Secondary Disulfonamides and Secondary Tetrasulfondiamides as Proposed New Biological Alkylating Agents

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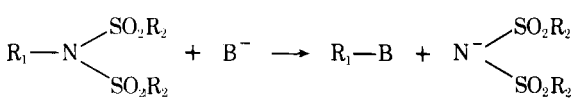
Abstract □ Secondary disulfonamides and secondary tetrasulfondiamides were prepared for antineoplastic activity testing. For the disulfonamides, one alkyl series (*n*-butyl), three aralkyl series (benzyl, phenethyl, and phenpropyl), and one diaralkyl series (diphenpropyl) were prepared. Two series of tetrasulfondiamides were made from diamines, one in which the central methylene chain was varied from four to six and another using the tetrasubstituted sulfonyl derivative of xylylenediamine. Thirteen final compounds were synthesized. Ten of these compounds and four intermediates have not been reported previously. Preliminary screening results for the final compounds are given.

Keyphrases □ Sulfonamides, secondary—synthesized, evaluated for antineoplastic activity □ Antineoplastic activity—various secondary disulfonamides and tetrasulfondiamides evaluated □ Structure–activity relationships—various secondary disulfonamides and tetrasulfondiamides evaluated for antineoplastic activity

Recently, the synthesis of a series of *N*-alkyl- and *N*-aralkyl-*N,N*-disulfonamides was reported (1) in a study involving the deamination of primary aliphatic amines. Compounds in which R_1 (Scheme I) was *n*-pentyl, isopentyl, *n*-hexyl, cyclohexyl, 1-methylhexyl, 1-methylheptyl, *n*-octyl, benzyl, and phenethyl and R_2 was phenyl, *p*-tolyl, *p*-bromophenyl, *p*-nitrophenyl, *m*-nitrophenyl, and trifluoromethyl were prepared (1). Only a few scattered reports of the intentional synthesis of this type of compound have appeared in the literature (1, 2). This class of compounds is known to undergo carbon–nitrogen bond cleavage in the presence of nucleophiles (3). [Typical nucleophiles are iodide, bromide, and aniline in dimethylformamide at about 100° for short periods (4).] In this way, a saturated carbon becomes bonded directly to the nucleophile. The leaving group is the disulfonamide anion, and the reaction has been reported to be near the S_N2 end of the spectrum for nucleophilic substitutions at a saturated carbon (3).



Scheme I

Secondary disulfonamides are potential biological alkylating agents. Furthermore, the corresponding compounds derived from diamines, *i.e.*, secondary tetrasulfondiamides[1]—previously unreported—have the potential to cross-link DNA by dialkylation. Thus, a new type of biological alkylating agent in which R_1 is the alkylating moiety is proposed. To explore this idea, representative disulfonamides and tetrasulfondiamides were synthesized for antineoplastic activity screening. In all cases, a primary amine or diamine was chosen so that the resulting disulfonamide or tetrasulfondiamide would be the least hindered to react most readily with cellular nucleophiles. The disulfonamides are monofunctional alkylating compounds. Many monofunctional agents have demonstrated significant anticancer activity; however, the most active agents are bifunctional (5).

In the disulfonamides, the alkylating moiety on the nitrogen is represented by alkyl, aralkyl, substituted aralkyl, and diaralkyl groups. The lengths of the methylene chains in the bifunctional compounds are varied slightly from that of busulfan.

This paper describes the synthesis and reports the preliminary antineoplastic activity of the 13 final compounds prepared.

RESULTS AND DISCUSSION

The intermediate primary sulfonamides and primary disulfonamides were prepared according to well-established procedures from the corresponding primary amines or diamines (6).

For the synthesis of the secondary disulfonamides and tetrasulfondiamides, the procedure of DeChristopher *et al.* (1) was used. This procedure involved the *in situ* generation of the sodium salt of the sulfonamide or disodium salt of the disulfonamide by sodium hydride. The sulfonamides or disulfonamides were dissolved in dry dimethylformamide, and a 50% oil dispersion of sodium hydride was added slowly with stirring. A 10% excess of the appropriate molar amount of the base was used. Stirring was continued for 30 min following addition of sodium hydride. A 10% excess of the appropriate molar amount of *p*-toluenesulfonyl chloride was then added; stirring was continued for another 30 min, except for the disulfonamide of hexamethylenediamine which required 1 hr of stirring because of the poor solubility of the disodium salt in dimethylformamide.

These reactions were run at room temperature in open beakers. The crude disulfonamides and tetrasulfondiamides were isolated by quenching the dimethylformamide reaction mixtures in water and filtering the crude products. The crude final products were washed with water and purified by recrystallization from the appropriate solvent(s). Tables I and II list the final compounds.

Table III shows the testing results obtained from the National Cancer Institute. Activity, host animal, tumor employed, vehicle used, and various dosage levels administered are shown for each compound. The intraperitoneal route was used. The parameter measured for antitumor activity in XI*b* and XII*b* was mean tumor weight; median survival time was used for all other compounds. Compound XI*b* showed presumptive activity in its initial test.

The tumors chosen for testing against the individual compounds were selected by the National Cancer Institute. Unfortunately, none of the compounds was tested against L-1210, which, according to protocol, should be employed in the current stage-one screen for synthetic compounds (7). Because of the limited number of compounds tested, conclusions regarding the antitumor activity of this new class of alkylating agents are premature.

EXPERIMENTAL

***N*-(3-Phenyl-1-propyl)-*p*-toluenesulfonamide (VIII*a*)**—Into a 250-ml round-bottom flask fitted with a mechanical stirrer were placed 6.75 g (0.05 mole) of 3-phenyl-1-propylamine, 5 ml of water, and 9.55 g (0.05 mole) of *p*-toluenesulfonyl chloride. To this mixture was added, with stirring, 20 ml of 10% NaOH in portions over 1 hr. The reaction was

[1] For the purpose of analogy, the difunctional compounds are referred to as secondary tetrasulfondiamides. However, in naming them chemically, they are probably better referred to as tetrasubstituted diamines.

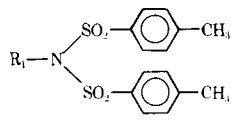
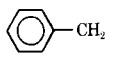
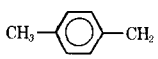
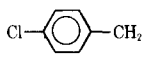
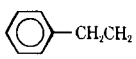
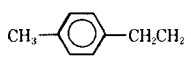
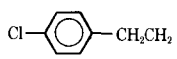
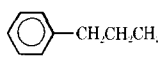
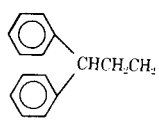


Table I—Physical Constants of Secondary Disulfonamides

Compound	R_1	Melting Point[a]	Yield, %	Empirical Formula	Analysis[b], % Calc.	Found
I*b*	n-C_4H_9	86–87°[c]	76.1	$C_{18}H_{23}NO_4S_2$	C 56.67 H 6.08 N 3.67	56.50 6.19 3.59
II*b*		158.5–160°[d]	83.1	$C_{21}H_{21}NO_4S_2$	C 60.70 H 5.09 N 3.37	60.75 5.03 3.39
III*b*		167–168°	65.7	$C_{22}H_{23}NO_4S_2$	C 61.52 H 5.40 N 3.26	61.49 5.42 3.20
IV*b*		125–127°	76.7	$C_{21}H_{20}ClNO_4S_2$	C 56.06 H 4.48 N 3.11	56.00 4.70 3.32
V*b*		100–101°[f]	82.6	$C_{22}H_{23}NO_4S_2$	Not determined	
VI*b*[e]		99–100.5°	78.7	$C_{23}H_{25}NO_4S_2$	C 62.28 H 5.68 N 3.16	62.45 5.81 3.35
VII*b*		120–121°	87.1	$C_{22}H_{22}ClNO_4S_2$	C 56.95 H 4.78 N 3.02	57.09 4.68 3.39
VIII*b*		112–113°	90.9	$C_{23}H_{25}NO_4S_2$	C 62.28 H 5.68 N 3.16	62.45 5.75 3.28
IX*b*[e]		143–144°	90.4	$C_{29}H_{29}NO_4S_2$	C 67.03 H 5.62 N 2.70	66.89 5.80 2.74

[a] Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. [b] Determined by Het-Chem-Co of Harrisonville, Mo. [c] Reference 8. [d] Reference 9. [e] New intermediate. [f] Reference 6.

heated on a steam bath during the addition of sodium hydroxide and for 1 additional hr. After cooling, the crude product was filtered, washed with water, and recrystallized from methanol–water (3:1), giving 9 g (62.5%), mp 64–65° [lit. (6) mp 66–67°]; IR ($CHCl_3$): 3370, 1330, and 1160 cm^{-1}.

***N*-(3-Phenyl-1-propyl)-*N*,*N*-di-*p*-toluenesulfonamide (VIII*b*)**—To a solution of 7.2 g (0.025 mole) of VIII*a* in 100 ml of dry dimethylformamide in an open beaker was added 1.32 g (0.0275 mole) of 50% NaH. After stirring for 30 min at room temperature, 5.2 g (0.0275 mole) of *p*-toluenesulfonyl chloride was added. Stirring was continued for 30 min, and the mixture was then poured into water. After standing overnight, the crude product was filtered, washed with water, and recrystallized from equal parts of acetone and ethanol, yielding 10 g (90.9%), mp 112–113°; IR ($CHCl_3$): NH stretching region blank, 1370 and 1165 cm^{-1}. The NMR ($CDCl_3$) spectrum had a trio of coupled triplets at 2.00, 2.59, and 3.68 ppm (J = 8 Hz) (2H each); an aromatic methyl singlet at 2.41 ppm (on top of the middle set of triplets) (6H); and aromatic multiplets at 6.90–8.00 ppm (13H).

Anal.—Calc. for $C_{23}H_{25}NO_4S_2$: C, 62.28; H, 5.68; N, 3.16. Found: C, 62.45; H, 5.75; N, 3.28.

***N*,*N*′-Di-(*p*-toluenesulfonyl)pentamethylenediamine (XI*a*)**—Into a 250-ml round-bottom flask fitted with a mechanical stirrer were placed 5.1 g (0.05 mole) of 1,5-diaminopentane, 5 ml of water, 19.1 g (0.1 mole) of *p*-toluenesulfonyl chloride, and 40 ml of 10% NaOH. The mixture was

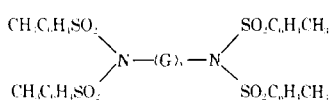


Table II—Physical Constants of Secondary Tetrasulfondiamides

Compound	G	x	Melting Point[a]	Yield, %	Empirical Formula	Analysis[b], % Calc.	Found
X*b*	CH_2	4	185–186°	76.2	$C_{32}H_{36}N_2O_8S_4$	C 54.53 H 5.15 N 3.97	54.51 5.49 4.06
XI*b*[c]	CH_2	5	129–130°	88.4	$C_{33}H_{38}N_2O_8S_4$	C 55.13 H 5.33 N 3.90	55.15 5.03 4.03
XII*b*	CH_2	6	214–215°	61.9	$C_{34}H_{40}N_2O_8S_4$	C 55.72 H 5.50 N 3.82	55.45 5.37 3.93
XIII*b*[c]		1	187–188°	80.2	$C_{36}H_{36}N_2O_8S_4$	C 57.43 H 4.82 N 3.72	57.28 4.72 3.79

[a,b] See Table I. [c] New intermediate.

Table III—Antitumor Testing Results

Compound	Activity[a]	Dose, mg/kg		PS[b]	B1[c]	WA[d]
I*b*	–	400		CDF_1 mouse		
		200				
		100		T[e]		
II*b*	×, –	400	100	CDF_1 mouse		
		200	50	T		
		100	25			
III*b*	–	400		CDF_1 mouse		
		200				
		100		T		
IV*b*	–	200		CDF_1 mouse		
		100				
		50		M[f]		
V*b*	–	200		CDF_1 mouse		
		100				
		50		M		
VI*b*	–	200		CDF_1 mouse		
		100				
		50		M		
VII*b*	–	200		CDF_1 mouse		
		100				
		50		M		
VIII*b*	–	200		CDF_1 mouse		
		100				
		50		M		
IX*b*	×, –	400	100	CDF_1 mouse		
		200	50			
		100	25	T		
X*b*	–	400		BDF_1 mouse		
		200				
		100		M		
XI*b*	+, –	150	400			Random bred albino rat
		75	200			
		37.5	100			
		18.7				
		9.4				0[g]
XII*b*	–, –	150	400			Random bred albino rat
		75	200			
		37.5	100			
		18.7				
		9.4				0
XIII*b*	–	400			BDF_1 mouse	
		200				
		100			M	

[a] Presumptive activity, +; no activity indicated, –; toxic doses, ×. [b] P-388 lymphocytic leukemia. [c] B16 melanocarcinoma. [d] Walker carcinosarcoma 256. [e] Saline with polysorbate 80. [f] Hydroxypropylcellulose. [g] Other.

heated on a steam bath with stirring for 2 hr. After cooling, the crude product was filtered, washed with water, and recrystallized from ethanol, yielding 15.4 g (75.2%) of tan crystals, mp 132–134°; IR ($CHCl_3$): 3320, 1330, and 1160 cm^{-1}.

***N,N,N′,N′*-Tetra-(*p*-toluenesulfonyl)pentamethylenediamine (XI*b*)**—To a solution of 6.15 g (0.015 mole) of XI*a* in 150 ml of dry dimethylformamide in an open beaker was added 1.584 g (0.033 mole) of 50% NaH. After stirring for 30 min at room temperature, 6.3 g (0.033 mole) of *p*-toluenesulfonyl chloride was added. Stirring was continued for 30 min, and the mixture was then poured into water. After standing overnight, the crude product was filtered, washed with water, and recrystallized from equal parts of acetone and ethanol, giving 9.6 g (88.4%), mp 129–130°; IR ($CHCl_3$): NH stretching region blank, 1370 and 1165 cm^{-1}. The NMR ($CDCl_3$) spectrum had an aliphatic region at 0.6–1.90 ppm (6H); an aromatic methyl singlet at 2.44 ppm (12H); an NCH_2 triplet centered at 3.60 ppm, J = 7 Hz (4H); and an aromatic *AA′BB′* quartet centered at 7.57 ppm, J_{ab} = 8 Hz (16H).

Anal.—Calc. for $C_{33}H_{38}N_2O_8S_4$: C, 55.13; H, 5.33; N, 3.90. Found: C, 55.15; H, 5.03; N, 4.03.

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