Alkylating Agents Related to 2,2'-Biaziridine. III.[1] The Stereoisomeric N,N'-Dimethanesulfonyl-2,2'-biaziridines

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The stereoisomeric N,N'-dimethanesulfonyl-2,2'-biaziridines (**8**), the related symmetrical position isomers of dimethanesulfonamidobutanediol bismethanesulfonates (**5**, **10**), and dihalogenodimethanesulfonamidobutanes (**4**, **9**) were prepared. Except for **4** the synthesis could be performed by two independent routes establishing the optical purity of the compounds. The results of an attempted preparation of 2,3-diamino-1,4-dibromobutane are mentioned. Available anticancer screening data of the compounds indicated that no outstanding antineoplastic activity of this group of bifunctional alkylating agents can be expected.

For reasons already discussed[2] and in order to get further information about the structure–activity relationship of bifunctional alkylating agents with regard to the antineoplastic effect the present communication deals mainly with the synthesis of *meso*-, DL-, (2*R*,2'*R*)-, and (2*S*,2'*S*)-*N*,*N*'-dimethanesulfonyl-2,2'-biaziridine [*meso*-**8**, DL-**8**, (*R*,*R*)-**8**, and (*S*,*S*)-**8**], the related symmetrical position isomers of the dimethanesulfonamidobutanediol bismethanesulfonates [*meso*-**5**, DL-**5**, (*R*,*R*)-**5**, and (*S*,*S*)-**5**; *meso*-**10**, DL-**10**, (*R*,*R*)-**10**, and (*S*,*S*)-**10**] and with the dihalogenodimethanesulfonamidobutanes [*meso*-**4**, DL-**4**, (*R*,*R*)-**4**, and (*S*,*S*)-**4**; *meso*-**9**, DL-**9**, (*R*,*R*)-**9**, and (*S*,*S*)-**9**].

Chemistry.—The synthetic route for the preparation of **5**, **8**, and **10** is summarized for one of the optically active compounds in Scheme I. The preparation of the dimethanesulfonylbiaziridines **8** from the diepoxide **3**[3] as well as from the dibenzyloxybutanediol bismethanesulfonates **14**[1] was attempted in order to prove the optical purity of the prepared compounds. The ring closure from **5** to **8** and the transformation of **5** into **4** proceed with Walden inversions and are the only steps involving attack at the optically active carbon atoms. The ring opening of the diepoxides **3** with methanesulfonamide to the dimethanesulfonamidobutanediols **2** was performed in boiling toluene. Hydrolysis of **2** yielded the stereoisomeric diaminobutanediols **1**, which were mesylated to the corresponding bismethansulfonates **5**; *meso*-**1**, DL-**1**, and (*S*,*S*)-**1** proved to be identical with authentic material prepared by other routes.[1,2]

Hydrolysis of (*R*,*R*)-**5** and (*S*,*S*)-**5** in moist $MeSO_3H$ yielded (*R*,*R*)-**6** and (*S*,*S*)-**6**; the latter was identical with material described earlier.[2]

Exchange of the mesyloxy groups in **5** and **10** for both Br and Cl by means of LiX at elevated temperature resulted in the halogeno compounds **4** and **9**, respectively. However, the isolation of *meso*- or (2*R*,3*R*)-2,3-dibromo-1,4-dimethanesulfonamidobutanes after reaction of *meso*- and (*S*,*S*)-**5** with LiBr failed. In both cases the isolable reactionproduct was *trans*-1,4-dimethanesulfonamido-2-butene (**7**), indicating that debromination and *cis*–*trans* isomerization take place under these conditions. On the other hand the *meso* 2,3-dibromo-1,4-dimethanesulfonamidobutane could be obtained by Br_2 addition to **7** at room temperature finally proving the *trans* configuration of **7**. This compound, the dihalides **9**, as well as the bismethanesulfonates **5** and **10**, smoothly yielded the corresponding biaziridines **8** by ring closure in aqueous NaOH. In our hands this reaction could not be extended to the 2,3-dichloro derivative **4**. The structure of **8** seems to be provided by the synthetic routes, but further evidence was supplied by a ring opening reaction with hydrohalic acids and $MeSO_3H$ resulting in the formation of **9** and **10**. Compound **10** was furthermore obtained from **14** in two steps. Unsuccessful attempts were made to prepare the desired (2*S*,3*S*)-2,3-diamino-1,4-dibromobutane by hydrolysis of (*S*,*S*)-**9b** in boiling HBr. (3*S*,4*S*)-Diaminotetrahydrofuran was formed, identical with authentic material obtained by hydrolysis of (2*S*,3*S*)-*N*,*N*'-dicarbethoxy-1,4-diamino-2,3-butanediol 2,3-bismethanesulfonate.[1] It is suggested that the ring closure is caused by a 1-bromo-4-hydroxybutane derivative, assumed to be in equilibrium with the dibromo compound under the prevailing conditions. This ring closure is furthermore in agreement with the investigated[4] tetrahydrofuran formation from 4-methanesulfonyloxy-1-butanol which proceeds very smoothly in H_2O at room temperature even under acidic conditions, and with the reported[5] conversion of mesylated polyalcohols into the corresponding anhydro sugar alcohols.

Treatment of **9**, **10**, or **11** with $SOCl_2$ under various conditions afforded the 3,4-dihalogenomethyl- and the 3,4-dimethanesulfonyloxymethyl-2,5-dimethanesulfonyl-1,2,5-thiadiazolidine 1-oxides (**13**).

Tosylation of *meso*- and (*S*,*S*)-**1** gave *meso*- and (2*S*,3*S*)-1,4-di-*p*-toluenesulfonamido-2,3-butanediol (*meso*-**15** and (*S*,*S*)-**15**) which were mesylated to the corresponding 2,3-bismethanesulfonates *meso*-**16** and (*S*,*S*)-**16**. Cyclization yielded *meso*- and (2*R*,2'*R*)-*N*,*N*'-di-*p*-toluenesulfonyl-2,2'-biaziridine (*meso*-**17** and (*R*,*R*)-**17**), which by ring opening with HBr and HCl afforded *meso*- and (2*S*,3*S*)-1,4-dihalogeno-2,3-di-*p*-toluenesulfonamidobutanes (*meso*- **18a**, **18b** and (*S*,*S*)-**18a**, **18b**).

Anticancer Screening.—For the selected compounds which were submitted to anticancer screening at the Cancer Chemotherapy National Service Center, National Institutes of Health; the screening data are

(1) Paper II: P. W. Feit and O. Tvaermose Nielsen, *J. Med. Chem.*, **10**, 927 (1967).

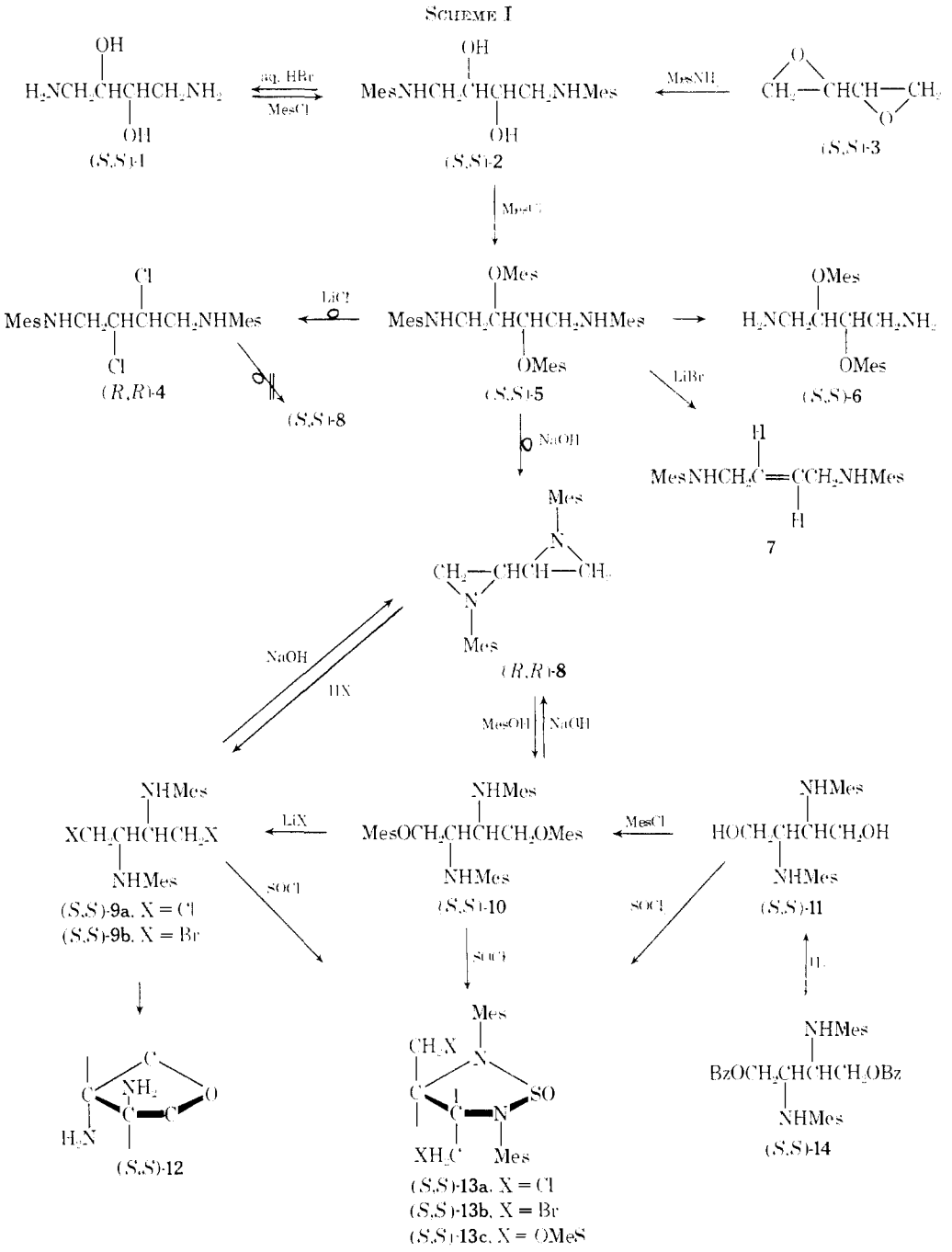
(2) P. W. Feit and O. Tvaermose Nielsen, *ibid.*, **10**, 697 (1967).

(3) (a) P. W. Feit, *Chem. Ber.*, **93**, 116 (1960); (b) P. W. Feit, *J. Med. Chem.*, **7**, 14 (1964).

(4) P. W. Feit, publication in preparation.

(5) (a) S. B. Brown and G. M. Timmis, *J. Chem. Soc.*, 3652 (1961); (b) P. W. Feit, *Chem. Ber.*, **96**, 712 (1963).

SCHEME I



included in Tables I, II, III, and IV. It appears from the rather limited data presented that compounds (*R,R*)-**8** (Table II), (*S,S*)-**9b** (Table III), and (*S,S*)-**10** (Table III) show some activity in the Carcinoma 1025 (mice) system. Testing was only extended for (*S,S*)-**9b** and a dose response was obtained.

Experimental Section[6]

1,4-Dimethanesulfonamido-2,3-butanediols (2). Method A. Part a (Table I).—A solution of **3** (43 g) and methanesulfonamide (143 g) in dry PhMe (400 ml) was refluxed for about 24 hr. On cooling the separated oil crystallized; trituration with MeCN (100 ml) gave 65–75 g of crude **2**.

(6) Analyses were performed by G. Cornali and W. Egger of these laboratories. Melting points were taken in open glass capillaries and rounded off to half degrees, using a Hershberg apparatus with thermometers subdivided in 0.1°. Analytical data are given as defined in footnote *b*, Table I.

Part b.—To a solution of 1·2HBr[2,7] (1.4 g) in 2 *N* NaOH (5 ml), MesCl (1.0 ml) and 2 *N* NaOH (6 ml) were simultaneously added dropwise over a period of 30 min with stirring at 0–5°. HCl (4 *N*, 2 ml) was added and the resulting precipitate washed with H_2O, EtOH, and Et_2O to give 0.2–0.3 g of crude **2**. The ir spectra (KBr), melting points and analyses were identical with those of the compounds prepared as in part a.

1,4-Di(*p*-toluenesulfonamido)-2,3-butanediols (15). Method B (Table I).—To a solution of 1·2HBr (14.1 g) and NaOH (15 g) in H_2O (100 ml), a solution of TsCl (28.5 g) in PhH (100 ml) was added dropwise over a period of 45 min while stirring vigorously at about 30°. After additional stirring for about 1.5 hr the aqueous layer was separated, washed with Et_2O, and then acidified with concentrated HCl (15 ml). The mixture was kept in a refrigerator for 20 hr and the precipitate washed with H_2O, a small amount of EtOH, and Et_2O, to give 8.0–11.5 g of crude **15**.

(2*R*,3*R*)-1,4-Diamino-2,3-butanediol Dihydrobromide [(*R,R*)-1·2HBr].—A solution of (*R,R*)-**2** (5.4 g) in 48% HBr (100 ml) was refluxed for 65 hr and then evaporated under reduced pres-

(7) G. W. Kilmer and H. McKennis Jr., *J. Biol. Chem.*, **152**, 103 (1944).

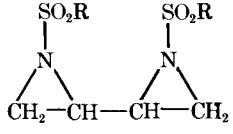
Table I

$RNHCH_2CHXCHXCH_2NHR$

No. and configuration	R	X	Mp, °C	Solvent of recrystn	$[\alpha]^{20}D$, deg	Method[a]	Formula	Analyses[b]	Tumor system,[c] 25[d]
meso-2	SO_2Me	OH	171–171.5	MeCN		A(a), (b)	$C_6H_{16}N_2O_6S_2$	C, H, N, S	
DL-2	SO_2Me	OH	131–132	MeCN		A(a)		C, H, N, S	
(*R*,*R*)-2	SO_2Me	OH	128–129.5	MeCN	+12.1[e]	A(a)		C, H, N, S	
(*S*,*S*)-2	SO_2Me	OH	128.5–129.5	MeCN	−12.2[e,f]	A(a), (b)		C, H, N, S	
meso-4	SO_2Me	Cl	180.5–181.5	MeCN		H	$C_6H_{14}Cl_2N_2O_4S_2$	C, H, Cl, N, S	86 (9) 500
DL-4	SO_2Me	Cl	176.5–177.5	MeCN		H		C*, H, Cl, N, S	
(*R*,*R*)-4	SO_2Me	Cl	167.5–168.5	EtOH	+13.2[g]	H		C, H, Cl, N, S	+(5) 500
(*S*,*S*)-4	SO_2Me	Cl	167.5–168.5	MeCN	−13.6[g]	H		C, H, Cl, N, S	98 (9) 250
meso-5	SO_2Me	OSO_2Me	156.5–157	MeCN		F	$C_8H_{20}N_2O_{10}S_4$	C, H, N, S	87 (9) 500
DL-5	SO_2Me	OSO_2Me	150.5–151.5	MeCN		F		C, H, N, S	88 (10) 500
(*R*,*R*)-5	SO_2Me	OSO_2Me	175–176.5	MeCN	−0.7[g]	F		C, H, N, S	89 (9) 500
(*S*,*S*)-5	SO_2Me	OSO_2Me	175.5–177	MeCN	+0.6[g]	F		C*, H, N, S	67 (10) 125
(*R*,*R*)-6·2$MeSO_3H$	H	OSO_2Me	201.5–202.5 dec	*h*	+26.0[e]	C	$C_6H_{16}N_2O_6S_2 \cdot 2CH_3SO_3H$	C, H, N, S	
(*S*,*S*)-6·2$MeSO_3H$	H	OSO_2Me	200–201 dec	*h*	−25.8[e]	C		C, H, N*, S[i]	
meso-15	$SO_2C_6H_4$(4-Me)	OH	157–157.5	EtOH		B	$C_{18}H_{24}N_2O_6S_2$	C, H, N, S	
(*S*,*S*)-15	$SO_2C_6H_4$(4-Me)	OH	141–142	EtOH	−5.6[j]	B		C, H, N, S	
meso-16	$SO_2C_6H_4$(4-Me)	OSO_2Me	203–204	MeCN		G	$C_{20}H_{28}N_2O_{10}S_4$	C, H, N, S	37 (9) 500[k]
(*S*,*S*)-16	$SO_2C_6H_4$(4-Me)	OSO_2Me	213.5–214.5	MeCN	+33.5[j]	G		C, H, N, S	80 (10) 500

[a] The letters relate to the general procedures in the Experimental Section. [b] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.25% of the theoretical values, or when marked with an asterisk within ±0.40% of the theoretical values. [c] The reported activities should be considered in a qualitative manner in comparing screening results. The number given is the mean tumor weight of test/control in per cent over the dose in milligrams per killogram. The number in parentheses is the number of animals surviving the test period out of 10 animals with Carcinoma 1025 (mice) and of 6 animals with Walker 256 (Subcutaneous). [d] Carcinoma 1025 (mice), administered i. p. once daily, day 1–5, sacrified for evaluation day 15. [e] *c* 2, H_2O. [f] For material prepared by method A(a); for material prepared by method A(b) the value was −12.1°. [g] *c* 2, DMF. [h] Purified by reprecipitation from H_2O acified with $MeSO_3H$ by addition of EtOH. [i] S: calcd, 27.27; found, 26.94. [j] *c* 2, MeCN. [k] Repeated, no effect.

Table II



No. and configuration	R	Mp, °C	Solvent of recrystn	$[\alpha]^{20}D$, deg	Method[a]	Formula	Analyses[b]	Tumor system[c] 25[d]	Tumor system[c] Wa[e]
meso-8	Me	155–159	MeCN		I(a), (b)	$C_6H_{12}N_2O_4S_2$	C, H, N, S	(5) 125	
DL-8	Me	165–166	MeCN		I(b)		C, H, N, S	(5) 125	
(*R*,*R*)-8	Me	183–184	MeCN	+208[f]	I(a), (b)		C, H, N, S	31(10) 15 42(8) 15	
(*S*,*S*)-8	Me	182.5–184	MeCN	−199[f]	I(b)		C, H, N, S*		56(6) 12[g]
meso-17	C_6H_4(4-Me)	137–138	MeCN		J	$C_{18}H_{20}N_2O_4S_2$	C, H, N, S		
(*R*,*R*)-17	C_6H_4(4-Me)	128–129.5	MeCN–H_2O	+111[f]	J		C, H, N, S		85(6) 50

[a–d] See corresponding footnotes in Table I. [e] See footnote *e*, Table III. [f] *c* 2, MeCN. [g] About 0.25 LD_{10} in untreated albino rats.

TABLE III

$XCH_2CHNHRCHNHRCH_2X$

No. and configuration	R	X	Mp, °C	Solvent of recrystn.	$[\alpha]^{20}D$, deg	Method[a]	Formula	Analyses[b]	Tumor system[c] 25[d]	Tumor system[c] Wa[e]
meso-9a	SO_2Me	Cl	226.5–227	MeCN		H	$C_6H_{14}Cl_2N_2O_4S_2$	C, H, Cl, N, S	77(9) 500	
DL-9a	SO_2Me	Cl	177–178	MeCN		H		C, H, Cl, N, S		64(6) 50
(*R*,*R*)-9a	SO_2Me	Cl	168.5–169.5	EtOH	−10.7[f]	K		C, H, Cl, N, S	93(10) 500	
(*S*,*S*)-9a	SO_2Me	Cl	168.5–169.5	EtOH	+11.2[f,g]	H, K		C, H, Cl, N, S	37(9) 500	
meso-9b	SO_2Me	Br	218–220 dec	Ethyl Cellosolve		K	$C_6H_{13}Br_2N_2O_4S_2$	C, H, Br*, N, S		
DL-9b	SO_2Me	Br	213.5–215 dec	Ethyl Cellosolve		H		C, H, N, S, Br[h]		61(6) 14[i]
(*R*,*R*)-9b	SO_2Me	Br	211.5–213	Ethyl Cellosolve	−6.9[f]	H		C, H, Br, N, S	0(8) 125 59(9) 62	
(*S*,*S*)-9b	SO_2Me	Br	212.5–213.5 dec	Ethyl Cellosolve	+6.7[f,j]	H, K		C, H, Br, N, S	75(10) 16 44(10) 32 45(10) 62.5 6(10) 125 (1) 250	
meso-10	SO_2Me	OSO_2Me	205.5–206.5	DMF–EtOH		F	$C_8H_{20}N_2O_{10}S_4$	H, N, S*, C[k]	45(10) 250	
DL-10	SO_2Me	OSO_2Me	185–186[l] dec	MeCN		F		C, H, N, S	44(10) 500	
(*R*,*R*)-10	SO_2Me	OSO_2Me	203.5–205.5	DMF–H_2O	−22.9[f]	M		H, N*, C[m]S[n]		
(*S*,*S*)-10	SO_2Me	OSO_2Me	209–210 dec	DMF–EtOH	+22.9[f,o]	F, M		C, H, N; S[p]	23(10) 63	
meso-11	SO_2Me	OH	180–182	MeCN		E	$C_6H_{16}N_2O_6S_2$	C, H, N, S		
DL-11	SO_2Me	OH	189–190	EtOH (90%)		E		C, H, N, S*		
(*S*,*S*)-11	SO_2Me	OH	156–156.5	EtOH	+29.3[q]	E		C, H, N, S		
meso-14	SO_2Me	$OCH_2C_6H_5$	158–159	EtOH		D	$C_{20}H_{28}N_2O_6S_2$	C, H, N, S		
DL-14	SO_2Me	$OCH_2C_6H_5$	122.5–123	EtOH		D		C, H, N, S		
(*S*,*S*)-14	SO_2Me	$OCH_2C_6H_5$	94.5–95	EtOH	+11.9[f]	D		C, H, N, S		
(*S*,*S*)-18a	$SO_2C_6H_4$(4-Me)	Cl	192–193	MeCN	+73.8[r]	L	$C_{18}H_{22}Cl_2N_2O_4S_2$	C, H, Cl, N, S		117(6) 25
(*S*,*S*)-18b	$SO_2C_6H_4$(4-Me)	Br	205–206	MeCN	+81.5[r]	L	$C_{18}H_{22}Br_2N_2O_4S_2$	C, H, Br, N, S		122(6) 50

[a–d] See corresponding footnotes in Table I. [e] Walker 256 (Subcutaneous). Assays were performed as reported in *Cancer Chemother. Rept.*, **25**, 11 (1962). [f] *c* 2, DMF. [g] For material prepared by method H; for material prepared by method K the value was +10.3°. [h] Calcd: Br, 39.75; found: 39.13. [i] About 0.25 LD_{50} in untreated albino rats. [j] For material prepared by both method H and method K. [k] Calcd: C, 22.21; found: 22.62. [l] A higher melting modification (mp 207.5–208.5) was isolated in one occasion. The infrared spectrum (KBr) of this material was identical with those of the optically active isomers. [m] Calcd: C, 22.21; found: 22.69. [n] Calcd: S, 29.65; found: 29.24. [o] For material prepared by method F; for material prepared by method M the value was +20.4°. [p] Calcd: S, 29.65; found: 29.17. [q] *c* 2, H_2O. [r] *c* 2, MeCN.

Table IV

No. and configuration	R	X	Mp, °C	Solvent of recrystn	$[\alpha]^{20}D$, deg	Method[a]	Formula	Analyses[b]	Tumor system[c] 25[d]	Tumor system[c] Ws[e]
(*R,R*)-13a	Me	Cl	173.5–174.5	MeCN–EtOH	+40.1[f]	N(a)	$C_6H_{12}Cl_2N_2O_5S_2$	C*, H, Cl, N, S		85(6) 25
(*S,S*)-13a	Me	Cl	173.5–174	MeCN–EtOH	−38.3[f]	N(b)		C, H, Cl*, N, S		
(*R,R*)-13b	Me	Br	160.5–161	MeCN–EtOH	+31.1[g]	N(a)	$C_6H_{12}Br_2N_2O_5S_2$	C*, H, N, S, Br[h]		88(6) 25
meso-13c	Me	OSO_2Me	214–215	Formamide		N(a)	$C_8H_{18}N_2O_{11}S_5$	C, H*, N, S[i]	13(10) 500	
DL-13c	Me	OSO_2Me	199–200.5	MeCH–EtOH		N(a)		C*, H, N, S	57(10) 250	

[a–d] See corresponding footnotes in Table I. [e] See footnote *e*, Table II. [f] *c* 2, DMF. [g] *c* 2, MeCN. [h] Calcd: Br, 35.66; found: 34.43. [i] Calcd: S, 33.50; found: 33.08.

sure. Trituration with Me_2CO gave 5.2 g of crude (*R,R*)-**1**·2HBr. After recrystallization from H_2O–EtOH the compound started to decompose above 250°, $[\alpha]^{20}D$ +20.3° (*c* 2, H_2O). *Anal.* ($C_4H_{12}N_2O_2$·2HBr) C, H, Br, N.

The **tetrabenzoate** had mp 156–157° (EtOH), $[\alpha]^{20}D$ +30.0° (*c* 2, DMF). *Anal.* ($C_{32}H_{28}N_2O_6$) C, H, N.

The **bissalicylaldehyde Schiff base** had mp 225.5–226.5° dec, lit.[8] mp 228–231° dec.

1,4-Diamino-2,3-butanediol 2,3-Bismethanesulfonate Dimethanesulfonates (Salts) (6·2MeSO$_3$H). Method C (Table I).—A mixture of **5** (6.5 g), $MeSO_3H$ (13.5 ml), and H_2O (1.5 ml) was heated to 130–135° for about 3.5 hr with stirring. After cooling, EtOH (30 ml) and Et_2O (75 ml) were added and the separated heavy oil triturated with hot EtOH (30 ml). The semi-solid residue was extracted with H_2O (35 ml), which after treatment with decolorizing C was removed under reduced pressure. The residue was triturated with EtOH (20 ml) to give 4.2 g of crude **6**·2MeSO$_3$H.

1,4-Dibenzyloxy-2,3-dimethanesulfonamidobutanes (14). Method D (Table III).—To a solution of 1,4-dibenzyloxy-2,3-diaminobutane dihydrochloride (18.7 g) in pyridine (75 ml), MesCl (12 ml) was added dropwise over a period of 1 hr while stirring at 0–5°. The mixture was kept in a refrigerator for about 20 hr and then poured into ice–2 *N* HCl (0.5:1). The resulting precipitate was washed with H_2O, EtOH, and Et_2O to give 15–20 g of crude **14**.

2,3-Dimethanesulfonamido-1,4-butanediol (11). Method E (Table III).—A suspension of **14** (13.7 g) in EtOH (225 ml) and H_2O (75 ml) acidified with 4 *N* HCl (5 ml) was hydrogenated in the presence of 10% Pd–C (3.0 g) under 1.1 atm of pressure. H_2 uptake was complete in 2–4 hr. The catalyst was removed by filtration and thoroughly washed with 50% EtOH and with H_2O. The combined filtrate was evaporated under reduced pressure and the residue triturated with EtOH (50 ml) to give 6.0–7.2 g of crude **11**.

2,3-Dimethanesulfonyloxy-1,4-dimethanesulfonamidobutane (5) and 1,4-Dimethanesulfonyloxy-2,3-dimethanesulfonamidobutane (10). Method F (Tables I and III).—To a solution or suspension of **2**(or 11) (27.6 g) in pyridine (150–300 ml), MesCl (25 ml) was added dropwise while stirring at 0–5°. After additional stirring for 1–2 hr, the mixture was poured into ice–2.5 *N* HCl (about 2 l.). The resulting precipitate[9] was washed with H_2O EtOH, and Et_2O to give 80–95% of crude **5** or 55–80% of crude **10**, respectively.

2,3-Dimethanesulfonyloxy-1,4-di-(*p*-toluenesulfonamido)butanes (16). Method G (Table I).—Method E was followed using (**15**) as starting material. The yield of crude **16** was 85–95%.

2,3-Dichloro-1,4-dimethanesulfonamidobutanes (4) and 1,4-Dihalogeno-2,3-dimethanesulfonamidobutanes (9a and 9b). Method H (Tables I and III).—A solution of LiBr (45 g) (or LiCl, 22 g) in ethyl-Cellosolve (350–500 ml) was dried by distilling off moist solvent (about 100 ml) until the boiling point was 134–135°. The starting material **5** (or **10**) (21.6 g) was added and the mixture was refluxed for 2.5–4 hr. After evaporation under reduced pressure the residue was triturated with H_2O to give 70–85% of crude **4**, **9a**, or **9b**, respectively.

***trans*-1,4-Dimethanesulfonamidobutene-2 (7).**—The compounds *meso*-**5**[or (*S,S*)-**5**] (8.6 g) were treated with LiBr using method H except that the reaction time was extended to about 22 hr. The yield of crude **7** was about 2.0 g. After recrystallization from MeCN the mp was 183–184.5°. *Anal.* ($C_6H_{14}N_2O_4S_2$) C, H, N, S.

***meso*-2,3-Dibromo-1,4-dimethanesulfonamidobutane.**—To a suspension of **7** (0.5 g) in $CHCl_3$ (10 ml), a solution of Br_2 (0.32 g) in $CHCl_3$ (10 ml) was added dropwise while stirring. After additional stirring for about 4 hr the precipitate was washed with $CHCl_3$ and with Et_2O to give 0.8 g of crude material with mp 186–193°. Recrystallization from MeCN raised the melting point to 198.5–200°. *Anal.* ($C_6H_{14}Br_2N_2O_4S_2$), C, H, N, S; calcd: Br, 39.75; found: 38.95.

1,1'-Dimethanesulfonyl-2,2'-biaziridines (8). Method I Part a (Table II).—To a solution of **9a** (6.3 g) in MeCN (100 ml), Ag_2O (12 g) was added and the mixture refluxed for 1 hr. The inorganic precipitate was removed by filtration and the re-

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(9) In the case of the stereoisomeric **10** the precipitation sometimes was very sluggish.

sulting clear solution evaporated under reduced pressure. Crude **8** was obtained in about 90% yield by trituration of the residue with Et_2O.

Part b.—The appropiate dihalogeno- or dimethanesulfonyloxydimethanesulfonamidobutanes (**5**, **9a**, **9b**, or **10**) (0.1 mol) was dissolved in 10% NaOH (about 450 ml). After a few moments the biaziridine started to separate. Washing with H_2O, EtOH, and Et_2O gave 75–90% of crude **8**.

1,1'-Di(*p*-toluenesulfonyl)-2,2'-biaziridines (17). Method J.—(Table II) Method I, Part b was followed using **16** as starting material. The yield of crude **17** was 60–70%.

1,4-Dihalogeno-2,3-dimethanesulfonamidobutanes (9a,b) by Opening of the Biaziridines 8 with Halo Acids. Method K (Table III).—The biaziridine **8** was dissolved in a large excess of the appropiate haloacid (5 *N* HCl or 3 *N* HBr). After a few moments the reaction product started to separate. Washing with H_2O, EtOH, and Et_2O gave 70–75% of crude **9a** or 90–95% of crude **9b**, respectively. The physical properties were identical with those of the compounds prepared as in method H.

1,4-Dihalogeno-2,3-di(*p*-toluenesulfonamido)butanes (18a and 18b). Method L (Table III).—To a solution of the biaziridine **17** (7.85 g) in MeCN (20 ml), the appropiate concentrated haloacid (20 ml) was rapidly added while stirring. After a few moments the reaction product started to separate. The mixture was diluted with H_2O (20 ml) and kept in a refrigerator for about 20 hr. Washing with H_2O, EtOH, and Et_2O gave 70–75% of crude **18a** or **18b**, respectively.

1,4-Dimethanesulfonyloxy-2,3-dimethanesulfonamidobutanes (10) by Opening of the Biaziridines 8 with $MeSO_3H$. Method M (Table III).—To a solution of the biaziridine **8** (4.8 g) in MeCN (50 ml), a mixture of $MeSO_3H$ (6.0 g) and H_2O (1.0 ml) was rapidly added while stirring. After additional stirring for about 2 hr the solvent was removed under reduced pressure. The residue was washed with Et_2O and triturated with MeCN (10 ml) to give about 2.6 g of crude **10**. The physical properties were identical with those of the compounds prepared as in Method E.

Attempts to open the biaziridine (*S,S*)-**17** with $MeSO_3H$ using method M resulted in **(2*S*,3*S*)-1-acetamido-4-methanesulfonyloxy-2,3-di-(*p*-toluenesulfonamido)butane,** mp 193.5–195° (MeCN), $[\alpha]^{20}D$ +66.0° (*c* 2, DMF). *Anal.* ($C_{29}H_{39}N_3O_8S_3$) H, N, S; Calcd C: 46.06; found: 45.48.

3,4-Disubstituted-2,5-dimethanesulfonyl-1,2,5-thiadiazolidine-1-oxides (13a,b, and c). Method N, Part a (Table IV).—A mixture of **9a**, **9b**, or **10** (0.01 mol), $SOCl_2$ (50 ml), pyridine[10] (3.0 ml), and $CHCl_3$ (20 ml) was refluxed for 4 hr. The resulting solution was evaporated under reduced pressure and the residue washed with H_2O, EtOH, and Et_2O to give 85–95% of crude **13a,b**, or **c**, respectively.

Part b.—Compound **11** was treated with $SOCl_2$ as in Part a except that no $CHCl_3$ and only a catalytical amount of pyridine was added. The yield of crude **13a** was about 45%.

(3*S*,4*S*)-3,4-Diaminotetrahydrofuran Dihydrobromide [(*S,S*)-12·2HBr].—A solution of **18b** (2.8 g) in 48% HBr (30 ml) and AcOH (30 ml) was refluxed for about 48 hr, evaporated under reduced pressure, and the residue triturated with Me_2CO to give 0.7 g of crude (*S,S*)-**12**·2HBr. After recrystallization from H_2O–48% HBr the material started to decomposes at about 270°, $[\alpha]^{20}D$ −20.9° (*c*, H_2O). *Anal.* ($C_4H_{10}N_2O$·2 HBr) C, H, Br, N.

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(10) When **9b** or **10** was reacted, pyridine was replaced by pyridine hydrobromide (4.5 g) or pyridine methanesulfonic acid salt (5.0 g), respectively.

Structure–Activity Relationships in Adenosine Deaminase Inhibitors[1]

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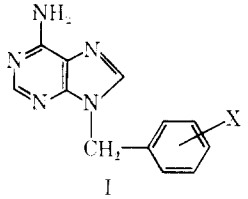
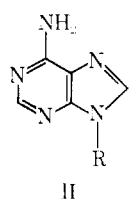
Structure–activity correlations for a series of 9-*n*-alkyladenines (II) and 9-(1-hydroxy-2-alkyl)adenines (III) as inhibitors of adenosine deaminase have shown a high dependence of inhibitory activity on the hydrophobic character (π) of the 9 substituent. The slope of the equation derived from compounds related to III is greater than the slope derived from compounds related to II. This increase in slope for III may reflect a conformational change in the enzyme. A comparison of some *meta* and *para* isomers of 9-benzyladenines (I) reveals that the *meta* isomers are correlated by an equation containing both a π and σ term. However, no correlation could be found for the *para*-substituted isomers. This variation in the binding regions of adenosine deaminase for the *meta* and *para* isomers of I is also reflected in the dramatic difference in the ability of the *para* and *meta* isomers of 9-(bromoacetamidobenzyl)adenines to cause irreversible inhibition of the enzyme.

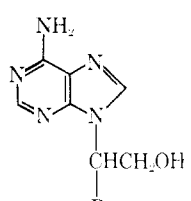
In continuing our study[2,3] of the structure–activity relationships in adenosine deaminase inhibitors we consider in this report derivatives of 9-benzyladenines (I).



I



II



III

In the present study a variety of substituents (X) have been placed in the 3 and 4 position of the benzyl moiety of I in order to assess their hydrophobic, electronic, and steric effects on inhibitory action.

In previous studies of the effect of substituents attached to adenine, as in II and III, a strong dependence of inhibitory action on hydrophobic binding has been established. The structure–activity relationship for the derivatives[4] in Table I is defined in eq 1 and that for the congeners[3] of Table II is contained in eq 2 and 3. The quality of the fit obtained with eq 1 and 2 as

Inhibitors Table I	n	r	s	
$-\log (I/S)_{0.5} =$				
$0.452(\pm 0.06)\pi - 1.194(\pm 0.15)$	8	0.992	0.078	(1)

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