SYNTHESIS AND ANTITUMOR ACTIVITY OF N-SULFANILYL-5-AMINOINDOLINES AND 9-INDOLINYLAMINOACRIDINES

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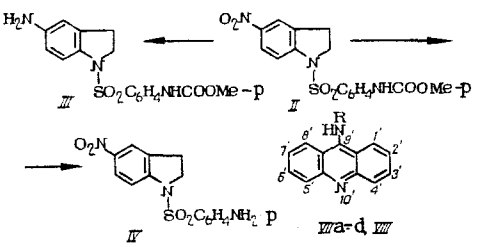
Some indoles have been reported to possess antitumor activity [2], while 9-aminoacridines have been found to possess antitubercular [8], antitumor [6, 7], and other types of biological activity. We have therefore synthesized the N-sulfanilylindolines (III) and (IV), together with compounds which combine the acridine and indole or indoline structures (VIIa-d), (VIII), and (IX).

The starting nitrosulfanilylindoline (II) was obtained by boiling 5-nitroindoline (I) [5] with p-methoxycarbonylaminobenzenesulfonyl chloride in pyridine. Reduction of the nitro-group in (II) with hydrazine hydrate in 2-propanol in the presence of Raney nickel, or alkaline hydrolysis of (II), afforded the sulfanilylaminoindoline (III) and the sulfanilylamino-nitroindoline (IV).

The 9-indolylaminoacridines (VIIa, b) and 9-indolinylaminoacridine (VIId) were obtained by reacting 9-chloroacridine (V) [3, 4] with 5-aminoindole (VIa), 3-(N,N-dimethylsulfamoyl)-5-aminoindole (VIb), or N-acetyl-5-aminoindoline (VId) [1, 5] in dry pyridine.

Acid hydrolysis of (VIId) afforded (VIIc), which on treatment with p-methoxycarbonyl-aminobenzenesulfonyl chloride was converted into 9-[5-(1-N-methoxycarbonylsulfanilyl)indolinyl]-aminoacridine (VIII).



The structures of (II-IV), (VII), and (VIII) were in good agreement with their elemental analyses and IR, PMR, and mass spectra (Tables 1 and 2).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UV-20 (Germany) in Vaseline grease, and PMR spectra on a Bruker WP-200SY (200 MHz) in DMSO or $CDCl_3$. Mass spectra were obtained on an MAT-112 GC-MS. The progress of the reactions and the purity of the products were followed by TLC on Silufol UV-254 plates in the systems ethyl acetate–chloroform (5:1) and 2-propanol–benzene–ammonia (10:5:1).

9-(5-Indolyl)aminoacridine (VIIa). A solution of 2 g (15 mmole) of 5-aminoindole and 3.2 g (15 mmole) of (V) in 150 ml of dry pyridine was boiled under argon for 3.5 h. The mixture was cooled, poured into 250 ml of ice-water, and basified with NaOH to pH 10. The solid which separated was filtered off, washed with water to pH 7, and dried to give 2 g of (VIIa).

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TABLE 1. PMR Spectra of (VIIa-d), (II-IV), (VIII), and (IX)

Compound	Chemical shifts, ppm and G values, Hz										Other signals
	1′-H; 8′-H (m)	2′-H, 7′-H (m)	3β-H 6′-H (m)	4′-H 5′-H (m)	1-H	2-H	3-H	4-H	6-H	7-H	
VIIa*	8,05 (2H)	7,00 (2H)	7,51 (2H)	7,61 (2H)	10,21 (1H, br.s) $G_{1,2}$=2,19	7,31 (1H, d.d) $G_{2,3}$=2,92	6,37 (1H, d.d) $G_{1,3}$=1,46	7,10 (1H, d) $G_{4,6}$=1,82	6,77 (1H, d.d) $G_{6,7}$=8,40	7,38 (1H, d) $G_{6,7}$=8,40	
VII b	8,19 (2H)	7,33 (2H)	7,92 (2H)	8,06 (2H)	12,40 (1H, br.s)	8,01 (1H, d) $G_{1,2}$=2,56		7,84 (1H, d) $G_{4,6}$=1,83	7,31 (1H, d.d) $G_{6,7}$=8,77	7,68 (1H, d) $G_{6,7}$=8,77	2,54 [N(CH$_3$)$_2$, s]
VIIc	8,87 (2H)	7,37 (2H)	7,91 (2H)	7,93 (2H)	5,84 (1H)	3,53 (2H, t) $G_{2,3}$=8,59	2,96 (2H, t) $G_{2,3}$=8,59	7,08 (1H, s) $G_{4,6}$=1,83	6,96 (1H, d) $G_{4,6}$=1,83	6,57 (1H, d) $G_{6,7}$=8,41	
VIId	7,86 (2H)	6,56 (2H)	7,19 (2H)	7,35 (2H)	—	4,03 (2H, t) $G_{2,3}$=8,40	3,02 (2H, t) $G_{4,6}$=2,02	6,56 (1H, d) $G_{4,6}$=2,02	6,42 (1H, d.d) $G_{6,7}$=8,58	7,78 (1H, d) $G_{6,7}$=8,58	2,11 (CH$_3$, s)
II*	—	—	—	—	—	4,12 (1H, t) $G_{2,3}$=8,40	3,19 (2H, t)	8,02 (1H, d) $G_{4,6}$=1,83	8,15 (1H, d.d) $G_{6,7}$=8,78	7,73 (1H, d) $G_{6,7}$=8,78	7,90 (2H, s) 7,72 (2H, s) G_{ortho}=8,77
III*	—	—	—	—	—	3,84 (2H, t) $G_{2,3}$=8,40	2,61 (2H, t)	6,42 (1H, d) $G_{4,6}$=2,19	6,52 (2H, d.d) $G_{6,7}$=8,40	7,30 (1H, d) $G_{6,7}$=8,40	7,61 (4H, m) 9,09 (NH, br.s) 4,50 (NH$_2$ br.s) 3,71 (CH$_3$, s)
IV*	—	—	—	—	—	4,03 (2H, t) $G_{2,3}$=8,67	3,16 (2H, t)	8,00 (1H, d) $G_{4,6}$=2,44	8,13 (1H, d) $G_{6,7}$=8,79	7,68 (1H, d.d) $G_{6,7}$=8,79	7,61 (2H, d) 6,73 (2H, d) G_{ortho}=8,79
VIII	8,14 (2H)	7,33 (2H)	7,92 (2H)	8,06 (2H)	—	3,99 (2H, t) $G_{2,3}$=8,40	3,99 (2H, t) $G_{2,3}$=8,40	2,90 (2H, t)	7,18 (1H, d)	7,20 (1H, d)	7,54 (NH$_2$, br.s) 7,52 (1H, d) 7,66 (2H, d) G_{ortho}=8,77 10,00 (NH, s) 3,71 (CH$_3$, s)

*Spectra obtained in d-neuteroacetone.

TABLE 2. Physicochemical Data for (VIIa, d), (II-IV), (VIII), and (IX)

Compound	Yield,%	MP, °C (solvent for crystallization)	Empirical formula	M+ (calculated and found)	IR spectrum, ν_{max}, cm^{-1}
VIIa	42	233—5 (ethanol)	$C_{21}H_{15}N_3$	309	3490 s (NHpyrrol), 1550—1600 (C=C pyrrol), 3310 (NH amine)
VIIb	45	308—10 (MeOH)	$C_{23}H_{20}N_4O_2S$	416	1150, 1180, 1340, 1375 (SO_2), 1320 s (CH_3) 3310 br.s (NH amine), 3460 s (NH pyrrol),
VIIc	57	286—8 (ethanol)	$C_{21}H_{17}N_3$	311	3350 w (NH amine)
VIId	58	258—60 (ethanol)	$C_{23}H_{19}N_3O$	353	1630 s (CO amide) 3310 s (NH amine), 2860 s (CH_3) 1360 w ($COCH_3$)
II	69	229—30 (ethanol)	$S_{16}H_{15}N_3O_6S$	377	1350 w (NO_2), 1160 s (SO_2Ar), 1145 w ($COOCH_3$), 1600 s (CO amide)
III	99	160—1 (MeOH)	$C_{16}H_{17}N_3O_4S$	347	1345 w, 1170 s (SO_2Ar), 1145 w ($COOCH_3$) 3450 s (NH_2), 1580 s (NHCO)
IV	85	170—1 (MeOH)	$C_{14}H_{13}N_3O_4S$	319	1370s 1180 s (SO_2Ar), 1640 s (NHCO), 1350 s (NO_2), 3450 s (NH_2)
VIII	70	233—5 (ethanol)	$C_{29}H_{24}N_4O_4S$	373*-M^+ — $C_6H_4NHCOOCH_3$	1370 s, 1180 s (SO_2Ar) 1650 s (NHCO), 3310 (NH amine)
IX	89	223—5	$C_{21}H_{18}N_3Cl$	—	—

*M^+ not seen as a result of the instability of (VIII) to electron impact.

TABLE 3. Biological Test Results

Compound	Dose, mg/kg	Inhibition of tumor growth (I_t)		ILA (%) of mice with P-388 leukemia
		Jensen's sarcoma	Walker's carcinosarcoma	
VIId	10	38	—	—
	20	56	13	21
	40	78	35	25
	60	78	40	—
VIIa	20	0	—	20
	40	29	40	32
	60	—	65	—
IX	20	20	—	25
	40	32	31	10
	60	—	63	—
VIIb	25	—	—	0
	40	20	0	0
	50	60	30	0
VIII	40	40	0	0
	60	45	0	0

9-(3-N,N-Dimethylsulfamoyl-5-indolyl)aminoacridine (VIIb) and 9-(1-Acetyl-5-indolyl)-aminoacridine (VIId) were obtained as for (VIIa), from (VIb) and (VId) respectively.

1-N-Methoxycarbonylsulfanilyl-5-nitroindoline (II). To a solution of 0.5 g (3 mmole) of (I) in 40 ml of dry pyridine was added at the boil with stirring under argon over 1.5 h 0.96 g (4 mmole) of p-methoxycarbonylaminobenzenesulfonyl chloride. The mixture was stirred at the boil for a further 3 h, cooled, and the solid (II) which separated was filtered off and washed with ether. The mother liquors were poured into 100 ml of water, basified with NaOH to pH 10, and the additional precipitate of (II) washed with water to pH 7, dried, and combined with the solid obtained previously, to give 0.8 g of (II).

1-Sulfanilyl-5-nitroindoline (IV). Potassium hydroxide (1.5 g, 2.7 mmole) was dissolved with heating in 20 ml of alcohol and 2 ml of water, and to the solution was added 1 g (3 mmole) of (II). The solution was boiled for 4 h, concentrated to half its original volume, cooled, poured into 25 ml of water, and the solid which separated filtered off and dried to give 0.7 g of (IV).

1-N-Methoxycarbonylsulfanilyl-5-aminoindioline (III). To a solution of 1 g (3 mmole) of (II) in 2-propanol was added 0.1 g of Raney nickel, the mixture brought to the boil, and 6 ml of hydrazine hydrate added dropwise with stirring.

The mixture was stirred for 4 h, filtered, the catalyst washed with a small amount of 2-propanol, the filtrates combined, evaporated to 1/3 of their initial volume, and the solid which separated filtered off and washed with 2-propanol to give 0.6 g of (III).

9-(5-Indolinyl)aminoacridine (VIIa). A mixture of 2 g (6 mmole) of (VIId), 30 ml of 35% HCl, and 15 ml of water was boiled for 0.5 h, filtered, and the filtrate cooled and neutralized cautiously with cooling with 25% ammonia. The solid which separated was filtered off, washed with water to pH 8, and dried to give 1 g of (VIIc).

9-(5-Indolinyl)aminoacridine Hydrochloride (IX). To a solution of 1 g (3 mmole) of (VI) in 100 ml of absolute ethanol was added a solution of HCl in ethanol to pH 2-3. The hydrochloride was precipitated with dry ether, filtered off, and washed with ether to give 1 g of (IX).

9-[5-(1-N-Methoxycarbonylsulfanilyl)indolinyl]aminoacridine (VIII). Obtained as for (II).

EXPERIMENTAL (PHARMACOLOGY)

The antitumor activity of the compounds was examined in the Laboratory for Antitumor Drugs, Central Drug Laboratory, All-Union Research Institute for Pharmaceutical Chemistry.

Tests were carried out on mongrel male rats weighing 110-120 g with transplated tumors (Jensen's sarcoma, Walker's carcinosarcoma), and on BDF_1 mice with P-388 lympholeucotic leukemia.

The test compounds were given intraperitoneally in 10% polyvinylpyrrolidone solution with the addition of Tween-80 to a concentration of 0.8%, once daily for eight days. Treatment was commenced 3-4 days following transplantation of the solid tumors (Jensen's sarcoma and Walker's adenosarcoma), and two days after induction of P-388 leukemia.

Antiblastic activity was expressed using the tumor growth inhibition index (I_t), given by the expression:

$$I_t = \frac{B_c - B_e}{B_c},$$

where B_c and B_e are the masses of the tumors in the control and experimental groups. Antileukemic activity was expressed as the increased lifespan of the animals (ILA, %) as a percentage of the controls.

The compounds were found to have moderate antitumor activity in rats with Jensen's sarcoma and Walker's adenocarcinoma, inhibiting tumor growth up to 78% when given in doses of 40 mg/kg and 60 mg/kg. Compounds (VIIa), (VIId), and (IX) showed antileukemic activity against leukemia P-388, the most active being (VIIa), which increased the mean lifespan of mice by 32% (Table 3).

LITERATURE CITED

1. Mandur Adel Khamed Mokhammed, Synthesis of sulfamoylindoles [in Russian], Diss. Cand. Chem. Sci., Moscow (1987).
2. M. D. Mashkovskii, Drugs, 10 edn., Moscow (1986), Part 2, pp. 464-466.
3. Ibid., Vol. 3, p. 36.
4. Ibid., Vol. 3, p. 36.
5. A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, et al., Zh. Obshch. Khim., 29, 2541 (1959).
6. B. F. Cain, G. J. Atwell, and W. A. Denny, J. Med. Chem., 18, 1110-1117 (1975).
7. J. M. Covery, K. W. Kohn, D. P. Kerrigan, et al., Cancer. Res., 48, No. 4, 860-863 (1980).
8. G. D. Jaycox, G. N. Griblle, and M. R. Hacker, J. Het. Chem., 24, 1405-1408 (1987).