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Synthesis and Evaluation of Antitumor Activity of 1-[*N*,*N*-Bis(2-chloroethyl)sulfamoylphenyl]-3,3-dialkyltriazenes

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Abstract □ Twenty-two 1-*p*-sulfamoylphenyl-3,3-dialkyltriazenes, 1-*p*-dialkylsulfamoylphenyl-3,3-dialkyltriazenes, and 1-*p*-[*N*,*N*-bis(2-chloroethyl)sulfamoylphenyl]-3,3-dialkyltriazenes were synthesized from their corresponding amines. Six of the compounds tested were devoid of antitumor activity.

Keyphrases □ Triazene derivatives—synthesis of 22 1-*p*-sulfamoylphenyl-, 1-*p*-dialkylsulfamoylphenyl-, and 1-*p*-[*N*,*N*-bis(2-chloroethyl)sulfamoylphenyl]-substituted 3,3-dialkyltriazenes, six compounds screened for antitumor activity □ Sulfamoylphenyltriazenes—synthesis of 22 derivatives, six screened for antitumor activity □ Antitumor activity—six of 22 synthesized sulfamoylphenyltriazenes screened

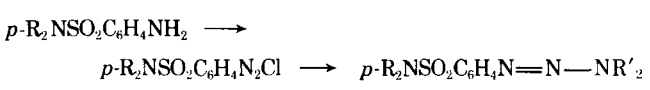
A number of 5-triazenoimidazoles with pronounced activity against experimental tumors were synthesized previously (1, 2). 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide, in particular, is clinically useful for the induction of temporary remission in malignant melanoma (3). Some derivatives of phenyltriazenes have exhibited antitumor activity (4, 5), and some derivatives of N^1,N^1-bis(2-chloroethyl)-sulfanilamide were also found to be active against experimental tumors (6). Several *p*-sulfonyl- and *p*-sulfamoylcarbanilic acid esters were found to be inactive in mouse lymphoid leukemia (7, 8).

To extend these observations, it was decided to prepare compounds having *p*-sulfamoylphenyl, *p*-dialkylsulfamoylphenyl, and bis(2-chloroethyl)sulfamoylphenyl groups and the triazeno moiety in their molecules. Sulfanilamide, N^1,N^1-dialkylsulfanilamide, and N^1,N^1-bis(2-chloroethyl)sulfanilamide were readily converted to the desired triazeno derivatives by treating the appropriate diazotized amines with the secondary amines in sodium carbonate solution (Scheme I). All prepared compounds are summarized in Table I.

Compounds VI*a*, II*b*, V*b*, Ic, III*c*, and V*c* were tested *in vivo* for antitumor activity against mouse lymphoid leukemia L-1210, resulting in a T/C percent of 120 or less at 400 mg/kg (increase in survival of treated animals).

EXPERIMENTAL[1]

1 [*N*,*N*-Bis(2-chloroethyl)sulfamoylphenyl] 3,3-pentamethylenetriazene (IVc) was obtained from 2.97 g (0.01 mole) of N^1,N^1-bis(2-chloroethyl)sulfanilamide prepared according to Brintzinger *et al.* (9). The sulfanilamide derivative was added to a mixture of 25 g of crushed ice and 3.5 ml of concentrated hydrochloric acid with vigorous stirring at 0–5°. Diazotization was achieved by the slow addition, accompanied by thorough agitation, of sodium nitrite [0.7 g (0.01 mole) dissolved in 5 ml of water]. After standing at 0–5° for 20 min, the solution was filtered rapidly



Scheme I

[1] Melting points were measured on a Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded on a Leitz model III spectrograph. NMR spectra were taken on a Varian A60A instrument. Mass spectra were recorded on a Varian Mat 111 spectrograph. UV spectra were obtained using a Varian-Techtron 635 recording instrument. All compounds were subjected to IR, NMR, and mass spectroscopy, and the results were as expected.

Table I—1-*p*-Sulfamoylphenyl- and 1-*p*-Dialkylsulfamoylphenyl-3,3-dialkyltriazenes

Compound	Melting Point	Yield, %	Formula	Analysis, % Calc.	Found
I*a*	178–182°	58	$C_8H_{12}N_4O_2S$	C 42.11	42.18
				H 5.26	5.31
II*a*	128°	63	$C_{10}H_{16}N_4O_2S$	C 46.88	46.95
				H 6.25	6.17
III*a*	118–120°	49	$C_{12}H_{20}N_4O_2S$	C 50.70	50.61
				H 7.04	6.92
IV*a*	206–210°	68	$C_{10}H_{14}N_4O_2S$	C 47.24	47.14
				H 5.51	5.52
V*a*	150–154°	75	$C_{11}H_{16}N_4O_2S$	C 49.25	49.37
				H 5.97	6.06
VI*a*	169–173°	69	$C_{10}H_{14}N_4O_3S$	C 44.44	44.63
				H 5.19	5.12
VII*a*	198–200°	48	$C_{12}H_{18}N_4O_2S$	C 51.06	51.17
				H 6.38	6.20
VIII*a*	200–202°	56	$C_{11}H_{17}N_5O_2S$	C 46.64	46.60
				H 6.01	5.93
I*b*	118–120°	63	$C_{10}H_{16}N_4O_2S$	C 46.88	46.78
				H 6.25	6.28
II*b*	104–107°	66	$C_{12}H_{20}N_4O_2S$	C 50.70	50.88
				H 7.04	7.14
III*b*	167–170°	78	$C_{12}H_{18}N_4O_2S$	C 51.06	51.01
				H 6.38	6.44
IV*b*	135–138°	81	$C_{13}H_{20}N_4O_2S$	C 52.70	52.88
				H 6.76	6.80
V*b*	143–146°	73	$C_{12}H_{18}N_4O_3S$	C 48.32	48.41
				H 6.04	6.02
VI*b*	135–136°	59	$C_{14}H_{22}N_4O_2S$	C 54.19	54.17
				H 7.10	7.20
VII*b*	133–136°	48	$C_{13}H_{21}N_5O_2S$	C 50.16	50.28
				H 6.75	6.79
I*c*	100–102°	57	$C_{12}H_{18}Cl_2N_4O_2S$	C 40.79	40.78
				H 5.10	5.25
II*c*	63–64°	53	$C_{14}H_{22}Cl_2N_4O_2S$	C 44.09	44.22
				H 5.77	5.66
III*c*	150–152°	64	$C_{14}H_{20}Cl_2N_4O_2S$	C 44.33	44.50
				H 5.28	5.21
IV*c*	101–103°	72	$C_{15}H_{22}Cl_2N_4O_2S$	C 45.80	45.72
				H 5.60	5.55
V*c*	117–118°	83	$C_{14}H_{20}Cl_2N_4O_2S$	C 42.53	42.68
				H 5.06	4.98
VI*c*	108–110°	56	$C_{16}H_{24}Cl_2N_4O_2S$	C 47.17	47.26
				H 5.90	5.83
VII*c*	110–114°	63	$C_{15}H_{23}Cl_2N_5O_2S$	C 44.12	44.30
				H 5.64	5.69

and the cold solution was carefully added to a solution of 1 ml (0.012 mole) of piperidine in 25 ml of water containing 2.12 g (0.02 mole) of anhydrous sodium carbonate. The precipitate was filtered, washed with cold water, and recrystallized from aqueous ethanol to give 2.82 g (72%), mp 101–103°, mol. wt. 393 (by mass spectroscopy); UV_{max} 322 nm; IR (KBr): ν_{max} 3330, 2880, 2775, 1582, 1448, 1420, 1392, 1338, 1286, 1258, 1219, 1187, 1165, 1147, 1101, 943, 869, 851, 842, 781, 746, and 711 cm^{-1}; NMR (CCl_4): δ 1.76 (m, 6H, piperidine H), 3.51 (m, 8H, CH_2—CH_2), 3.80 (m, 4H, piperidine H), and 7.33–7.80 (q, 4H, ArH).

All other triazene derivatives reported in Table I were prepared similarly.

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