New Antifilarial Agents. 1. Epoxy Sulfonamides and Ethynesulfonamides[1]

Marie-Josèphe Brienne,*† Daniel Varech,† Martine Leclercq,† Jean Jacques,† Nathalie Radembino,‡ Marie-Christine Dessalles,‡ Georges Mahuzier,‡ Chantal Gueyouche,§ Christian Bories,§ Philippe Loiseau,§ and Philippe Gayral*§

Chimie des Interactions Moléculaires, ER 285 CNRS, Collège de France, 75005 Paris, France, and Laboratoire de Chimie analytique II and Laboratoire de Parasitologie, Faculté de Pharmacie, Université Paris XI, 92290 Chatenay-Malabry, France.
Received December 8, 1986

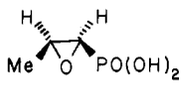
Two series of 2-substituted 1,2-epoxyethanesulfonamides **2** and ethynesulfonamides **5** were synthesized and evaluated for their antifilarial activity. The trans epoxides **2T** were stereospecifically prepared by a Darzens reaction between aldehydes and halomethanesulfonamides. The cis isomers **2c** were obtained from ethynesulfonamides **5** by semihydrogenation followed by KOCl epoxidation. 2-Substituted ethynesulfonamides **5** were synthesized from appropriate *trans*-ethenesulfonamides by a bromination/dehydrobromination sequence. These products, as well as several synthetic intermediates, were evaluated for antifilarial activity against *Molinema dessetae* either in vivo in its natural host, the rodent *Proechimys oris*, or in vitro by a new test using cultures of the infective larvae. Most of the epoxides **2T** and acetylenic derivatives **5** bearing a 2-aryl substituent were active in vitro. Among these compounds, four epoxides **2T** and one acetylenic derivative **5** showed marked *macrofilaricidal* activity in vivo without any microfilaricidal activity. The differences between the in vivo and in vitro results may be due, in part, to the low chemical stability of the epoxy sulfonamides **2T**. Despite this limitation, the activities observed in this reliable animal model suggest further development and testing of both series **2T** and **5** as macrofilaricides.

Despite numerous efforts in the last decades, eradication of filarial infections, which affect more than 200 000 000 people, remains one of the major health problems in tropical areas. Chemotherapeutic solutions to this problem are still extremely sparse and inappropriate. In this regard, onchocerciasis (or river blindness), which affects about 30 000 000 people, is particularly illustrative. Control of this disease is presently restricted to the use, on a large scale, of insecticides (acting against *Simulii*, the vectors of this infection) since no efficient and safe drug is available. In infected people, the drugs that kill the microfilariae laid by females often provoke severe reactions, mainly allergic in nature, which make the treatment unpopular and unacceptable in mass therapy. On the other hand, the few drugs able to kill the adult worms (or macrofilariae) are too toxic to be safely recommended in human prophylaxis. Thus, development of a potent and nontoxic filaricide, especially a macrofilaricide for onchocerciasis, remains a priority.[2]

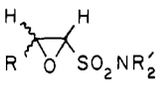
Research in this area is difficult for several reasons. One difficulty is that appropriate experimental filariae in animals do not yet exist, that would mimic the pathology observed in humans or show the same sensitivity to antifilarial compounds as human parasites. On the other hand, the antifilarial activity of drugs varies with the filaria species and with the stage of its life cycle: the adult worms are often less sensitive to chemotherapeutic agents than microfilariae, which mainly dwell in the bloodstream and superficial tissues. Also, knowledge of the parasite biochemistry is still too scanty to be of help in a rational approach to new potentially active molecules.

Previously, some of us have developed a new animal model,[3] which uses *Molinema* (ex *Dipetalonema*) *dessetae* in its natural host, *Proechimys oris*, a small brazilian rodent.[4] This model was found to be remarkably sensitive to the major known filaricides[3b] (see Table IV) and was thus suitable as a screen test for antifilarial activities. In this way, a weak *macrofilaricidal* activity was found for fosfomycin (**1**) [(−)-(1*R*,2*S*)-(1,2-epoxypropyl)phosphonic acid], a well-known antibiotic.[5]

This finding prompted us to explore a series of epoxides of general structure **2** (cis or trans), bearing a sulfonamide



1



2C *(cis)*

2T *(trans)*

group which could be regarded as a nonclassical isostere (following a suggestion of Thornber[6]) of the phosphonic group of **1**. It soon became obvious that this approximate analogy could not account for the observed activities. In fact, only the trans epoxy sulfonamides **2T** were active in killing adult worms while the model molecule **1** has a cis configuration. In addition, we found interesting activities for several intermediate ethynesulfonamides **5**. We also examined these two series in vitro against the infective larvae of *M. dessetae*, by using a test recently described by us.[7] The results of these investigations are reported here.

Chemistry

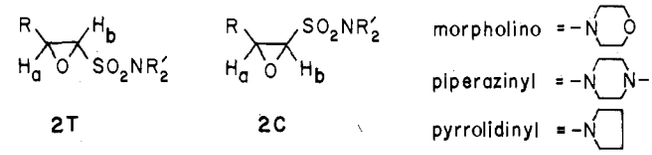
1. Syntheses. The synthetic approaches to compounds **2** (Table I) and **5** (Table II) are depicted in Scheme I. Most of the trans epoxy sulfonamides **2T** were stereospecifically obtained in fair to good yields by reaction of halomethanesulfonamides **3** with appropriate aldehydes (Darzens reaction[8]) in the presence of HK or HNa (methods A, B). Cis epoxy sulfonamides **2c** were syn-

† Collège de France.
‡ Laboratoire de Chimie analytique II.
§ Laboratoire de Parasitologie.

(1) Previously reported, in part, in the following patent: Jacques, J.; Brienne, M.-J.; Gayral, P.; Varech, D. French Demande 85. 00575, 1985.
(2) Although transmission of onchocerciasis is expected to virtually stop at the end of the Vector Control Programme (by 1990), there is still an urgent need for a macrofilaricidal drug. This point was recently reaffirmed at the *Filariasis Seminar* '86 held by the Wellcome Foundation, in collaboration with the WHO, Onchocerciasis Chemotherapy Project; London, 13 Nov 1986.
(3) (a) Gayral, Ph.; Dreyfuss, G.; Gantier, J.-C. *Cah. ORSTOM, Sér. Ent. Méd. Parasitol.* **1982**, *XX*, 81. (b) Gayral, Ph.; Dreyfuss, G.; Gantier, J.-C. *J. Pharmacol.* **1982**, *13*, 49.
(4) Bain, O. *Bull. Mus. Hist. Nat. (Paris), 3e Série* **1973**, *116*, 309.
(5) Gayral, Ph.; Dreyfuss, G. *C. R. Seances Acad. Sci., Ser. 3* **1981**, *292*, 717.
(6) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563.
(7) Bories, C.; Loiseau, P.; Gueyouche, C.; Gayral, Ph. *J. Pharmacol.* **1986**, *17*, 301.
(8) (a) Golinski, J.; Makosza, M. *Synthesis* **1978**, 823. (b) Truce, W. E.; Christensen, L. W. *J. Org. Chem.* **1971**, *36*, 2538.

0022-2623/87/1830-2232$01.50/0

Table I. Physical Properties of Trans and Cis Epoxy Sulfonamides **2T** and **2C**

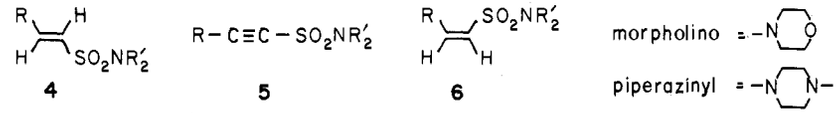


2T **2C**

no.	R	NR'_2	meth[a]	yield, %	mp,[b] °C	formula[c]	NMR[d] H_a	NMR[d] H_b
2aT	Ph	NMe_2	A	76	67	$C_{10}H_{13}NO_3S$	4.34	4.16
2aC	Ph	NMe_2	C	48	82	$C_{10}H_{13}NO_3S$	4.35	4.29
2bT	Ph	morpholino	A	80	112[e]	–	4.36	4.15
			C	40				
2bC	Ph	morpholino	C	70	99.5	$C_{12}H_{15}NO_4S$	4.36	4.27
2cT	Ph	4-Me-1-piperazinyl	A	70	95 dec	$C_{13}H_{18}N_2O_3S$	4.34	4.13
2cC	Ph	4-Me-1-piperazinyl	C	48	99 dec	$C_{13}H_{18}N_2O_3S$	4.35	4.25
2dT	Ph	4-*n*-Pr-1-piperazinyl	A	40	92.5 dec	–[f]	4.34	4.12
2eT	Ph	4-CO_2Et-1-piperazinyl	A	50	88	$C_{15}H_{20}N_2O_5S$	4.36	4.13
2fT	Ph	4-Ph-1-piperazinyl	A	70	127	$C_{18}H_{20}N_2O_3S$	4.38	4.17
2gT	Ph	4-(*m*-$CF_3C_6H_4$)-1-piperazinyl	A	70	108.5	$C_{19}H_{19}F_3N_2O_3S$	4.39	4.18
2hT	Ph	pyrrolidinyl	A	70	95.5	$C_{12}H_{15}NO_3S$	4.35	4.15
2iT	*p*-ClC_6H_4	morpholino	B	65	109	$C_{12}H_{14}ClNO_4S$	4.34	4.11
2jT	3,4-$Cl_2C_6H_3$	morpholino	A	34	140	$C_{12}H_{13}Cl_2NO_4S$	4.32	4.14
2kT	3,4-$Cl_2C_6H_3$	pyrrolidinyl	B	30	95	$C_{12}H_{13}Cl_2NO_3S$	4.33	4.14
2lT	*o*-MeC_6H_4	morpholino	A	78	113	$C_{13}H_{17}NO_4S$	4.48	4.03
2mT	*m*-MeC_6H_4	morpholino	A	70	87	$C_{13}H_{17}NO_4S$	4.32	4.15
2nT	*p*-hexyl-C_6H_4	morpholino	A	28	69.5	$C_{18}H_{27}NO_4S$	4.33	4.16
2oT	*p*-$NO_2C_6H_4$	morpholino	C	42	166 dec	$C_{12}H_{14}N_2O_6S$	4.47	4.14
2pT	*m*-MeC_6H_4	4-Me-1-piperazinyl	A	44	98 dec	$C_{14}H_{20}N_2O_3S$	4.32	4.13
2qT	*p*-MeC_6H_4	4-Me-1-piperazinyl	A	50	dec	$C_{14}H_{20}N_2O_3S$	4.31	4.12
2rT	Me	NMe_2	A	15	34	$C_5H_{11}NO_3S$	3.43	3.85[g]
2sT	Me	morpholino	A	26	66	$C_7H_{13}NO_4S$	3.50	3.86[g]
2sC	Me	morpholino	C	40	65	$C_7H_{13}NO_4S$	3.33	3.96[h]

[a] See Experimental Section and footnote *a*, Scheme I. [b] These compounds were recrystallized from CH_2Cl_2/Et_2O or $MeOH/i\text{-}Pr_2O$ except for **2nT**, which was recrystallized from Et_2O/pentane. [c] Analytical results for C, H were within ±0.4% of the theoretical values. [d] ^1H NMR (200 MHz): chemical shifts δ ($\delta_{TMS} = 0$) of epoxy ring protons, J = 1.5–1.6 Hz in trans isomers **2T**, and J = 3.8–3.9 Hz in cis isomers **2C**. Where R = aryl (**2a–q**), H_a and H_b assignment was based on the evidence of a weak coupling between H_a and aromatic ortho protons. [e] Mp 108–109.5 °C in ref 8a. [f] Solvated with $0.5H_2O$ as deduced from analytical results for ($C_{15}H_{22}N_2O_3S \cdot 0.5H_2O$): calcd C 56.40, H 7.26; found C 56.4, H 7.2. [g] δ Me 1.43, (d, J = 5.3 Hz). [h] δ Me 1.69, (d, J = 5.9 Hz).

Table II. Physical Properties of Unsaturated Sulfonamides **4–6**



4 **5** **6**

no.	R	NR'_2	mp, °C	recrystn solvent	formula[a]
4a	Ph	NMe_2	103[b]	EtOH	–
4b	Ph	morpholino	112[c]	EtOH	–
4c	Ph	4-Me-1-piperazinyl	92	acetone/$i\text{-}Pr_2O$	$C_{13}H_{18}N_2O_2S$
4d	*p*-$NO_2C_6H_4$	NMe_2	178	methoxyethanol	$C_{10}H_{12}N_2O_4S$
4e	*p*-$NO_2C_6H_4$	morpholino	210	methoxyethanol	$C_{12}H_{14}N_2O_5S$
5a	Ph	NMe_2	94	MeOH	$C_{10}H_{11}NO_2S$
5b	Ph	morpholino	95	MeOH	$C_{12}H_{13}NO_3S$
			102.5		
5c	Ph	4-Me-1-piperazinyl	81	Et_2O/pentane	$C_{13}H_{16}N_2O_2S$
5d	*p*-$NO_2C_6H_4$	NMe_2	154 dec	acetone	$C_{10}H_{10}N_2O_4S$
6a	Ph	NMe_2	78	AcOEt/hexane	$C_{10}H_{13}NO_2S$
6b	Ph	morpholino	112	AcOEt/hexane	$C_{12}H_{15}NO_3S$
6c	Ph	4-Me-1-piperazinyl	80	Et_2O/pentane	$C_{13}H_{18}N_2O_2S$
6d	Me	morpholino	liq	–	–[d]

[a] Analytical results for C, H were within ±0.4% of the theoretical values. [b] Melting point 103–104 °C in ref 8a; mp 104 °C in ref 28. [c] Melting point 113.5–115 °C in ref 24. [d] The product was impure and was not analyzed (see Experimental Section).

thesized by epoxidation of *cis*-ethanesulfonamides **6** (Table II), obtained by semihydrogenation of either ethynesulfonamides **5** (R = aryl) or allenesulfonamide **11**.

In general, the requisite ethynesulfonamides **5** were best prepared from the corresponding *trans*-ethenesulfonamides **4** by standard procedures (bromination followed by dehydrobromination with *t*-BuOK). An alternative route (**7** → **8** → **5**) was used when the bromination of unsaturated amides **4** failed (for **4c**, NR'_2 = 4-methyl-1-piperazinyl). The allenic compound **11** was prepared and semihydrogenated without difficulty by conventional procedures.

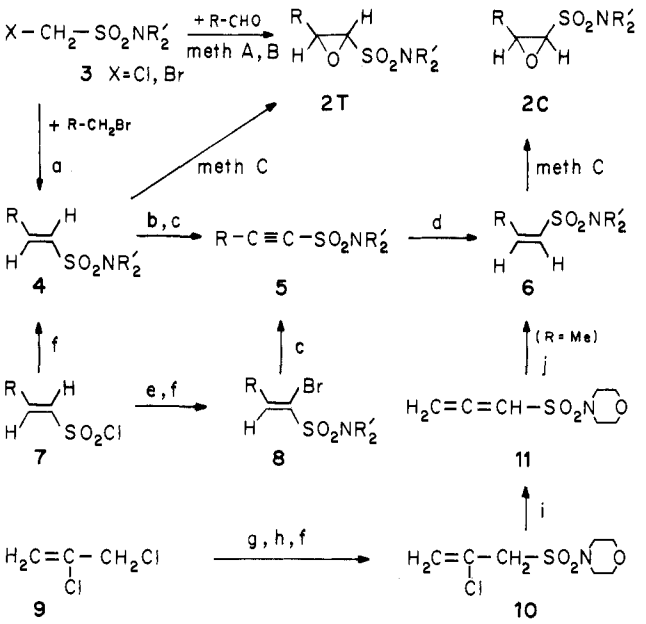
Catalytic hydrogenation of ethynesulfonamides **5** was difficult, presumably due to partial hydrogenolysis of the sulfonamide group and subsequent catalyst poisoning. Alternatively, compounds **6** were conveniently obtained, although in moderate yields, by catalytic transfer hydrogenation in aqueous ethanol with sodium hypophosphite as a hydrogen donor and Pd catalysts. These conditions, however, led to some hydration of the acetylenic bond,

Table III. Kinetics of Decomposition of **2bT** and **2cT** in Solution

		2bT		2cT	
solvent	temp, °C	k,[a] day^{-1}	dec[b] time	k,[a] day^{-1}	dec[b] time
DMSO[c]	0	0.02	230 days	–	–
	20	0.12	38 days	0.41	11 days
	37	0.39	12 days	–	–
MeOH[c]	20	0.30	15 days	0.91	5 days
	37	1.16	4 days	–	–
H_2O[d]	20	42	158 min	117	57 min
	37	89	75 min	–	–

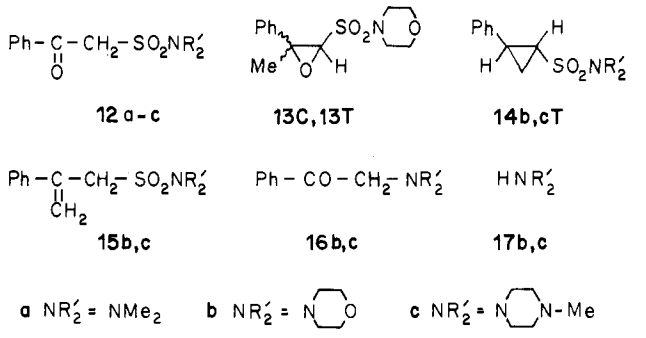
[a] Rate constant. [b] Time necessary to decompose 99% of product. [c] Concentration = 20 g/L. [d] Concentration = 0.2 g/L.

Scheme I[a]



[a] Reagents: (a) 50% NaOH, $Bu_4N^+HSO_4^-$, HMPT (ref 8a); (b) Br_2, CCl_4, reflux; (c) *t*-BuOK, *t*-BuOH, dioxane, room temperature; (d) $NaPO_2H_2$, Pd/C or $Pd/BaSO_4$, EtOH, H_2O, reflux; (e) Br_2, CCl_4, room temperature, then 1 equiv of NEt_3, Et_2O, −5 °C (ref 21); (f) HNR'_2, CH_2Cl_2, 0–10 °C; (g) Na_2SO_3, H_2O, reflux; (h) PCl_5, 120 °C; (i) NaOMe, MeOH, room temperature; (j) H_2, Pd/C, MeOH; (method A) **3** (X = Cl), KH, THF, −78 °C; (method B) **3** (X = Br), NaH, THF, 0 °C; (method C) KOCl, KOH (pH >12), $Bu_4N^+HSO_4^-$, Et_2O and (or) CH_2Cl_2, 20 °C.

resulting in the formation of ketones **12** as the major byproducts.



Successful epoxidation of *cis*-ethenesulfonamides **6** was realized by treatment with alkaline potassium hypochlorite. This reagent was previously used by Curci et al.,[9] for epoxidation of unsaturated sulfones, at 40 °C in aqueous dioxane. In view of the lability of some of the epoxy sulfonamides **2** in aqueous media (see below), epoxidation of **6** was best performed under phase transfer conditions at 20 °C, in Et_2O and (or) CH_2Cl_2/H_2O, with catalytic amounts of tetrabutylammonium salt (method C).[10] Some of the *trans*-ethenesulfonamides **4** could also be epoxidized under these conditions, although in moderate yields. In the cases where the Darzens route failed (for example, **2oT**, Table I), this method was a valuable alternative to prepare the trans epoxy sulfonamides.

In addition, for comparison of biological activities, the structurally related sulfonamides **13–15** were synthesized by literature procedures (see Experimental Section).

2. Stability. The chemical stability of these compounds was investigated because erratic biological results were observed for some of the epoxy sulfonamides **2T** when the injected suspensions were not freshly prepared. We now report a few kinetic data regarding some biologically active compounds. More details will be published elsewhere.

Epoxy sulfonamides **2**, upon heating beyond their melting points, underwent stepwise decomposition (first step ca. 130–180 °C, second step ca. 180–230 °C; see Experimental Section) with loss of volatile material. The major product of the first decomposition step (up to 160 °C) of the morpholino derivative **2bT** was identified as *N*-phenacylmorpholine (**16b**). The formation of this ketone did not arise from the transformation of oxosulfonamide **12b**, which would be expected in the thermal rearrangement[11] of **2bT**, since **12b**, which displayed greater stability (decomposition > 230 °C), did not afford amino ketone **16b** upon heating. Comparatively, the 4-methyl-1-piperazinyl derivatives were more labile than the morpholino derivatives since for all of them melting and decomposition occurred simultaneously.

In solution, epoxy sulfonamides **2** decomposed relatively easily, even at room temperature, to give complex mixtures. The kinetic data in Table III indicate that the decomposition of **2bT** and **2cT** proceeds more rapidly in hydroxylic solvents (MeOH, H_2O) than in an aprotic solvent such as DMSO. Both compounds decompose ca. 3 times faster in MeOH and ca. 300 times faster in H_2O than in DMSO. It should be noted that these reactions are insensitive to light exposure.

In DMSO, decomposition of **2b** afforded substantial amounts (ca. 30%) of amino ketone **16b**, which was unstable under these conditions with formation of morpholine (**17b**). In hydroxylic solvents, **16b** was not detected. Only two products were found in appreciable amounts: morpholine (**17b**) (ca. 40%, in MeOH solution) and a product of unidentified structure (ca. 30%, presumed molecular mass 150).

Comparatively, the 4-methyl-1-piperazinyl derivative **2cT** decomposed ca. 3 times faster than **2bT**, which is consistent with their thermal behavior. The decomposition process seems much more complex. Amino ketone **16c** and 1-methylpiperazine (**17c**) were found in very small amounts (1% and 10%, respectively, in DMSO or MeOH), which suggests that decomposition of **2cT** may follow a different pathway.

(9) Curci, R.; DiFuria, F. *Tetrahedron Lett.* **1974**, 4085.

(10) Concentrated (at least 1.8 M) KOCl solutions, prepared from $Ca(OCl)_2$ (ref 15), were used in large excess. At the same concentration (1.8 M), NaOCl solutions, either from commercial source or prepared from $Ca(OCl)_2$, were found less effective (slower rates and increasing amounts of byproducts). Similar observations were recently reported for the conversion of ureas to hydrazines (Hofmann and Shestakov rearrangements). See: Enders, D.; Fey, P.; Kipphardt, H. *Org. Prep. Proced. Int.* **1985**, *17*, 1. Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891.

(11) Newman, M. S. In *Organic Reactions*; Wiley: New York, 1949; Vol. 5, pp 413–440.

Table IV. Antifilarial Activity against *M. dessetae* in Vivo against Adult Worms and in Vitro against Infective Larvae

	in vivo activity				in vitro activity			in vivo activity				in vitro activity	
	dose,[a]	nr[b]	act.[c]		EC_{50}[d]	EC_{90}[d]		dose,[a]	nr[b]	act.[c]		EC_{50}[d]	EC_{90}[d]
no.	mg/kg	*P. oris*	m	f	range	range	no.	mg/kg	*P. oris*	m	f	range	range
	Epoxy Sulfonamides (Table I)							Unsaturated Sulfonamides (Table II)					
2aT	200	2	+	+	B	C	**4b**	200	2	0	0	D	D
	50	2	0	+			**4c**	200	1	0	0	C	D
2aC	–	–	–	–	C	C	**5a**	200	2	+	0	C	D
2bT	100	3	+	+	B	B	**5b**	200	2	+	+	A	A
2bC	200	2	0	0	B	C		100	2	+	+		
2cT	10	4	+	+	B	B		10	2	0	0		
2cC	100	2	0	0	B	C	**5c**	200	1	0	0	A	A
2dT	200	2	0	0	B	C	**6a**	–	–	–	–	C	C
2eT	200	2	0	0	A	B	**6b**	–	–	–	–	C	D
2fT	100	2	0	0	B	B							
2gT	200	2	0	0	B	B		Oxo Sulfonamides (See the Text)					
2iT	200	2	0	0	B	C	**12b**	200	2	0	0	D	D
2jT	200	2	+	+	A	B	**12c**	–	–	–	–	D	D
2kT	–	–	–	–	B	B							
2lT	200	1	0	0	A	A		Cyclopropane and Methylene Sulfonamides (See the Text)					
2mT	200	2	0	0	A	A	**14bT**	200	2	0	0	–	–
2nT	200	1	0	0	–	–	**14cT**	200	2	0	0	C	D
2oT	–	–	–	–	A	A	**15c**	–	–	–	–	C	D
2pT	–	–	–	–	C	C							
2qT	200	2	0	0	B	C		Degradation Products of **2bT** and **2cT** (See the Text)					
2rT	200	2	0	0	B	C	**16b**	100	2	0	0	D	D
2sT	200	2	0	0	D	D	**16c**	100	1	0	0	D	D
2sC	–	–	–	–	C	D	**17b**	–	–	–	–	D	D
							17c	–	–	–	–	D	D
	Epoxy Sulfonamides (See the Text)												
13T	200	2	0	0	D	D		Reference Compounds[e]					
13C	200	2	0	0	D	D	DEC[f]	200	2	+	+	D	D
							suramin[f]	40	2	+	+	C	C
							Mel W	100	2	+	+	A	A
							ivermectin[f]	0.2	2	+	+	A	A
							1, Na salt	1000	2	+	+	D	D

[a] Dose administered subcutaneously once a day for 5 days. [b] Number of infected *P. oris*. [c] Activity on adult worms; m = male, f = female; + = active, 0 = inactive, – = not tested. [d] Effective concentrations of product necessary to kill 50% or 90% of infective larvae after 7 days. EC ranges: A < 20, B = 20–100, C = 100–500, D > 500 (μM). [e] DEC = diethylcarbamazine, Mel W = melarsonyl potassium salt. [f] At the indicated dose the compound also showed microfilaricidal activity.

As will be seen below, none of the degradation products **16** and **17** showed any antifilarial activity in our in vitro and in vivo experiments.

As expected, ethynesulfonamides **5**, especially in solution, exhibit considerably greater stability. For example, **5b** remained unchanged after 1 month at 20 °C in MeOH, while disappearance of **2bT** was virtually complete after 15 days.

Biological Results

The preceding compounds were evaluated for in vivo antifilarial activity against *M. dessetae* in *P. oris*, the natural host, as previously described in detail.[3b] The products were administered subcutaneously at doses that ranged from 10 to 200 mg/kg per day for 5 days. No drug-related toxicity was observed at the highest dose used, during the test period. These compounds were also evaluated in vitro, as we have recently described.[7] This new test used the infective larvae, maintained in culture in an artificial medium for 7 days. The results are shown in Table IV. Data on **1** and various standards are included for comparative purposes.

Five compounds showed in vivo *macrofilaricidal* activity on both male and female worms: **2aT**, **2bT**, **2cT**, **2jT** (epoxy sulfonamides), and **5b** (ethynesulfonamide). The most potent were **2cT** (at 10 mg/kg) and **5b** (at 10–100 mg/kg) while the others were less active (at 100–200 mg/kg). Even at 200 mg/kg, **5a** was only active against male worms. This range of activities is similar to that obtained with established standards (DEC, suramin, Mel W). Especially interesting was the lack of significant activity against microfilariae for all the new compounds, which contrasts with the marked microfilaricidal activity observed for DEC, ivermectin, or suramin.

The behavior of ethynesulfonamide **5b** was more unusual. At 200 mg/kg per day for 5 days, no sign of toxicity was observed, in noninfected *P. oris*, white rats, and laboratory mice. The same treatment, applied to infected *P. oris*, led to the death of the rodents after 2 days. At the autopsy, the adult filariae were found dead in a caseous substance. However, at 100 mg/kg, the treatment was effective and well-tolerated. These toxicity symptoms could be related to a shock reaction following a highly efficient treatment, as often observed in the chemotherapy of heavily infected animals.

All the compounds selected as macrofilaricides in vivo were found active in vitro against infective larvae. The most potent compounds killed larvae at effective concentrations (EC_{50}) below 20 μM (range A, Table IV). Ethynesulfonamides **5b**,**c** were the most active (range A, EC_{50} ca. 3–6 μM). Most of the trans epoxy sulfonamides **2T** were moderately active (ranges A, B, EC_{50} ca. 10–40 μM) except for **2pT**, **2qT** ranges B, C, EC_{50} ca. 70–110 μM) and **2sT** (range D). Comparatively, the cis isomers **2C** were less active (ranges B, C).

No significant in vivo and in vitro activity was seen for the substituted epoxides **13**, the cyclopropane derivatives **14**, and the degradation products **16** and **17**.

Discussion

In light of these results, we can point out a few structural features likely to be essential to the observed activities. The presence of an epoxy ring or an acetylenic bond was clearly important. Replacement of these functions by either a cyclopropyl ring as in **14** or an ethylenic bond as in **4** and **6** resulted in complete loss of activity. The bio-

logical activity was markedly dependent on the nature and stereochemistry of the epoxy ring substitution. Only those isomers bearing an aryl groups trans to the sulfonamido group showed significant in vitro (**2a–oT**) or in vivo (**2a–cT**, **2jT**) activity. The effect of altering the stereochemistry is particularly clear in the comparison of the in vivo activities of **2cT** and **2cC**. While trans epoxide **2cT** is the most potent compound of this series, its cis isomer **2cC** is completely inactive at a 10-fold dose level. Introduction of a cis or trans methyl substituent at the 2-position on the epoxy ring (**13**) was not favorable either. Furthermore, while the 4-methyl-1-piperazinyl residue caused a marked in vivo activity enhancement (**2cT** compared to **2aT** or **2bT**), no generalization can be made since other 4-methyl-1-piperazinyl derivatives were inactive in vivo (**2pT**, **2qT**, **5c**). (It should be noted, however, that **5c** retained a high in vitro activity.)

For both series, epoxy sulfonamides **2T** and ethynesulfonamides **5**, the in vitro evaluations support the in vivo activities. However, since there is no close correlation between the two sets of data, the in vivo activities could not be predicted from the in vitro results. One possible explanation for these discrepancies could result from variations in the resorption and diffusion processes of the injected compounds. Another possibility is that epoxy sulfonamides **2**, which proved relatively unstable in aqueous media, were certainly unstable under our assay conditions as well. The fact that no in vivo and in vitro activities were found for the degradation products **16** and **17** (from **2bT** and **2cT**) and, especially, for aged suspensions of **2bT** or **2cT** (allowed to stand at room temperature for several days before injection) suggests that the activity is actually due to the epoxides (or their metabolites). In any case, the amount of product that is really absorbed would remain unpredictable.

Despite these limitations, the above activities observed against *M. dessetae* are of interest since this animal model displays a very good sensitivity to known filaricides. Thus, our in vivo and in vitro tests are certainly valuable tools for the systematic study of new chemical classes. Moreover, the in vitro model, which is likely to be more sensitive to macrofilaricidal agents, should be recommended as a rapid screening test for such activities. Further studies will be needed to confirm the antifilarial activity of these compounds against other kinds of filariae, especially against human parasites.[12] The fact that no microfilaricidal activity was found in these compounds may be advantageous since it often results in undesirable side effects, which preclude the use of such drugs in mass campaign. Studies are underway to further explore these two series, which may offer new therapeutic opportunities in filarial diseases.

Experimental Section

Chemistry. IR spectra were recorded with a Perkin-Elmer 297 spectrometer. Melting points were either taken on a Kofler hot-stage apparatus or recorded on a Perkin-Elmer DSC2 differential scanning calorimeter with simultaneous control of the purity. ^{1}H NMR spectra were obtained in $CDCl_3$ on either a Perkin-Elmer R32 (at 90 MHz) or a Brucker AM200SY spectrometer (at 200 MHz) with an Aspect 3000 computer. Chemical shifts are given in parts per million with tetramethylsilane as an internal standard. Column chromatography was performed either on silica gel 60 (Merck, 230–400 mesh) or on alumina 90 (Merck, activity II–III, 70–230 mesh). Thin-layer chromatography (TLC) was carried out on silica gel 60 F254 (Merck). Microanalyses were performed by the Service Central d'Analyse of CNRS. Where analyses are indicated by the symbols of elements, the analytical results for those elements were within ±0.4% of the theoretical values.

Unless otherwise specified, usual workup is as follows: quenching of the reaction mixture with water, extraction with CH_2Cl_2, washing of the extracts with water, drying of the organic phase over anhydrous Na_2SO_4, and evaporation to dryness in vacuo.

Chloromethanesulfonyl chloride was prepared as described in literature.[13]

Bromomethanesulfonyl Chloride. The procedure described by Truce et al.[14] was modified as follows. A mixture of CH_2Br_2 (350 g, 2 mol), Na_2SO_3 (252 g, 2 mol), tetrabutylammonium hydrogen sulfate (10 g, 0.03 mol), and H_2O (800 mL) was refluxed for 26 h with vigorous stirring. The solvent was evaporated in vacuo and the resulting solid residue dissolved in a warm mixture of H_2O (320 mL) and EtOH (1800 mL). After filtration of some insoluble material, the filtrate was cooled at −20 °C. The crystalline sodium salt was collected by filtration: 300 g (77%).

A mixture of this sodium salt (197 g, 1 mol) and PCl_5 (220 g, 1.05 mol) was vigorously stirred until the mixture liquified (exothermic reaction for ca. 15 min). The mixture was heated at 130 °C for 45 min and then at 70 °C for 30 min. Workup was performed as previously described[14] to give 157 g (81%), bp 93–95 °C (20 mm) [lit.[14] bp 87–89 °C (15 mm)].

Preparation of Epoxy Sulfonamides 2. Physical properties and yields are listed in Table I.

Method A. Dry THF (5 mL) was added to KH (35% dispersion in oil, 1.35 g, 11.5 mmol) under nitrogen. To the stirred mixture cooled at −78 °C was added a solution of the appropriate chloromethanesulfonamide **3** (10 mmol) in THF (5 mL). After 15 min, a solution of aldehyde (11 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 15 min at −78 °C and 1 h at 0 °C. After usual workup (the organic extracts were evaporated at temperature <40 °C), the solid residue was recrystallized.

Method B. The procedure was similar to the preceding method, with the following modifications: (a) NaH (50% dispersion in oil, 0.53 g, 11 mmol) was used to generate the anion of the appropriate bromomethanesulfonamide **3** at 0 °C; (b) after the addition of aldehyde, the reaction mixture was allowed to warm to room temperature.

Method C. 1. Preparation of 2sC. A mixture of **6d** (ca. 80% purity, 3.8 g, 16 mmol), tetrabutylammonium hydrogen sulfate (0.54 g, 1.6 mmol), concentrated KOH (35 mL, 336 mmol), ca. 2.1 M KOCl (160 mL) (prepared[15] from $Ca(OCl)_2$, 65% active chlorine), and CH_2Cl_2 (240 mL) was vigorously stirred at 20 °C for 20 h. After usual workup (the organic extracts were evaporated at temperature <30 °C), the residue (3.8 g) was purified by silica gel chromatography (300 g) with Et_2O as the eluent. After elimination of the first eluted fraction (0.95 g of unidentified products), epoxide **2sC** (1.91 g) was obtained. It was then recrystallized from CH_2Cl_2/Et_2O at −20 °C.

2. Preparation of 2aC, 2bC, 2cC, 2bT, and 2oT. Specific conditions, solvent (mL/mmol of substrate), reaction time: **2aC**,

(12) Some compounds were evaluated against *Brugia pahangi* in *Meriones* and were found inactive. This screening test was carried out by Dr. D. A. Denham (London School of Tropical Medicine and Hygiene); see: Denham, D. A. In *Proceedings of Symposium of the Royal Zoological Society*; Owen, D. G.; Ed.; Macmillan: London, 1981; pp 93–104. The lack of activity observed for our compounds is not quite unexpected since it is now agreed that this model shows low sensitivity to most of the known filaricides. In fact, significant activity was only found for arsenical compounds; see: Court, J. P.; Lees, G. M.; Martin-Short, M. *Trop. Med. Parasit.* **1986**, *37*, 75. Bories, C.; Loiseau, Ph.; Gayral, Ph.; Denham, D. A.; Wolf, J. G.; Madaule, Y. *Réunion de la Société Francaise de Parasitologie*, Poitiers, France, 5–8 May 1986.

(13) Paquette, L. A.; Wittenbrook, L. S. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 231.

(14) Truce, W. E.; Abraham, D. J.; Son, P. J. *Org. Chem.* **1967**, *32*, 990.

(15) Newman, M. S.; Holmes, H. L. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 428. Preparation of KOCl solutions was conveniently performed at room temperature. Amounts of water were slightly decreased so as to obtain 1.8–2.2 M concentrations (iodometrically determined).

CH_2Cl_2 (8 mL) and Et_2O (16 mL), 14 h; **2bC**, CH_2Cl_2 (10 mL), 14 h; **2cC**, $Bu_4N^+HSO_4^-$ (68 mg, 0.2 mmol), Et_2O (20 mL), 14 h, filtration on alumina; **2bT**, addition of KCl (2 g, 27 mmol), CH_2Cl_2 (3 mL) and Et_2O (7 mL), 14 h; **2oT**, addition of KCl (2 g, 27 mmol), CH_2Cl_2 (30 mL) and Et_2O (20 mL), 10 h.

Preparation of Halomethanesulfonamides 3. A solution of halomethanesulfonyl chloride (0.15 mol) in CH_2Cl_2 (150 mL) was added dropwise (internal temperature <10 °C) either to a mixture of the appropriate secondary amine (0.165 mol) and NEt_3 (0.165 mol) (for **3e–g**) or to the secondary amine alone (0.33 mol for **3a,b,h–j** or 0.165 mol for **3c**,d) dissolved in CH_2Cl_2 (150 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 3 h. For **3a,b,e,h–j**, the organic phase was washed with 2 N HCl (2 × 200 mL), and for **3c**,d,**f,g** 1 N NaOH (250 mL) was added. After usual workup, the solid residue was recrystallized.

For the following compounds are given, successively, compound number (X, NR'_2); melting point (°C) (recrystallization solvent); and analysis (formula) C, H or literature reference. **3a** (Cl, NMe_2); 45 ($EtOH/H_2O$).[16] **3b** (Cl, morpholino); 71 (EtOH).[17] **3c** (Cl, 4-Me-1-piperazinyl); 78 ($MeOH/Et_2O$); ($C_6H_{13}ClN_2O_2S$). 3d (Cl, 4-*n*-Pr-1-piperazinyl); 82 (*i*-PrOH); ($C_8H_{17}ClN_2O_2S$). **3e** (Cl, 4-CO_2Et-1-piperazinyl); 75 (acetone/hexane); ($C_8H_{15}ClN_2O_4S$). **3f** (Cl, 4-Ph-1-piperazinyl); 115 (*i*-Pr_2O); ($C_{11}H_{15}ClN_2O_2S$). **3g** [Cl, 4-(*m*-$CF_3C_6H_4$)-1-piperazinyl]; 84.5 ($EtOH/H_2O$); ($C_{12}H_{14}ClF_3N_2O_2S$). **3h** (Cl, 1-pyrrolidinyl); 80 ($EtOH/H_2O$); ($C_5H_{10}ClNO_2S$). **3i** (Br, NMe_2); 95 (EtOH).[18] **3j** (Br, morpholino); 133 (EtOH).[19]

Preparation of *trans*-2-Arylethenesulfonamides 4. 2-Phenylethenesulfonamides **4a** and **4b** were prepared according to literature procedure [8a] by condensation of benzyl bromide and bromomethanesulfonamides **3i** and **3j**, respectively. Amides **4c–e** were obtained as described for amides **3**, by starting from the appropriate 2-arylethenesulfonyl chloride **7** (R = Ph, Aldrich) or **7** (R = *p*-$NO_2C_6H_4$[20]): NMR (90 MHz) δ 7.5 (d, 1 H, *J* = 15 Hz, PhCH=) and 6.7 (d, 1 H, *J* = 15 Hz, $=CHSO_2$). Recrystallization solvents and melting points are listed in Table II.

Preparation of 2-Arylethynesulfonamides 5a,b,d. These compounds were prepared as described for **5b**: IR (Nujol). 2190 cm^{-1} (C≡C). Recrystallization solvents and melting points are listed in Table II.

***N*-[(2-Phenylethynyl)sulfonyl]morpholine (5b).** A solution of Br_2 (3.4 mL, 62 mmol) in CCl_4 (30 mL) was added dropwise (ca. 30 min) to a refluxed solution of amide **4b** (15.18 g, 60 mmol) in CCl_4 (150 mL). After the addition was complete, refluxing was continued for 2.5 h, and the solvent was removed in vacuo. The residue was dissolved in dry dioxane (150 mL) and *t*-BuOH (150 mL), and *t*-BuOK (13.65 g, 120 mmol) was added. The mixture was stirred under nitrogen for 3 h and then poured into ice water (900 mL). The precipitated product was collected by filtration, dried (14.4 g), and chromatographed on silica gel (300 g), with CH_2Cl_2 as the eluent, to yield **5b**: 13.5 g (89%).

1-Methyl-4-[(2-phenylethynyl)sulfonyl]piperazine (5c) was obtained in 54% yield by reaction of amide **8** with *t*-BuOK (1 equiv) as described for **5b**.

Preparation of *cis*-2-Phenylethenesulfonamides 6a,b. These compounds were obtained as described for **6a**. NMR (90 MHz) δ 7.1 (d, 1 H, *J* = 13 Hz, PhCH=) and 6.2 (d, 1 H, *J* = 13 Hz, $=CHSO_2$). Recrystallization solvents and melting points are listed in Table II.

***cis*-*N*,*N*-Dimethyl-2-phenylethenesulfonamide (6a).** A mixture of **5a** (2 g, 9.6 mmol), sodium hypophosphite (3 g, 34 mmol), EtOH (50 mL), and H_2O (25 mL) was refluxed in the presence of 10% Pd/C (1.5 g) for 15 h with stirring. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue (containing ca. 20% of ketone **12a** and small amounts of the saturated amide) was dissolved in CH_2Cl_2. The organic phase was washed with 1 N NaOH (3 × 10 mL) to remove ketone **12a** and with water and then was dried over Na_2SO_4. The solvent was removed in vacuo and the residue (0.87 g) chromatographed on alumina (30 g) with CH_2Cl_2 as the eluent to give 0.8 g (40%) of **6a**.

The preceding alkaline phase was acidified (concentrated HCl). Usual workup afforded ketone **12a** identical with the compound described below.

***cis*-1-Methyl-4-[(2-phenylethenyl)sulfonyl]piperazine (6c).** The procedure described for **6a** was modified as follows: **5c** (2 g, 7.6 mmol), sodium hypophosphite (3.3 g, 37.5 mmol), EtOH (125 mL), H_2O (20 mL), and 5% Pd/$BaSO_4$ (2 g). After removal of ketone **12c**, the crude product (0.9 g) was chromatographed on alumina (50 g) with AcOEt/hexane (1:1) as the eluent to give 0.54 g (27%) of **6c**. Recrystallization solvent and melting point are given in Table II. Ketone **12c**, identical with the compound described below, was obtained from the alkaline aqueous phase after neutralization with AcOH and usual workup.

***N*-(*cis*-1-Propen-1-ylsulfonyl)morpholine (6d).** A solution of NaOMe (3.78 g, 70 mmol) in MeOH (70 mL) was added dropwise to a stirred solution of amide **10** (15.78 g, 70 mmol) in MeOH (70 mL). Stirring was continued for 30 min and the solvent removed in vacuo. After usual workup, the crude allene **11** [13.5 g; IR (neat) 1940, 1970 cm^{-1} (CH_2=C=C)] was dissolved in MeOH (150 mL) and hydrogenated (1.4 L of H_2, 30 min) in the presence of 5% Pd/C (400 mg). After filtration of the catalyst, the filtrate was evaporated in vacuo and the residue distilled under reduced pressure to give 12.3 g, bp 110–116 °C (0.05 mm), of a pale yellow oil, which was shown by ^1H NMR to contain ca. 80% of **6d**. This material was used in the next step without further purification: NMR (200 MHz) δ 2.14 (dd, 3 H, *J* = 7.35 Hz, *J* = 1.8 Hz, Me), 3.17 and 3.78 (2 m, 8 H, morpholino), 6.04 (dq, 1 H, *J* = 11.3 Hz, *J* = 1.8 Hz, $=CHSO_2$), 6.50 (dq, 1 H, *J* = 7.35 Hz, *J* = 11.3 Hz, MeCH=).

***N*-[(1-Bromo-2-phenylethenyl)sulfonyl]morpholine (8b).** This compound was obtained as described for **3b**, by reaction of morpholine with 1-bromo-2-phenylethenesulfonyl chloride prepared[21] from commercial 2-phenylethenesulfonyl chloride (**7**, R = Ph). The crude amide (200 mg) was purified by TLC on a silica gel plate (2 mm) with AcOEt/hexane (3:7) as the eluent to give amide **8b**: 90 mg (ca. 40% yield based on **7**). An analytical sample was recrystallized from Et_2O/*i*-Pr_2O: mp 87.5 °C; NMR (200 MHz) δ 3.41 and 3.77 (2 m, 8 H, morpholino), 7.45 and 7.80 (2 m, 5 H, Ph), 8.04 (s, 1 H, PhCH=). Anal. ($C_{12}H_{14}BrNO_3S$) C, H.

1-Methyl-4-[(1-bromo-2-phenylethenyl)sulfonyl]piperazine (8c). This compound was obtained as described for **3c**, by reaction of 1-methylpiperazine with 1-bromo-2-phenylethenesulfonyl chloride prepared as above. The crude piperazinyl amide was purified via its 3,5-dinitrobenzoate, which was recrystallized from EtOH, mp 179 °C (40%). Anal. ($C_{13}H_{17}BrN_2O_2S \cdot C_7H_4N_2O_6$) C, H. Treatment of this salt with 1 N NaOH followed by usual workup afforded pure **8c**. An analytical sample was recrystallized from Et_2O/*i*-Pr_2O: mp 93 °C; NMR (90 MHz) δ 2.3 (s, 3 H, Me), 2.48 and 3.43 (2 m, 8 H, piperazinyl), 7.42 and 7.75 (2 m, 5 H, Ph), 8.0 (s, 1 H, PhCH=). Anal. ($C_{13}H_{17}BrN_2O_2S$) C, H.

***N*-[(2-Chloro-2-propen-1-yl)sulfonyl]morpholine (10).** 1,2-Dichloro-2-propene (**9**) (56 g, 0.5 mol) was added dropwise to a solution of Na_2SO_3 (63 g, 0.5 mol) in H_2O (400 mL) with stirring and heating at 55 °C. The mixture was then refluxed for 3 h and the solvent evaporated in vacuo. To the residue was added EtOH (500 mL), and the mixture was refluxed with stirring for 10 min. After removal of some insoluble material by filtration of the hot mixture, the filtrate was cooled. The crystalline sodium 2-chloro-2-propene-1-sulfonate was collected by filtration: 51.8 g (65%).

A mixture of this sodium salt (0.324 mol) and PCl_5 (72.7 g, 0.349 mol) was stirred vigorously until the mixture liquified (exothermic reaction for ca. 10 min). The mixture was then rapidly heated at 120 °C, cooled, and poured onto ice with vigorous stirring. The reaction mixture was allowed to stand for 30 min (temperature

(16) Jakobsen, H. J.; Senning, A.; Kaae, S. *Acta Chem. Scand.* **1971**, *25*, 3031.
(17) Christensen, L. W.; Seaman, J. M.; Truce, W. E. *J. Org. Chem.* **1973**, *38*, 2243.
(18) Sheehan, J. C.; Zoller, U.; Ben-Ishai, D. *J. Org. Chem.* **1974**, *39*, 1817.
(19) Truce, W. E.; Christensen, L. W. *Tetrahedron* **1969**, *25*, 181.
(20) Bordwell, F. G.; Colbert, A. B.; Alan, B. *J. Am. Chem. Soc.* **1946**, *68*, 1778.
(21) Rondestvedt, C. S., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 1926.

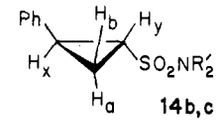
<20 °C) and extracted with CH_2Cl_2. The organic phase was washed with ice water, 5% $NaHCO_3$ solution (2 × 150 mL), and water, then dried, and evaporated in vacuo. The residue (57 g) was distilled under reduced pressure to give 2-chloro-2-propenesulfonyl chloride: 46.3 g (82%); bp 112 °C (30 mm); n^{25}_D 1.5028 [lit.[22] bp 60 °C (0.6 mm)].

A solution of morpholine (33.2 g, 0.38 mol) in CH_2Cl_2 (130 mL) was added dropwise to a solution of the preceding chloride (33.21 g, 0.19 mol) in CH_2Cl_2 (130 mL), with stirring and cooling at −50 °C. After the addition was complete, the mixture was stirred at 20 °C for 1 h, washed with 2 N HCl (2 × 150 mL), and worked up as usual. The crude product [39.5 g, containing ca. 15% of *N*-[(2-chloro-1-propen-1-yl)sulfonyl]morpholine] was triturated with Et_2O (50 mL). The crystalline amide **10** was collected by filtration, washed with Et_2O (2 × 20 mL), and dried: 32.0 g (75%); mp 123 °C; NMR (90 MHz) δ 3.35 and 3.75 (2 m, 8 H, morpholino), 3.93 (s, 2 H, CH_2), and 5.62 (s, 2 H, $=CH_2$). An analytical sample was recrystallized from CH_2Cl_2/Et_2O. Anal. ($C_7H_{12}ClNO_3S$) C, H.

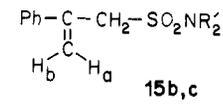
Preparation of 2-Oxo-2-phenylethanesulfonamides 12a–c. Dry dimethoxyethane (DME, 10 mL) was added to KH (35% dispersion in oil, 3.1 g, 27 mmol) under nitrogen. To the stirred mixture was added a solution of the appropriate methanesulfonamide (10 mmol) and methyl benzoate (1.5 mL, 12 mmol) in DME (10 mL), with stirring at room temperature. The reaction mixture was refluxed for 1 h (H_2 was evolved) and cooled. Water was added (10 mL) and the mixture extracted with Et_2O. The organic phase was washed with 1 N NaOH (3 × 10 mL). The combined alkaline phases were acidified with concentrated HCl (for **12a** and **12b**) or with AcOH up to pH 7–8 (for **12c**). The crude crystalline ketone was collected by filtration, dried, chromatographed on alumina (20–40 g) with CH_2Cl_2 as the eluent, and recrystallized: IR (Nujol) 1680 cm^{-1} (C=O); NMR (90 MHz) δ 4.55 (s, 2 H, CH_2). **12a**: mp 81 °C (CH_2Cl_2/Et_2O); 78%. Anal. ($C_{10}H_{13}NO_3S$) C, H. **12b**: mp 136 °C (CH_2Cl_2/Et_2O); 72%. Anal. ($C_{12}H_{15}NO_4S$) C, H. **12c**: mp 82.5 °C (acetone/pentane); 60%. Anal. ($C_{13}H_{18}N_2O_3S$) C, H.

***cis*- and *trans*-*N*-[(1,2-Epoxy-2-phenylpropyl)sulfonyl]morpholine (13C and 13T).** A 1:1 mixture of isomeric epoxides **13**, prepared according to a procedure of Golinski and Makosza,[8a] from acetophenone (1.2 g) and chloromethanesulfonamide **3b**, was chromatographed on alumina with Et_2O as the eluent. First to elute was **13T** (1.15 g): mp 90 °C; NMR (200 MHz) δ 2.06 (s, 3 H, Me), 3.45 and 3.78 (2 m, 8 H, morpholino), 3.86 (s, 1 H, H), 7.36 (s, 5 H, Ph). Anal. ($C_{13}H_{17}NO_4$) C, H. Eluting next was **13C** (1.37 g): mp 111 °C; NMR (200 MHz) δ 1.70 (s, 3 H, Me), 3.12 and 3.61 (2 m, 8 H, morpholino), 4.18 (s, 1 H, H), 7.39 (s, 5 H, Ph). Anal. ($C_{13}H_{17}NO_4$) C, H. (Lit.[8a] mp 71–74.5 °C for 1:1 mixture.)

***trans*-*N*-[(2-Phenylcyclopropyl)sulfonyl]morpholine (14bT) and *N*-[(2-Phenyl-2-propen-1-yl)sulfonyl]morpholine (15b).** These compounds were prepared by the general procedure for the preparation of cyclopropanes described by Kaiser et al.,[23] by reaction of dimethylsulfoxonium methylide (13 mmol) with **4b** (2.56 g, 10 mmol) in DMSO (30 mL). The reaction was allowed to proceed at 60 °C for 4 h instead of 1 h. The crude product was chromatographed on alumina (300 g) with CH_2Cl_2/hexane mixtures. First to elute was **14bT**, which was recrystallized from MeOH: 1.3 g (50%); mp 107 °C (lit.[24] mp 124–125 °C); NMR (200 MHz) δ 1.48 (m, 1 H, H_b), 1.75 (m, 1 H, H_a), 2.48 (m, 1 H, H_y), 2.70 (m, 1 H, H_x), 3.30 and 3.76 (2 m, 8 H, morpholino), 7.1 and 7.3 (2 m, 5 H, Ph), J_{ax} = 11, J_{ay} = 5, J_{bx} = 6.5, J_{by} = 8.5, J_{ab} = 5, J_{xy} = 4.5 Hz. Anal. ($C_{13}H_{17}NO_3S$) C, H. Eluting next was **15b**, which was recrystallized from MeOH: 0.2 g; mp 90 °C; NMR (200 MHz) δ 3.15 and 3.55 (2 m, 8 H, morpholino), 4.15 (d, 2 H, CH_2), 5.53 (m, 1 H, H_a), 5.72 (d, 1 H, H_b), 7.4 (m, 5 H, Ph), J_{ab} ca. 0.7, J_{ax} ca. 0.8 Hz. Anal. ($C_{13}H_{17}NO_3S$) C, H.



14b,cT



15b,c

***trans*-1-Methyl-4-[(2-phenylcyclopropyl)sulfonyl]piperazine (14cT) and 1-methyl-4-[(2-phenyl-2-propen-1-yl)sulfonyl]piperazine (15c)** were obtained as described for **14bT** and **15b**, starting from **4c**. **14cT**: mp 127 °C; NMR (200 MHz) δ 1.44 (m, 1 H, H_b), 1.74 (m, 1 H, H_a), 2.31 (s, 3 H, Me), 2.47 (m, 1 H, H_y), 2.68 (m, 1 H, H_x), 2.49 and 3.34 (2 m, 8 H, piperazinyl), 7.1 and 7.3 (2 m, 5 H, Ph), same *J* values as for **14bT**. Anal. ($C_{14}H_{20}N_2O_2S$) C, H. **15c**: mp 108 °C; NMR (200 MHz) δ 2.25 (s, 3 H, Me), 2.34 and 3.22 (2 m, 8 H, piperazinyl), 4.14 (d, 2 H, CH_2), 5.51 (m, 1 H, H_a), 5.71 (d, 1 H, H_b), 7.4 (m, 5 H, Ph), same *J* values as for **15b**. Anal. ($C_{14}H_{20}N_2O_2S$) C, H.

***N*-Phenacylmorpholine (16b)** was prepared according to the procedure of Chapman and Triggle,[25] from phenacyl bromide (10 g, 50 mmol) and morpholine (8.7 g, 100 mmol). The crude free base (10.6 g) was distilled under reduced pressure [6.5 g (63%); bp 120–130 °C (0.5 mm)] and recrystallized from Et_2O/pentane at −20 °C to give pure **16b**: mp 50 °C (lit.[26] mp 50–52 °C); NMR (200 MHz) δ 2.65 and 3.80 (2 m, 8 H, morpholino), 3.85 (s, 2 H, CH_2), 7.5 and 8.0 (2 m, 5 H, Ph). As already mentioned,[26] this product is relatively unstable at room temperature and must be kept in the cold (it becomes gradually yellow on standing for several days).

1-Methyl-4-phenacylpiperazine (16c) was prepared according to the procedure of Zaugg et al.,[27] from phenacyl bromide (10 g, 50 mmol) and 1-methylpiperazine (5.5 g, 55 mmol). The crude free base (8.4 g) was converted to its perchlorate salt, which was recrystallized from EtOH/H_2O: 11.2 g (53%). Decomposition of this salt with 1 N NaOH followed by extraction with CH_2Cl_2 afforded the free base, which was recrystallized from hexane: mp 69 °C (lit.[27] mp 69–70 °C); NMR (200 MHz) δ 2.31 (s, 3 H, Me), 2.53 and 2.65 (2 m, 8 H, piperazinyl), 3.82 (s, 2 H, CH_2), 7.5 and 8.0 (2 m, 5 H, Ph).

Thermal Stability. The thermal behavior of sulfonamides **2**, **5**, and **12** was investigated by DSC (sample weights 1–3 mg, heating rate 10 K/min, temperature range 50–300 °C). Typically, the thermograms display an endothermic peak (melting) followed by one or two exothermic peaks (decomposition). In the following examples are given successively the beginning, the first maximum, and the second maximum of decomposition (temperatures roughly estimated in °C): **2aT**, 70, 135, 185; **2aC**, 145, 185, –; **2bT**, 125, 170, 225; **2bC**, 120, 180, 240; **2cT**, 95, 130, 190; **2cC**, 95, 125, 190; **2iT**, 125, 180, 230; **2oT**, 165, 180, –; **2qT** (no melting peak), 130, 150, 195; **2sT**, 105, 175, –; **2sC**, 140, 160, 185; **5a**, 150, 220, –; **5b**, 145, 205, 230; **5c**, 125, 185, 215; **5d**, 150, 200, 300; **12a**, 250, 270, –; **12b**, 230, 260, –; **12c**, 200, 220, –.

Some samples of **2bT** were heated (DSC) up to 150–160 °C. ^1H NMR (200 MHz) showed the major product to be **16b**.

Stability in Solution. DMSO and distilled MeOH were dried over molecular sieves.

The products resulting from the decomposition of **2bT** and **2cT** (**16b**, **16c**, **17b**, **17c**, and the product of presumed molecular mass 150) were identified by GC/MS (Girdel 300 chromatograph with an OV 101 silica capillary column coupled to a Nermag R-10-10 mass spectrometer with a quadripole separator) and by TLC (Merck, neutral alumina 60 F254 type E, two successive elutions with MeOH/H_2O, 8:2, then AcOEt/hexane, 2:8).

The decomposition kinetics of **2bT** and **2cT** were followed by HPLC (Chromatem pump 380, Brownlee C18 Spheri 5 column, phosphate buffer pH 7 and acetonitrile in varying proportions as the mobile phase, UV detector at 207 nm). The amounts of products were determined by HPLC with 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (nitrazepam) as an internal standard, except for the amounts of **17b** and **17c**, which were

(22) Bradamante, S.; Del Buttero, P.; Maiorana, S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 612.
(23) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972.
(24) Truce, W. E.; Goralski, C. T. *J. Org. Chem.* **1968**, *33*, 3849. Although the melting point of **14bT** does not agree with that reported by Truce, NMR data are consistent with a trans configuration.
(25) Chapman, N. B.; Triggle, D. J. *J. Chem. Soc.* **1963**, 1385.
(26) Mason, J. P.; Ross, S. D. *J. Am. Chem. Soc.* **1940**, *62*, 2882.
(27) Zaugg, H. E.; Michaels, R. J.; Glenn, H. J.; Swett, L. R.; Freifelder, M.; Stone, G. R.; Weston, A. W. *J. Am. Chem. Soc.* **1958**, *80*, 2763.
(28) Cardillo, G.; Savoia, D.; Umani-Ronchi, A. *Synthesis* **1975**, 453.

measured by GC (split injector, fused silica capillary column coated with RSL 160 BP, flame ionization detector).

Biology. Evaluation of antifilarial activities was carried out by following the previously described protocols,[3,7] which are briefly summarized below.

In Vivo Screening. Rodents *P. oris* of both sexes were infected by injection of 200 infective larvae, obtained by dissection of the mosquitoes *Aedes aegypti*. After control of the microfilaremia, they were treated between 150 and 180 days after infectation. Compounds were administered subcutaneously in 1% (carboxymethyl)cellulose suspension to two rodents for 5 consecutive days. Microfilaremia was controlled for 6 weeks. At the end, adult filariae were counted at the autopsy. A compound would present a statistically significant ($p = 0.12$) macrofilaricidal effect if not a single male and not more than 1.6 female filaria were found.

In Vitro Screening. Infective larvae isolated from the intermediate host were maintained in a biphasic culture medium composed of a cell feeder layer (L 929) with RPMI (90 mL), fetal calf serum (10 mL), penicillin (1000 IU/mL medium), and streptomycin (100 IU/mL medium). Twenty larvae were put in the medium (1.5 mL) after decontamination in a sterile medium.

Compounds were dissolved in DMSO (100 μL) at several concentrations, and 10 μL of each solution was added to 20 larvae. Each run was duplicated. The percentage of survival larvae corrected by control was determined.

Registry No. **2aT**, 110380-88-6; **2aC**, 110417-67-9; **2bT**, 110380-87-5; **2bC**, 110381-01-6; **2cT**, 110380-91-1; **2cC**, 110417-68-0; **2dT**, 110417-69-1; **2eT**, 110380-92-2; **2fT**, 110380-93-3; **2gT**, 110380-94-4; **2hT**, 110380-89-7; **2iT**, 110417-70-4; **2jT**, 110380-90-0; **2kT**, 110417-71-5; **2lT**, 110417-72-6; **2mT**, 110417-73-7; **2nT**, 110417-74-8; **2oT**, 110417-75-9; **2pT**, 110417-76-0; **2qT**, 110417-77-1; **2rT**, 110380-97-7; **2sT**, 110380-96-6; **2sC**, 110417-78-2; **3a**, 35427-68-0; **3b**, 39542-27-3; **3c**, 3967-02-0; **3d**, 110417-46-4; **3e**, 110381-05-0; **3f**, 110381-06-1; **3g**, 110381-07-2; **3h**, 98069-37-5; **3i**, 51270-39-4; **3j**, 22457-12-1; **4a**, 56631-61-9; **4b**, 17299-32-0; **4c**, 110417-47-5; **4d**, 110417-48-6; **4e**, 110417-49-7; **5a**, 110381-00-5; **5b**, 110380-99-9; **5c**, 110417-50-0; **5d**, 110417-51-1; **6a**, 110417-52-2; **6b**, 110381-12-9; **6c**, 110417-53-3; **6d**, 110417-54-4; **7** (R = Ph), 52147-97-4; **7** (R = 4-$O_2NC_6H_4$), 52148-00-2; **8** (R = Ph, NR′ = Cl), 55129-82-3; **8b**, 110417-59-9; **8c**, 110417-60-2; **8c**·3,5-$(O_2N)_2C_6H_3CO_2H$, 110417-80-6; **9**, 78-88-6; **10**, 110417-57-7; **11**, 110417-58-8; **12a**, 73281-91-1; **12b**, 110417-55-5; **12c**, 110417-56-6; **13c**, 110417-62-4; **13T**, 110417-63-5; **14bT**, 17299-25-1; **14cT**, 110417-65-7; **15b**, 110417-64-6; **15c**, 110417-66-8; **16b**, 779-53-3; **16c**, 41298-85-5; **16c**·$HClO_4$, 110417-79-3; **17b**, 110-91-8; **17c**, 109-01-3; CH_2Br_2, 74-95-3; $BrCH_2SO_3H$·Na, 34239-78-6; $BrCH_2SO_2Cl$, 10099-08-8; $ClCH_2SO_2Cl$, 3518-65-8; $PhCH_2Br$, 100-39-0; $PhCO_2Me$, 93-58-3; PhCOMe, 98-86-2; PhCHO, 100-52-7; $H_2C{=}C(Cl)CH_2SO_3H$·Na, 55947-45-0; $H_2C{=}C(Cl)CH_2SO_2Cl$, 40644-59-5; $MeSO_2NMe_2$, 918-05-8; 4-ClC_6H_4CHO, 104-88-1; 3,4-$Cl_2C_6H_3CHO$, 6287-38-3; 2-MeC_6H_4CHO, 529-20-4; 3-MeC_6H_4CHO, 620-23-5; 4-$H_3C(CH_2)_5C_6H_4CHO$, 49763-69-1; 4-MeC_6H_4CHO, 104-87-0; MeCHO, 75-07-0; 1-propylpiperazine, 21867-64-1; 1-phenylpiperazine, 92-54-6; 1-methylpiperazine, 109-01-3; pyrrolidine, 123-75-1; 1-piperazinecarboxylic acid ethyl ester, 120-43-4; 3-piperazinyl-1-(trifluoromethyl)benzene, 15532-75-9; phenylacyl bromide, 70-11-1; 1-(methylsulfonyl)-4-methylpiperazine, 59039-17-7; *N*-(methylsulfonyl)morpholine, 1697-34-3; *N*-(1-(2-chloro-2-propenyl)sulfonyl)morpholine, 110417-61-3.

Synthesis of New Antiinflammatory Steroidal 20-Carboxamides: (20*R*)- and (20*S*)-21-(*N*-Substituted amino)-11β,17,20-trihydroxy-3,21-dioxo-1,4-pregnadiene

Hyun P. Kim, John Bird, Ann S. Heiman, George F. Hudson, Irach B. Taraporewala, and Henry J. Lee*

Center for Anti-inflammatory Research, College of Pharmacy, Florida A&M University, Tallahassee, Florida 32307.
Received February 9, 1987

The synthesis and antiinflammatory activities of new steroidal 20-carboxamides, (20*R*)- and (20*S*)-21-(*N*-substituted amino)-11β,17,20-trihydroxy-3,21-dioxo-1,4-pregnadiene (**5–8**) are described. These compounds were prepared from the respective isomer of 20-dihydroprednisolonic acid, (20*R*)- and (20*S*)-11β,17,20-trihydroxy-3-oxo-1,4-pregnadien-21-oic acid (**4a** and **4b**), by coupling with primary amines after the activation of the steroid acid with N,N^1-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole. Confirmation of the configurational assignment at C-20 of the 20-carboxamides was achieved by reduction of methyl (20*R*)- and (20*S*)-11β,17,20-trihydroxy-3-oxo-1,4-pregnadien-21-oate (**3a** and **3b**) to the known stereochemistry at C-20 of (20*R*)- and (20*S*)-11β,17,20,21-tetrahydroxy-3-oxo-1,4-pregnadiene (**2a** and **2b**). The topical antiinflammatory activities of these steroidal 20-carboxamides were assessed by the croton oil induced ear edema assay and their local and systemic antiinflammatory activities by the cotton pellet granuloma bioassay. Results of these investigations suggest a structure–activity relationship where carboxamide derivatives with the 20(*R*)-hydroxy configurations exhibit higher potency than those with the 20-(*S*)-hydroxy configurations. The amides of steroidal 21-oic acids with high local antiinflammatory potency exhibited systemic activities unlike the corresponding esters of steroidal 21-oic acids, which are devoid of systemic activities.

The limiting factor in the use of corticosteroids for the chronic treatment of inflammatory conditions has been their adverse systemic side effects.[1] Therapeutic approaches such as dosage forms for local application, alternate-day administration, and concomitant "protective" therapy have been employed to reduce the adverse systemic effects of potent steroids. As a synthetic approach to the design of safer antiinflammatory steroids, we have introduced the antedrug concept. The term antedrug can be applied to an active synthetic derivative that is inactivated by the first metabolic step upon entry into the circulation. Thus, a true antedrug acts only locally and undergoes only one predictable metabolic step to an inactive metabolite.[2,3] Compounds that have at least one active intermediary metabolite can be considered as partial antedrugs. It has recently been established that methyl 11β,17-dihydroxy-3,20-dioxo-1,4-pregnadien-21-oate and the isomers of methyl (20*R*)- and (20*S*)-11β,17,20-trihydroxy-3-oxo-1,4-pregnadien-21-oate (**3a** and **3b**) retain significant local antiinflammatory activity, but are devoid of prednisolone-like side effects, such as pituitary adrenal suppression and thymus involution.[2-4] It has been sug-

(1) Popper, T. L.; Watnick, A. S., in *Medicinal Chemistry*; Scherrer, R. A., Whitehouse, M. W., Eds; Academic: New York, 1974; Vol. 2, pp 245–294.

(2) Lee, H. J.; Soliman, M. R. I. *Science (Washington, D.C.)* **1982**, *215*, 989.

(3) Lee, H. J.; Khalil, M. A.; Lee, J. W. *Drugs. Exp. Clin. Res.* 1984, *10*, 835.

(4) Soliman, M. R. I.; Nathoo, Z. M.; Heiman, A. S.; Cook, E. B.; Lee, H. J. in *Progress in Research and Clinical Application of Corticosteroids*; Lee, H. J., Fitzgerald, T. J., Eds.; Hayden: Philadelphia, 1982; pp 253–267.

0022-2623/87/1830-2239$01.50/0