Synthesis and Antihypertensive Activity of a Series of Spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one]s[1]

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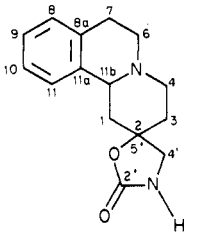
Received November 22, 1982

The 2*R**,11b*S** and 2*S**,11b*S** diastereoisomers of the spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one] system were prepared by stereoselective methods. Evaluation of these compounds for antihypertensive activity by oral administration to the spontaneously hypertensive rat showed the 2*S**,11b*S** series was the more potent. Within that series it was found that small alkyl substituents at positions 3 and 4′ enhanced antihypertensive activity and that methoxyl substitution at positions 9 and 10 was optimal. (2*S*,3*S*,11b*S*)-Spiro-[2-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one] [(−)-**9e**] was one of the most efficacious compounds of this series, while its antipode, (+)-**9e**, was inactive. Selected compounds in this series were shown to be α-adrenoceptor antagonists.

In extending our study of α-adrenoceptor blocking, antihypertensive 1-oxo-3,8-diazaspiro[4.5]decan-2-ones,[2] we chose to investigate the spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one] system **1**. An example of this system (**2**, 4′ = Et) had been

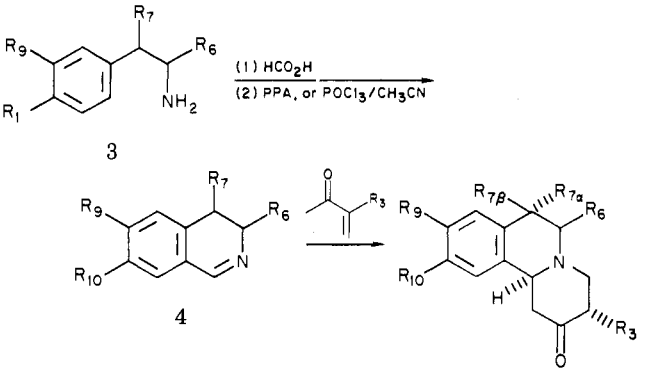


1
2, 4′ = Et

described without accompanying biological data.[3] Compound **2** had been synthesized without control of stereochemistry, and, therefore, it could have been a mixture of as many as four diastereoisomers. Since, in principle, a system of fused rings such as **1** allows for defined stereochemistry and conformation, we decided to exploit those stereochemical features in following up on the earlier report of compound **2**. Our major goal in this study was to assess the antihypertensive structure–activity relationships of system **1** by preparing the two major diastereoisomers (2,5′ isomerism) and then to evaluate systematically the effects on activity resulting from variations of substituents about the periphery.

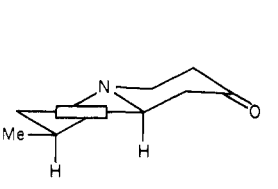
Chemistry. The 1,3,4,6,7,11b-hexahydro-2*H*-benzo-[*a*]quinolizin-2-ones **5a**-t in Table I were prepared according to known methods, as outlined in Scheme I.[4-7] Many of the 3,4-dihydroisoquinoline intermediates **4** were made by using modified Bischler–Napieralski conditions wherein the cyclization of the formamide precursors with phosphorus oxychloride proceeded at room temperature in acetonitrile.[8]

Scheme I

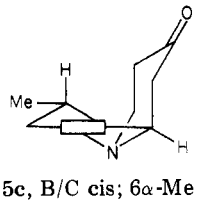


3 **4** **5a-t**

The condensation of 3,4-dihydroisoquinolines with methyl vinyl ketones to give benzoquinolizinones can exhibit variable degrees of stereoselectivity with regard to the ultimate conformation of substituents. A rigorous stereochemical analysis of the synthesis of 7-phenyl-substituted **5f** has been published.[6] Essentially no conformational preference was seen in that system when equilibrating conditions were used; however, the 7α-phenyl **5f** could be obtained in high yield under what were presumably conditions of kinetic control. In the present work, the conditions used to produce the 7-methylbenzoquinolizinones were only modestly stereoselective: 7β-methyl **5d** and 7α-methyl **5e** were obtained in 66% total yield and in a ratio of 1:1.7. The assignments of stereochemistry for **5d** and **5e** were made on the basis of their ^{13}C NMR spectra, which showed the 7α-methyl at 4.2 ppm higher field than the 7β-methyl due to strong peri interaction of the pseudoequatorial 7α-methyl and the proton at C-8. The 6-methyl compound **5c** was obtained as the sole product in 50% yield from the condensation of its precursor dihydroisoquinoline with methyl vinyl ketone. The assignment of the 6β stereochemistry to the methyl group in **5c** was made after examination of Dreiding



5c, B/C trans; 6β-Me



5c, B/C cis; 6α-Me

models, which showed a strong preference for a 6β-methyl substituent and a B/C *trans* conformation for the benzoquinolizinone. The appearance of strong Bohlmann bands

(1) Contribution no. 640 from the Institute of Organic Chemistry.
(2) Caroon, J. M.; Clark, R. D.; Kluge, A. F.; Nelson, J. T.; Strosberg, A. M.; Unger, S. H.; Michel, A. D.; Whiting, R. L. *J. Med. Chem.* **1981**, *24*, 1320.
(3) Maillard, J.; Langlois, M.; Delaunay, P.; Vo Van, T.; Chenu, J.; Morin, R.; Benharkate, M.; Manuel, C.; Motosso, F. *J. Med. Chem.* **1972**, *15*, 1123.
(4) Beke, D.; Szantay, C. *Chem. Ber.* **1962**, *95*, 2132.
(5) (a) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1449. (b) *Ibid.* **1963**, 1461.
(6) Maryanoff, B. E.; McComsey, D. F.; Taylor, Jr., R. J.; Gardocki, J. E. *J. Med. Chem.* **1981**, *24*, 79.
(7) Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119.
(8) McDonald, E.; Suksamararn, A. *J. Chem. Soc.* **1978**, 434.

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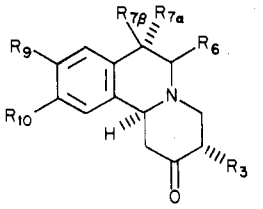
Table I. Intermediate 1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-ones

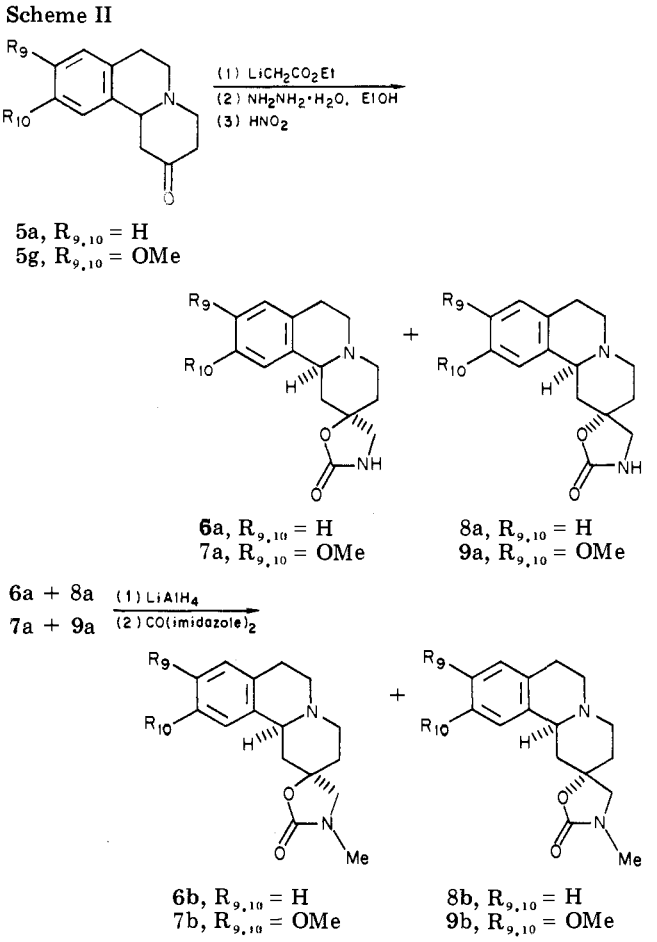


compound	mp, °C	formula	ref
5a (R_{3-10} = H)	76–77	$C_{13}H_{15}NO$	4
5b (R_3 = Et; R_{6-10} = H)	95–97	$C_{15}H_{19}NO$	5a
5c (R_6 = CH_3; $R_{3,7,9,10}$ = H)	77–80	$C_{14}H_{17}NO$	
5d ($R_{7\beta}$ = CH_3; $R_{3,7\alpha,9,10}$ = H)	89–90	$C_{14}H_{17}NO$	
5e ($R_{7\alpha}$ = CH_3; $R_{3,7\beta,9,10}$ = H)	96–97	$C_{14}H_{17}NO$	
5f ($R_{7\alpha}$ = C_6H_5; $R_{3,7\beta,9,10}$ = H)	139–140	$C_{19}H_{19}NO$	6
5g ($R_{9,10}$ = OCH_3; R_{3-7} = H)	152–153	$C_{15}H_{19}NO_3$	4
5h (R_3 = CH_3; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	140–142	$C_{16}H_{21}NO_3$	5a
5i (R_3 = C_2H_5; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	106–107	$C_{17}H_{23}NO_3$	5a
(+)-5i	117–120	$C_{17}H_{23}NO_3$	5b
(−)-5i	116–119	$C_{17}H_{23}NO_3$	5b
5j (R_3 = *n*-C_3H_7; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	104–105	$C_{18}H_{25}NO_3$	5a
5k (R_3 = *n*-C_4H_9; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	105–106	$C_{19}H_{27}NO_3$	5a
5l (R_3 = C_6H_5; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	150–153	$C_{21}H_{23}NO_3$	5a
5m (R_3 = $CH_2C_6H_5$; $R_{9,10}$ = OCH_3; $R_{6,7}$ = H)	148–150	$C_{22}H_{23}NO_3$	4
5n (R_3 = C_2H_5; R_9 = OCH_3; R_{10} = OC_2H_5; $R_{6,7}$ = H)	120–121	$C_{18}H_{25}NO_3$	
5o (R_3 = C_2H_5; R_9 = OC_2H_5; R_{10} = OCH_3; $R_{6,7}$ = H)	108–111	$C_{18}H_{25}NO_3$	
5p (R_9-R_{10} = OCH_2O; R_{3-7} = H)	130–133	$C_{14}H_{15}NO_3$	7
5q (R_9-R_{10} = OCH_2O; R_3 = C_2H_5; $R_{6,7}$ = H)	149–151	$C_{16}H_{19}NO_3$	7
5r (R_9 = OCH_3; R_{10} = O-*n*-C_3H_7; $R_{3,6,7}$ = H)	89–92	$C_{17}H_{23}NO_3$	
5s (R_9 = OCH_3; R_{10} = O-*n*-C_3H_7; $R_{3,6,7}$ = H)	98–101	$C_{17}H_{23}NO_3$	
5t (R_9 = OCH_3; R_{10} = O-*n*-C_4H_9; $R_{3,6,7}$ = H)	74–74	$C_{18}H_{25}NO_3$	

in the infrared spectrum of **5c** provided evidence for assigning a B/C trans conformation and against assigning the alternative 6α-methyl B/C cis formulation to **5c**.[9] The condensation reactions that produced the 3-substituted benzoquinolizinones uniformly afforded single isomers, which were assigned 3α stereochemistry in accord with the preference in this system for equitorial substituents and a B/C trans conformation. The presence of strong Bohlmann bands in the infrared spectra of these compounds and the absence of signals attributable to H-11b below δ 3.8[10] in their ^{1}H NMR spectra provided evidence for such a B/C trans-fused conformation.

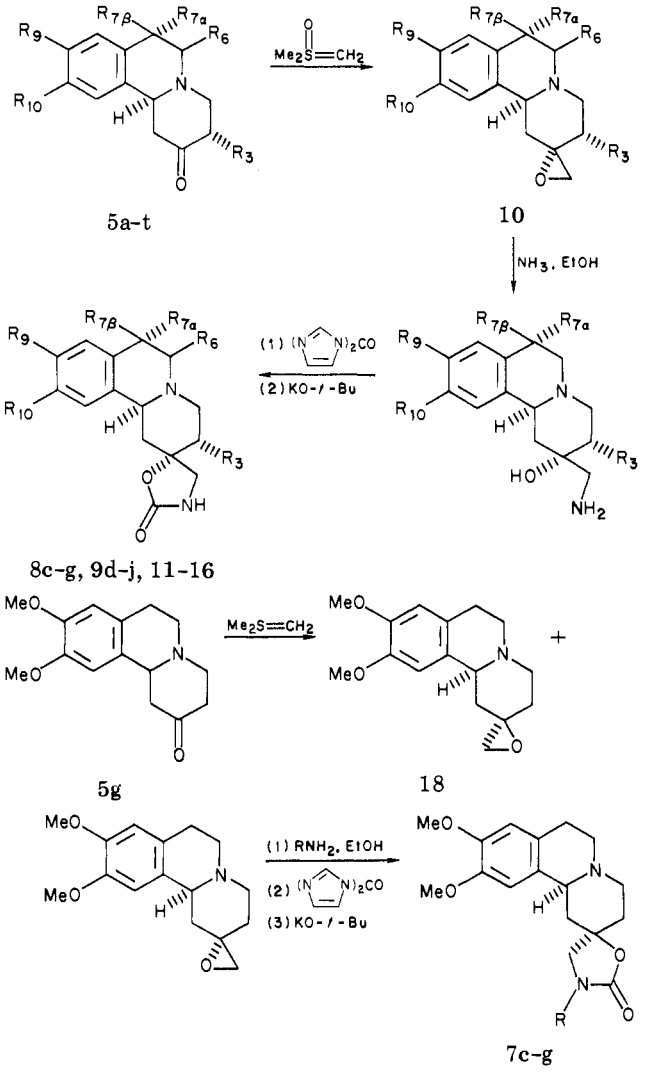
The initial syntheses of the two possible 2,5′-isomeric spiro[benzoquinolizine-oxazolidinone]s produced both the unsubstituted pair **6a**, **8a** and the 9,10-dimethoxy pair **7a**, **9a** using the three-step sequence shown in Scheme II. We were unable to assess directly the stereochemistry of the addition of lithioethyl acetate to the ketones **5a** and **5g**, since the epimeric 1,2-adducts did not separate conveniently by chromatography. These 1,2-adducts were transformed through hydrazide formation and subsequent Curtius rearrangement into mixtures of isomers, which were separated by column chromatography: **6a**, **8a** = 2.35:1; **7a**, **9a** = 2.9:1. The assignments of stereochemistry for the isomeric pairs were made on the basis of ^{13}C NMR spectroscopy, where in the pseudoaxial methylene (C-4′) in **6a** was at 2.66 ppm higher field than C-4′ in **8a**, and C-4′ in **7a** was at 2.6 ppm higher field than C-4′ in **9a**. These relative positionings were in accord with expectations

Scheme II

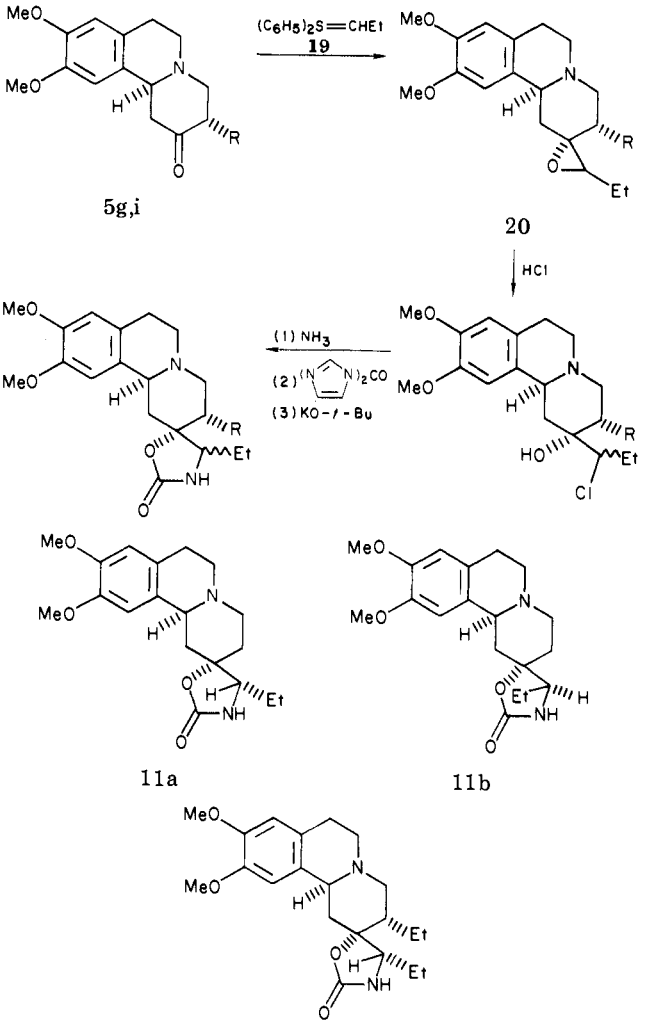


(9) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(10) Uskokovic, M.; Bruderer, H.; von Planta, C.; Williams, T.; Brossi, A. *J. Am. Chem. Soc.* **1964**, *86*, 3364.

Scheme III



Scheme IV



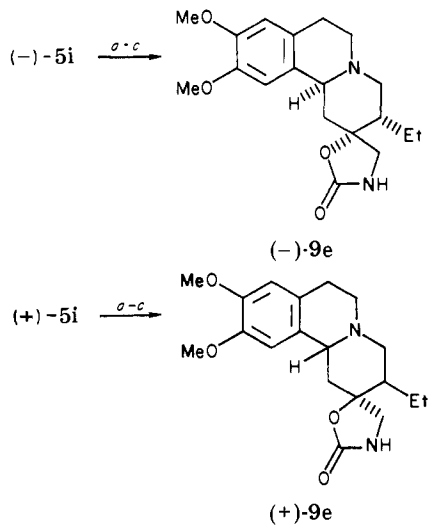
based on the well-known upfield steric compression shift found with axial substituents.[11] Also shown in Scheme II is the further transformation of the spiro[benzoquinolizine-2,5′-oxazolidinone]s **6a–9a** to their *N*-methyl (3′) congeners **6b–9b** in two steps using lithium aluminum hydride reduction, followed by cyclization with *N,N′*-carbonyldiimidazole.

Since it became evident that the spiro[benzoquinolizine-2,5′-oxazolidinone]s that were derived from 1,2-addition of lithioethyl acetate to the β-face of the benzoquinolizinone were the more active isomers in the antihypertensive assay (Table II), a more stereoselective method of synthesis of this series had to be developed. This problem was solved conveniently by using the epoxide-based route outlined in Scheme III. Reaction of ketones **5a–t** with dimethylsulfoxonium methylide gave with high stereoselectivity epoxides **10** having the 2*S**,11b*S** stereochemistry. The reaction of dimethylsulfonium methylide with ketone **5g** gave a mixture of epoxides, from which **18** having the 2*R**,11b*S** stereochemistry could be isolated conveniently.[12] These epoxides were then reacted with amines to give aminocarbinols, which were cyclized with *N,N′*-carbonyldiimidazole and potassium *tert*-butoxide to give the spiro[benzoquinolizine-2,5′-oxazolidinone]s listed in Table II.[13]

The 4′-ethyl-substituted compounds **9j**, **11a**, and **11b** were prepared according to Scheme IV. Reactions of ketones **5g** and **5i** with sulfonium ylide **19** were expected to be subject to thermodynamic control, since the addition to the carbonyl should be reversible, and the product-forming step should be controlled by the requirement that the bulky diphenylsulfonium moiety occupy the less hindered equatorial position in the transition state[14,15] leading to pseudoequatorial methylene stereochemistry in epoxides **20**. Starting with **5g**, we obtained **11a** and **11b**, which were separated by chromatography and assigned structures on the basis of ^{13}C NMR spectroscopy. In particular, C-1 and C-3 were subject to the shielding influence of the ethyl

(11) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972, p 163 ff.
(12) Davis, R.; Kluge, A. F.; Maddox, M. L.; Sparacino, M. L. *J. Org. Chem.* **1983**, *48*, 255.
(13) TLC analysis of product mixtures from the reaction of the intermediate aminocarbinols with *N,N′*-carbonyldiimidazole frequently showed two components, one that proved to be the desired product and another that was presumably a mixed urea composed of one part aminocarbinol and one part imidazole. Treatment of this two-component mixture with potassium *tert*-butoxide resulted in the rapid transformation of the mixture into a single component, which was the desired spiro[benzoquinolizine-2,5′-oxazolidinone].
(14) See, for example, Johnson, A. W.; Hruby, V. J.; Williams, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 918.
(15) The same argument applies to the stereoselectivity observed in the reaction of dimethylsulfoxonium methylide with 4-*tert*-butylcyclohexanone: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

Scheme V



[a] Me_2SOCH_2. [b] NH_3, EtOH, 150 °C. [c] Carbonyldiimidazole.

group at C-3′ (**11a**: C-1 at 42.29 and C-3 at 30.20 ppm; **11b**: C-1 at 36.70 and C-3 at 35.89 ppm). Starting with **5i**, we obtained only **9j** (Scheme IV). Since we did not characterize all of the products from the epoxidation or the chlorohydrin-forming reactions, we cannot say definitely whether the formation of the single diastereomer **9j** represents a true stereoselectivity in the epoxidation reaction or merely an adventitious result determined by the relative insolubility of the isolated chlorohydrin that was used to prepare **9j**.

The optically active compounds (+)-**9e** and (−)-**9e** were prepared by starting with the known (+) and (−) enantiomers of **5i**[5b] according to Scheme V. The absolute stereochemical assignments for the enantiomers of **5i**, and thus for the anantiomers of **9e**, are based on the known conversion of (−)-**5i** into (−)-emetine.[5b]

Structure–Activity Relationships. The compounds in Table II were evaluated for their antihypertensive effects in male, Okamoto-Aoki strain, spontaneously hypertensive rats (SHR). Data in Table II represent the percentage decrease in systolic blood pressure for the drug-treated group relative to the value for the untreated control.

Within the 2*R**,11b*S** series (**6a,b**, **7a–g**) most compounds were inactive. Comparison of **7b** with **6b** showed that methoxyl substituents at positions 9 and 10 increased activity. An increase in the size of the 3′-substituent led to an activity maximum with the 3′-ethyl-substituted **7c**. Activity declined with 3′-substituents with a chain length greater than two carbons and with a steric bulk greater than that of an ethyl group; moreover, the fact that **7e** (3′-*i*-Pr) and **7g** (3′-*t*-Bu) were active, whereas **7d** (3′-*n*-Pr) was inactive, showed that the antihypertensive activity of these compounds was relatively more sensitive to the length of the 3′-substituent than it was to the steric bulk of that substituent.

The structure–activity relationships within the 2*S**,11b*S** series followed a different set of correlations than were seen in the 2*R**,11b*S** series. For example, inverting the stereochemistry at position 2 for the active compound **7c** gave the less active compound **9c**. Both the unsubstituted **8a** and the 9,10-dimethoxy-substituted **9a** were active, while their 2*R**,11b*S** isomeric counterparts **6a** and **7a** were inactive. In the 2*S**,11b*S** series, substitution of a methyl at N-3′ of **8a** gave the inactive compound **8b**, whereas the same modification applied to the 9,10-dimethoxy-substituted **9a** gave **9b**, a compound having essentially the same level of activity as its parent. A further increase in the size of the N-3′ substituent with the 3′-ethyl compound **9c** resulted in a drop in the duration of activity.

For the 2*S**,11b*S** series the following additional points apply in summarizing the structure–activity relationships: (a) The 11b*S* absolute stereochemistry is preferred over the 11b*R* [(−)-**9e** vs. (+)-**9e**]. (b) Activity drops when the size of the alkoxy substituents at positions 9 and 10 is increased beyond methoxy. (c) A 4′-ethyl substituent is favorable in either absolute configuration (**11a,b**). (d) For 9,10-dimethoxy compounds, alkyl substitution at position 3 is favorable (**9d,e**); however, activity drops when the size of the substituent exceeds two carbons. (e) For 9,10-unsubstituted compounds, activity drops when substituents are added at positions 3, 6, or 7 (**8c–g**).

In Vitro Studies. The α-adrenoceptor blocking activities of **9a**, (±)-**9e**, (−)-**9e**, and (+)-**9e** were shown by in vitro studies. These compounds shifted the dose–response curve to the right for norepinephrine (NE) stimulated contraction of isolated rat aortic strips. The shifts in the dose–response curves were dose dependent, and the shifted curves were parallel to the NE control curve, which suggested that the compounds competed with NE for the receptor site. The pA_2 values were as follows: (−)-**9e** = 6.31; (±)-**9e** = 5.97; **9a** = 5.90; (+)-**9e** = 4.72. Since the receptor mediating NE contraction is the α-adrenoceptor, it can be concluded that the four compounds functioned as α-adrenoceptor antagonists in the dose range tested (10^{-4}–10^{-7} M).[16] These in vitro measurements indicated that compounds in the spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine-2,5′-oxazolidin-2′-one] series lower blood pressure through α-adrenoceptor blockade, and thus, they were similar in mechanism to the structurally related 8-substituted 1-oxa-3,8-diazaspiro[4.5]decan-2-ones.[2]

Experimental Section

Melting points (uncorrected) were obtained on a Fisher-Johns apparatus. Infrared spectra were obtained with a Perkin-Elmer 237 grating instrument. ^{13}C NMR spectra were obtained with a Bruker 90. Mass spectra were obtained with either an Atlas-werke CH-4 or CH-7 instrument. Combustion analyses were obtained from Syntex Analytical Research and from Alfred Bernhardt, Muhlheim/Ruhr.

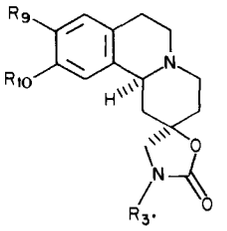
Antihypertensive Screen and Anesthetized Dog Studies. Compounds were evaluated as previously described.[2]

Aortic Strip Preparation. The thoracic aorta was removed from the rat, and the adventitial connective tissue was carefully removed. The aorta was cut into a helical strip of 2 to 3 mm in width and 3 cm in length.[17] The strips were mounted vertically in an organ bath containing 10 mL of modified Krebs' solution, maintained at 37 °C and equilibrated with a 95% O_2/5% CO_2 gas mixture. The composition of the modified Krebs' solution (in millimolar concentrations) was as follows: NaCl, 118.2; KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 2.5; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; dextrose, 10.0; $NaHCO_3$, 24.8. An initial resting tension of 1 g was applied to the tissue, and the system was allowed to equilibrate for at least 1 h before exposure to drugs. Isometric contractions were recorded on a Grass polygraph with a Grass FT.03 force-displacement transducer. A norepinephrine dose–response curve was first obtained cumulatively by a stepwise increase in concentration as soon as a steady response was reached from the preceding dose. After the washout and relaxation, the aortic strip was incubated for 10–15 min with a test compound at the lowest concentration,

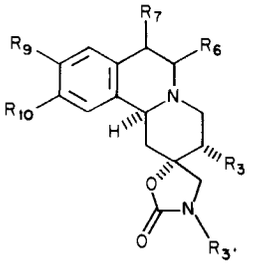
(16) Work with isolated rat vas deferens has shown that compounds in this series function as α_1- and α_2-adrenoceptor antagonists (Dr. R. Whiting, personal communication). The results of these studies will be published separately.

(17) Furchgott, R. F.; Bhadrakom, S. J. *J. Pharmacol. Exp. Ther.* **1953**, *108*, 129.

Table II. Spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one]s and Antihypertensive Activity in Spontaneously Hypertensive Rats



2*R**,11b*S** series
(6a,b and 7a–g)



2*S**,11b*S** series
(8a–g, 9a–j, 11a,b, 12a–c, and 13–16)

compound	yield,[a] %	mp, °C	formula[b]	dose, mg/kg po	% fall in systolic blood pressure[c] 1 h	2 h	3 h	4 h
6a ($R_{3',9,10}$ = H)	57	221–223	$C_{15}H_{18}N_2O_2$	50	*	*	*	*
6b ($R_{3'}$ = CH_3; $R_{9,10}$ = H)	11	156–158	$C_{16}H_{20}N_2O_2$	50	*	+10[e]	+12[e]	*
7a ($R_{3'}$ = H; $R_{9,10}$ = OCH_3)	21	222–230	$C_{17}H_{22}N_2O_4$	50	*	*	*	*
7b ($R_{3'}$ = CH_3; $R_{9,10}$ = OCH_3)	5	213–215	$C_{18}H_{24}N_2O_4$	50	27	*	*	18
7c ($R_{3'}$ = C_2H_5; $R_{9,10}$ = OCH_3)	11	indefinite[d]	$C_{19}H_{27}N_2O_4Cl$	25	*	*	*	*
				50	43	30	*	18
7d ($R_{3'}$ = *n*-C_3H_7; $R_{9,10}$ = OCH_3)	18	228–233[d]	$C_{20}H_{29}N_2O_4Cl$	50	*	*	*	*
7e ($R_{3'}$ = *i*-C_3H_7; $R_{9,10}$ = OCH_3)	12	indefinite[d]	$C_{20}H_{29}N_2O_4Cl$	50	29	16	*	*
7f ($R_{3'}$ = *n*-C_4H_9; $R_{9,10}$ = OCH_3)	26	228–235[d]	$C_{21}H_{31}N_2O_4Cl$	50	*	*	*	*
7g ($R_{3'}$ = *t*-C_4H_9; $R_{9,10}$ = OCH_3)	14	202–208[d]	$C_{21}H_{31}N_2O_4Cl$	50	39	20	*	*
8a ($R_{3',4',3,6,7,9,10}$ = H)	29	184–185	$C_{15}H_{18}N_2O_2$	50	22	26	14	12
				25	20	*	*	25
8b ($R_{3'}$ = CH_3; $R_{4',3,6,7,9,10}$ = H)	5	156–158	$C_{16}H_{20}N_2O_2$	50	*	*	*	*
8c (R_3 = C_2H_5; $R_{3',4',6,7,9,10}$ = H)	50	236–240	$C_{17}H_{22}N_2O_2$	50	25	*	*	*
8d (R_6 = CH_3; $R_{3',4',3,7,9,10}$ = H)	34	indefinite[f]	$C_{16}H_{21}N_2O_2Cl$	50	*	*	*	*
8e ($R_{7\beta}$ = CH_3; $R_{3',4',3,6,7\alpha,9,10}$ = H)	16	191–193	$C_{16}H_{20}N_2O_2$	50	*	*	*	*
8f ($R_{7\alpha}$ = CH_3; $R_{3',4',3,6,7\beta,9,10}$ = H)	12	178–179	$C_{16}H_{20}N_2O_2$	50	16	*	*	*
8g ($R_{7\alpha}$ = C_6H_5; $R_{3',4',6,7,9,10}$ = H)	19	260–270[f]	$C_{21}H_{23}N_2O_2Cl$	50	*	*	*	*
9a ($R_{3',4',3,6,7}$ = H; $R_{9,10}$ = OCH_3)	9	263–267[f]	$C_{17}H_{23}N_2O_4Cl$[k]	50	20	13	12	15
				25	22	19	*	*
9b ($R_{3'}$ = CH_3; $R_{4',3,6,7}$ = H; $R_{9,10}$ = OCH_3)	2	230–240[f]	$C_{18}H_{25}N_2O_4Cl$	50	28	14	*	21
9c ($R_{3'}$ = C_2H_5; $R_{4',3,6,7}$ = H; $R_{9,10}$ = OCH_3)	2[d]	193–195	$C_{19}H_{26}N_2O_4$	50	31	*	*	*
9d (R_3 = CH_3; $R_{3',4',6,7}$ = H; $R_{9,10}$ = OCH_3)	21	262–265[f]	$C_{18}H_{25}N_2O_4Cl \cdot {}^1/_2H_2O$	50	47	41	37	25
				25	27	19	*	15
(±)-**9e** (R_3 = C_2H_5; $R_{3',4',6,7}$ = H; $R_{9,10}$ = OCH_3)	21	263–265	$C_{19}H_{26}N_2O_4$	50	45	37	29	33
(+)-**9e**	50	289–292[g]	$C_{19}H_{26}N_2O_4$	25	*	*	*	*
(−)-**9e**	51	287–291[h]	$C_{19}H_{26}N_2O_4$	50	52	40	33	28
				25	44	30	*	*
9f (R_3 = *n*-C_3H_7; $R_{3',4',6,7}$ = H; $R_{9,10}$ = OCH_3)	40	258–262[i]	$C_{20}H_{29}N_2O_4Cl \cdot H_2O$	50	41	27	17	16
9g (R_3 = *n*-C_4H_9; $R_{3',4',6,7}$ = H; $R_{9,10}$ = OCH_3)	42	230–231	$C_{21}H_{30}N_2O_4$	50	34	21	13	13

9h ($R_3 = C_6H_5$; $R_{3',4',6,7} = H$; $R_{9,10} = OCH_3$)	26	278–282[j]	$C_{23}H_{27}N_2O_4Cl \cdot {}^1/_2H_2O$[l]	50	*	*	+9	*
9i ($R_3 = CH_2C_6H_5$; $R_{3',4',6,7} = H$; $R_{9,10} = OCH_3$)	34	250–253	$C_{24}H_{28}N_2O_4$	50	27	*	*	19
9j ($R_{4'S^*,3S^*} = C_2H_5$; $R_{3',6,7} = H$; $R_{9,10} = OCH_3$)	20	223–225[f]	$C_{21}H_{31}N_2O_4Cl \cdot H_2O$	50	43	48	30	24
11a ($R_{4'S^*} = C_2H_5$; $R_{3',3,6,7} = H$; $R_{9,10} = OCH_3$)	10	220–224[i]	$C_{19}H_{27}N_2O_4Cl \cdot H_2O$	50	45	37	30	27
11b ($R_{4'R^*} = C_2H_5$; $R_{3',3,6,7} = H$; $R_{9,10} = OCH_3$)	9	215–218[j]	$C_{19}H_{27}N_2O_4Cl \cdot {}^1/_2H_2O$	50	41	38	25	25
12a ($R_{3',4',3,6,7} = H$; $R_9 = OCH_3$; $R_{10} =$ O-*i*-C_3H_7)	14	78–82	$C_{19}H_{26}N_2O_4$	50	19	*	8	*
12b ($R_{3',4',3,6,7} = H$; $R_9 = OCH_3$; $R_{10} =$ O-*n*-C_3H_7)	13	248–250[j]	$C_{19}H_{27}N_2O_4Cl \cdot {}^1/_2H_2O$	50	*	*	*	*
12c ($R_{3',4',3,6,7} = H$; $R_9 = OCH_3$; $R_{10} =$ O-*n*-C_4H_9)	16	118–120	$C_{20}H_{28}N_2O_4$	50	15	*	*	*
13 ($R_{3',4',3,6,7} = H$; R_9-$R_{10} = OCH_2O$)	7	265–270	$C_{16}H_{18}N_2O_4$	50	28	*	14	*
14 ($R_{3',4',6,7} = H$; $R_3 = C_2H_5$; R_9-$R_{10} =$ OCH_2O)	30	indefinite[j]	$C_{18}H_{23}N_2O_4Cl \cdot {}^1/_2H_2O$	50	*	*	*	*
15 ($R_{3',4',6,7} = H$; $R_3 = C_2H_5$; $R_9 = OCH_3$; $R_{10} = OC_2H_5$)	8	176–177	$C_{20}H_{28}N_2O_4$	50	25	22	17	*
16 ($R_{3',4',6,7} = H$; $R_3 = C_2H_5$; $R_9 = OC_2H_5$; $R_{10} = OCH_3$)	52	228–232	$C_{20}H_{29}N_2O_4Cl \cdot H_2O$[m]	50	39	32	17	*
9a methiodide		210–215	$C_{18}H_{25}N_2O_4I$	50	*	*	*	*
indoramin				25	27	28	34	30
				12.5	*	*	*	*
prazosin				1.25	26	46	36	31
				0.31	19	31	21	26

[a] Overall yield from the corresponding 1,3,4,6,7,11b-hexahydrobenz[a]quinolizin-2-one 5. [b] Elemental analyses were within 0.4% of theory except where otherwise noted. [c] There were four rats per dosage group. Percentage falls in systolic blood pressure relative to the control group were recorded at the indicated times after dosing on the 2nd day of dosing. Systolic pressures in the controls started at about 200 mmHg and varied over the range of 180 to 200 mmHg during the 4-h measurement period. Values in the table are statistically significant ($p < 0.05$) relative to control values; asterisks indicate nonsignificant difference ($p > 0.05$) between treated and control group. Drug was dosed in solution or suspended in 0.3% aqueous Tween-80. Control groups were treated with vehicle only. [d] Free base was an oil; compound was characterized as its HCl salt. [e] A statistically significant ($p < 0.05$) rise in systolic pressure relative to control was observed. [f] Melting point of hydrochloride salt. [g] $[\alpha]_D$ +32.8° (*c* 1.11, $CHCl_3$); HCl salt $[\alpha]_D$ −6.8° (*c* 2, H_2O). [h] $[\alpha]_D$ −32.3° (*c* 1.12, $CHCl_3$); HCl salt $[\alpha]_D$ +7.0° (*c* 1.98, H_2O). [i] Melting point of hydrochloride salt monohydrate. [j] Melting point of hydrochloride salt hemihydrate. [k] C: calcd, 57.54; found, 56.98. [l] N: calcd, 6.37; found, 5.96. [m] H: calcd, 7.53; found, 7.06.

and the norepinephrine dose–response was repeated. For each dose–response curve, the concentration of test compound was increased 10 times until four or more dose–response curves were obtained. Since the compounds produce dose-related parallel displacements of norepinephrine dose–response curves without affecting their slope or maximum, pA_2 values were calculated according to the methods of Arunlakshana and Schild.[18] No attempt was made to distinguish α_1- from α_2-receptors.

7α-Methyl- (5e) and 7β-Methyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (5d). A mixture formed by cautious addition of 25 g (185 mmol) of 1-amino-2-phenylpropane and 9.07 g (197 mmol) of formic acid was heated in an open flask in an oil bath at 160 °C for 5 h. The cooled mixture was dissolved in 250 mL of diethyl ether, and the resulting solution was washed successively with 50-mL portions of 1 N HCl, water, and 5% sodium bicarbonate. Evaporation gave an oil that was purified by Kugelrohr distillation (160 °C, 0.1 mm) to give 26 g of the crude formamide. A mixture of this material and 100 g of polyphosphoric acid was stirred at 150 °C for 4 h under argon. The hot mixture was poured with stirring into 500 mL of ice–water containing 30 mL 1 N HCl. This mixture was extracted with two 150-mL portions of diethyl ether. The aqueous layer was basified with concentrated sodium hydroxide solution, the product was evaporated, and the oily residue was dissolved in 50 mL of absolute ethanol. This solution was made acidic by passing in HCl gas. Evaporation and heating at 80 °C and 0.1 mm gave 18.1 g of crude 4-methyl-3,4-dihydroisoquinoline hydrochloride as a hydroscopic solid. This salt was mixed with 75 mL of methyl vinyl ketone, and the mixture was heated at 90 °C for 1.5 h. Evaporation left a residue, which was added to 250 mL of 0.01 N HCl.

This mixture was extracted with diethyl ether, and the extract was basified with concentrated ammonium hydroxide. Extraction with ethyl acetate and evaporation gave an oil, which was purified by medium-pressure (50 psi) chromatography from 350 g of silica gel (200 mesh) by using 50% ethyl acetate/hexane. The first compound eluted was **5d**: yield 5.2 g (13% from starting amine); mp 89–90 °C; IR ($CHCl_3$) 2935, 2800, 2750, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, J = 6.5 Hz), 2.3–3.3 (m, 9 H), 3.53 (q, J = 3 and 12 Hz, 1 H), 6.94–7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 23.02 (7-CH_3), 33.94 (C-7), 41.22 (C-3), 47.56 (C-1), 54.84 (C-4), 56.92 (C-6), 61.93 (C-11b), 124.80, 126.17, 126.72, 128.87, 136.54, 139.89, 209.00 (C-2); mass spectrum, m/e 215 (M^+).

The second eluted was **5e**: yield 7.6 g (19% from starting amine): mp 96–97 °C; IR ($CHCl_3$) 2960, 2825, 2770, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.5 Hz, 3 H), 2.0–3.4 (m, 9 H), 3.6 (q, J = 3.5 and 12 Hz, 1 H), 6.94–7.39 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 18.82 (7-CH_3), 32.87 (C-7), 40.99 (C-3), 47.27 (C-1), 54.71 (C-4), 58.71 (C-6), 62.29 (C-11b), 124.71, 126.20, 126.88, 127.01, 136.70, 139.34, 208.58 (C-2); mass spectrum, m/e 215 (M^+).

(2*R,11b*S**)- (6a) and (2*S**,11b*S**)-Spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one] (8a).** To a solution of 5.35 g (53 mmol) of diisopropylamine in 100 mL THF at −70 °C under argon was added 34 mL of 1.57 M n-butyllithium (53.4 mmol). After 5 min, 4.66 g (64.7 mmol) of ethyl acetate was added dropwise over 5 min. To this solution was added dropwise over 20 min a solution of 9.8 g of **5a** (48.8 mmol) in 60 mL of THF. The mixture was allowed to warm to room temperature and poured into 500 mL of diethyl ether. This solution was washed with water and dried over sodium sulfate. Evaporation gave 14.2 g of an oil (ca. 100%): mass spectrum, m/e 289 (M^+). A mixture of this ester, 15 mL 85% hydrazine hydrate, and 75 mL ethanol was heated at reflux for 2 h. The solvent was removed by rotary vacuum evaporation. The residue was dissolved in 250 mL of toluene; this solution was heated at reflux, and excess water was removed with a Dean–Stark separator. After the solution was cooled, the product was isolated by vacuum rotary evaporation: yield 13.5 g of the acyl hydrazide as a foam (ca. 100%). A mixture of 5.9 g of the crude hydrazide (ca. 18.4 mmol) and 25 mL of water was made acidic with concentrated HCl. To this solution at 5 °C was added a solution of 1.34 g of sodium nitrite in 5 mL of water over 15 min. This solution was heated at 60 °C for 20 min and then basified with sodium hydroxide solution. The product was isolated through dichloromethane extraction, and, after evaporation, the mixture was separated by medium-pressure chromatography using 6% methanolic dichloromethane. The first compound eluted was **6a**: yield 1.6 g; IR (KBr) 1750,1710 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 29.16, 35.18, 41.19, 48.70, 50.39, 51.46, 58.32, 80.53, 124.90, 125.71, 126.07, 128.64, 134.33, 137.12, 157.93. The next compound eluted was **8a**: yield 0.68 g; IR (KBr) 1740 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 29.13, 34.98, 41.38, 51.07, 51.36, 57.96, 79.62, 124.64, 125.71, 126.01, 128.70, 134.49, 137.55, 157.96.

(2*S,4′*S**,11b*S**)- (11a) and (2*S**,4′*R**,11b*S**)-Spiro-[9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizine-2,5′-4′-ethyloxazolidin-2′-one] (11b).** Propyldiphenylsulfonium tetrafluoroborate[19] (4.7 g, 15 mmol) was stirred in 15 mL of THF under argon. The mixture was cooled to −70 °C and 7.5 mL of 2 M *tert*-butyllithium in hexane (15 mmol) was added over 5 min. After 30 min, a solution of 2.6 g in 60 mL of THF was added over 30 min. The mixture was stirred at −70 °C for 1 h. The mixture was poured into 1 N HCl, washed twice with diethyl ether, and basified with ammonium hydroxide. The product was extracted into dichloromethane. Evaporation gave a residue from which 1.35 g of an impure mixture of epoxide diastereoisomers was isolated by chromatography using ca. 100 g of silica gel and eluting with 6% methanolic dichloromethane. A portion (0.5 g) of this epoxide was dissolved in ca. 50 mL of 6 N HCl. After 1 h this solution was extracted with ethyl acetate, and the extract was basified with sodium carbonate. The product was extracted into ethyl acetate. After drying and evaporating there was obtained 0.5 g of a mixture of chlorohydrins: mass spectrum, m/e 339, 341 (M^+). This mixture was heated in a stainless-steel bomb for 6 h at 150 °C with 10 mL of 30% ammonia in methanol. This carbinolamine was identical by TLC (10% CH_3OH–CH_2Cl_2) with that obtained by heating the crude epoxide with 30% ammonia in methanol at 140 °C overnight. A mixture of 1.5 g of the carbinolamine, 2 g of carbonyldiimidazole, and 100 mL of THF was heated at reflux for 6 h. The solvent was evaporated, and the residue was dissolved in dichloromethane and washed with water. Evaporation of the dichloromethane left a residue, which was dissolved in 25 mL of THF and stirred with 1 g of potassium *tert*-butoxide for 1 h. Evaporation left a residue that was partitioned between water and dichloromethane. Evaporation of the dichloromethane gave a solid, which was chromatographed from ca. 100 g of silica gel with 7% CH_3OH–CH_2Cl_2. The first compound eluted was **11a**: yield 0.38 g; ^{13}C NMR ($CDCl_3$) δ 11.09, 22.44, 29.16, 30.20, 42.29, 52.53, 52.85, 55.88, 56.14, 57.90, 63.75, 83.94, 107.87, 111.67, 126.82, 129.19, 147.40, 147.69, 159.26. The next compound eluted a mixed fraction of **11a** and **11b** (yield 0.6 g), followed by **11b** (yield 0.38 g): ^{13}C NMR ($CDCl_3$) δ 11.22, 23.34, 29.26, 35.89, 36.70, 51.72, 51.79, 55.88, 56.27, 57.64, 63.95, 84.00, 108.13, 111.67, 126.98, 129.32, 147.43, 147.69, 159.26.

Registry No. **3a**, 64-04-0; **3b**, 60-15-1; **3c**, 582-22-9; **3d**, 3963-62-0; **3e**, 120-20-7; **3f**, 36377-59-0; **3g**, 86456-97-5; **3h**, 1484-85-1; **3i**, 86456-98-6; **3j**, 86456-99-7; **3k**, 86457-00-3; **4a**, 3230-65-7; **4b**, 14123-78-5; **4c**, 86457-01-4; **4c**·HCl, 86457-02-5; **4d**, 6187-58-2; **4e**, 3382-18-1; **4f**, 86457-03-6; **4g**, 86457-04-7; **4h**, 6882-28-6; **4i**, 86457-05-8; **4j**, 86457-06-9; **4k**, 82354-47-0; **5a**, 715-52-6; **5b**, 86457-07-0; **5c**, 86457-08-1; **5d**, 86457-09-2; **5e**, 86457-10-5; **5f**, 86457-11-6; **5g**, 841-95-2; **5h**, 33081-47-9; **5i**, 47136-76-5; (+)-**5i**, 2609-33-8; (−)-**5i**, 2609-32-7; **5j**, 86457-12-7; **5k**, 86457-13-8; **5l**, 86457-14-9; **5m**, 86457-15-0; **5n**, 86457-16-1; **5o**, 86457-17-2; **5p**, 86457-18-3; **5q**, 86457-19-4; **5r**, 86457-20-7; **5s**, 86457-21-8; **5t**, 86457-22-9; **6a**, 86457-23-0; **6b**, 86457-24-1; **7a**, 83917-86-6; **7b**, 86457-25-2; **7c**, 86457-26-3; **7c**·HCl, 86457-27-4; **7d**, 86457-28-5; **7d**·HCl, 86457-29-6; **7e**, 86457-30-9; **7e**·HCl, 86457-31-0; **7f**, 86457-32-1; **7f**·HCl, 86457-33-2; **7g**, 86457-34-3; **7g**·HCl, 86457-35-4; **8a**, 86457-36-5; **8b**, 86457-37-6; **8c**, 86470-92-0; **8d**, 86457-38-7; **8d**·HCl, 86495-73-0; **8e**, 86457-39-8; **8f**, 86495-74-1; **8g**, 86457-40-1; **8g**·HCl, 86495-75-2; **9a**, 83917-85-5; **9a**·HCl, 86457-41-2; **9a** methiodide, 86457-42-3; **9b**, 86457-43-4; **9b**·HCl, 86457-44-5; **9c**, 86457-45-6; **9c**·HCl, 86457-46-7; **9d**, 86457-47-8; **9d**·HCl, 86495-76-3; (±)-**9e**, 86457-48-9; (+)-**9e**, 86495-77-4; (+)-**9e**·HCl, 86540-84-3; (−)-**9e**, 86495-78-5; (−)-**9e**·HCl, 86540-85-4;

(18) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.

(19) Prepared by the general method given by Franzen, V.; Schmidt, H.-J.; Mertz, C. *Chem. Ber.* **1961**, *94*, 2942.

9f, 86457-49-0; **9f**·HCl, 86495-79-6; **9g**, 86470-93-1; **9h**, 86457-50-3; **9h**·HCl, 86495-80-9; **9i**, 86457-51-4; **9j**, 86457-52-5; **9j**·HCl, 86495-81-0; **11a**, 86457-53-6; **11a**·HCl, 86495-82-1; **11b**, 86495-83-2; **11b**·HCl, 86540-86-5; **12a**, 86457-54-7; **12b**, 86457-55-8; **12b**·HCl, 86457-56-9; **12c**, 86457-57-0; **13**, 86457-58-1; **14**, 86457-59-2; **14**·HCl, 86495-84-3; **15**, 86457-60-5; **16**, 86457-61-6; **16**·HCl, 86495-85-4; **20** (R = H) (isomer 1), 86457-62-7; **20** (R = H) (isomer 2), 86495-86-5; **20** (R = H) (isomer 1) chlorohydrin derivative, 86457-63-8; **20** (R = H) (isomer 2) chlorohydrin derivative, 86495-87-6; **20** (R = Et) (isomer 1), 86457-64-9; **20** (R = Et) (isomer 2), 86495-88-7; diphenylpropylsulfonium tetrafluoroborate, 14264-05-2; *N*-(2-phenylpropyl)formamide, 85070-52-6; methyl vinyl ketone, 78-94-4; ethyl acetate, 141-78-6; 3-(phenylmethyl)-3-buten-2-one, 25522-79-6; 3-methyl-3-buten-2-one, 814-78-8; 3-ethyl-3-buten-2-one, 4359-77-7; 3-propyl-3-buten-2-one, 25409-10-3; 3-butyl-3-buten-2-one, 65818-30-6; 3-phenyl-3-buten-2-one, 32123-84-5; 2-(1-aminopropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-ol (isomer 1), 86496-35-7; 2-(1-aminopropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-ol (isomer 2), 86457-65-0.

Synthesis and Antihypertensive Activity of Some New Quinazoline Derivatives

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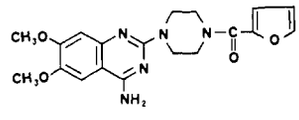
A series of substituted 2-piperidino-4-amino-6,7-dimethoxyquinazolines was synthesized and screened as potential antihypertensive agents. The hypotensive effect of all the new compounds was studied after intravenous administrations in urethane-anesthetized normotensive rats. The furoylpiperazine moiety in the prazosin molecule could be replaced by a more stable substituted piperidine group without loss of the blood pressure lowering activity. However, the nature of the substituent profoundly influenced the hypotensive potency as well as the duration of the hypotensive action. Some of the new compounds were found to be as potent as prazosin. On the basis of potency and the duration of the hypotensive action in the anesthetized rats, five of the most promising compounds were selected for further studies. Each of these agents exerted an antihypertensive effect upon oral administrations in conscious spontaneously hypertensive rats. At small doses, the new compounds appeared to be somewhat less potent than prazosin, but at the higher doses of 10–100 μmol/kg, two of them appeared to be even more efficacious antihypertensive agents than prazosin.

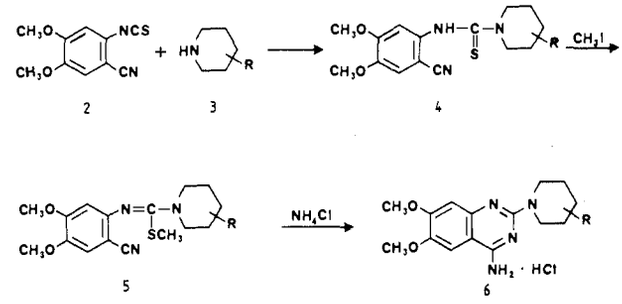
Prazosin, 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (1), is a novel, highly active and selective antagonist of α_1-adrenoceptors and can be considered an important advancement both pharmacologically and therapeutically, since this compound, in contrast to the classical α-adrenoceptor blocking agents, is effective for the treatment of high blood pressure. Prazosin lacks direct smooth muscle relaxing properties, and, unlike many vasodilatators, in doses that decrease blood pressure it does not produce undesirable tachycardia or increases the heart rate only slightly. The most serious side effect of prazosin is known as the "first dose phenomenon", which can sometimes lead to syncope.[1] Prazosin is well absorbed from the gastrointestinal tract and entirely eliminated after undergoing extensive metabolism. The bioavailability of prazosin is rather low, and the elimination half-life is quite short, being only about 2–3 h. A typical metabolic pathway of prazosin is the easy elimination of the furoyl group from the piperazine ring, leading to metabolites of very low antihypertensive activity.[2] The piperazine ring is also very sensitive toward enzymatic hydroxylation.



1

The purpose of this investigation was to study the possibility of replacing the labile furoylpiperazine moiety in prazosin by a more stable piperidino group so that the antihypertensive activity of the new derivatives remains unaltered but possess longer duration of action due to the increased stability against enzymatic degradation.

Scheme I



Therefore, a series of new 2-piperidino-4-amino-6,7-dimethoxyquinazoline derivatives substituted with various chemical groups in the piperidino moiety was synthesized. The compounds synthesized and their hypotensive activity compared to prazosin are presented in Table IV.

Chemistry. The new quinazoline derivatives **6** can be synthesized in different ways as described previously.[3] However, the most practical route used in the synthesis of prazosin[4] is shown in Scheme I.

3,4-Dimethoxy-6-isothiocyanatobenzonitrile (**2**) was condensed first with the substituted piperidine derivatives **3** to give the thioureas **4**. After methylation of **4** with methyl iodide, the *S*-methylisothioureas (**5**) formed were cyclized to the quinazolines (**6**) with an excess of ammonium chloride. The overall yield from **2** to **6** is, in general,

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(1) Gavero, I.; Roach, A. G. *Life Sci.* **1980**, *27*, 1525.
(2) Hess, H. J. In "Prazosin—Evaluation of a New Antihypertensive Agent" (*Excerpta Med.*); Elsevier: Amsterdam, 1974; pp 3–15.
(3) Honkanen, E.; Hietava, M.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. European Patent 34471, 1981.
(4) Honkanen, E.; Pippuri, A.; Kairisalo, P.; Thaler, H.; Koivisto, M.; Tuomi, S. *J. Heterocycl. Chem.* **1980**, *17*, 797.

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