carotid artery was ligated, the incision was sutured, and the animal was allowed to recover from anesthesia. The ECG was continuously monitored for a period of approximately 4 h. During this observation period, only occasional, isolated premature ventricular beats occurred.

Twenty-four hours after myocardial infarction, during the period of maximal ventricular ectopic activity,[12] the animals were returned to the laboratory and allowed to lie quietly on a table while an adhesive ECG electrode was again attached to each limb and a 23-gauge Butterfly infusion set was introduced into a foreleg vein and secured for drug injection. Prior to the initiation of any experimental procedure, animals were allowed a period of approximately 30–45 min to adjust to the laboratory surroundings. Throughout this period a lead II ECG was continuously recorded on a Beckman R-611 dynograph and simultaneously monitored at a fast trace speed on a storage oscilloscope. In all experiments it was noted that during this period approximately 80–85% of all ECG complexes arose from a ventricular pacemaker site and that the proportion of ectopic beats remained relatively constant. At the conclusion of the observation period, drugs being evaluated for antiarrhythmic activity were injected iv in incremental doses until conversion to a normal sinus rhythm occurred or until a total dose of 3.0 mg/kg was reached. Compounds **1–3** were administered in 0.3 mg/kg increments at 2-min intervals; **4** was administered in 0.1 mg/kg increments at 2-min intervals. Solutions of each drug were prepared fresh daily in 5% dextrose in water. Compound **5** was administered in 5 μg/kg increments at 2-min intervals in isotonic dextrose containing 5% propylene glycol (v/v). Several animals received only the 5% propylene glycol–isotonic dextrose solution to serve as controls; no change in cardiac rhythm was observed in any of the control animals. Lidocaine hydrochloride was administered in saline in 0.5 mg/kg increments at 1-min intervals. The concentration of each solution was adjusted so that each dosage increment of drugs employed was contained in 0.5 mL. Each animal received only one drug.

At the conclusion of each experiment, the animals were sacrificed and the hearts removed. At this time the location of the bead in the left coronary circulation and the location of the infarct were noted. In addition, the area of the aorta surrounding the left coronary ostium and the ostium itself were examined for damage incurred during catheterization. No evidence of trauma was noted in the area of the left coronary ostium in any animal. In all instances it was noted that the occlusion occurred distal to the first diagonal branch of the left anterior descending coronary artery, and the infarct involved only the anterior wall of the left ventricle.

Hemodynamic Effects of 5. Three dogs anesthetized with pentobarbital sodium (30 mg/kg) had cannulae positioned in a femoral artery and vein for blood-pressure monitoring and drug injection, respectively. A cardiac cannula was positioned in the left ventricle via the left carotid artery for recording left ventricular pressure, which was electronically differentiated to obtain left ventricular dp/dt. Needle electrodes were placed in each limb for recording lead II ECG and heart rate was electronically derived from the ECG signal. All parameters were recorded on a Beckman R611 dynograph at a paper speed of 100 mm/s in order to determine the left ventricular dp/dt at a developed left ventricular pressure of 50 mmHg (dp/dt/50) for evaluation of changes in myocardial contractility and to allow accurate determination of the ECG PR interval and QRS duration. All animals were allowed to stabilize approximately 30 min after surgical preparation before iv administration of **5**.

Statistics. All statistical comparisons were made using Student's t test for paired or unpaired data utilizing a Monroe 1930 calculator. In each instance, statistical significance was defined as $p < 0.05$.

Acknowledgment. The authors thank Ms. Patricia Huffstutler and Ms. Elizabeth McCloskey for their expert technical assistance and Ms. Linda Kopaciewicz for preparing the figures for this paper. This work was supported in part by an intramural research grant from the University of South Alabama College of Medicine (to J.D.H.) and by a grant-in-aid from the American Heart Association and with funds contributed in part by the American Heart Association, Northwestern Ohio Chapter, Inc. (to R.D.W.)

Synthesis and Some Pharmacological Properties of [8-L-Tryptophan]oxytocin

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Condensation of (*tert*-butyloxycarbonyl)tocinoic acid with L-prolyl-L-tryptophylglycinamide produced the Boc derivative of a nonapeptide (disulfide) which on deprotection afforded [8-L-tryptophan]oxytocin. In assays on the rat uterus in vitro and in vivo the new analogue acts as both an agonist and an antagonist. The duration of both actions is prolonged.

The conformation of oxytocin has been extensively studied, mostly by NMR spectra.[1] It seemed to us desirable to seek confirmation of the proposed[2] architecture of the molecule of the hormone, particularly to find new, independent evidence for the folding of the C-terminal tripeptide segment over the cyclic hexapeptide. In order to measure the distance between two parts of the structure through a fluorescence energy transfer experiment,[3] a donor–acceptor pair is necessary. The presence of a tyrosine (donor) residue in the ring prompted us to synthesize an oxytocin analogue with tryptophan (acceptor) replacing

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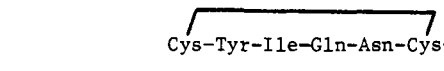


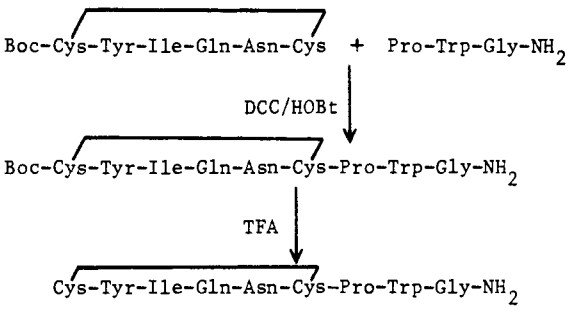
Figure 1. The amino acid sequence of [8-L-tryptophan]oxytocin

one of the amino acids in the side chain. Since proline in position 7 might have a major effect on conformation and a change of glycine for tryptophan would be far from conservative, position 8, occupied by leucine, seemed to be most suitable for substitution. Replacement of the leucine residue by other hydrophobic amino acids usually had no major effect on biological activities[4] and, hence, probably also little effect on conformation. Therefore, we embarked on the synthesis of [8-L-tryptophan]oxytocin (Figure 1).

The pharmacological properties of the new analogue turned out to be quite interesting. It is both an agonist and an antagonist, with markedly prolonged duration of action. Because of the rather unusual combination of the biological effects, we report here the synthesis and pharmacological properties of [8-L-tryptophan]oxytocin, while the energy-transfer experiment will be discussed in a separate publication, which will also include an alternative synthesis of the same analogue.

Synthesis. An obvious choice for the synthesis of the new analogue could have been the stepwise strategy, first demonstrated on a synthesis of oxytocin.[5] The sensitivity of tryptophan, however, cautioned against repeated deprotections with HBr in acetic acid. Therefore, a segment condensation approach was chosen: coupling of (*tert*-butyloxycarbonyl)tocinoic acid[6] to the C-terminal tripeptide amide, L-prolyl-L-tryptophylglycinamide. The latter was prepared via (benzyloxycarbonyl)-L-tryptophylglycine which was converted to the amide by reaction of its mixed anhydride with ammonia. In this manner the formation of a hydantoin derivative[7] during ammonolysis was circumvented. Hydrogenolysis of the protected dipeptide amide, followed by acylation with (benzyloxycarbonyl)-L-proline *p*-nitrophenyl ester, produced the protected tripeptide amide which was deblocked by catalytic hydrogenation. Thus, the segment L-prolyl-L-tryptophylglycinamide could be secured without exposing the tryptophan moiety to acidic conditions. The Boc-derivative of tocinoic acid was obtained as described in the synthesis of [8-L-methionine]oxytocin,[8] that is, by a modification of the procedures of Hruby et al.[9] and Mühlmann et al.[10] For the condensation of the two segments the dicyclohexylcarbodiimide–hydroxybenzotriazole method[11] was applied. The protected nonapeptide, the cyclic disulfide form of *N*-(*tert*-butyloxycarbonyl)-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-tryptophylglycinamide was purified by chromatography, deblocked with trifluoroacetic acid in the presence of a

Scheme I. Synthesis of [8-L-Tryptophan]oxytocin



tenfold excess of the scavenger acetyl-L-tryptophan *n*-butyl ester, prepared for this purpose.[12] The crude peptide was chromatographed on a column of silica gel. On TLC and on LC the purified peptide appeared homogeneous and it also gave correct amino acid analaysis. From its UV absorption spectrum the expected 1:1 ratio could be calculated for tryptophan and tyrosine.[13] The synthesis is summarized in Scheme I.

Pharmacological Activities. [8-L-Tryptophan]-oxytocin has unusual actions on the rat uterus. In assays on the isolated rat uterus suspended in a medium without Mg^{2+} (cf. ref 14), the analogue caused contraction when applied in concentrations of 5 to 40 ng/mL. When these were compared to responses by the same uteri to USP posterior pituitary standard, the agonist activity of [8-L-tryptophan]oxytocin appeared equivalent to about 55 U/mg. After the analogue was washed out of the chamber, subsequent responses to the standard were markedly inhibited for as long as 30 min. This made quantitative assays of agonistic potency impossible.

In assays on the isolated uterus in a medium[14] containing 0.5 mM Mg^{2+}, responses to [8-tryptophan]oxytocin indicated agonistic activity equivalent to about 15 U/mg. There was some inhibition of responses to subsequent additions of the standard, but this was less consistent and weaker than that seen in assays done without Mg^{2+} in the medium.

[8-L-Tryptophan]oxytocin was also assayed by intravenous injection into anesthetized rats pretreated with diethylstilbestrol. Intrauterine pressure was recorded. Comparisons of changes in integrated uterine activity during 10-min periods following injections[15,16] indicated

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(12) The indole moiety in the side chain of tryptophan residues can suffer oxidative degradation in acid media and also alkylation during the acidolytic removal of protecting groups based on stable carbocations. (Cf., e.g., Jaeger, E.; Thamm, P.; Schmidt, I.; Knof, S.; Moroder, L.; Wünsch, E. *Hoppe-Seylers Z. Physiol. Chem.* **1978**, *359*, 155. Wünsch, E.; Jaeger, E.; Kisfaludy, L.; Low, M. *Angew. Chem.* **1977**, *89*, 330. Masu, Y.; Chino, *N.*; Sakakibara, S. *Bull. Chem. Soc. Jpn* **1980**, *53*, 464.) Suppression of these side reactions by the addition of indole or scatole to the reaction mixture is effective, but the objectionable odor of the reagents prompted us to seek a new scavenger which can be handled without inconvenience. We found N^{α}-acetyl-L-tryptophan methyl ester not entirely satisfactory, because it was only sparingly soluble in ether and in ethyl acetate. The *n*-butyl ester, however, could be readily eliminated after deprotection, e.g., with trifluoroacetic acid, simply by washing the trifluoroacetate salt of the partially deprotected peptide with ether and ethyl acetate.
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that [8-L-tryptophan]oxytocin had activity equivalent to about 50 U/mg. Responses to 25 to 100 μg/kg of the analogue were more persistent than those to oxytocin and usually lasted for 20 to 40 min from the time of injection. Responses to subsequent injections of oxytocin were depressed for as long as an hour after injection of these doses of [8-tryptophan]oxytocin.

[8-L-Tryptophan]oxytocin has weak vasopressor activity when injected intravenously into anesthetized rats pretreated with phenoxybenzamine[17] equivalent to less than 0.25 U/mg. There was no clear indication of antagonistic activity in this assay preparation.

Experimental Section

Capillary melting points are reported uncorrected. Thin-layer chromatography (TLC) was performed on precoated (Merck) silica gel plates in the following solvent systems (ratios by volume): A, $CHCl_3$–CH_3OH–AcOH (8:1:1); B, $CHCl_3$–CH_3OH (8:2); C, EtOAc–pyridine–AcOH–H_2O (60:20:6:11); D, EtOAc–pyridine–AcOH–H_2O (30:20:6:11); E, *n*-BuOH–AcOH–H_2O (4:1:1). Spots were revealed by ninhydrin, fluorescamine, charring, and their absorption in the UV. For amino acid analysis, samples were hydrolyzed with constant-boiling HCl in evacuated sealed ampules at 110 °C for 16 h and analyzed on a Beckman-spinco instrument.

(Benzyloxycarbonyl)-L-tryptophylglycine. A sample of glycine (0.75 g, 10 mmol) was dissolved in H_2O (4 mL), and the pH of the solution adjusted to 9 by the addition of 1 N NaOH. After dilution with H_2O (6 mL) and pyridine (20 mL), Z-L-Trp-ONp[18] (2.3 g, 5 mmol) was added and the pH of the suspension was maintained (Radiometer pH stat) at 9 ± 0.5 by the addition of 1 N NaOH. Acylation was complete in about 0.5 h. The solution was diluted with H_2O (50 mL), neutralized with 1 N HCl, evaporated in vacuo to a small volume, rediluted with H_2O (50 mL), and acidified to pH 2 with 1 N HCl. The precipitate was extracted into EtOAc, and the organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo to a small volume. On addition of hexane the product crystallized. It was collected on a filter, washed with a mixture of EtOAc and hexane, and dried in vacuo: yield 1.88 g (95%); mp 148–150 °C. A sample recrystallized from EtOAc–hexane melted at 156–157 °C (lit.[19] 156 °C, lit.[20] 158–159 °C): TLC R_f (A) 0.55; $[\alpha]^{22}_D$ −24.0° (*c* 1, MeOH) [lit.[20] −24.6° (*c* 1, MeOH)]. Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

(Benzyloxycarbonyl)-L-tryptophylglycinamide. The protected dipeptide (1.73 g, 4.4 mmol) and *N*-methylmorpholine (0.50 mL, 4.4 mmol) were dissolved in tetrahydrofuran (20 mL), cooled to −15 °C, and treated with isobutyl chlorocarbonate[21] (0.60 mL, 4.4 mmol). After 5 min a stream of NH_3 was passed over the solution for about 5 min. The mixture was stirred at −15 °C for 0.5 h and evaporated to dryness. The residue was dissolved in EtOAc, and the solution was washed with H_2O, dried over $MgSO_4$, and evaporated to a small volume. On dilution with hexane the protected dipeptide amide crystallized. It was filtered and washed with a mixture of EtOAc and hexane and then with hexane. The dry product, 1.52 g (88%), melted at 118–119 °C: $[\alpha]^{24}_D$ +4.0° (*c* 0.5, AcOH); TLC R_f (B) 0.55. Anal. ($C_{31}H_{22}N_4O_4$) C, H, N.

(Benzyloxycarbonyl)-L-prolyl-L-tryptophylglycinamide. A solution of the protected dipeptide amide (1.45 g, 3.68 mmol) in 95% EtOH (20 mL) was hydrogenated in the presence of a 10% Pd on charcoal catalyst (0.2 g) for 3 h. The catalyst was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in DMF (10 mL) and treated with Z-L-Pro-ONp[5] (1.48 g, 4 mmol) and 1-hydroxybenzotriazole monohydrate[22] (0.57 g, 3.7 mmol). The next day the solvent was evaporataed in vacuo, and the residue was dissolved in EtOAc (20 mL) and diluted with hexane until slight turbidity. Gradually crystals formed: they were collected on a filter, washed with ether, and dried: yield 1.6 g (88%); mp 129–130 °C; TLC R_f (B) 0.50; $[\alpha]^{22}_D$ −57° (*c* 0.3, MeOH). The product gave the expected NMR (CD_3OD) and UV spectra (ϵ_{280} 5400). Anal. ($C_{26}H_{29}N_5O_5$) C, H, N.

L-Prolyl-L-tryptophylglycinamide. A sample of the protected tripeptide amide (0.50 g, 1 mmol) in 95% EtOH (20 mL) was hydrogenated in the presence of Pd on charcoal catalyst (50 mg) for 5 h. The catalyst and the solvent were removed and the residue triturated with ether. The product was washed with ether and dried: yield 0.42 g (100%); TLC R_f (C) 0.07, R_f (E) 0.27. The compound has no well-defined melting point. Anal. ($C_{18}H_{23}N_5O_3 \cdot 0.5\ H_2O$) C, H, N.

Cyclic Disulfide with the Sequence *N*-(*tert*-Butyloxycarbonyl)-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-tryptophylglycinamide. A sample of (*tert*-butyloxycarbonyl)tocinoic acid (100 mg, 0.112 mmol) and 1-hydroxybenzotriazole monohydrate (24 mg, 0.15 mmol) were dissolved in DMF (1.0 mL) and L-Pro-Trp-Gly-NH_2 (cf. above, 72 mg, 0.2 mmol) was added, followed by dicyclohexylcarbodiimide (31 mg, 0.15 mmol). The mixture was kept at room temperature overnight. The dicyclohexylurea was filtered off, the solvent was removed in vacuo, and the residue was triturated with EtOAc. The solid was collected by centrifugation, washed with EtOAc and with ether, and dried in vacuo: yield 144 mg (more than the calculated amount). This crude material (135 mg) was chromatographed on a column of silica gel (2 × 25 cm) in the the system EtOAc–pyridine–acetic acid–water (60:20:6:11). After the first 100-mL eluent, 5-mL fractions were collected. The desired material was detected (TLC) in fractions no. 13–18. After pooling, these fractions yielded 65 mg (51%) of protected nonapeptide amide: TLC R_f (D) 0.60; mp 199–200 °C dec; $[\alpha]^{25}_D$ −53° (*c* 0.5, DMF). Anal. ($C_{53}H_{73}N_{13}O_{14}S_2$) C, H, N.

[8-L-Tryptophan]oxytocin. A sample of the Boc–nonapeptide amide (55 mg) was dissolved in a 7:3 mixture of trifluoroacetic acid and acetic acid (2 mL) containing acetyl-L-tryptophan *n*-butyl ester (cf. below, 135 mg). The mixture was kept under N_2 at 0 °C for 1.5 h and evaporated in vacuo, and the residue was triturated with EtOAc. On TLC some starting material could be detected in the product; therefore, it was redissolved in trifluoroacetic acid (2 mL) containing the scavenger (135 mg) and kept under N_2 at 0 °C for 1 h. Precipitation with EtOAc and washing with ether yielded 35 mg of crude [8-L-tryptophan]-oxytocin (trifluoroacetate salt), which was chromatographed on a column of silica gel (1.5 g, 0.5 × 15 cm) in the system used for the purification of the Boc derivative. Fractions of 0.25 mL were collected; the elution was monitored on TLC (system D). Fractions no. 20–30 contained homogeneous material (14 mg), while fractions no. 10–14 yielded 11 mg, slightly contaminated. From fractions no. 31 to 35 more (3 mg) impure material was obtained. The product from fractions no. 20 to 30 was used for the study of the properties of [8-L-tryptophan]oxytocin. The purified sample of the new analogue, R_f (D) 0.50, R_f (E) 0.30, gave the expected ratios of amino acids after hydrolysis: Asp, 1.03; Glu, 1.02; Pro, 0.90, Gly, 0.91; $^1/_2$-Cys, 2.02; Ile, 1.00; Tyr, 1.00. From the UV absorption of the peptide in H_2O, Tyr (0.9) and Trp (1.0) were calculated.[13] On LC [Dupont 850; Zorbax C-8, 0.46 × 24 cm; 23-nmol load; eluted at 1.5 mL/min with a gradient of A [3% CH_3CN in 0.1 M KH_2PO_4 (pH 2.2)] and B [75% CH_3CN in 0.1 M KH_2PO_4 (pH 2.2)] [10 to 20% B in 5 min, 20 to 55% B in 10 min, 55 to 100% B in 10 min], monitored at 215 and 275 nm], the peptide emerged as a sharp peak with a retention time of 13.5 min, corresponding to 40% CH_3CN.

Acetyl-L-tryptophan *n*-Butyl Ester. A sample of acetyl-L-tryptophan[23] (15 g, 61 mmol) and *p*-toluenesulfonic acid monohydrate (11.4 g, 60 mmol) were dissolved in 1-butanol (100 mL). The solution was warmed to about 50 °C for 0.5 h, stirred at room temperature for 4 h, and evaporated in vacuo. The residue was dissolved in EtOAc (150 mL), and the solution was washed with 0.1 M $KHCO_3$ and with H_2O and dried ($MgSO_4$). Evaporation left a crystalline residue, which was triturated with a hexane–EtOAc mixture (10:1), filtered, and dried in vacuo: yield 16.6 g

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(90%); mp 113–114.5 °C; TLC R_f (A) 0.50. The expected signals were seen in the NMR spectrum. Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

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Synthesis and Adrenergic Blocking Effects of 2-(Alkylamino)-3,4-dihydroquinazolines

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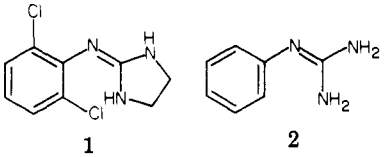
Based on the known biological activity of a variety of guanidine-containing agents, several N-substituted 3,4-dihydroquinazolines were synthesized. These compounds can be considered to be rigid analogues of phenylguanidines. In anesthetized rats the compounds decreased blood pressure and were antagonists of the pressor response to norepinephrine.

The literature is replete with examples of guanidine or guanidine-containing compounds which possess interesting pharmacological properties.[1] In addition, the number of clinically useful agents incorporating the guanidine functionality is similarly substantial.[2] Recently, interest has been stimulated in the area of arylguanidines by way of investigating the centrally active antihypertensive clonidine (1).[3] Studies have indicated that a wide variety of modifications can be made on the clonidine framework with the retention of activity.[4,5]



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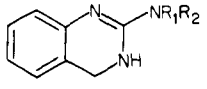
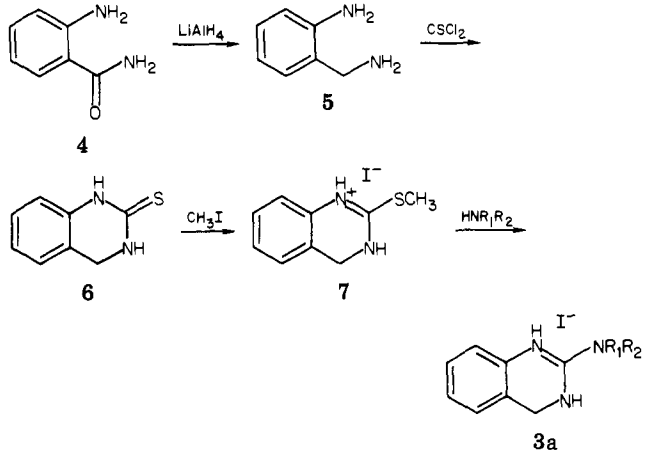


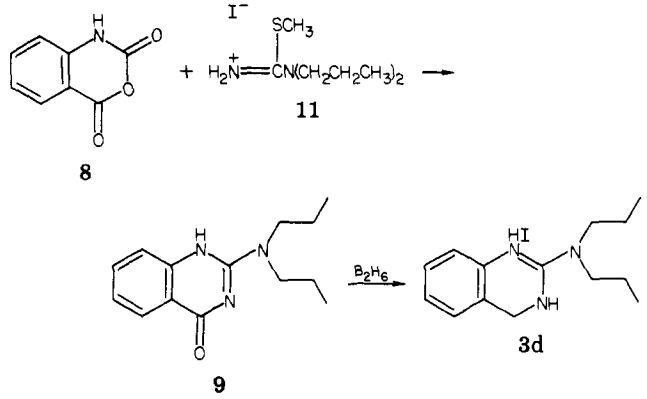
3a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = CH_3; R_2 = CH_3
d, R_1 = n-C_3H_7, R_2 = n-C_3H_7

In the course of our examination of semirigid analogues of a variety of biologically active flexible parent compounds,[6,7] it seemed of interest to prepare the conformationally defined analogue of phenylguanidine (2), 2-amino-3,4-dihydroquinazoline (3a). It was speculated that this rigid structure might exhibit significant cardiovascular activity, based upon the known activity of the parent, 2,[4] and of other multicyclic congeners.[8,9]

Scheme I



Scheme II



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