}N_2O_3S$	0,47
IIId	61,4	226—228	$C_{13}H_{16}N_2O_3S$	0,48
IIIe	65,6	196—198	$C_{13}H_{14}N_2O_3SCl_2$	0,57*
IIIf	67,1	205—207	$C_{13}H_{14}N_2O_4S$	0,50
IIIg	52,7	144—146	$C_{14}H_{18}N_2O_3S$	0,45

*Mobile phase chloroform—acetone, 3:2.

In studying the biological action of the synthesized compounds we noted that the toxicity and antiblastic activity of the 5-sulfonamide derivatives of indole-3-carboxylic acid changes somewhat dependent upon the place and nature of the substituents. Thus, 5-dimethylaminosulfonylindole-3-carboxylic acid (IVa) turned out to be practically non-toxic (LD_{100} >5000 mg/kg). At therapeutic doses it exhibited marked antitumor activity in the treatment of rats with sarcoma 45 (T = 65%, $\alpha > 0.99$), moderately suppressed the growth of Pliss's sarcoma (T = 45.5%, $\alpha > 0.95$) and extended the longevity of experimental mice with ascitic Ehrlich's carcinoma by 20% in comparison to the control. The therapeutic dose for compound IVa was optimal since its administration was accompanied by general toxic phenomena in the form of significant emaciation in the experimental animals (growth coefficient = from —7.6 to —10.8%).

The replacement of a hydrogen atom connected to the indole nitrogen by a methyl group in compound IVa did not result in any significant changes in the antitumor activity of the synthesized compound IVb which turned out to be slightly toxic (LD_{100} = 3000 mg/kg). On the other hand the replacement of a hydrogen atom by an ethyl group resulted in the practically non-toxic compound IVc, although some loss of antitumor activity was observed.

Our examination of compounds IVd and IVf, where the CH_3 substituent in the sulfonamide group was replaced by an ethyl or morpholine group, showed that they are devoid of antiblastic properties when tested against experimental tumors, although they were only slightly toxic. Compound IVe with a chloroethyl group also turned out to be practically non-toxic. It exhibited reliable antitumor activity only against sarcoma 45 (T = 55%, $\alpha > 0.95$).

As can be seen, the placement of an alkyl radical either in position 1 or in the sulfonamide group reduced the antitumor activity of the synthesized compounds. This was confirmed by the lack of activity in compound IVg.

The replacement of a carboxyl group by a methyl group in compound V resulted in significant toxicity changes. Its toxicity differed little from that of compounds IVa and IVb in solid tumors (sarcoma 45, Pliss' lymphosarcoma).

We also examined compound VI whose indole molecule lacks a carboxyl group. It turned out to be only slightly toxic (LD_{100} = 4000 mg/kg), although in contrast to compound IVa, it did not exhibit antitumor activity on the tested experimental tumor models.

Consequently, the presence of a carboxyl group in the compounds under study plays a specific role.

Our experimental results demonstrated that compound IVa was a comparatively active antitumor substance among the 5-sulfonamide derivatives of indole-3-carboxylic acid.

EXPERIMENTAL CHEMICAL

IR-spectra were recorded on a UR-20 instrument in petroleum jelly. PMR-spectra were recorded on a Varian T-60 spectrometer with an operating frequency of 60 MHz, TMS internal standard. TLC was performed on Silufol UF-254 plates. Development by a 5% ethanol solution of phosphomolybdic acid.

5-Chlorosulfonyl-3-formylindole (II). A 58 g (0.4 mole) portion of compound I was added upon stirring in small segments to 132 ml (233 g, 2 mole) of chlorosulfonic acid cooled to —10°C. The temperature was brought up to room temperature and the mixture was heated for 2 h at 70°C after which it was cooled and decanted onto ice. The separated precipitate was

filtered and washed on a filter with water until neutralized. The resultant product was recrystallized from a dioxane–water mixture with activated charcoal. Yield of compound II was 54.5 (56%), R_f 0.41 (3:2 chloroform–acetone), mp 180°C (decomp.), PMR-spectrum (DMSO-d_6), δ, ppm: 7.7 m (2-H, 7-H and 8-H), 8.4 d (H, 4-H, J = 20 Hz), 8.6 s (H-,2-H), 10 s (H, CHO). $C_9H_6NO_3SCl$.

Product II can be used in the following reaction without recrystallization.

3-Formyl-5-(dialkylaminosulfonyl)indoles (IIIa, d-f). A 52.5 g (0.21 mole) portion of sulfochloride II was added in portions upon stirring at a rate that kept the temperature from rising above 30-35°C to a solution of 0.7 mole of the corresponding amine in 150 ml of water and 70 ml of tetrahydrofuran — THF (in the case of dimethylamine, 140 ml of its 30% aq. solution is taken). Then the excess of the amine and THF was distilled off. The separated precipitate was filtered, washed with water, and recrystallized from a 2:1 methanol–water mixture (Table 1). TLC, mobile phase — ethyl acetate. IR-spectrum of IIIa-g, ν, cm^{-1}; 1660-1665 (C=O), 1330-1340, 1140-1160 (—SO_2N<). PMR-spectrum (DMSO-d_6) IIIa, δ, ppm: 2.60 s (6-H, 2-CH_3), 7.63 d (2-H, 6-H and 7-H), 8.2 s (1-H, 2-H); 8.6 d (1-H, 4-H); 10.28 s (1-H, CHO). PMR-spectra of the remaining compounds in the 7.63-10.28 region are similar.

1-Alkyl-3-formyl-5-(dialkylaminosulfonyl)indoles (IIIb, c, g). Compounds IIIb, g were obtained by alkylating IIIa and IIId with dimethylsulfate by the same method as in [4]. Compound IIIc was obtained by alkylating IIIa with ethyl iodide by method [8]. The physicochemical properties and yields of IIIa-g are given in Table 1. The experimental analytical data satisfied the calculated values.

1-R-5-(dialkylaminosulfonyl)indole-3-carboxylic acids (IVa-g). An 11.06 g (0.07 mole) portion of potassium permanganate was added in small portions while stirring to a solution of 0.05 mole of IIIa-g in 150 ml of acetone and 100 ml of water. The temperature of the reaction mixture was maintained within the range of 30-35°C for 2 h after which the precipitate was filtered off. The filtrate was acidified to pH 2.0. The separated precipitate was recrystallized from a 2:1 methanol–water mixture (Table 2). TLC, mobile phase — ethyl acetate. IR-spectrum of IVa, ν, cm^{-1}: 1680-1690 (C=O). PMR-spectrum (DMSO-d_6) IVa, δ, ppm: 2.56 s (6H, 2CH_3), 7.5 q (1-H, 7-H, J= 8 Hz, J = 2 Hz), 7.7 d (1H, 6-H, J = 8 Hz), 8.2 d (1-H, 4-H, J = 2 Hz), 12.2 s (1-H COOH). PMR-spectra of the remaining compounds in the 7.6-12.5 region are similar.

1-3-Dimethyl-5-(dimethylaminosulfonyl)indole (V) was obtained by method [6]. Yield of V was 63.4%, mp 153-154°C, R_f 0.86. $C_{12}H_{16}N_2O_2S$. PMR-spectrum, δ, ppm: (methanol–d_4): 2.33 s (3-H, CH_3), 2.65 s (6-H, $(CH_3)_2N$), 3.76 s (3-H, CH_3N), 7.06 m (1-H, 7-H), 7.46 s (1-H, 2-H), 7.48 m (1-H, 6-H), 7.86 m (1-H, 4-H).

5-(Dimethylaminosulfonyl)indole (VI). A 2.7 g (0.01 mole) portion of IVa was heated until the onset of decarboxylation (238-240°C) after which this temperature was maintained for 30 min. After cooling, the residue was recrystallized from ethanol, and then from benzene with activated charcoal. Yield of VI was 0.7 g (31.2%), R_f 0.68 (3:1 chloroform–acetone), mp 122-124°C. According to data of [2], mp 123.5-125°C. PMR-spectrum of VI ($CDCl_3$), δ, ppm: 2.7 s (6-H, $(CH_3)_2N$), 6.6 m (H, 3-H), 7.3 m (H, 2-H), 7.5 m (2H, 6-H and 7-H), 8.1 m (H, 4-H); 9.1 s (H, N—H). $C_{10}H_{12}N_2O_2S$.

EXPERIMENTAL BIOLOGICAL

The antitumor activity of the synthesized compounds IVa-g, V, and VI was tested by the recognized method [1] on rats with sarcoma 45, Pliss' lymphosarcoma, and on mice with Ehrlich's ascitic carcinoma. The single therapeutic dose for each substance was found by testing its

TABLE 2. 1-R-5-(Dialkylaminosulfonyl)Indole-3-Carboxylic Acids

Compound	Yield, %	mp, °C (methanol–water)	Empirical formula	R_f
IVa	47,0	234—236	$C_{11}H_{12}N_2O_4S$	0,48
IVb	50,1	204—206	$C_{12}H_{14}N_2O_4S$	0,51
IVc	48,1	185—186	$C_{13}H_{16}N_2O_4S$	0,56
IVd	50,1	241—243	$C_{13}H_{16}N_2O_4S$	0,50
IVe	46,5	242—245	$C_{13}H_{14}N_2O_4SCl_2$	0,52
IVf	49,1	231—233	$C_{13}H_{14}N_2O_5S$	0,64
IVg	52,1	216—218	$C_{14}H_{18}N_2O_4S$	0,52

TABLE 3. Toxicity and Antitumor Activity Data for 5-Sulfonamide Derivatives of Indole-3-Carboxylic Acid

Compound	LD_{100} mg/kg	Max. tolerated dose mg/kg	24 h dose, mg/kg	Sarcoma 45 T. %	Sarcoma 45 growth coeff. %	Pliss' lymphosarcoma T. %	Pliss' lymphosarcoma growth coeff. %	24 h dose, mg/kg	Ehlrich's ascitic carcinoma, longevity exten., %
IVa	5000	—	250	65	—10,8	45,5	—7,6	500	20,5*
IVb	3000	1400	150	50	—12	57,5	—3	300	0
IVc	5000	—	250	0		37,5*	—3	500	0
IVd	3000	2000	150	0		35*	—2,7	300	0
IVe	5000	—	250	55	—12,5	25*	—10	500	0
IVf	3000	2000	150	0		0		300	0
IVg	5000	—	250	0		0		—	—
V	1000	700	50	60	—10,6	38,5	—9,5	100	0
VI	4000	—	200	0		0		300	0

*Unreliable.

acute toxicity when administered ip to white non-pedigree mice weighing 18-21 g. The water-insoluble compounds were administered to the animals in the form of a suspension prepared in a 0.5% solution of carboxymethylcellulose once a day over an eight day period to rats and over a six day period to mice at a dose equivalent to $^1/_{20}$ and $^1/_{10}$ of the LD_{100} respectively. Antitumor activity of the compounds was evaluated by the percent inhibition of solid tumor growth (T, %) and the longevity extension of mice with ascites (life prolongation, %). The growth coefficient (C_g, %) was used to determine the overall toxic effect on the animals.

The experimental results were statistically processed by the Student–Fisher method; data were reliable at $\alpha \geq 0.95$. A total of 195 rats and 84 non-pedigree mice of both sexes were used in the experiments.

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