4.5; $NaHCO_3$, 25; $MgCl_2$, 1.25; dextrose, 10; (Ca/Na_2) EDTA, 0.025. After a cumulative dose–response curve was obtained for l-norepinephrine bitartrate (NE), the test compound was added in a volume of between 0.01 and 0.1 mL, and the cumulative dose–response curve for NE was again determined in the presence of the test compound incubated for 10 min. The test compounds and prazosin hydrochloride (PZ) were dissolved in dimethyl sulfoxide. Phentolamine mesylate (PT) and NE were diluted with saline. PA_2 values were determined according to the method of Van Rossam.[19]

Acknowledgment. The authors thank Drs. Y. Masuda and T. Kobayashi for their continuing interest and encouragement during this work.

Registry No. **3a**, 84050-18-0; **3a** (base), 70842-66-9; **3b**·HCl, 84050-26-0; **3b** (base), 84050-25-9; **3c**, 84050-28-2; **3d**, 84050-29-3; **3d** (base), 84050-45-3; **3e**, 70842-70-5; **3f**, 84050-30-6; **3f** (base), 84050-46-4; **3g**, 84050-31-7; **3g** (base), 84050-47-5; **3h**, 70842-73-8; **3i**, 84050-32-8; **3i** (base), 84050-48-6; **3j**, 70842-75-0; **3k**, 84050-33-9; **3k** (base), 84050-49-7; **3l**, 70842-78-3; **3m**, 70842-79-4; **3n**, 84050-34-0; **3n** (base), 84050-50-0; **3o**, 70842-85-2; **3p**, 84050-35-1; **3p** (base), 70842-86-3; **3q**, 84050-36-2; **3q** (base), 84050-51-1; **3r**, 70842-87-4; **3s**, 84056-88-2; **3s** (base), 84050-52-2; **4a**·HCl, 84050-27-1; **4a** (base), 84050-19-1; **4b**, 84050-37-3; **4c**, 84050-38-4; **4c** (base), 84050-53-3; **4d**, 84050-39-5; **4d** (base), 70843-21-9; **4e**, 84050-40-8; **4e** (base), 84050-54-4; **4f**, 84050-41-9; **4f** (base), 84050-55-5; **5a**, 84050-20-4; **5a** (base), 84050-56-6; **5b**, 70842-93-2; **5c**, 84050-42-0; **5c** (base), 84050-57-7; **5d**, 84050-43-1; **5d** (base), 84050-58-8; **5e**, 84050-44-2; **5e** (base), 84050-59-9; **6**, 23680-84-4; **7**·HCl, 84050-21-5; **8**·HCl, 84050-22-6; **8** (base), 60547-97-9; **9a**, 621-82-9; **9b**, 2373-76-4; **9c**, 3029-79-6; **9d**, 17451-22-8; **9e**, 3368-21-6; **9f**, 6099-03-2; **9g**, 6099-04-3; **9h**, 830-09-1; **9i**, 69038-81-9; **9j**, 2373-79-7; **9k**, 20718-97-2; **9l**, 16909-11-8; **9m**, 33130-03-9; **9n**, 1615-02-7; **9o**, 1202-39-7; **9p**, 1200-07-3; **9q**, 555-68-0; **9r**, 779-89-5; **9s**, 1199-77-5; **10a**, 1124-65-8; **10b**, 1195-52-4; **10c**, 40527-55-7; **10d**, 77741-66-3; **10e**, 14770-88-8; **10f**, 41914-51-6; **11a**, 539-47-9; **11b**, 39244-10-5; **11c**, 84050-60-2; **11d**, 14779-25-0; **11e**, 75426-52-7; **14**, 84050-23-7; **15a**, 55486-27-6; **15b**, 70842-48-7; **15c**, 70842-53-4; **15d**, 70842-55-6; **15e**, 70842-49-8; **15f**, 70842-56-7; **15g**, 70842-57-8; **15h**, 70842-64-7; **15i**, 84050-62-4; **16a**, 58955-26-3; **16b**, 70843-15-1; **16c**, 70843-13-9; **16d**, 84050-63-5; **17a**, 84050-24-8; **17b**, 84050-61-3; cinnamoyl chloride, 102-92-1; acryloyl chloride, 814-68-6; formylpiperazine, 7755-92-2; 2-thiophenecarboxaldehyde, 98-03-3; propionic anhydride, 123-62-6; piperazine hydrobromide, 14007-05-7; ethyl chlorocarbonate, 541-41-3; 4-ethoxycinnamic acid, 2373-79-7.

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Synthesis and Antihypertensive Activity of 2-Sulfonamido- and 2-Sulfamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines

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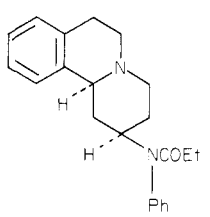
The synthesis of a series of 2-sulfonamido- and 2-sulfamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines is reported. Compounds in which the 2-substituent is equatorial were synthesized stereoselectively and shown to possess greater antihypertensive activity than the 2-axial isomers. *N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methanesulfonamide (**5**) was shown to possess antihypertensive activity in the DOCA rat at 10–50 mg/kg, and its pharmacology was examined in detail.

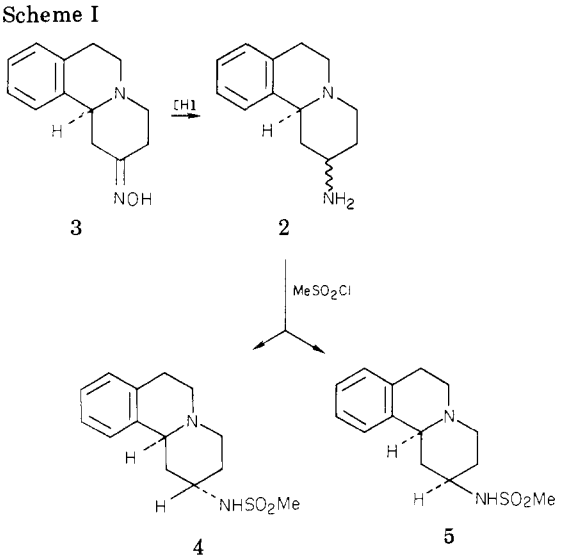
Some years ago, a series of amide derivatives of 2-aminobenzoquinolizine was reported and examined for antihypertensive activity.[1] Of particular interest from this series was compound **1**, which showed vasodilating activity



1

and was chosen for further evaluation.[2] Despite this interest in amides of 2-aminobenzoquinolizine, the related sulfonamides remained unexplored. We were therefore prompted to prepare a series of 2-sulfonamidobenzoquinolizines for evaluation as antihypertensive agents. A number of these sulfonamides have shown marked antihypertensive activity.

Scheme I



Chemistry. In initial experiments, the required intermediate, 2-aminobenzoquinolizine (**2**), was prepared by reduction of the oxime **3** over Raney nickel (Scheme I). Treatment of **2**, prepared in this way, with methane-

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sulfonyl chloride gave an approximately 1:1 mixture (TLC) of isomeric sulfonamides, which were separated by fractional crystallization. The IR spectra of both compounds showed strong "Bohlmann" bands at 2750 and 2800 cm^{-1}, characteristic of a trans ring fusion at the 5,11b-positions.[3,4] Therefore, the products only differ in the stereochemistry at the 2-position and must possess structures **4** and **5** (Scheme I) in which the 2-protons occupy equatorial and axial positions, respectively. The NMR signals for equatorial protons in six-membered rings are well known to occur at slightly lower field than the equivalent axial protons.[5] The position of the 2-proton signal has therefore been used previously to assign stereochemistry to isomeric pairs of 2-substituted benzoquinolizines.[6] The ^1H NMR spectrum (in chloroform) of the low R_f isomer obtained above showed the 2-proton as a complex multiplet at δ 3.8, downfield from the unresolved aliphatic backbone protons. In the spectrum of the high R_f isomer, the 2-proton signal was assigned to a shoulder at δ 3.5 on the broad aliphatic backbone signals. On the basis of this chemical-shift data, the low R_f isomer is assigned structure **4** in which the 2-proton is equatorial and conversely the high R_f isomer is assigned structure **5**. Similar pairs of isomers were isolated from reaction of amine **2** with ethane- and benzenesulfonyl chlorides. At this point it became apparent that biological activity was greater in the derivatives that were stereochemically related to **5**. Accordingly, a stereoselective synthesis of **2** in which the amino group is equatorial was required. In the absence of overwhelming steric effects, reduction of the oxime **3** (Scheme I) should lead predominantly to the more stable isomer in which the amino group is equatorial. Because Raney nickel/hydrogen has a large steric requirement, attack from the least-hindered face of **3** is favored and leads to undue preponderance of the less thermodynamically stable (but kinetically favored) unwanted axial amino compound, resulting in a mixture of isomers as observed above. We reasoned that the use of a sterically undemanding reducing agent, such as sodium–ethanol, to reduce **3** would favor the required equatorial isomer of **2**. When amine **2** prepared in this way was reacted with methanesulfonyl chloride, TLC showed almost exclusive formation of **5**. This provides further evidence for the validity of our structural assignments from NMR data. In subsequent experiments, amine prepared by this second route was used, and all products are therefore assumed to possess stereochemistry analogous to **5**. The secondary amine intermediate to compound **11** was prepared from **2** by formylation, followed by reduction with lithium aluminium hydride. In addition to sulfonamides, we also prepared examples of the closely related sulfamides **16–22** (Table I). These were generally prepared by reaction of sulfamyl chlorides with **2**, except for compounds **14** and **20**, which were prepared by reaction of sulfamide with the appropriate 2-aminobenzoquinolizine.

Pharmacological Results and Discussion

The antihypertensive activity of compounds in Table I was evaluated in DOCA/saline hypertensive rats.[7,8] Systolic blood pressure (BP) and heart rate (HR) were measured by an indirect tail-cuff technique.[9] All compounds were tested initially at an oral dose equivalent to 50 mg/kg of compound as its free base. BP and HR were measured at 2, 6, and 24 h, all of the compounds being inactive at the 24-h time point. The more active compounds were retested at lower doses as shown; results for the less active compounds at higher doses have not been reported.

As already indicated, initial results obtained on compounds **4–7** showed that optimum cardiovascular activity was present in compounds in which the sulfonamide group is equatorial, and further discussion of structure–activity relationships (SAR) is confined to this latter class. The methane- and ethanesulfonamides **5** and **6** showed marked activity, but **5** was marginally more potent and longer acting. Further extension of the side chain to propyl (**8**) reduced activity. Interestingly, the ethanesulfonamide **12** was more potent than the methane- or propanesulfonamides in the N-methylated series **11–13**. The effect of substituents at the 9/10-positions was unfavorable in the two examples studied, **14** and **15**. SAR for the closely related sulfamides **16–22** followed that observed for the sulfonamides, and the least substituted example **16** showed the greatest antihypertensive activity.

The effect of the compounds on heart rate is notable. Tachycardia occurred frequently in this series and may reflect a reflex mediated response to lowered BP. However, the severity of tachycardia does not always parallel the severity of BP reduction. For example, **5** elicited marked tachycardia at 10 mg/kg but had no effect on heart rate at 25 mg/kg, despite the greater fall in BP produced by the higher dose. Compound **5** was selected for further studies to define its cardiovascular profile.

Central (icv) administration of **5** to conscious, normotensive rats evoked similar decreases in BP to those evoked by the same dose given peripherally, but the onset of action was delayed. These experiments suggested that the mode of action was mainly peripheral.

In anesthetized rats (ganglion blocked with pentolinium to maintain a stable basal BP), **5** elicited dose-dependent reductions in norepinephrine-induced pressor responses, suggesting α-adrenergic blockade or a direct action on vascular smooth muscle. A direct action on smooth muscle was ruled out, since **5** at 10^{-5} M neither antagonized contractions elicited by barium or potassium ions on the rat isolated perfused mesentery nor inhibited spontaneous myogenic contractions of the rat isolated portal vein. In further isolated tissue studies, **5** was devoid of 5-hydroxytryptamine, histamine H_1, and β_1- or β_2-adrenoceptor antagonist actions.

In renal hypertensive cats implanted with aortic cannulas[10] **5** decreased mean arterial pressure by 37, 46, and 39% at doses of 5, 10, and 25 mg/kg orally. Heart rate rose by 25% at 5 mg/kg but was decreased by 15 and 30%, respectively, at the higher doses. In contrast to the effects observed in the cat and rat, **5** had no significant effect on BP but increased heart rate in conscious renal hypertensive dogs at 5 and 10 mg/kg.

Species specificity and the presence of tachycardia precluded further development of **5** as an antihypertensive agent. However, continuing studies on related compounds have led to the discovery of agents having selective α_2-antagonist activity.[11] Structure–activity relationships for

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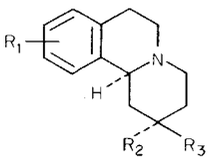
Table I. Benzoquinolizines[a]



no.	R_1	R_2	R_3	crystn solv	mp, °C	method	yield,[c] %	formula[d]	dose, mg/kg, po	antihypertensive act.: DOCA/saline rat[b] % fall BP[e] 2 h	% fall BP[e] 6 h	% rise HR[e] 2 h	% rise HR[e] 6 h
1	H	H	N(Ph)COEt						50	*	*	*	*
									75	*	15 ± 6	*	*
4	H	$NHSO_2Me$	H	MeOH	251–254	C	40	$C_{14}H_{20}N_2O_2S \cdot HCl$	50	*	*	*	*
5	H	H	$NHSO_2Me$	EtOH	253–254	D	74.2	$C_{14}H_{20}N_2O_2S \cdot HCl$	50	53 ± 3	68 ± 3	*	*
						C	12.7		25	50 ± 4	50 ± 5	*	*
									10	28 ± 7	*	39 ± 6	*
6	H	H	$NHSO_2Et$	MeOH	227–228	C	24	$C_{15}H_{22}N_2O_2S \cdot HCl$	50	56 ± 3	43 ± 3	*	22 ± 6
									25	42 ± 6	*	*	*
									10	37 ± 7	*	*	*
7	H	$NHSO_2Et$	H	MeOH	234–236	C	26	$C_{15}H_{22}N_2O_2S \cdot HCl$	50	*	*	*	*
8	H	H	$NHSO_2$-*n*-Pr	EtOH	227–232	D	57.4	$C_{16}H_{24}N_2O_2S \cdot HCl$	50	28 ± 10	46 ± 10	14 ± 5	*
9	H	H	$NHSO_2Ph$	EtOH	245–246	D	57.7	$C_{19}H_{22}N_2O_2S \cdot HCl$	50	*	*	*	*
						C	16						
10	H	$NHSO_2Ph$	H	EtOH	255	C	18	$C_{19}H_{22}N_2O_2S \cdot HCl$	50	*	18 ± 1	*	*
11	H	H	$N(Me)SO_2Me$	MeOH	228	D	53.8	$C_{15}H_{22}N_2O_2S \cdot HCl$	50	*	*	*	*
12	H	H	$N(Me)SO_2Et$	EtOH	230–233[f]	D	27	$C_{16}H_{24}N_2O_2S \cdot HCl$	25[g]	36 ± 7	*	*	*
13	H	H	$N(Me)SO_2$-*n*-Pr	EtOH	240–250[f]	D	55.2	$C_{17}H_{26}N_2O_2S \cdot HCl$	50	38 ± 7	*	15 ± 8	21 ± 6
									25	*	*	*	*
14	9,10-$(OMe)_2$	H	$NHSO_2Me$	MeOH	220–223[f]	D	39.5	$C_{16}H_{24}N_2O_4S \cdot HCl \cdot 0.25H_2O$	50	44 ± 3	35 ± 4	16 ± 6	*
15	10-Cl	H	$NHSO_2Me$	EtOH	223–233[f]	D	11.8	$C_{14}H_{19}ClN_2O_4S \cdot HCl \cdot 0.5H_2O$	50	*	*	*	*
16	H	H	$NHSO_2NH_2$	H_2O	205–205.5	E	20.3	$C_{13}H_{19}N_3O_2S \cdot HCl$	50	48 ± 4	50 ± 3	24 ± 6	*
									10	*	*	24 ± 5	*
17	H	H	$NHSO_2NHMe$	EtOH	206.5–208[f]	D	24.7	$C_{14}H_{21}N_3O_2S \cdot HCl$	50	35 ± 4	18 ± 3	23 ± 3	*
18	H	H	$NHSO_2NMe_2$	EtOH	201.5–202.5[f]	D	46.2	$C_{15}H_{23}N_3O_2S \cdot HCl$	50	45 ± 12	31 ± 6	*	*
19	H	H	$NHSO_2NEt_2$	IPA	120–140[f]	D	21.2	$C_{17}H_{27}N_3O_2S \cdot HCl \cdot 0.25H_2O$	50	29 ± 6	*	*	*
20	H	H	$NHSO_2$-c-NC_4H_8	EtOH	206–207[f]	D	34.1	$C_{17}H_{25}N_3O_2S \cdot HCl \cdot 0.5H_2O$	50	*	*	22 ± 7	*
21	H	H	$NHSO_2NHPh$	EtOH	210–213[f]	D	17.4	$C_{19}H_{23}N_3O_2S \cdot HCl \cdot 0.5H_2O$	50	*	*	*	*
22	9,10-$(OMe)_2$	H	$NHSO_2NH_2$	MeOH	215–217[f]	E	12.9	$C_{15}H_{23}N_3O_4S \cdot HCl \cdot 0.5H_2O$	50	22 ± 7	*	*	*
hydrallazine									2	22 ± 2	*	28 ± 4	*
phentolamine									10	36 ± 6	*	23 ± 8	*

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structure. [b] There were four rats per group in each experiment. [c] Yield of analytically pure material; yields were not optimized. [d] C, H, and N analyses were within ±0.4% of theoretical values for the formulas given. [e] Means ± SE; all results were analyzed for statistically significant differences from control values using analysis of variance; nonsignificant values ($p > 0.05$) are indicated by an asterisk. [f] Decomposition. [g] Toxic at 50 mg/kg.

the agents having this new pharmacological activity will be the subject of a future communication.

Experimental Section

Melting points were obtained on a Reichert microscope heating stage and are uncorrected. IR spectra were obtained as Nujol mulls with a Perkin-Elmer Model 521 spectrophotometer. NMR spectra were determined on a Varian EM 360 instrument. C, H, and N analyses were within ±0.4% of theoretical values. TLC separations were performed on Merck silica gel 60 F_{254} plates (0.25-mm thickness) and were visualized under UV light.

1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2α- and -2β-ylamine (2). Method A. A suspension of the oxime hydrochloride **3**[1] (8.2 g, 0.0324 mol) in a mixture of 200 mL of ethanol and 200 mL of H_2O was basified to about pH 12 with 50% NaOH. The mixture was stirred vigorously and maintained below 30 °C while nickel–aluminium alloy powder (50% Ni, 8.2 g) and 20 mL of 50% NaOH were added concurrently over 5 min. The mixture was stirred for an additional 2.5 h and then filtered, and the ethanol was removed from the filtrate by evaporation in vacuo. The aqueous residue was extracted with four 100-mL portions of $CHCl_3$. The extracts were dried and evaporated, and the residual oil was dissolved in 10 mL of ethanol, acidified with ethanolic HCl, and diluted with 30 mL of EtOAc to precipitate the crystalline dihydrochloride (6.8 g, 76.5%).

1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-ylamine (2). Method B. Sodium chips (165 g) were added over 1 h to a vigorously stirred refluxing solution of oxime **3**·HCl (98 g, 0.39 mol) in 1650 mL of ethanol. After the addition was complete, stirring and refluxing were maintained for an additional 3 h. The solvent was then evaporated in vacuo, and the residue was diluted with H_2O and extracted with ether. The extract was dried and evaporated to yield the title compound, which was converted to the dihydrochloride (86.7 g, 81.5%) as described in the previous preparation.

***N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)formamide.** Acetic anhydride (43.5 mL) was added at room temperature to a stirred solution of amine **2** base (31.2 g, 0.0876 mol), obtained by method B, in 75 mL of formic acid. After stirring for an additional 1.75 h, the mixture was heated at reflux for 2.5 h. The solvent was then evaporated in vacuo, and the residue was treated with 600 mL of sodium carbonate solution (10%) and extracted with CH_2Cl_2. The extract was dried and evaporated, and the residue was crystallized from ethanol–hexane to give the title compound (26.9 g, 75.8%) mp 152–154 °C. Anal. ($C_{14}H_{18}N_2O$) C, H, N.

***N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methylamine.** A solution of the above formamide (26.9 g, 0.117 mol) in 400 mL of dry THF was added slowly to a stirred suspension of lithium aluminium hydride (15.3 g, 0.4 mol) in 300 mL of dry THF. The mixture was heated at reflux for 24 h under nitrogen and then decomposed by the dropwise successive addition of 15 mL of H_2O, 15 mL of 4 N NaOH, and 45 mL of H_2O. After filtration, the solution was evaporated in vacuo to give the title compound as an oil (20.6 g, 81.6%). A sample converted to the hydrochloride in ethanol gave mp 248–251 °C dec. Anal. ($C_{14}H_{20}N_2$·2HCl) C, H, N.

***N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2α-yl)methanesulfonamide (4 and 5). Method C.** The amine dihydrochloride **2** (1.38 g, 0.005 mol) obtained by method A was suspended in a stirred, ice-cooled mixture of triethylamine (2.8 mL, 0.02 mol) and 10 mL of CH_2Cl_2. To the above suspension was added dropwise a solution of methanesulfonyl chloride (0.63 g, 0.0055 mol) in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1 h, then poured into water, and the CH_2Cl_2 layer was separated, dried, and evaporated to yield an oil containing equal amounts of **4** and **5**: TLC (toluene/ethanol/ammonia, 80:20:1) R_f 0.40 and 0.54. The oil was dissolved in 10 mL of a 1:1 mixture of ethanol and EtOAc; on acidification with ethanol–HCl, **4**·HCl separated (0.56 g, 35.5%). The mother liquors were evaporated, basified, and extracted with $CHCl_3$. The extract was dried and evaporated, and the residue was crystallized from acetonitrile to give **5** (0.2 g, 14.6%).

***N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methanesulfonamide (5). Method D.** The amine dihydrochloride **2** (5.5 g, 0.02 mol) obtained by method B was dissolved in a stirred, ice-cooled mixture of K_2CO_3 (11 g, 0.08 mol), H_2O (40 mL), and CH_2Cl_2 (40 mL). To the above mixture was added dropwise methanesulfonyl chloride (3 g, 0.026 mol) over 5 min. After stirring for a further 0.5 h, the organic phase was separated, dried, and evaporated to yield a residue containing essentially a single product (TLC). The product was dissolved in 12 mL of ethanol and acidified with ethanol–HCl to precipitate **5**·HCl (4.27 g, 67.5%), identical by TLC and spectroscopic comparison with the high R_f isomer from method B.

***N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)sulfamide (16). Method E.** A solution of amine **2** (2.26 g, 0.011 mol) obtained by method B and sulfamide (1.34 g, 0.014 mol) in 50 mL of 1,2-dimethoxyethane was heated at reflux for 21 h. The clear supernatent solution was decanted free from a black tar and evaporated in vacuo. The residue was dissolved in 25 mL of CH_2Cl_2 and washed with two 15-mL portions of H_2O; on standing, the title compound crystallized from solution (0.9 g, 29.7%), mp 192–193 °C, and was converted to the hydrochloride with ethanol–HCl (0.71 g, 20.3%).

DOCA Hypertensive Rat Assay. Female Charles River rats (50–70 g) were rendered hypertensive by subcutaneous implantation of deoxycorticosterone acetate (DOCA) pellets (30 mg) and unilateral nephrectomy under halothane anesthesia. The drinking water was replaced with 0.9%, w/v, saline for the subsequent 4 weeks. After an additional 2 weeks, systolic blood pressures were measured in a 37 °C constant-temperature housing by a tail-cuff technique. Tail pulses were detected by a pneumatic pulse transducer (Narco Biosystems) and recorded on a Devices MX2 recorder. Rats with systolic pressures below 155 mmHg were discarded.

Groups of four hypertensive rats were dosed orally with the test substance in 0.5% (hydroxypropyl)methylcellulose/0.9% saline vehicle (10 mL/kg) or vehicle alone. Blood pressures were recorded before dosing and at 2, 6, and 24 h after dosing. Heart rates were derived from the pulse traces. Results were appraised statistically by an analysis of variance.

Central and Peripheral Administration to Conscious Normotensive Rats. Rats were prepared with chronically implanted brain cannulas.[12] Blood pressure and heart rate were recorded from a carotid arterial cannula. Groups of four rats were given **5** (2 mg/kg) in saline vehicle either via the brain cannula (icv) or via the arterial cannula (ia). Control groups were given vehicle alone, 10 μL (icv) or 1 mL/kg (ia).

Ganglion-Blocked Rats. Rats were anesthetized with sodium pentobarbitone (60 mg/kg ip). A carotid artery and jugular vein were cannulated for the recording of blood pressure and the administration of compounds, respectively. Ganglion blockade was induced with pentolinium (5 mg/kg), and periodic challenges with nicotine (100 μg/kg) were made to ensure maintenance of the blockade. Response curves to norepinephrine were made before and 15 min after single doses of **5** (1, 10, and 50 mg/kg).

Renal Hypertensive Cats. Cats were prepared with chronically implanted aortic cannulas and made hypertensive by inducing perinephritis with cellophane.[10] Gelatine capsules filled with lactose or **5** (5, 10 or 25 mg/kg) were administered orally. Blood pressure and heart rate were recorded continuously.

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Registry No. **1**, 23548-26-7; 2α-**2**, 84051-73-0; 2α-**2**·2HCl, 84051-74-1; 2β-**2**, 73799-46-9; 2β-**2**·2HCl, 73799-52-7; **3**·HCl, 84051-63-8; **4**, 84051-76-3; **4**·HCl, 84051-64-9; **5**, 84051-75-2; **5**·HCl, 84051-65-0; **6**·HCl, 84051-66-1; **7**·HCl, 84051-67-2; **8**·HCl, 84051-68-3; **9**·HCl, 84051-69-4; **10**·HCl, 84051-70-7; **11**·HCl, 82059-27-6; **12**·HCl, 82059-28-7; **13**·HCl, 82059-29-8; **14**·HCl, 84051-71-8; **15**·HCl, 84051-72-9; **16**, 73799-47-0; **16**·HCl, 73799-48-1; **17**·HCl,

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(12) Harvey, E. A.; Stephens, R. J. *J. Pharm. Pharmacol.* **1975**, *27*, 43.

73799-54-9; 18·HCl, 73799-56-1; 19·HCl, 73799-62-9; 20·HCl, 73799-60-7; 21·HCl, 73799-58-3; 22·HCl, 73799-51-6; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)formamide, 82059-25-4; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methylamine, 75054-28-3; methanesulfonyl chloride, 124-63-0; sulfamide, 7803-58-9; 9,10-dimethoxy-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-ylamine, 73799-49-2; 10-chloro-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-ylamine, 84051-77-4; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methylamine dihydrochloride, 84051-78-5.

(*E*)-3-(4-Oxo-4*H*-quinazolin-3-yl)-2-propenoic Acids, a New Series of Antiallergy Agents

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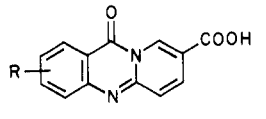
A series of substituted (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids was prepared and evaluated in the rat passive cutaneous anaphylaxis (PCA) test for antiallergic activity. Alkoxy, alkylthio, and isopropyl substituents at the 6- or 8-positions provided highly potent compounds. Conversion to the *Z* isomer, reduction of the side chain double bond, or reduction of the quinazoline ring resulted in substantial loss of activity. Among the analogues that exhibited oral activity in the PCA test, (*E*)-3-[6-(methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic acid (5i) was the most potent.

Disodium cromoglycate (DSCG) is the only antiallergy drug currently available for the prophylactic treatment of bronchial asthma believed to act by inhibiting the release of mediators of allergic reactions from sensitized mast cells. Since the introduction of DSCG, which is not orally active, numerous compounds that have similar pharmacological properties but are orally active in animal models have been described in the scientific literature.[1]

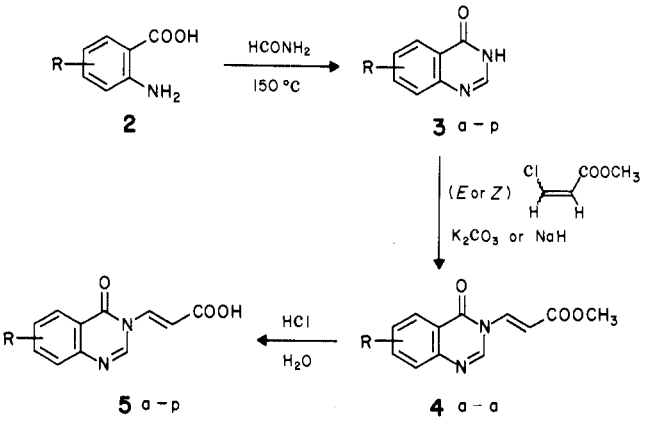
Several recent publications,[2,3] have disclosed the antiallergic activity of substituted pyrido[2,1-*b*]-quinazolinecarboxylic acids (1). We describe here a new series of potential antiallergy agents, the (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids (5), which can be considered bicyclic analogues of 1.



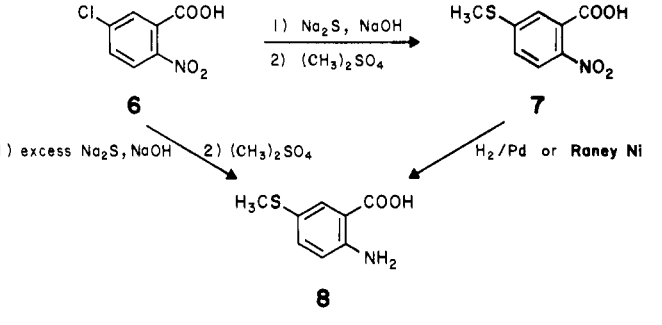
1, R = 2-OCH_3, 2-$CH(CH_3)_2$

Chemistry. The (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids (5) were prepared as shown in Scheme I. The crucial intermediates required were the quinazolin-4(3*H*)-ones (3) and the methyl ester of 3-chloro-2-propenoic acid. The substituted anthranilic acids (2) needed for the preparation of the quinazolin-4(3*H*)-ones were prepared either by literature procedures or as described under Experimental Section. Special attention was given to development of an efficient procedure for the synthesis of 2-amino-5-(methylthio)benzoic acid (8), which is the intermediate needed for the preparation of the most potent analogue (5i). Initially, 8 was prepared (Scheme II) by catalytic hydrogenation of 7, which required several catalyst loadings. During the course of this work we examined the reported[4] reaction of 6 with 1 equiv of sodium sulfide in base, followed by methylation with dimethyl sulfate to give 7. In the presence of excess sodium sulfide, a facile reduction also occurred, providing an extremely efficient conversion of 6 directly to 8. Heating the anthranilic acids (2) with formamide[5] gave the quinazolin-4(3*H*)-ones (3, Table I).

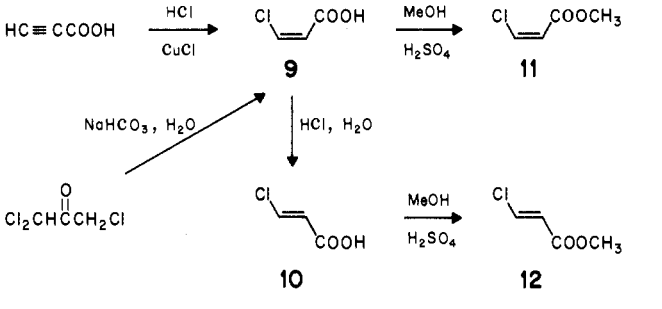
Scheme I



Scheme II



Scheme III



Two different literature methods were used to prepare the required 3-chloro-2-propenoic acids (Scheme III).

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