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Inhibitors of the Luteinizing Hormone-Releasing Hormone Based upon Modifications in the 2, 3, and 6 Positions[1]

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[Leu^2,Leu^3,D-Ala^6]-LH-RH (<Glu-Leu-Leu-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2) and [Val^2,Leu^3,D-Ala^6]-LH-RH completely inhibited the release of LH and FSH induced by 0.3 ng/ml of medium of LH-RH on isolated rat pituitaries, at a dosage of 10 μg. [Leu^2,Val^3,D-Ala^6]-LH-RH and [Val^2,Val^3,D-Ala^6]-LH-RH also completely inhibited this response but were one-tenth as active as [Leu^2,Leu^3,D-Ala^6]-LH-RH. All of the analogs were devoid of agonist activities. The incorporation of the D-Ala residue in position 6 into the [Leu^2,Leu^3]-LH-RH sequence, therefore, increased the inhibition potency as much as tenfold.

Humphries et al.[2a] recently reported that the decapeptide amide, <Glu-Leu-Leu-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 ([Leu^2,Leu^3]-LH-RH), inhibited the LH-RH-induced release of LH and FSH at a 300000-fold dosage, in vitro, from isolated rat pituitaries.

Previously, Vale et al.[2b] had found that [des-His^2]- and [Gly^2]-LH-RH were competitive inhibitors of LH-RH for LH release in a monolayer culture assay. Later studies by these investigators showed that inhibitors could be formed by other single substitutions in the 2 or in the 3 positions of LH-RH in which the analogs modified in the 2 position were more potent[3] and also that Ac-[des-<Glu^1,des-His^2]-LH-RH acted as an inhibitor.[4]

Monahan et al.[3] reported that [D-Ala^6]-LH-RH was 300–500% more active than LH-RH and hypothesized that this enhancement of activity occurred because the D-Ala residue in position 6 favored a conformational population which had increased binding affinity for the LH-RH receptor.

Fujino et al.[5] reported that replacement of the carboxyl terminal Pro-Gly-NH_2 unit by Pro-NHEt enhanced the agonist activity of LH-RH by 300–500%, possibly by reduction of enzymatic degradation and by other effects.

On the basis of these reports, the replacement of Gly in position 6 by D-Ala, and Pro-Gly-NH_2 at the C terminus by Pro-NHEt, may constitute structural changes to include in the synthesis of other analogs of LH-RH. One may presume that no gross changes would be made on the overall conformation by these modifications since these changes may only affect binding and enzymatic degradation, and the resulting analogs are highly potent agonists. One may also presume that the conformation of an effective competitive inhibitor of LH-RH would be essentially similar to that of LH-RH. The enhancement of the agonist properties by these changes in LH-RH has been applied by Coy et al.[6] for [D-Ala^6,des-Gly^{10}]-LH-RH ethylamide, which showed on infusion into immature male rats 1600% of the LH-releasing activity and 1200% of the FSH-releasing activity of LH-RH. Similar enhancements of potency have been observed in the [des-His^2]-LH-RH series of inhibitors. [Des-His^2,D-Ala^6]-LH-RH inhibited the LH response of LH-RH threefold better than [des-His^2]-LH-RH[3], and [des-His^2,D-Ala^6,des-Gly^{10}]-LH-RH ethylamide was reported to be active in vivo.[7,8] Whether the Pro^9-NHEt modification increases inhibition potency, rather than duration, is not clear since Amoss et al.[9] reported that [des-His^2]-LH-RH and [des-His^2,des-Gly^{10}]-LH-RH ethylamide were active as inhibitors of LH-RH, in vivo, at the same molar ratios. In the in vivo assay system used by Coy et al.,[10] [des-His^2,D-Ala^6,des-Gly^{10}]-LH-RH ethylamide was found to be more effective as an inhibitor than [des-His^2,D-Ala^6]-LH-RH. It is sometimes difficult to compare agonist or antagonist activities of analogs because of the different assay systems used by various investigators. Coy et al.[10] has also reported that [des-His^2,Leu^3,D-Ala^6,des-Gly^{10}]-LH-RH ethylamide, [des-His^2,Leu^3,des-Gly^{10}]-LH-RH ethylamide, and [Gly^2,Leu^3,des-Gly^{10}]-LH-RH ethylamide inhibited the response to LH-RH, in vivo, in rats.

We now report further modification of our [Leu^2,-Leu^3]-LH-RH sequence[2a] in which the Leu residues have been replaced by Val. This analog series offers the advantage that substitutions are made in both the biologically important 2 and 3 positions[11] and maintains a decapeptide structure.

Experimental Section

General Solid-Phase Procedure. The peptide analogs were synthesized by the solid-phase methodology on a Beckman 990 peptide synthesizer. Commercial amino acid derivatives were supplied by either Beckman Instruments, Inc., or by Bachem, Inc. α-Amino functions were protected by the *tert*-Boc group and side-chain functionalities were protected as benzyl (Ser), 2,6-

dichlorobenzyl (Tyr), and Tos (Arg). Boc-D-Ala was prepared from D-Ala according to the method of Schnabel.[12] Coupling reactions, with a threefold excess of amino acid derivative and DCC, were generally performed in CH_2Cl_2, except for Boc-Arg(Tos), which was coupled in DMF, and <Glu, which was incorporated either as <Glu-OH, in DMF, or as Z-<Glu-OH, in DMF–CH_2Cl_2.

The coupling program used for peptide elongation involved the following successive operations (number of times each step performed, mixing time): (1) CH_2Cl_2 (3 washes, 2 min); (2) 50% TFA in CH_2Cl_2 (v/v) (1 prewash, 2 min); (3) 50% TFA in CH_2Cl_2 (1 deprotection, 30 min); (4) CH_2Cl_2 (6 washes, 2 min); (5) 10% NEt_3 (redistilled from NaOH pellets) in CH_2Cl_2 (v/v) (2 prewashes, 2 min); (6) 10% NEt_3 in CH_2Cl_2 (1 neutralization, 10 min); (7) CH_2Cl_2 (5 washes, 2 min); (8) amino acid derivative (1 addition, 10 min); (9) DCC (coupling); (10) CH_2Cl_2 (2 washes, 2 min); (11) DMF (4 washes, 2 min); (12) CH_2Cl_2 (4 washes, 2 min).

The coupling reactions were monitored by the ninhydrin test[13] and were generally complete in 2–4 hr.

The completed, protected peptide resin was finally washed with EtOH (5 times), CH_2Cl_2 (3 times), EtOH (5 times), DMF (5 times), EtOH (5 times), and with CH_2Cl_2 (5 times).

Cleavage and Deblocking Procedures. The protected peptide resin ester was cleaved by stirring in NH_3-saturated (at 0°) anhydrous MeOH (ca. 60 ml) for 3 days at room temperature in a closed vessel.[14] The mixture was filtered and the residual polymer was washed with MeOH (3–6 times) and the combined solutions were evaporated to dryness to yield the protected peptide amide.

Deblocking of the protected peptide amide, or deblocking and simultaneous cleavage of the peptide-benzhydrylamine (BHA) resins, was accomplished in anhydrous (CoF_3) liquid HF containing 10–20% anisole for 1 hr at 0°.[15] After the reaction, the HF was removed as rapidly as possible under reduced pressure and the oily residue left in vacuo over P_2O_5 and NaOH pellets for 3–4 hr. Anisole and anisole by-products were removed by washing the solution of peptide amide in 10% aqueous AcOH, with Et_2O and EtOAc prior to lyophilization. In the case of the HF treatment of the peptide resins, the dried reaction mixture was first washed with Et_2O and EtOAc before extracting the peptide amide into 10% AcOH. Generally, the crude solid peptide amide obtained on lyophilization was relyophilized from 10% aqueous AcOH before being purified.

Purification Procedures. Gel filtration over Bio-Gel P-2 with 1.3% aqueous AcOH, partition chromatography over Sephadex G-25 with either 0.1% AcOH–1-BuOH–pyridine (11:5:3) or 1-BuOH–AcOH–H_2O (4:1:5), and ion-exchange chromatography on CM-cellulose with NH_4OAc buffers (2, 50, and 75 m*M*) have been used. Chromatographic profiles were recorded at 254 nm or by the Folin–Lowry method.[16] Those fractions corresponding to the target peptide peak were evaluated by TLC, after each column, and cuts were made for purity at the high expense of product yield.

Synthesis. [Leu^2,Leu^3,D-Ala^6]-LH-RH. The chloromethylated resin (Sigma Chemical Co.) was esterified with Boc-Gly,[16] and the Boc-Gly-resin ester (2.5 g, 0.68 m*M*/g of Gly) was taken through nine successive coupling cycles to give the protected resin, <Glu-Leu-Leu-Ser(Bzl)-Tyr(2,6-Cl_2-Bzl)-D-Ala-Leu-Arg(Tos)-Pro-Gly-resin ester. Cleavage with NH_3 in MeOH followed by deblocking with HF gave the free peptide amide. Purification over Bio-Gel P-2, partition chromatography with the 11:5:3 system, and ion-exchange chromatography gave 193.5 mg (10%) of the target peptide, homogeneous in five TLC systems.

[Val^2,Leu^3,D-Ala^6]-LH-RH. The BHA resin (Beckman Instruments, Inc., 0.5 mequiv of amine/g) was acylated with 2.5 equiv of Boc-Gly and DCC, and a portion (1.27 g, 0.49 m*M*/g of Gly) was taken through nine successive coupling cycles to give Z-<Glu-Val-Leu-Ser(Bzl)-Tyr(2,6-Cl_2-Bzl)-D-Ala-Leu-Arg-(Tos)-Pro-Gly-BHA-resin. The free peptide was liberated with HF and purified by partition chromatography with the 4:1:5 system to yield 372 mg (55%).

[Leu^2,Val^3,D-Ala^6]-LH-RH was obtained (297 mg, 47%) from Boc-Gly-BHA resin (1.2 g, 0.49 m*M*/g of Gly), and [Val^2,-Val^3,D-Ala^6]-LH-RH was obtained (331 mg, 53%) from the same resin (1.2 g) by a similar synthesis and purification procedure to that described for [Val^2,Leu^3,D-Ala^6]-LH-RH. The chemical and physical properties of these LH-RH analogs are shown in Table I.

Table I. Chemical and Physical Properties of Synthetic LH-RH Analogs

[Leu^2,Leu^3,D-Ala^6]-LH-RH (<Glu-Leu-Leu-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2): amino acid analysis[a] Glu 0.93, Leu 3 × 1.0, Ser 0.89, Tyr 1.14, Ala 1.01, Arg 1.02, Pro 0.96, Gly 0.98; TLC data[b] R_f^{I} 0.69, R_f^{II} 0.63, R_f^{III} 0.80, R_f^{IV} 0.59, R_f^{V} 0.67; $[\alpha]^{24}D$[c] −55.377° (*c* 1.685, 1% AcOH)

[Val^2,Leu^3,D-Ala^6]-LH-RH (<Glu-Val-Leu-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2): amino acid analysis Glu 1.02, Val 0.93, Leu 2 × 0.95, Ser 0.98, Tyr 1.12, Ala 1.01, Arg 1.00, Pro 1.00, Gly 1.00; TLC data R_f^{I} 0.66, R_f^{II} 0.62, R_f^{III} 0.71, R_f^{V} 0.58, R_f^{VI} 0.58; $[\alpha]^{25}D$ −54.40° (*c* 1.00, MeOH)

[Leu^2,Val^3,D-Ala^6]-LH-RH (<Glu-Leu-Val-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2): amino acid analysis Glu 1.02, Leu 2 × 1.0, Val 0.96, Ser 0.90, Tyr 1.05, Ala 0.98, Arg 0.99, Pro 0.95, Gly 1.00; TLC data R_f^{I} 0.66, R_f^{II} 0.62, R_f^{III} 0.71, R_f^{V} 0.57, R_f^{VI} 0.58; $[\alpha]^{25}D$ −49.8° (*c* 1.07, MeOH)

[Val^2,Val^3,D-Ala^6]-LH-RH (<Glu-Val-Val-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2): amino acid analysis Glu 1.04, Val 2 × 0.91, Ser 0.83, Tyr 1.12, Ala 1.02, Leu 1.06, Arg 1.04, Pro 1.14, Gly 1.04; TLC data R_f^{I} 0.64, R_f^{II} 0.62, R_f^{III} 0.70, R_f^{V} 0.54, R_f^{VI} 0.53; $[\alpha]^{25}D$ −42.84° (*c* 1.02, MeOH)

[a] The peptides were hydrolyzed in vacuo in 6 *N* HCl, either overnight at 110° or for 3 hr at 130°, and then analyzed on a Beckman 119 amino acid analyzer set up for one-column methodology. [b] TLC systems (silica gel): I, 1-BuOH–AcOH–EtOAc–H_2O (1:1:1:1); II, EtOH–H_2O (7:3); III, EtOAc–pyridine–AcOH–H_2O (5:5:1:3); IV, 1-BuOH–pyridine–AcOH–H_2O (30:20:6:24); V, 2-propanol–1 *N* AcOH (2:1); VI, $CHCl_3$–MeOH–concentrated NH_4OH (60:45:20). The peptides were located by iodine and chlorotolidine reagents and were negative to ninhydrin. [c] Optical rotations were measured on a Perkin-Elmer 141 digital readout polarimeter.

Biological Assays. The analogs were assayed, in vitro, for release of LH and FSH and for inhibition of the LH-RH-induced release of LH and FSH from isolated rat pituitaries, according to our published procedures.[2a]

Results and Discussion

The agonist and inhibitor results are shown in Table II, which also includes the data[2a] for [Leu^2,Leu^3]-LH-RH for comparison. All of the analogs were practically devoid of agonist activity.

Although a 300000-fold dosage of [Leu^2,Leu^3]-LH-RH was necessary to inhibit completely the release of LH and FSH,[2a] a 30000-fold dosage of [Leu^2,Leu^3,D-Ala^6]-LH-RH produced the same inhibition. Therefore, the replacement of Gly by D-Ala in position 6 enhanced the potency of inhibition by a factor of 10.

In repeated studies, the potency of inhibition observed for [Val^2,Leu^3,D-Ala^6]-LH-RH has always been slightly greater than that observed for [Leu^2,Leu^3,D-Ala^6]-LH-RH. However, both analogs completely inhibited the release of LH and just about completely the FSH at a 30000-fold dosage.

The side chain of Leu has a γ branch, $-CH_2CHMe_2$, and that of Val has a β branch, $-CHMe_2$, and our results indicate that this chain shortening in the 2 position was perhaps somewhat favorable in increasing the inhibition potency. When Leu^3 of [Leu^2,Leu^3,D-Ala^6]-LH-RH, is changed to Val^3, the inhibition potency was reduced $^1/_{10}$. [Leu^2,Val^3,D-Ala^6]-LH-RH completely inhibited the release of LH and FSH at a 300000-fold dosage and, thus, this analog had the same potency as [Leu^2,Leu^3]-LH-RH. Therefore, the 3 position is more sensitive than the 2 position for the Leu-Val substitutions. The reduction of the inhibition potency when Leu^3 is replaced by Val^3 could be a consequence of the change in chain branching, i.e.,

Table II. Assay, in Vitro, for Agonist and Antagonist Activities of Analogs on Isolated Rat Pituitaries[a]

Peptide analog	Dose, ng/ml of medium: Peptide	Dose, ng/ml of medium: LH-RH	LH: Δ, ng/ml of medium	LH: SEM	LH: p value vs. LH-RH	FSH: Δ, ng/ml of medium	FSH: SEM	FSH: p value vs. LH-RH
[Leu^2,Leu^3,D-Ala^6]-LH-RH		0.3	552	±58		8859	±811	
	100000		26	±23	ns	1692	±226	ns
	1000	0.3	460	±59	ns	9278	±1384	ns
	10000	0.3	3	±67	<0.001	2697	±871	<0.001
[Val^2,Leu^3,D-Ala^6]-LH-RH		0.3	327	±74		5381	±598	
	100000		−9	±45	ns	158	±274	ns
	1000	0.3	246	±22	ns	6171	±1190	ns
	10000	0.3	28	±11	<0.001	1260	±603	<0.001
[Leu^2,Val^3,D-Ala^6]-LH-RH		0.3	262	±65		3032	±452	
	100000		−37	±42	ns	−185	±220	ns
	10000	0.3	150	±43	ns	3766	±311	ns
	100000	0.3	13	±20	<0.01	−399	±138	<0.001
[Val^2,Val^3,D-Ala^6]-LH-RH		0.3	282	±51		4990	±804	
	100000		17	±6	ns	850	±206	~0.02
	10000	0.3	313	±57	ns	4813	±766	ns
	100000	0.3	35	±11	<0.001	770	±201	<0.001

[a] Incubation for 5 or 6 hr. Medium changed hourly ($P_1, P_2, I_3, I_4, I_5, I_6$). Experiments were performed by adding the LH-RH analog to I_3-I_6 and LH-RH to I_5 and I_6. Values were obtained by subtraction of P_2 from I_3, I_4, I_5, and I_6 and each value recorded is the mean of 3-9. For brevity, results tested at other dosages have been omitted.

Table III. Antagonist Activity of the Analogs

Analog	Minimal active antagonist dose, μg/ml of medium: LH	Minimal active antagonist dose, μg/ml of medium: FSH	Ratio analog-LHRH
[Leu^2,Leu^3]-LH-RH[a]	100	100	300000:1
[Leu^2,Leu^3,D-Ala^6]-LH-RH	10	10	30000:1
[Val^2,Leu^3,D-Ala^6]-LH-RH	10	10	30000:1
[Leu^2,Val^3,D-Ala^6]-LH-RH	100	100	300000:1
[Val^2,Val^3,D-Ala^6]-LH-RH	100	100	300000:1
[Des-His^2]-LH-RH[b]	30	30	100000:1

[a] From ref 2a. [b] Described by Vale et al.[2b]

γ vs. β branching. The closer proximity of the methyl groups in Val to the peptide backbone, in this biologically important part of the molecule, could have a greater effect on conformation than the γ branching of the Leu side chain. The decreased inhibition potency of the analog, [Val^2,Val^3,D-Ala^6]-LH-RH, is presumably a result of changing the more sensitive 3 position in accordance with the above concepts.

A better comparison of the potencies of inhibition of [Leu^2,Leu^3,D-Ala^6]-LH-RH and [Val^2,Leu^3,D-Ala^6]-LH-RH with other reported inhibitors of LH release is not possible due to differences of assay systems being used. However, Table III shows the antagonist activities of our analogs in relation to [des-His^2]-LH-RH in our in vitro assay. These data indicate that [Leu^2,Leu^3,D-Ala^6]-LH-RH and [Val^2,Leu^3,D-Ala^6]-LH-RH are three times more potent than [des-His^2]-LH-RH.

In our in vivo system, [Val^2,Leu^3,D-Ala^6]-LH-RH has been found to be effective in inhibiting the release of LH by LH-RH at a 100:1 dosage ratio.[17]

Although these analogs are found to inhibit completely the LH-RH-induced release of both LH and FSH, Folkers et al.[18] reported that [des-His^2]-LH-RH, [Leu^2,Leu^3]-LH-RH, and [Val^2,Leu^3,D-Ala^6]-LH-RH do not inhibit, in vitro, the release of FSH from partially purified FSH-RH. Such data support the reports[19-21] that a separate hypothalamic hormone, other than LH-RH, may control the secretion of FSH.

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Synthesis and Evaluation of 1,ω-Diaryl-1,ω-alkanediamines Related to the Fibrinolytic Bis(tetrahydroisoquinolines) and Bis(benzylamines)[1a]

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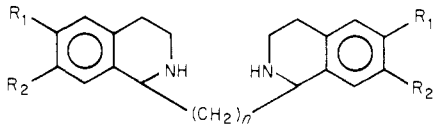
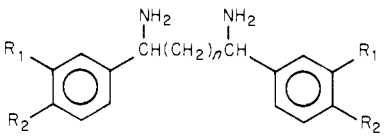
Since the previously investigated bis(tetrahydroisoquinolines) **1** and bis(benzylamines) **2** may be classified as 1,ω-diaryl-1,ω-alkanediamines, it appeared worthwhile to examine this structural concept as a guideline for predicting significant fibrinolytic activity. The prototype bis compounds **7**, **14**, **15**, and **29–31**, which were synthesized for this purpose, incorporate such molecular modifications as replacement of the tetrahydroisoquinoline nuclei of series **1** with tetrahydrobenzazepine (**7**) and tetrahydropyridoindole (**14–15**) nuclei. The latter compounds, as well as **29–31** which possess features common to both series **1** and **2**, showed good to moderate activity in the standard rat (ip) screen. Significant departures from the 1,ω-diaryl-1,ω-alkanediamine structural concept led to compounds (**35** and **40**) of weak to moderate activity.

Previous papers have described the synthesis, structure–activity relationships, and pharmacology of two series of potential fibrinolytic agents: the bis(tetrahydroisoquinolines) **1** and the bis(benzylamines) **2**.[2] Additional



1a, $R_1 = R_2 = CH_3O$; $n = 4$
b, $R_1 = CH_3O$; $R_2 = H$; $n = 4$
c, $R_1 = CH_3O$; $R_2 = H$; $n = 7$



2a, $R_1 = R_2 = CH_3O$; $n = 4$

studies on the synthesis, pharmacology, and mechanism of action of bis(tetrahydroisoquinolines) have been subsequently reported.[3] Structures **1** and **2** are related by inclusion within the generic classification of 1,ω-diaryl-1,ω-alkanediamines, and the present report documents our efforts to extend this structural concept to the design of new fibrinolytic agents.

The diverse prototype compounds **7**, **14**, **15**, **29–31**, **35**, and **40**, which were synthesized for this purpose, combine within the desired framework those features which were found to confer optimal fibrinolytic activity in series **1** and **2**. Thus emphasis has been placed on 1,ω-diaryl-1,ω-alkanediamines with chain lengths of four to seven methylene groups, one or two methoxy substituents on the aromatic portions of the molecules, and primary or secondary amino functions as appropriate. In structures **7**, **14**, and **15**, the tetrahydroisoquinoline nuclei of series **1** have been replaced with tetrahydrobenzazepine and tetrahydropydroindole nuclei, respectively, while structures **29–31** combine features common to both series **1** and **2**.

Compounds **35** and **40** represent molecular modifications which depart substantially from the generic classification described above, **35** being, in fact, a bis(phenethylamine) rather than a bis(benzylamine) of type **2**.

Chemistry. The three-step synthetic sequence (Scheme I) leading to the bis(tetrahydrobenzazepine) **7** is similar to that utilized in the preparation of the bis(tetrahydroisoquinolines) **1**,[2a] and both the condensation and reduction steps leading to **5** and **7**, respectively, proceeded in good yield. Since polyphosphate ester (PPE) has been found effective in the Bischler–Napieralski-type cyclization of 3,4-dimethoxybenzenepropanamine amides to the corresponding 4,5-dihydro-3*H*-2-benzazepines,[4] the cyclization of **5** to **6** was attempted with this reagent. Despite a number of variations in temperature and time of heating, however, the maximum yield of **6** obtained by this method was 15%. The uv and ir spectra of **6** and **7** were in accord with the spectroscopic properties of such systems.[4]

A condensation–cyclization–reduction sequence of reactions was also applicable to the synthesis of the bis(tetrahydropyridoindoles) **14** and **15** (Scheme II). The intermediate bis(methoxydihydropyridoindoles) **12** and **13** were prepared, in fact, by methods which have been reported to yield a similar series of bis(demethoxydihydropyridoindoles) starting from tryptamine and various dibasic acids.[5] While in the demethoxy series several attempts at effecting reduction to the tetrahydro derivatives led to poorly characterized products,[5] **12** and **13** were cleanly reduced to **14** and **15**, respectively, with $NaBH_4$.

Compounds **29–31** (Scheme III) were variations of particular interest since they combine in one structure both the tetrahydroisoquinoline and benzylamine moieties. The ω-aroylaliphatic acids **17–19** required for condensation with **16** were prepared by the general procedure of Papa et al.[6a] Bischler–Napieralski cyclization of amides **20–22** to the corresponding dihydroisoquinolines **23–25** was effected in satisfactory yield with $POCl_3$. It may be noted that with hot PPA an alternate type of intramolecular cyclization has been reported for a demethoxy analog of **20** [viz. *N*-[2-(3,4-dimethoxyphenyl)ethyl]-ε-oxobenzenehexanamide] leading to a hexahydroazepino[2,1-*a*]isoquinolone derivative.[6b] Although the neutral fraction from the reaction of **20** and $POCl_3$ was not examined in detail, the intervention of this alternate cyclization mode might account for the lower yield of **23** vs. **24** or **25**. Synthesis of the desired bisamines **29–31** was completed in a straightforward manner by conversion of ketones **23–25** to their oximes, **26–28**, followed by simultaneous catalytic reduction of the oxime and imine functions.

Scheme IV outlines the preparation of the bis(phenethylamine) **35** by application of the well-known phenethylamine synthesis. The condensation of aromatic aldehydes (2 mol) with 1,ω-dinitroalkanes has been described