the resin and simultaneously deprotected by reaction with anhydrous HF (10 mL) in the presence of *p*-cresol (1 g) for 30 min at 0 °C. The peptide was dissolved in CF_3CO_2H (100 mL), and the resin was removed by filtration. The solvent was removed by rotary evaporation, and the crude product was isolated by trituration with ether and filtration. Yield 200–300 mg. The crude product obtained after the reaction with HF was dissolved in 7% acetic acid (10 mL), clarified by centrifugation, and purified by HPLC.

Preparative Reversed-Phase HPLC. Purification of peptides was accomplished with use of a Varian HPLC system equipped with a Vista 401 microprocessor controller. Separations were achieved on a Bio-Rad Hi-Pore 318 reversed-phase preparative column (25.0 × 2.15 cm) at 25 °C with a stepped linear gradient of acetonitrile in 0.1% CF_3CO_2H at a flow rate of 7.5 mL/min. Automated repetitive injections of peptides (5 × 5 mg) were made from a nitrogen pressurized Rheodyne injector with a 2.0-mL sample loop. One-fifth of the total sample was injected during each run by lowering the flow rate to 4.0 mL/min for a 0.1-min "inject" period. One cycle consisted of the following events: 0 → 10 min, 7.5 mL/min, 90% H_2O/10% of 1% aqueous CF_3CO_2H; 10 → 11 min, → 4.0 mL/min; 11 → 11.1 min, "inject"; 11.1 → 13 min, → 7.5 mL/min, → 70% H_2O/20% CH_3CN/10%; of 1% CF_3CO_2H; 13 → 30 min, → 45% H_2O/45% CH_3CN/10% of 1% CF_3CO_2H; 30 → 42 min, → 90% CH_3CN/10% of 1% CF_3CO_2H; 42 → 50 min, → 100% H_2O.

Fractions were collected at 0.1-min intervals with a Gilson Model 201 fraction collector programmed to collect for a 5-min period centered around the elution time (27–29 min) of the major product. The fraction collector was restarted by the Vista 401 at the beginning of each HPLC run so that the material eluting with the same retention time was repeatedly deposited in the same tubes. Elution of the peptide was detected simultaneously from the absorbances at 254 nm (Varian UV-1) and 230 nm (Kratos SF769Z). Fractions containing the required peptide were pooled; after removal of CH_3CN on a rotary evaporator at 40 °C, the fractions were lyophilized and stored at −20 °C. Yield 5–20%.

Amino acid analyses (Beckman 121 M) were carried out after acid hydrolysis in 6 N HCl (containing 1% cresol to prevent loss tyrosine) at 100 °C for 18 h in vacuo. The purity of products was established by analytical HPLC reruns and by thin-layer chromatography (TLC). TLC was carried out with precoated silica gel on glass (Merck Kieselgel 60 F254) TLC plates. The two solvent systems used were 1-butanol–pyridine–acetic acid–water (15:10:3:6) (BPAW) and chloroform–methanol–acetic acid–water (15:10:2:3:) (CMAW). Peptides were detected by fluorescence quenching under UV light followed by development with ninhydrin (0.3%) in 1-butanol/acetic acid (100:3, v/v).

Rat Uterus Bioassay. Defatted uterine horns from diethylstilbestrol-primed virgin Sprague–Dawley rats (150–250 g) were cut in half, and each tissue was suspended under 1 g of tension in a 3-mL tissue bath containing 150 mM NaCl, 5.6 mM KCl, 0.18 mM $NaHCO_3$, and 1.4 mM glucose at pH 7.0 gassed with oxygen. Contractions were monitored with Gould Metripak 763341-4202 isotonic transducers coupled to Gould 13-4615-50 transducer amplifiers housed in a Gould 2600S recorder. Agonist activities of peptides were determined by matching the response with an equivalent response to ANG II (human). Antagonist activities (pA_2) were determined as the negative logarithm of the concentration of antagonist required to reduce the response to an EC_{50} dose of ANG II to the response to half the EC_{50} dose.

Registry No. Sarmesin, 88874-29-7; [Me_2Gly^1,Tyr(Me)^4]ANG II, 114396-29-1; [EtGly^1,Tyr(Me)^4]ANG II, 114396-30-4; [Aib^{1}Tyr(Me)^4]ANG II, 114396-31-5; [MeAib^{1}Tyr(Me)^4]ANG II, 114396-32-6; [Acp^1, Tyr(Me)^4]ANG II, 114396-33-7; [Oxm^1, Tyr (Me)^4]ANG II, 114396-34-8; [Sar^1, Nle^3, Tyr(Me)^4]ANG II, 114396-35-9; [des^1, Nle^2, Tyr(Me)^4]ANG II, 114396-36-0; [des^1, Sar^3, Tyr(Me)^4]ANG II, 114396-37-1; [Aib^1, Tyr(Me)^4, Ile^8]ANG II, 114396-38-2; [MeAib^1, Tyr(Me)^4, Ile^8]ANG II, 114422-57-0; [Acp^1, Tyr(Me)^4, Ile^8]ANG II, 114396-39-3; [Oxm^1, Tyr(Me)^4, Ile^8]ANG II, 114396-40-6; [Sar^1, Ile^8]ANG II, 37827-06-8.

Synthesis and Structure–Activity Relationships of 2-Sulfonamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines as α_2-Adrenoceptor Antagonists

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A series of 2-sulfonamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines were synthesized and examined for α_2- and α_1-adrenoceptor antagonist activity on the rat vas deferens and anococcygeus muscle, respectively. A number of compounds in this series were shown to be potent and selective α_2-adrenoceptor antagonists. Studies on the resolved enantiomers of compounds **6**, **10**, and **16** showed that α_2-adrenoceptor antagonist activity resided primarily in the 2*R*,11b*S* isomers, related to the absolute configuration of the α_2-antagonist yohimbine, such that the benzene ring and sulfonamide groups in this series were superimposable on the pyrrole and ester groups of yohimbine.

α-Adrenoceptors have been classified into α_1 or α_2 subtypes depending on the relative affinities of various agonists and antagonists.[1,2] Initially the two receptors were also defined anatomically, α_1-adrenoceptors being located postsynaptically and α_2-adrenoceptors at presynaptic sites on sympathetic nerve terminals. Subsequently α_2-adrenoceptors were identified at postsynaptic sites in several organs and in platelets.[3] Presynaptic α_2-adrenoceptors mediate a negative-feedback mechanism which modulates release of norepinephrine from nerve endings.[1] It follows that blockade of central presynaptic α_2-adrenoceptors should lead to enhanced neuronal release of norepinephrine, an effect which is predicted from the catecholamine theory[4] of depressive illness to be of potential value for the treatment of depression. Furthermore chronic treatment of rats with desipramine produces a

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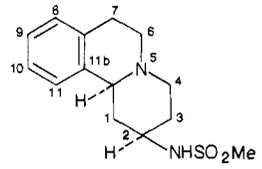
Table I

compd	proton shift,[a] δ 11b-H	2-H
3	3.2 (a)	2.8 (a)
4	3.55 (a)	3.05 (e)
5	4.35 (e)	3.75 (a)
6	3.2 (a)	4.0 (a)

[a] Assignment: a = axial, e = equatorial.

gradual decrease in presynaptic α_2-adrenoceptor sensitivity.[5,6] α_2-Adrenoceptors are also implicated in adrenergic control of lipolysis,[7-9] insulin[10,11] and growth hormone secretion,[12] vasoconstriction,[13-15] and platelet aggregation.[16] It follows that selective antagonists of α_2-adrenoceptors may have therapeutic potential in a number of disease areas and this has led in recent years to a search for selective α_2-adrenoceptor antagonists of various structural types.

In a previous publication we described a series of sulfonamidobenzoquinolizines which were examined for antihypertensive activity.[17] Of particular interest from this series was compound **1**, which showed excellent antihypertensive activity.



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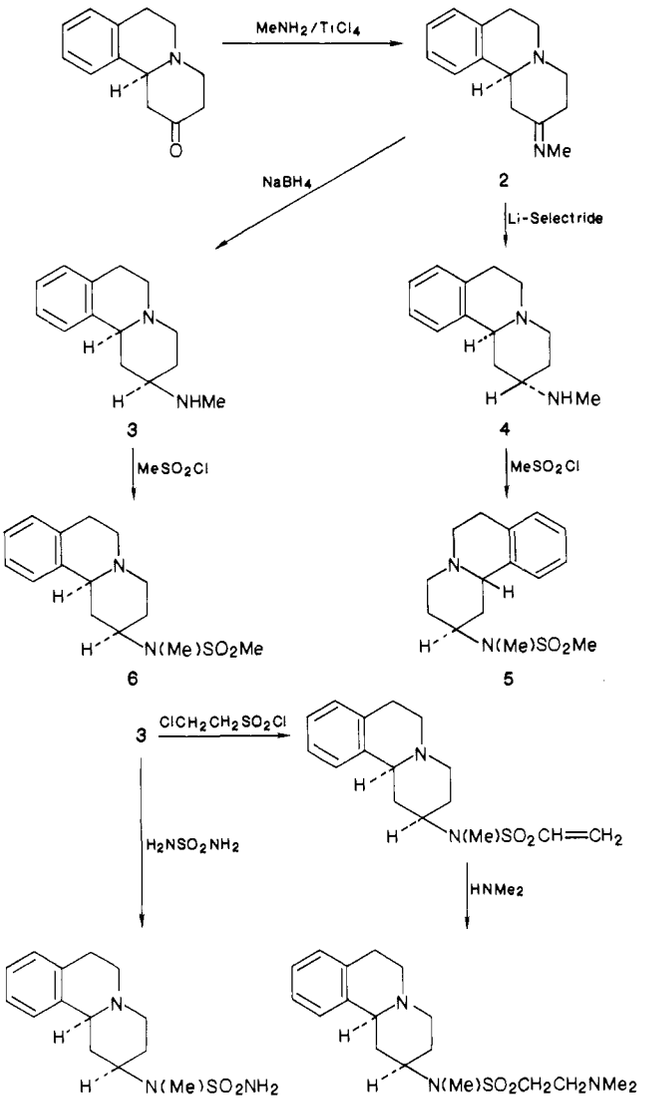
During the course of studies aimed at elucidating the mechanism by which **1** exerted its hypotensive effects, we found the compound to be a moderately potent adrenoceptor antagonist which displayed about 10-fold selectivity in favor of α_2-adrenoceptor blockade over α_1-adrenoceptor blockade. This discovery prompted us to reexamine other members of the series[18] and to carry out systematic modifications to the sulfonamide group of **1** to determine the optimum structural requirements for selective α_2-adrenoceptor blockade. These studies resulted in the discovery of a number of potent and selective compounds from this new class of adrenoceptor antagonists.

Chemistry

Most of the compounds listed in Table I were prepared by sulfonation or acylation of an aminobenzoquinolizine with the appropriate acid chloride (method A). The required intermediate aminobenzoquinolizines were prepared as described previously,[17] or by reduction of an imine such as **2** (Scheme I). The stereochemistry of the amine produced by reduction of **2** varies with the nature of the reducing agent. Reduction of **2** with sodium borohydride gave the product corresponding to **3** in which the amino group is equatorial; on the other hand, reduction of **2** with lithium tri-*sec*-butylborohydride gave the axial amine **4**. Interestingly, sulfonation of **4**, under standard conditions, proceeded with inversion of the bridgehead nitrogen atom to give a product (**5**) in which the sulfonamide group is equatorial. The assignment of stereochemistry to the products of these reactions was in accord with IR and NMR data obtained on the free bases. For example, the IR spectra of **3**, **4**, and **6** show strong "Bohlmann bands" in the region 2700–2800 cm^{-1} characteristic of a trans ring junction at the 5,11b-positions;[19] these bands are absent in **5**. NMR signals for equatorial protons in six-membered rings are well known to occur at lower field than the equivalent axial protons.[20,21] Accordingly comparison of

Scheme I



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the shift positions for the 2- and 11b-protons in the isomeric pairs **3**/**4** and **5**/**6**, as the free bases in $CDCl_3$, allowed us to assign equatorial and axial protons as indicated (Table I).

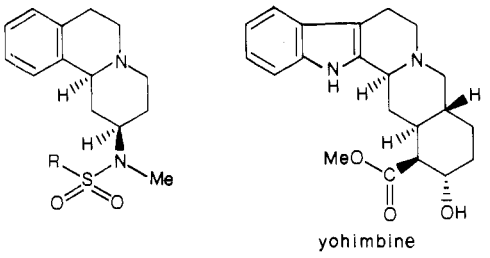
Reaction of 2-chloroethanesulfonyl chloride with **3** in the presence of excess base gave the vinyl sulfonamide **23**, which readily underwent Michael additions (method B) with secondary amines to give β-aminoethanesulfonamides (**24**, **25**). Sulfamides **35–38** were generally prepared by method A, with the exception of the parent compound **35**, which was prepared by reaction of **3** with sulfamide (method C).

The intermediate amine **3** was resolved into its enantiomers by fractional crystallization of its ditoluoyltartrate salts. Attempts to determine the enantiomeric purity of resolved **3** by NMR measurements using chiral shift reagents were unsuccessful, due to the presence of two sites for coordination of the reagent. Reaction of the resolved isomers of **3** with methanesulfonyl chloride gave the individual enantiomers (**6a**, **6b**) of **6**, which could then be evaluated for their chiral purity by NMR experiments using the chiral shift reagent praseodymium tris(*d*-3-(trifluoroacetyl)camphorate). The best separation of NMR signals on racemic **6** occurred at the *N*-methyl group, where a separation of 3 Hz was observed between the two enantiomers on a 60-Hz NMR instrument. The chiral purity of **6a** and **6b** was estimated to be greater than 95% by integration in the presence of the shift reagent. The same batches of resolved **3** were also used to prepare the individual enantiomers of **10** and **16** (Table III), under similar conditions. Similar optical purities to **6a**/**6b** were assumed for these higher homologues, although chiral NMR experiments could not be used to determine accurate optical purities due to the presence of additional aliphatic protons which obscured the *N*-methyl signal in these latter examples. X-ray diffraction studies on (+)-**3** hydrochloride showed this to have the absolute configuration 2*S*,11b*R* and allowed us to assign absolute configurations to products derived from (+)-**3** and (−)-**3** (Table III).

Results and Discussions

The potency and selectivity of compounds as antagonists of α_2- and α_1-adrenoceptors are listed in Table II. Antagonist activity at the α_1-adrenoceptor was assessed by determining the pA_2 value for inhibition of methoxamine-induced contractions on the isolated rat anococcygeus muscle.[22] α_2-Antagonist activity was assessed from the pA_2 value obtained aginst clonidine-induced inhibition of electrically stimulated contractions in the rat vas deferens.[23] Values for the α_2-antagonists yohimbine and idazoxan[24] are also reported for comparative purposes.

The secondary sulfonamide **1** showed moderate potency and selectivity for the α_2-adrenoceptor. Replacement of the sulfonamide N-H of **1** by methyl (**6**) greatly enhanced potency and selectivity, but the higher *N*-alkyl homologues (**7**, **8**) showed reduced potency/selectivity, indicating an unfavorable steric or hydrophobic interaction. The diastereoisomer (**5**) of **6** in which the nitrogen bridgehead ring fusion is cis instead of trans showed little activity. Accordingly further studies concentrated on tertiary *N*-methyl sulfonamides related to **6**. For the normal alkanesulfonamides (**6**, **9–10**, **12–14**), potency and selectivity for the α_2-receptor peaked at three carbon atoms (**10**)



yohimbine

Figure 1.

although activity was retained for chains at least up to five carbon atoms. A limiting value for the length of the *n*-alkyl chain is indicated by the poor activity and nonselectivity of the *n*-dodecanesulfonamide (**14**). Increasing the bulk around the sulfonamide groups by branching (**16–19**) was well tolerated and even favorable, compound **16** being among the most potent compounds in our series. These results may indicate the presence of a hydrophobic pocket on the α_2-receptor, able to accept a bulky R_1 side chain. Some support for this hypothesis is provided by the reduced potency of analogues **24**, **25** bearing a hydrophilic tertiary amine substituent on the R_1 side chain. The aromatic sulfonamides (**26–34**) contained a number of potent examples. Substituents on the aromatic ring were well tolerated and bulky bicyclic rings (**31**, **34**) seemed to confer favorable effects on potency. Examination of the ring-substituted phenyl sulfonamides by multiple linear regression analysis failed to identify any correlation with π, σ, or MR. Further studies showed these aromatic sulfonamides to be associated with unwanted 5-hydroxytryptamine antagonist activity. The sulfonamide function could be replaced by the closely related sulfamide group (**35–38**) with retention of activity, although the open chain analogues (**35–37**) were less potent than the lower alkyl sulfonamides.

In order to gain further insights into the stereochemical requirements for activity in this series, the resolved enantiomers of **6**, **10**, and **16** were also prepared and studied (Table III). The results shown in Table III indicate that affinity for the α_2-adrenoceptor resides primarily in the isomers having the absolute configuration 2*R*,11b*S*. The diastereomeric and absolute configuration of the more active members of this series are therefore related to the configuration of the α_2-antagonist yohimbine, such that the benzene ring and sulfonamide fragments of our series are superimposable on the pyrrole and ester fragments of the alkaloid (Figure 1).

In order to investigate the relationship between yohimbine and our benzoquinolizine series further, we replaced sulfonyl in our series by the methyl ester grouping present in yohimbine to give the urethane **39**. Interestingly **39** showed good potency and selectivity, comparable to that of the methyl sulfonamide **6**. However, in contrast to the sulfonamides **9** and **16**, higher alkyl ester substitution (**40**, **41**) caused a marked fall in selectivity; further, again in contrast to the sulfonamides, branching (**41**) reduced rather than enhanced potency. The inability of the α_2-adrenoceptor to accept antagonists with higher alkyl substitution on the ester group may reflect the different directional properties of the planar ester carbonyl carbon atom compared to the tetrahedral sulfur atom of the sulfonamides. It follows from these contrasting structure–activity relationships between the esters and sulfonamides that the sulfonamide function is not a simple surrogate for the ester group in these yohimbine-related compounds but confers unique affinity for the α_2-adrenoceptor. Indeed, further attempts to replace sulfonyl by related groups such as amide (**42–44**), urea (**45**), or phosphoramide (**46**) consist-

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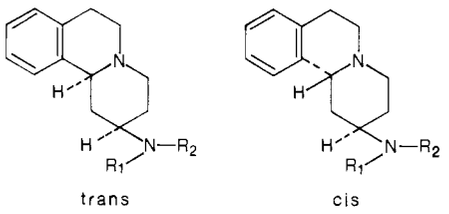
Table II[a]



no.	stereochem	R_1	R_2	method	crystn solv	mp, °C	yield,[b] %	formulae[e]	pA_2 (n)[c] α_2	pA_2 (n)[c] α_1	selectivity[d] ratio
1	trans	$MeSO_2$	H	A	EtOH	253–254	74.2	$C_{14}H_{20}N_2O_2S\cdot HCl$	6.27 (4)[f]	5.33 (4)[f]	9
5	cis	$MeSO_2$	Me	A	*i*-PrOH	253–254	56.6	$C_{15}H_{22}N_2O_2S\cdot HCl$	5.7 (6)[f]	NT	
6	trans	$MeSO_2$	Me	A	MeOH	228	53.8	$C_{15}H_{22}N_2O_2S\cdot HCl$	7.81 (6)[f]	6.04 (4)[f]	59
7	trans	$MeSO_2$	Et	A	EtOH/EtOAc	217–221[g]	26.8	$C_{16}H_{24}N_2O_2S\cdot HCl\cdot 0.5H_2O$	7.39 (4)	6.61 (3)	6
8	trans	$MeSO_2$	*n*-Pr	A	EtOH/EtOAc	220–224[g]	38.8	$C_{17}H_{26}N_2O_2S\cdot HCl$	6.77 (4)	6.44 (6)	2
9	trans	$EtSO_2$	Me	A	EtOH	230–233[g]	27	$C_{16}H_{24}N_2O_2S\cdot HCl$	7.7 (3)	6.17 (4)	34
10	trans	*n*-$PrSO_2$	Me	A	EtOH	240–250[g]	55.2	$C_{17}H_{26}N_2O_2S\cdot HCl$	8.08 (6)[f]	6.34 (6)[f]	55
11	cis	*n*-$PrSO_2$	Me	A	EtOH	168–169[g]	38.6	$C_{17}H_{26}N_2O_2S\cdot HBr$	5.78 (2)	5.86 (2)	1
12	trans	*n*-$BuSO_2$	Me	A	EtOH/EtOAc	224–226	57.6	$C_{18}H_{28}N_2O_2S\cdot HCl$	7.87 (2)[f]	6.6 (2)[f]	19
13	trans	*n*-amylSO_2	Me	A	EtOH/EtOAc	100–110	29.6	$C_{19}H_{30}N_2O_2S\cdot HCl\cdot H_2O$	7.74 (2)	6.8 (2)	9
14	trans	*n*-dodecylSO_2	Me	A	H_2O	93–100	14.2	$C_{26}H_{44}N_2O_2S\cdot HCl\cdot 1.25H_2O$	<5 (2)	NT	
15	trans	*i*-$BuSO_2$	H	A	EtOH/EtOAc	210–213[g]	55.6	$C_{17}H_{26}N_2O_2S\cdot HCl$	6.34 (4)[f]	6.55 (3)[f]	0.6
16	trans	*i*-$BuSO_2$	Me	A	EtOH/EtOAc	217–220[g]	64.3	$C_{18}H_{28}N_2O_2S\cdot HCl$	8.16 (12)[f]	6.49 (4)[f]	47
17	trans	*i*-$BuSO_2$	Et	A	EtOH	160–168	15.8	$C_{19}H_{30}N_2O_2S\cdot C_4H_4O_4$	7.61 (3)[f]	6.65 (2)[f]	9
18	trans	$Me_3CCH_2SO_2$	Me	A	EtOAc	205–215[g]	35.4	$C_{19}H_{30}N_2O_2S\cdot HCl$	8.11 (2)[f]	6.5 (4)[f]	41
19	trans	c-$C_3H_5CH_2SO_2$	Me	A	EtOH/EtOAc	215–228[g]	38.8	$C_{18}H_{26}N_2O_2S\cdot HCl$	7.7 (2)[f]	6.7 (2)[f]	10
20	trans	$ClCH_2SO_2$	Me	A	EtOH/EtOAc	225–230[g]	46.6	$C_{15}H_{21}ClN_2O_2S\cdot HCl$	8.26 (6)[f]	6.61 (6)[f]	45
21	trans	CF_3SO_2	Me	A	EtOH/EtOAc	235–239[g]	15.1	$C_{15}H_{19}F_3N_2O_2S\cdot HCl$	7.15 (6)[f]	5.49 (6)[f]	46
22	trans	$CF_3CH_2SO_2$	Me	A	EtOH	227–230[g]	71.9	$C_{16}H_{21}F_3N_2O_2S\cdot HCl$	7.56 (6)[f]	5.93 (6)[f]	43
23	trans	$CH_2{=}CHSO_2$	Me	A	EtOH/EtOAc	≈190[f]	46.1	$C_{16}H_{22}N_2O_2S\cdot HCl$	7.93 (2)[f]	6.32 (2)	41
24	trans	$Me_2NCH_2CH_2SO_2$	Me	B	EtOH/EtOAc	258–261[g]	89.8	$C_{18}H_{29}N_3O_2S\cdot 2HCl\cdot 0.5H_2O$	7.26 (2)[f]	5.6 (2)	46
25	trans	c-$C_5H_{10}NCH_2CH_2SO_2$	Me	B	EtOH/EtOAc	262–263[g]	90.9	$C_{21}H_{33}N_3O_2S\cdot 2HCl$	7.5 (2)[f]	6.11 (2)	24.5
26	trans	$C_6H_5SO_2$	Me	A	EtOH/EtOAc	227–233[g]	88.2	$C_{20}H_{24}N_2O_2S\cdot HCl$	8.44 (4)[f]	7.05 (11)[f]	24.5
27	trans	4-$MeC_6H_4SO_2$	Me	A	EtOH	258–261[g]	83.3	$C_{21}H_{26}N_2O_2S\cdot HCl$	8.1 (3)[f]	6.84 (2)[f]	18
28	trans	2-$MeC_6H_4SO_2$	Me	A	EtOH/H_2O	197–203[g]	58.0	$C_{21}H_{26}N_2O_2S\cdot HCl\cdot 0.25H_2O$	7.87 (2)[f]	6.27 (2)	40
29	trans	4-$ClC_6H_4SO_2$	Me	A	EtOH/H_2O	>230	51.4	$C_{20}H_{23}ClN_2O_2S\cdot HCl$	7.6 (2)[f]	6.09 (2)[f]	32
30	trans	4-$MeOC_6H_4SO_2$	Me	A	EtOH/H_2O	>220	61.9	$C_{21}H_{26}N_2O_3S\cdot HCl$	8.1 (2)[f]	6.5 (2)	40
31	trans	1-naphthylSO_2	Me	A	EtOH	225–230[g]	73.8	$C_{24}H_{26}N_2O_2S\cdot HCl\cdot 0.75H_2O$	8.06 (2)	7.1 (4)	9
32	trans	3-pyridylSO_2	Me	A	EtOH	≈190[f]	39.9	$C_{19}H_{23}N_3O_2S\cdot HCl$	8.22 (2)[f]	6.73 (2)[f]	31
33	trans	3-thienylSO_2	Me	A	EtOH/EtOAc	220–223[g]	41.7	$C_{18}H_{22}N_2O_2S_2\cdot HCl$	7.94 (4)[f]	6.65 (4)[f]	19.5
34	trans	8-quinolylSO_2	Me	A	EtOH	176–181[g]	64.9	$C_{23}H_{25}N_3O_2S\cdot HCl\cdot H_2O$	8.46 (4)[f]	6.84 (4)[f]	42
35	trans	H_2NSO_2	Me	C	EtOH	225[f]	35.0	$C_{14}H_{21}N_3O_2S\cdot HCl$	7.1 (4)[f]	5.7 (6)	25
36	trans	$MeNHSO_2$	Me	A	EtOH	205–206[g]	63.3	$C_{15}H_{23}N_3O_2S\cdot HCl$	7.44 (6)[f]	6.19 (6)[f]	18
37	trans	Me_2NSO_2	Me	A	MeOH	240–248[g]	60.8	$C_{16}H_{25}N_3O_2S\cdot HCl$	7.4 (8)	5.95 (2)	28
38	trans	c-$C_4H_8NSO_2$	Me	A	MeOH	228–235[g]	49.3	$C_{18}H_{27}N_3O_2S\cdot HCl$	8.1 (2)[f]	6.7 (2)[f]	25
39	trans	MeO_2C	Me	A	MeOH-MeAc	180–185[g]	19.8	$C_{16}H_{22}N_2O_2\cdot HCl\cdot 0.75H_2O$	7.9 (22)	6.56 (2)	22
40	trans	EtO_2C	Me	A	EtOH/EtOAc	216–218[g]	45.7	$C_{17}H_{24}N_2O_2\cdot HCl$	7.77 (3)	6.93 (2)	7
41	trans	*i*-BuO_2C	Me	A	*i*-BuOH	130–132	46.3	$C_{19}H_{28}N_2O_2\cdot HBr\cdot 0.5H_2O$	7.1 (4)[f]	7.0 (2)[f]	1
42	trans	MeCO	Me	A	EtOH/EtOAc	165–175[g]	19.4	$C_{16}H_{22}N_2O\cdot HCl\cdot 0.5H_2O$	6.5 (3)	NT	
43	trans	C_6H_5CO	Me	A	EtOH	220–227[g]	79.0	$C_{21}H_{24}N_2O\cdot HCl$	6.62 (2)[f]	NT	
44	trans	*i*-BuCO	Me	A	EtOH/EtOAc	206–212[g]	55.7	$C_{19}H_{28}N_2O\cdot HCl$	6.45 (2)	NT	
45	trans	H_2NCO	Me	C	EtOH/EtOAc	194–197[g]	20.2	$C_{16}H_{21}N_3O\cdot HCl$	6.0 (2)	NT	
46	trans	$(MeO)_2PO$	Me	A	EtOH/Et_2O	171–173	55.4	$C_{16}H_{25}N_2O_3P\cdot HCl\cdot 0.5H_2O$	6.63 (2)	NT	
idazoxan									8.04 (4)[f]	6.16 (4)[f]	76
yohimbine									7.58 (6)[f]	6.58 (4)[f]	10

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structure. [b] Yield of analytically pure material, yields not optimized. [c] n = number of determinations. [d] Antilog (α_2 pA_2 − α_1 pA_2). [e] C, H, and N analysis were within ±0.4% of theoretical values for the formulae given. [f] Calculated by Schild plot analysis of three or more antagonist concentrations; all other pA_2 values were calculated from results with one concentration assuming a Schild plot slope of unity. [g] decomposition. [h] Maleate.

ently gave compounds having lower potency at the α_2-adrenoceptor than their closest related sulfonamide analogues (Table II).

In summary, the potency and selectivity of a series of 2-sulfonamidobenzoquinolizines as antagonists at the α_2-adrenoceptor were studied. Optimum activity was ob-

Table III

compd	stereochem	pA_2 (n) α_2	α_1
6a	2*S*,11b*R*	<5 (4)	5.3 (4)
6b	2*R*,11b*S*	8.05 (7)[a]	6.48 (8)[a]
10a	2*S*,11b*R*	7.1 (4)[a]	5.8 (4)
10b	2*R*,11b*S*	8.5 (4)[a]	7.2 (8)[a]
16a	2*S*,11b*R*	<5 (4)	5.2 (2)
16b	2*R*,11b*S*	8.05 (6)[a]	6.9 (4)[a]

[a] Calculated by Schild plot analysis of three or more antagonist concentrations; all other pA_2 values were calculated from results with one concentration assuming a Schild plot slope of unity.

served for tertiary *N*-methyl sulfonamides bearing moderately bulky side chains. Studies of the resolved enantiomers of this series showed that activity resided primarily in the 2*R*,11b*S* isomers related to yohimbine. Following these initial test results, compounds **10** and **16** were selected for more extensive studies which have appeared elsewhere, confirming their selectivity and potency as antagonists of the α_2-adrenoceptor both in vivo and vitro[25] as well as their ability to penetrate the CNS.[26] Further clinical development of **10** and **16** was precluded by adverse toxicologial findings. However, based on these new lead compounds, further studies in these and other laboratories have led to analogues having enhanced α_2-antagonist properties.[27,28]

Experimental Section

Melting points were obtained on a Reichert microscope heating stage and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer. NMR spectra were determined on a Brucker WP200 or a Varian EM360 instrument. C, H, and N analyses were within ±0.4% of theoretical values unless otherwise stated.

***N*-((2α,11bα)-1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)methanamine (4).** Methylamine gas (7.5 g, 0.25 mol) was condensed by means of a dry ice cooled condenser into a solution of 2-oxo-1,3,4,6,7,11bα-hexahydrobenzoquinolizine (5 g, 0.025 mol) in a mixture of 100 mL of Et_2O and 100 mL of toluene under nitrogen. The solution was then ice-cooled and titanium tetrachloride (5 mL) added dropwise. After the solution was stirred for 4 h, IR showed complete imine formation and the solution was filtered and evaporated in vacuo to give the imine **2**. The residue was dissolved in 50 mL of anhydrous Et_2O, and 40 mL of a 1 M solution of lithium tri-*sec*-butylborohydride was added over 0.5 h under nitrogen with ice cooling. The mixture was then allowed to stand at ambient temperature for 24 h and then diluted with 50 mL of Et_2O and extracted twice with 1 M aqueous hydrochloric acid. The acid extracts were basified with NaOH solution and back-extracted into Et_2O. The Et_2O extract was dried (Na_2SO_4) and evaporated to give the product base as an oil, 5.2 g. The base was dissolved in 30 mL of 2-propranol and acidified with ethanolic HCl to precipitate the product hydrochloride: 2.35 g (32.5%), mp >210 °C; IR (Nujol) 2686, 2594, 2487, 1459, 1309, 1155, 1009, 741 cm^{-1}; NMR (CD_3OD) δ 2.8 (s, 3 H, CH_3), 2–3.9 (m, 11 H, $(CH_2)_5$ + 2b-H), 5.18 (dd, 1 H, 11b-H), 7.25–7.55 (m, 4 H, aryl H). Anal. ($C_{14}H_{20}N_2$·2HCl) C, H, N.

***N*-((2β,11bα)-1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)methanamine (3).** The imine **2** prepared as above was dissolved in 100 mL of ethanol, immediately followed by addition of sodium borohydride (1 g), and stirred overnight. The solvent was then evaporated in vacuo, diluted with water, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give the base, which was treated with ethanolic HCl in 2-propanol to give **3** hydrochloride: 4 g (55.3%), mp >210 °C; IR (Nujol) 3510, 3390, 2530, 2450, 1640, 1060, 945, 775, 758 cm^{-1}; NMR (CD_3OD) δ 2.0 (dq, 1 H, 1α-H), 2.05 (dq, 1 H, 3α-H), 2.5 (d, 1 H, 3β-H), 2.8 (s, 3 H, CH_3), 3–3.9 (m, 8 H, $(CH_2)_3$ + 2α-H + 1β-H), 4.67 (dd, H, 11b-H), 7.3–7.5 (m, 4 H, aryl H). Anal. ($C_{14}H_{20}N_2$·2HCl) C, H, N.

***N*-Methyl-*N*-((2β,11bα)-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)ethenesulfonamide (23). Method A.** A solution of 2-chloroethanesulfonyl chloride (1.63 g, 0.011 mol) in 25 mL of CH_2Cl_2 was added slowly to a stirred, ice-cooled solution of **3** base (2.16 g, 0.01 mol) and Et_3N (1.2 g) in 25 mL of CH_2Cl_2. The solution was then allowed to stand for 3 days, washed with aqueous Na_2CO_3 solution, dried, and evaporated. The residue was chromatographed on silica gel eluted with 10% EtOH in EtOAC to give a gum (1.56 g). This was dissolved in 5 mL of EtOH, acidified with ethanolic HCl and diluted with 7 mL of EtOAC to precipitate the title hydrochloride, 1.58 g (41.6%), with no clear melting point but decomposing above 190 °C: IR (Nujol) 2527, 2447, 1323, 1160, 966, 800 cm^{-1}; NMR (CD_3OD) δ 2.8 (s, 3 H, CH_3), 2–3.9 (m, 10 H, $(CH_2)_5$), 4.29 (tt, 1 H, 2-H), 4.67 (dd, 1 H, 11b-H), 6.08 (d, 1 H, CH_2=), 6.24 (d, 1 H, CH_2=), 6.78 (dd, 1 H, CH=), 7.25–7.4 (m, 4 H, aryl H). Anal. ($C_{16}H_{22}N_2O_2S$·HCl).

***N*-Methyl-*N*-((2β,11bα)-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)-2-(dimethylamino)ethanesulfonamide (24). Method B.** Compound **23** base (1.18 g, 0.0038 mol) was dissolved in 25 mL of ethanolic dimethylamine (33% w/v) and allowed to stand overnight. The solvent was then evaporated, and the residue was dissolved in 5 mL of hot EtOH, acidified with ethanolic HCl, and diluted with 15 mL of EtOAC to give on cooling **24** dihydrochloride: 1.5 g (94.5%), mp 258–261 °C; IR (Nujol) 2515, 2441, 1453, 1345, 1319, 1159, 960, 801 cm^{-1}; NMR (CD_3OD) δ 2.94 (s, 3 H, CH_3), 3.0 (s, 6 H, NMe_2), 2–3.9 (m, 14 H, $(CH_2)_7$), 4.38 (tt, 1 H, 2-H), 4.72 (dd, 1 H, 11b-H), 7.25–7.5 (m, 4 H, aryl H). Anal. ($C_{18}H_{29}N_3O_2S$·HCl) C, H, N.

***N*-Methyl-*N*-((2β,11bα)-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)sulfamide (35). Method C.** A solution of **3** base (4.64 g, 0.0215 mol) and sulfamide (2.61 g, 0.027 mol) in 50 mL of 1,2-dimethoxyethane was heated at reflux for 17 h. After cooling, the solution was decanted free from a red gum and evaporated and the residue was crystallized from CH_2Cl_2. The base was suspended in 10 mL of hot EtOH and acidified with ethanolic HCl to give the title hydrochloride: 2.49 g (34.9%), mp 200–202 °C dec; IR (Nujol) 3257, 3169, 3075, 2555, 1428, 1391, 960, 801 cm^{-1}; NMR (CD_3OD) δ 2.8 (s, 3 H, CH_3), 2-3.85 (m, 10 H, $(CH_2)_7$), 4.27 (tt, 1 H, 2-H), 4.65 (dd, 1 H, 11b-H), 7.25–7.4 (m, 4 H, aryl H). Anal. ($C_{14}H_{22}N_3O_2S$) C, H, N.

Resolution of *N*-((2β,11βα)-1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)methanamine (3). A solution of (−)-di-*p*-toluoyl-L-tartaric acid (19.34 g, 0.05 mol) in 50 mL of hot EtOH was added with stirring to a hot solution of racemic **3** base (21.6 g, 0.1 mol) in 50 mL of EtOH. Crystallization commenced rapidly, and after cooling, the crystalline precipitate, crop A, was collected and triturated twice with hot EtOH. The salt was then basified with aqueous NaOH and extracted twice with CH_2Cl_2. The extract was dried and evaporated to give (+)-**3**, 7.43 g (34.4%). A sample of (+)-**3** (1 g) was treated with ethanolic HCl and EtOAC to give (+)-**3** hydrochloride: 1.27 g (95%), mp >210 °C; $[\alpha]^{21}_D$ +44° (*c* 1, MeOH). Anal. ($C_{14}H_{20}N_2$·2HCl) C, H, N. The filtrate obtained after collection of crop A was evaporated in vacuo, basified with aqueous NaOH solution, and extracted into $CHCl_3$ (2 × 50 mL). The extracts were dried and evaporated, and the residue was dissolved in 25 mL of hot EtOH and treated with a solution of (+)-di-*p*-toluoyl-D-tartaric acid (10.8 g) in 25 mL of hot EtOH. Crystallization again commenced rapidly, and after cooling, crop B was collected and treated as for crop A to give (−)-**3**, 7.79 g (36.1%). A sample of the base (1

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g) was again treated with ethanolic HCl and EtOAc to give (−)-**3** hydrochloride: 1.22 g (90%), mp >210 °C; $[\alpha]^{21}_D$ −44.5° (*c* 1, MeOH). Anal. ($C_{14}H_{20}N_2$·2HCl) C, H, N.

Chiral Purity of the Enantiomers of 6. The resolved enantiomers of **6** were examined, as their bases, by NMR in a 9:1 mixture of $C_6D_6/CDCl_3$ in the presence of 0.3 mol of praseodymium tris(*d*-3-(trifluoroacetyl)camphorate)/mol of **6**. The best separation of signals was found for the *N*-Me singlet which occurred at δ 1.15 and 1.20 for (+)-**6** and (−)-**6**, respectively. The chiral purity was determined by integration and estimated to be greater than 95% for each isomer.

Estimation of α_2-Adrenoceptor Antagonism on the Rat Isolated Vas Deferens. Rats (200–250 g) were killed with a blow to the head and a section (2 cm) cut from the prostatic region of the vas deferens, which was desheathed and suspended in an organ bath (6 mL) at 34.5 °C in Krebs solution gassed with a 95% O_2/5% CO_2 mixture. Platinum ring electrodes, one above and one below the tissue, were used for field stimulation (0.1 Hz, 1-ms pulse width, 100 mA). Isometric twitch responses were recorded at a resting tension of 0.5 g. Concentration–response curves for the inhibitory effect of clonidine were obtained by cumulative addition of clonidine (10^{-9} to 10^{-8} M) to the bath, a 4-min contact time with each concentration of clonidine being allowed. Clonidine was then washed from the bath and an antagonist equilibrated with the tissue for 30 min, after which time a clonidine concentration–response curve was again obtained.

Estimation of α_1-Adrenoceptor Antagonism on the Rat Isolated Anococcygeus Muscle. Anococcygeus muscles were suspended in organ baths (6 mL) in Krebs solution at 37 °C, gassed with a 95% O_2/5% CO_2 mixture. Isotonic contractions (0.5 g tissue load) were obtained by cumulative addition of the α_1-adrenoceptor selective agonist methoxamine (3×10^{-8} to 3×10^{-6} M) to the bath (10-min contact time for each concentration of methoxamine). Methoxamine was washed from the bath and an antagonist equilibrated with the tissue for 30 min, when a concentration–response curve to methoxamine was again obtained.

Calculation of pA_2 Values. Compounds which demonstrated marked antagonist activity were tested at a minimum of three concentrations. Agonist concentration–ratios were used to calculate a pA_2 by the Schild plot method.[29] Where compounds showed weak antagonist activity, a pA_2 value was estimated from each tissue from the agonist concentration–ratio obtained with a single concentration of antagonist (usually 10^{-5} M) assuming a Schild plot slope of unity.

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Registry No. (±)-**2**, 114131-35-0; (±)-**2** (ketone), 114131-34-9; (±)-**2** (*N*-ethyl analogue), 114132-18-2; (±)-**2** (*N*-propyl analogue), 114132-19-3; (±)-**2** (*N*-demethyl analogue), 114132-23-9; (±)-**3**, 114132-17-1; (±)-**3**·2HCl, 114131-36-1; (+)-**3**, 114182-23-9; (+)-**3**·2HCl, 114246-98-9; (+)-**3**·di-*p*-toluoyl-L-tartrate, 114246-96-7; (−)-**3**, 114182-24-0; (−)-**3**·2HCl, 114247-00-6; (−)-**3**·d-*p*-toluoyl-L-tartrate, 114246-97-8; (−)-**3**·di-*p*-toluoyl-D-tartrate, 114246-99-0; (±)-**3** (*N*-ethyl analogue), 114132-20-6; (±)-**3** (*N*-propyl analogue), 114132-21-7; (±)-**3** (*N*-demethyl analogue), 114132-22-8; (±)-**4**, 114132-16-0; (±)-**4**·2HCl, 114131-37-2; (±)-**5**, 114131-78-1; (±)-**5**·HCl, 114131-38-3; (±)-**6**, 114132-25-1; (±)-**6**·HCl, 114132-24-0; **69**, 114182-22-8; **6a**·HCl, 114246-95-6; **6b**, 114182-25-1; **6b**·HCl, 114247-01-7; (±)-**7**, 114131-79-2; (±)-**7**·HCl, 114131-39-4; (±)-**8**, 114155-48-5; (±)-**8**·HCl, 114131-40-7; (±)-**9**, 114131-80-5; (±)-**9**·HCl, 114131-41-8; (±)-**10**, 106967-17-3; (±)-**10**·HCl, 114131-42-9; **10a**, 114182-26-2; **10a**·HCl, 114247-02-8; **10b**, 114182-27-3; **10b**·HCl, 114247-03-9; (±)-**11**, 114131-81-6; (±)-**11**·HBr, 114131-43-0; (±)-**12**, 114131-82-7; (±)-**12**·HCl, 114131-44-1; (±)-**13**, 114131-83-8; (±)-**13**·HCl, 114131-45-2; (±)-**14**, 114131-84-9; (±)-**14**·HCl, 114131-46-3; (±)-**15**, 114131-85-0; (±)-**15**·HCl, 114131-47-4; (±)-**16**, 114131-86-1; (±)-**16**·HCl, 114131-48-5; **16a**, 114182-28-4; **16a**·HCl, 114247-04-0; **16b**, 114182-29-5; **16b**·HCl, 114247-05-1; (±)-**17**, 114131-49-6; (±)-**17**·$C_4H_4O_4$, 114131-50-9; (±)-**18**, 114131-87-2; (±)-**18**·HCl, 114131-51-0; (±)-**19**, 114131-88-3; (±)-**19**·HCl, 114155-46-3; (±)-**20**, 114131-89-4; (±)-**20**·HO, 114131-52-1; (±)-**21**, 114131-90-7; (±)-**21**·HCl, 114131-53-2; (±)-**22**, 114131-91-8; (±)-**22**·HCl, 114131-54-3; (±)-**23**, 114131-92-9; (±)-**23**·HCl, 114155-47-4; (±)-**24**, 114131-93-0; (±)-**24**·2HCl, 114131-55-4; (±)-**25**, 114131-94-1; (±)-**25**·2HO, 114131-56-5; (±)-**26**, 114131-95-2; (±)-**26**·HCl, 114131-57-6; (±)-**27**, 114131-96-3; (±)-**27**·HCl, 114131-58-7; (±)-**28**, 114131-97-4; (±)-**28**·HCl, 114131-59-8; (±)-**29**, 114131-98-5; (±)-**29**·HCl, 114131-60-1; (±)-**30**, 114131-99-6; (±)-**30**·HCl, 114131-61-2; (±)-**31**, 114132-00-2; (±)-**31**·HCl, 114131-62-3; (±)-**32**, 114132-01-3; (±)-**32**·HCl, 114131-63-4; (±)-**33**, 114132-02-4; (±)-**33**·HCl, 114131-64-5; (±)-**34**, 114132-03-5; (±)-**34**·HCl, 114131-65-6; (±)-**35**, 114132-04-6; (±)-**35**·HCl, 114131-66-7; (±)-**36**, 114132-05-7; (±)-**36**·HCl, 114131-67-8; (±)-**37**, 114132-06-8; (±)-**37**·HCl, 114131-68-9; (±)-**38**, 114132-07-9; (±)-**38**·HCl, 114131-69-0; (±)-**39**, 114132-08-0; (±)-**39**·HCl, 114131-70-3; (±)-**40**, 114132-09-1; (±)-**40**·HCl, 114131-71-4; (±)-**41**, 114132-10-4; (±)-**41**·HBr, 114131-72-5; (±)-**42**, 114132-11-5; (±)-**42**·HCl, 114131-73-6; (±)-**43**, 114132-12-6; (±)-**43**·HCl, 114131-74-7; (±)-**44**, 114132-13-7; (±)-**44**·HCl, 114131-75-8; (±)-**45**, 114132-14-8; (±)-**45**·HCl, 114131-76-9; (±)-**46**, 114132-15-9; (±)-**46**·HCl, 114131-77-0; $Cl(CH_2)_2SO_2Cl$, 1622-32-8; *n*-$BuSO_2Cl$, 2386-60-9; *n*-$C_5H_{11}SO_2Cl$, 6303-18-0; *n*-$C_{12}H_{25}SO_2Cl$, 10147-40-7; *i*-$BuSO_2Cl$, 35432-36-1; $Me_3CCH_2SO_2Cl$, 53333-76-9; c-$C_3H_5CH_2SO_2Cl$, 114132-26-2; $ClCH_2SO_2Cl$, 3518-65-8; CF_3SO_2Cl, 421-83-0; $CF_3CH_2SO_2Cl$, 1648-99-3; 2-$MeC_6H_4SO_2Cl$, 133-59-5; 4-$ClC_6H_4SO_2Cl$, 98-60-2; 4-$MeOC_6H_4SO_2Cl$, 98-68-0; $MeNHSO_2Cl$, 10438-96-7; Me_2NSO_2Cl, 13360-57-1; *c*-$C_4H_8NSO_2Cl$, 1689-02-7; (−)-di-*p*-toluoyl-L-tartaric acid, 32634-66-5; (+)-di-*p*-toluoyl-D-tartaric acid, 32634-68-7; 1-naphthalenesulfonyl chloride, 85-46-1; 3-pyridinesulfonyl chloride, 16133-25-8; 3-thiophenesulfonyl chloride, 51175-71-4; 8-quinolinesulfonyl chloride, 18704-37-5.