Synthesis and Reactions of 2-Amino-7,8-Dimethoxy-1*H*-3-Benzazepines. Competitive Formation of 2-Amino-1*H*-3-benzazepines *VS.* 2-Benzylimidazoles

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A short synthesis of 2-amino-7,8-dimethoxy-1*H*-3-benzazepine (**1a**) from 3,4-dimethoxyphenylacetonitrile (**8a**) is reported. The synthesis of several other 2-amino-1*H*-3-benzazepines **1** is also discussed. Conditions which favor the formation of **1** *versus* the formation of the isomeric 2-benzylimidazoles **11** are evaluated. Several reactions of **1a** are also described.

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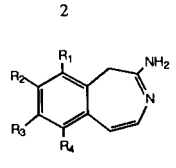
The anti-hypertensive activity of several 2-amino-1*H*-3-benzazepines **1** has recently been reported [1,2]. In connection with the study of this series of compounds, we required a synthesis of 2-amino-7,8-dimethoxy-1*H*-3-benzazepine hydrochloride (**1a**) which would be amenable to use on a large scale.

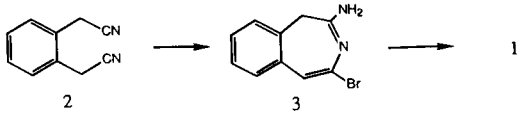


2

1

a, R_1=R_4=H, R_2=R_3=CH_3O

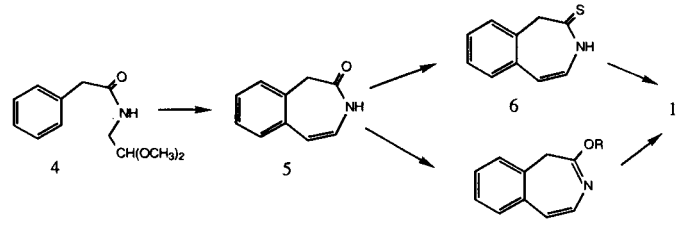
The literature reveals two existing methods of synthesis of 2-amino-1*H*-3-benzazepines. One reported method is the reaction of the dinitriles **2** with hydrogen bromide to generate 4-bromo-2-amino-1*H*-3-benzazepines **3** which can be reduced to give 2-amino-1*H*-3-benzazepines **1** [3-6]. The relative inaccessibility of the dinitrile **2a** needed for the synthesis of **1a** discouraged us from considering this route [7].



2 3 1

A second synthetic method (Scheme I) which has been used to prepare 2-amino-1*H*-3-benzazepines (and specifically **1a**) involves conversion of amide **4** to lactam **5** which can be converted *via* either the 2-thiolactam **6** or the 2-alkoxy-1*H*-3-benzazepine **7** to **1** by reaction with ammonia in an autoclave [2,8]. This method is lengthy, and requires either phosphorus pentasulfide or a trialkyloxonium fluoroborate to convert **5** to **6** or **7**, and an autoclave to convert **6** or **7** to **1**.

Scheme I

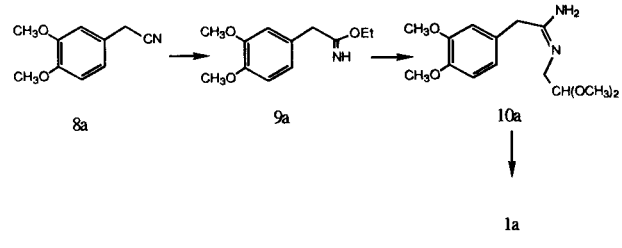


4 5 6 1

We describe herein a short and economical synthesis of **1a** from readily available raw materials (Scheme II) [9]. Thus, conversion of 3,4-dimethoxyphenylacetonitrile (**8a**) to the corresponding imidate **9a** was accomplished using standard methods (anhydrous hydrogen chloride, ethanol) in 88% yield [10]. Conversion of **9a** to oily amidine **10a** [11] was carried out by reaction of **9a** and aminoacetaldehyde dimethylacetal in THF or dimethoxyethane at room temperature. Addition of acetic acid and anhydrous hydrogen chloride to the resulting two phase mixture of **10a** and solvent at 50° converted **10a** to **1a** which precipitated from the reaction mixture in 78% yield from **9a**. Alternatively, **10a** can be reacted with methanesulfonic acid in acetic acid to give after neutralization the free base of **1a** in 70-75% yield from **9a**.

The new methodology is a vast improvement over the existing synthetic methods since it requires readily available raw materials and reagents and involves only one isolated intermediate. The new route (using anhydrous hydrogen chloride) was found to be very easily scaled up and **1a** has been made in this way in 100 gallon equipment.

Scheme II



8a 9a 10a

1a

It is well known that amidine acetals such as **10** are valuable intermediates for the synthesis of imidazoles. Indeed, several reports describe the preparation of 2-benzylimidazoles from analogs of **10** [12-14]. Based on these reports, one would expect the imidazole **11a**, isomeric with **1a**, to result from contact of **10a** with acidic media. We carefully examined the reaction of **10a** with three equivalents of hydrogen chloride in acetic acid and found only small amounts of **11a** in the filtrate after isolation of **1a**. On further experimentation with the hydrogen chloride/-acetic acid medium we found that **10a** was converted cleanly to **1a** only when three or more equivalents of hydrogen chloride was present. However, **10a** was converted exclusively to **11a** when one equivalent of hydrogen chloride was present and to a mixture of **1a** and **11a** when two equivalents of hydrogen chloride were present. With methanesulfonic acid in acetic acid one equivalent of acid was sufficient to convert **10a** to **1a**.

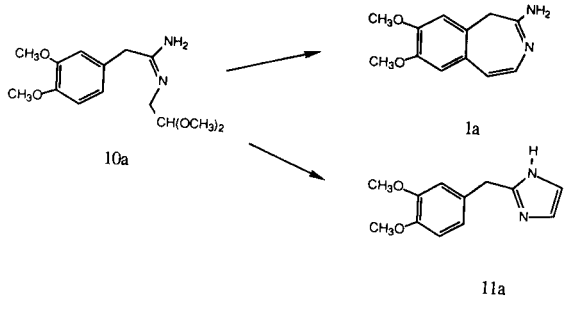
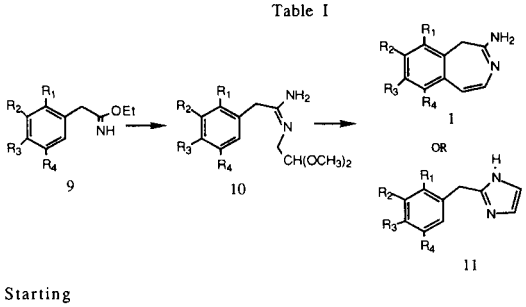


Table I



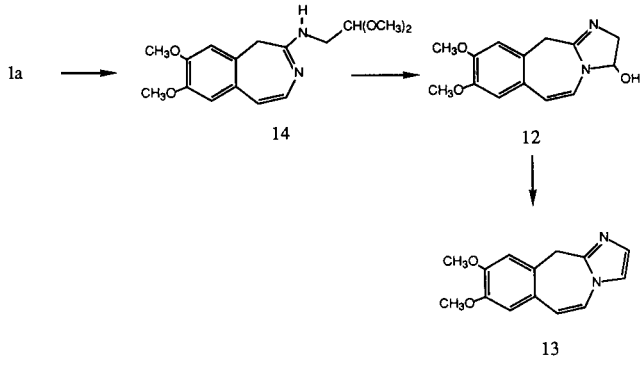
Starting Material	R_1	R_2	R_3	R_4	Product	Yield
9a	H	CH_3O	CH_3O	H	1a	78%[a]
9a	H	CH_3O	CH_3O	H	11a	62%[b]
9b	H	CH_3O	CH_3O	CH_3O	1b	50%[c]
9c	H	CH_3O	H	H	1c	82%[c,d]
9d	CH_3O	H	CH_3	CH_3O	11d	58%[a]

[a]. Using excess HCl. [b] Using 1 equivalent of HCl. [c] Using 1.25 equivalents of methanesulfonic acid. [d] Yield of free base.

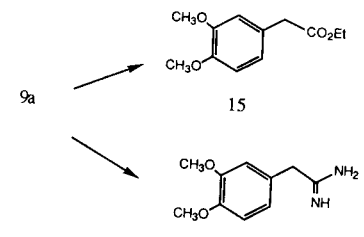
On examination of the reaction of analogs of **10a** with hydrogen chloride in acetic acid, it became clear that the cyclization was very sensitive to electronic effects. Compounds with an electron donating group *para* to the point of cyclization gave aminobenzazepines provided enough acid was present; those that were more electron deficient gave imidazoles even in the presence of greater than three equivalents of acid [15]. The conversion of **10** to imidazoles or 2-amino-1*H*-3-benzazepines was conveniently followed by nmr; the ring protons of the imidazole hydrochlorides appear as a singlet at approximately δ 7.6 [16,17] while the benzazepine hydrochloride ring protons appear as a pair of doublets at δ 6.3 to 6.7 [8,18]. Several examples of the cyclization of 2,2-dimethoxyethylamidines **10** to 2-amino-1*H*-3-benzazepines or imidazoles are collected in Table I.

Except for the conversion of **10a** to **1a**, we have not examined in detail the effects of varying amounts of acid catalysts on the conversion of **10** to **1** or **11**. However, we have found that only one equivalent of methanesulfonic acid is required to convert **10a**, **10b**, or **10c**, to **1a**, **1b**, or **1c**, respectively. In addition, we have observed that reaction of **10d** even with an excess of hydrogen chloride gas in acetic acid gives only **11d**; under these conditions no **1d** is detected.

Although recrystallization of crude **1a** from acetic acid gave very pure **1a**, two minor impurities (< 1%) identified as **12** and **13** could be detected in crude **1a**. These compounds probably derive from the reaction of **1a** with aminoacetaldehyde dimethylacetal to give **14**, although the reaction of **10a** with aminoacetaldehyde dimethylacetal followed by cyclization to **14** would also be possible. Authentic samples of **12** and **13** were prepared from **1a** *via* **14** [19].

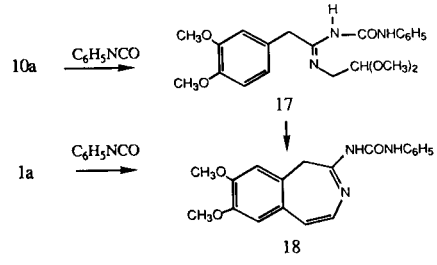


Two other by-products isolated from the filtrate after isolation of **1a** were the ester **15** and the amidine **16**. Compound **15** results from reaction of **9a** with traces of water. Compound **16** results from reaction of **9a** with ammonium chloride (formed during conversion of **9a** to **15**). Synthesis of authentic **16** was achieved by reaction of **9a** with liquid ammonia.



Acid catalysts in addition to anhydrous hydrogen chloride and methanesulfonic acid which have been investigated for the conversion of **10a** to **1a** include trifluoroacetic acid, sulfuric acid, and aqueous hydrochloric acid. Although all of these gave acceptable results, none appeared superior to the anhydrous hydrogen chloride method.

During the course of this study we sought to further characterize compound **10a** by conversion to a solid derivative. This was accomplished by reaction of **10a** with phenylisocyanate to give **17**. Subsequently, it was found that **17** could be cyclized to the benzazepine **18** under the same conditions we had used earlier for the conversion of **10** to **1**. Compound **18** could also be prepared by reaction of **1a** with phenylisocyanate [20].



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were recorded on a JEOL-FX-90Q or Varian EM390 spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT CH-5 spectrometer. The hplc analyses were run on a Waters Associates instrument equipped with a DuPont CN column using 96% 0.1*N* ammonium acetate containing 20 ml of glacial acetic acid per liter/4% acetonitrile as mobil phase with a flow rate at 2 ml/min and uv detection at 240 nm.

3,4-Dimethoxyphenylacetonitrile (**8a**), 3,4,5-trimethoxyphenylacetonitrile (**8b**), and 3-methoxyphenylacetonitrile (**8c**) were commercially available. 2,5-Dimethoxy-4-methylphenylacetonitrile (**8d**) was prepared according to a literature procedure [21].

Phenylacetimidates. General Procedure [10,22].

Phenylacetimidate hydrochlorides were prepared by saturating with gaseous hydrogen chloride a solution of 100 mmole of nitrile in 80 ml of 2B ethanol. The resulting solution was stirred overnight at room temperature and filtered at 0-5°. The filtrate was concentrated and the residual solid slurried in ether and filtered. The following compounds were obtained analytically pure by this method:

Ethyl 3,4,5-Trimethoxyphenylacetimidate Hydrochloride (**9b**).

This compound was obtained in 91% yield, mp 121-122°.

Anal. Calcd. for $C_{13}H_{20}ClNO_4$: C, 53.89; H, 6.96; Cl, 12.24; N, 4.83. Found: C, 53.64; H, 6.98; Cl, 12.17; N, 5.04.

3-Methoxyphenylacetimidate Hydrochloride (**9c**).

This compound was obtained in 92% yield, mp 107-109°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.52; H, 7.02; Cl, 15.43; N, 6.10. Found: C, 57.30; H, 6.92; Cl, 15.63; N, 6.40.

2,5-Dimethoxy-4-methylphenylacetimidate Hydrochloride (**9d**).

This compound was obtained in 90% yield, mp 138-140°.

Anal. Calcd. for $C_{13}H_{20}ClNO_3$: C, 57.04; H, 7.36; N, 5.12. Found: C, 56.77; H, 7.51; N, 5.23.

2-Amino-7,8-dimethoxy-1*H*-3-benzazepine Hydrochloride (**1a**).

Procedure A.

To a suspension of 3.0 g (11.6 mmoles) of ethyl 3,4-dimethoxyethanimidate hydrochloride (**9a**) [9] in 12 ml of dimethoxyethane at 15° was added 1.21 g (11.6 mmoles) of aminoacetaldehyde dimethylacetal. The mixture was allowed to warm to room temperature and stirred overnight. After addition of 12 ml of glacial acetic acid to the resulting suspension of **10a**, anhydrous hydrogen chloride was bubbled subsurface into the reaction mixture. When the solution was saturated, the solution was heated to 50° and held for 4 hours. The resulting suspension was cooled to room temperature and filtered to give 2.3 g (78%) of **1a**, mp 280-281° (lit mp 269-271° [2]) which was 99.8% pure by hplc and identical to an authentic sample [2]; ^{1}H-nmr (DMSO-d_6): δ 3.64 (2H, CH_2, s), 3.77 (3H, CH_3, s), 3.80 (3H, CH_3, s), 6.4-6.7 (2H, CH=, dd, J = 7), 6.9 (1H, ArH, s), 7.0 (1H, ArH, s), 9.2 (NH, broad), 9.9 (NH, broad).

Anal. Calcd. for $C_{12}H_{15}ClN_2O_2$: C, 56.59; H, 5.94; Cl, 13.92; N, 11.00. Found: C, 56.35; H, 6.13; Cl, 13.63; N, 10.77.

2-Amino-7,8-dimethoxy-1*H*-3-benzazepine (**1a**).

Procedure B.

The suspension of **10a** prepared as above from 3.0 g (11.6 mmoles) of **9a** was concentrated to a viscous oil which was dissolved in 12 ml of acetic acid. To this solution at room temperature was added 2.23 g (23.2 mmoles) of methanesulfonic acid and the resulting mixture stirred at room temperature overnight, poured into ice water, and made basic with 25% sodium hydroxide solution. The resulting suspension was filtered and the solid product washed with water and dried *in vacuo* to give 2.0 g (79%) of **1a** as the free base, mp 171-174° (lit [2] mp 183-185°).

Procedure C.

Similarly, **10a** was converted to **1a** (free base) by stirring **10a** from 3.0 g of **9a** at room temperature in 15 ml of trifluoroacetic acid at 50° for 5 hours. Basification and isolation as above gave 2.0 g (79%) of crude **1a** as the free base, mp 170-172°.

Procedure D.

Similarly, **10a** was converted to **1a** by stirring **10a** (from 3.0 g of **9a**) at room temperature in 20 ml of 48% sulfuric acid for 3 days. Basification and isolation as above gave 1.9 g (75%) of crude **1a** as the free base, mp 168-170°.

2-Amino-6,7,8-trimethoxy-1*H*-3-benzazepine Hydrochloride (**1b**).

To a suspension of 2.0 g (6.91 mmoles) of **9b** in 10 ml of dry THF at 5° was added 0.72 g (6.91 mmoles) of aminoacetaldehyde dimethylacetal. The mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was concentrated to a foam which was dissolved in 20 ml of glacial acetic acid. Methanesulfonic acid (0.85 g, 8.6 mmoles) was added at room temperature and the mixture was stirred overnight. The suspension which resulted was filtered and washed with glacial acetic acid to give 0.5 g of **1b**, mp 274-275°, identical to an authentic sample [2].

The filtrate was poured into 25% sodium hydroxide and the resulting precipitate removed by filtration, washed with water, and dried to give 0.8 g of **1b** as the free base, mp 155-162°. A solution of this material in 10 ml of glacial acetic acid was saturated with gaseous hydrogen chloride, cooled to 0°, and filtered to give 0.53 g of additional **1b** as the hydrochloride, mp 276-278° (total yield 1.03 g, 50%); ^{1}H-nmr (DMSO-d_6): δ 3.6 (2H, CH_2, s), 3.7 (3H, CH_3, s), 3.75 (3H, CH_3, s), 3.80 (3H, CH_3, s), 6.55 (2H, CH=, dd, J = 8), 6.7 (1H, ArH, s).

2-Amino-8-methoxy-1*H*-3-benzazepine Hydrochloride (**1c**).

The free base of the title compound was prepared from 2.3 g (10 mmoles) of **9c** as described for the preparation of **1a** (Procedure B) except that THF was used instead of dimethoxyethane. The free base was isolated by filtration, washed with water, and dried to give 1.54 g (82%) of the free base, mp 171-176°, which was converted to the hydrochloride, **1c**, mp 252-254° (lit [2] mp 250-252°); ^{1}H-nmr (DMSO-d_6): δ 3.68 (2H, CH_2, s), 3.75 (3H, CH_3, s), 6.5 (2H, CH=, dd, J = 8), 6.8-7.1 (2H, ArH, m), 7.2-7.4 (1H, ArH, m).

Anal. Calcd. for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; Cl, 15.78; N, 12.47. Found: C, 58.77; H, 5.66; Cl, 15.65; N, 12.24.

2-[(3,4-dimethoxyphenyl)methyl]-1*H*-imidazole Monohydrochloride (**11a**).

To a slurry of 15.0 g (57.9 mmoles) of **9a** in 60 ml of dimethoxyethane at 10° was added 6.08 g (57.9 mmoles) of aminoacetaldehyde dimethylacetal and the mixture was stirred at room temperature overnight. Glacial acetic acid (60 ml) was added and 2.0 g (55 mmoles) of gaseous hydrogen chloride was bubbled in subsurface. The resulting solution was held overnight at 50°, cooled to 5°, and filtered to give 9.11 g (62%) of **11a**, mp 212-214°. After stirring in ethanol and filtering, 8.0 g of **11a** was isolated, mp 217-219°; ^{1}H-nmr (DMSO-d_6): δ 3.72 (3H, CH_3, s), 3.77 (3H, CH_3, s), 4.25 (2H, CH_2, s), 6.90 (2H, ArH, s), 7.19 (1H, ArH, s), 7.54 (2H, CH=, s).

Anal. Calcd. for $C_{12}H_{15}ClN_2O_2$: C, 56.59; H, 5.94; Cl, 13.92; N, 11.00. Found: C, 56.46; H, 5.97; Cl, 13.87; N, 10.77.

[(2,5-Dimethoxy-4-methylphenyl)methyl]-1*H*-imidazole Hydrochloride (**11d**) [23].

To a suspension of 2.74 g (10 mmoles) of **9d** in 8 ml of dimethoxyethane at 15° was added 1.05 g (10 mmoles) of aminoacetaldehyde dimethylacetal. The mixture was allowed to warm to room temperature and stirred overnight. After addition of 9 ml of glacial acetic acid, the mixture was saturated with gaseous hydrogen chloride and heated to 50-60° for 5.5 hours. The resulting solution was cooled and poured into 15 ml of 10% sodium hydroxide at 0-5°. The precipitated solid was isolated by filtration, washed with water, dried, and converted to the hydrochloride with gaseous hydrogen chloride in ethanol to give 1.56 g (58%) of **11d**, mp 214-216°; ^{1}H-nmr (DMSO-d_6): δ 2.05 (3H, CH_3, s), 3.60 (3H, CH_3, s), 3.65 (3H, CH_3, s), 4.2 (2H, CH_2, s), 6.75 (1H, ArH, s), 7.0 (1H, ArH, s), 7.4 (2H, CH=, s).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_2$: C, 58.10; H, 6.38; Cl, 13.19; N, 10.42. Found: C, 57.84; H, 6.50; Cl, 13.43; N, 10.24.

N-(2,2-Dimethoxyethyl)-7,8-dimethoxy-1*H*-3-benzazepin-2-amine (**14**).

Aminoacetaldehyde dimethylacetal (24.8 g, 236 mmoles), 30.0 g (118 mmoles) of **1a**, 19.35 g (236 mmoles) of anhydrous sodium acetate, and 500 ml of methanol were combined. After stirring overnight at room temperature, the solids were removed by filtration and the filtrate concentrated to a solid which was slurried in hexane and filtered. The resulting crude solid was slurried in 200 ml of 25% sodium hydroxide, filtered, washed with water, and dried to give 32.94 g (91%) of **14**, mp 110-111°; ^{1}H-nmr (DMSO-d_6): δ 3.1 (2H, CH_2, d, J = 3), 3.2 (8H, 2 CH_3 and CH_2, s), 3.7 (3H, CH_3, s), 3.75 (3H, CH_3, s), 4.4 (1H, CH, t, J = 3), 6.0 (1H, CH=, d, J = 8), 6.7 (1H, ArH and CH=, m).

Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.55; H, 7.52; N, 8.89.

2,11-Dihydro-8,9-dimethoxy-3*H*-imidazo[2,1-*b*][3]benzazepin-3-ol, Hydrochloride (**12**).

A crude mixture (47.76 g) containing **14** was obtained by stirring overnight at room temperature a mixture of 30.0 g (118 mmoles) of **1a**, 24.8 g (236 mmoles) of aminoacetaldehyde dimethylacetal, 19.35 g (236 mmoles) of sodium acetate, and 300 ml of absolute methanol, concentrating to a solid, and filtering from hexane and 25% sodium hydroxide as described above. Crude **14**, thus obtained (47.76 g), was combined with 200 ml of glacial acetic acid and 100 ml of 1*N* hydrochloric acid, stirred 2 hours at room temperature and poured over ice and water. Aqueous 25% sodium hydroxide was added and the material extracted with methylene chloride. The extracts were washed with water and dried to give 32.56 g of crude foam. This material was dissolved in 160 ml of glacial acetic acid and acidified by bubbling gaseous hydrogen chloride subsurface into the solution until saturation was achieved. The solution was then concentrated to a solid which was slurried in 300 ml of ether, filtered, and dried to give 31.17 g (81%) of crude **12**, mp 263-265°. Recrystallization from acetic acid/ether gave 26.69 g of **12**, mp 265-266°. The analytical sample, mp 267-269°, was obtained by slurrying 1.0 g of crude material in 10 ml of 1*N* HCl and isolation of **12** by filtration. ^{1}H-nmr (DMSO-d_6): 3.77 (3H, CH_3, s), 3.795 (3H, CH_3, s), 3.67-4.0 (4H, CH_2, CH_2, m), 5.64-5.82 (1H, CH, m), 6.7 (2H, CH=, dd, J = 8), 6.9 (1H, ArH, s), 7.0 (1H, ArH, s); ms: electron impact, m/e 242; field desorption, m/e 260, 242.

Anal. Calcd. for $C_{14}H_{17}ClN_2O_3$: C, 56.66; H, 5.77; Cl, 11.95; N, 9.44. Found: C, 56.64; H, 5.62; Cl, 11.82; N, 9.46.

8,9-Dimethoxy-11*H*-imidazo[2,1-*b*][3]benzazepine Hydrochloride (**13**).

A solution of **14**, prepared as above from 10.0 g (39.4 mmoles) of **1a**, 150 ml of glacial acetic acid and 20 ml of concentrated hydrochloric acid was stirred overnight at 70°. After cooling, the solution was poured into ice water and basified with 25% sodium hydroxide. The resulting precipitate was isolated by filtration and recrystallized from methylene chloride/ether to give 5.13 g (54%) of **13**, mp 124-126°. The analytical sample, mp 125-127°, was recrystallized two additional times from methylene chloride/-

ether. ^{1}H-nmr (DMSO-d_6): δ 3.74 (3H, CH_3, s), 3.79 (3H, CH_3, s), 3.87 (2H, CH_2, s), 6.5 (1H, CH=, d, J = 8), 6.9-7.3 (5H, ArH, CH=, m).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.45; H, 5.79; N, 11.47.

3,4-Dimethoxybenzeneethanimidamide Hydrochloride (**16**).

To a solution of 40 g (174 mmoles) of **9a** [10] in 120 ml of 2B ethanol at −50° in a dry ice/acetone bath was added 40 ml of liquid ammonia. The mixture was allowed to warm to 0°, held for 2 hours, and concentrated. The residual solid was slurried in acetone and filtered to give 34.46 g (97%) of **16**, mp 164-166°. The analytical sample was recrystallized from ethanol/ethyl acetate to give purified **16**, mp 168-170°; ^{1}H-nmr (DMSO-d_6): δ 3.69 (2H, CH_2, s), 3.74 (3H, CH_3, s), 3.77 (3H, CH_3, s), 7.0-7.3 (3H, ArH, m), 8.8 (NH_2, broad).

Anal. Calcd. for $C_{10}H_{15}ClN_2O_2$: C, 52.06; H, 6.55; Cl, 15.37; N, 12.14. Found: C, 51.90; H, 6.65; Cl, 15.55; N, 11.94.

N'-(2,2-Dimethoxyethyl)-3,4-dimethoxy-*N*-[(phenylamino)carbonyl]benzeneethanimidamide Monohydrochloride (**17**).

To a suspension of **10a**, prepared from 5.2 g (20 mmoles) of **9a** and 2.1 g (20 mmoles) of aminoacetaldehyde dimethylacetal in 10 ml of dimethoxyethane as described for the preparation of **1a**, was added 40 ml of 1.25*N* sodium hydroxide solution. The resulting solution was extracted with methylene chloride and the extracts dried over sodium sulfate. Concentration of the extracts gave 6.2 g of the free base as an oil. Phenylisocycanate (2.4 g, 20 mmoles) was added dropwise to this oil in 25 ml of toluene at room temperature and the mixture was stirred overnight at room temperature. A small amount of white precipitate was removed by filtration and the filtrate concentrated to give 9.1 g of a viscous oil which was converted with hydrogen chloride in methanol to 8.0 g of **17** as a foam. A small sample was recrystallized from methanol/hexane to give the purified hydrochloride, mp 148-150°; ^{1}H-nmr (DMSO-d_6): 3.36 (6H, CH_3, s), 3.66 (3H, CH_3, s), 3.74 (5H, CH_3, CH_2, m), 3.76 (2H, CH_2, d), 4.14 (1H, CH, m), 4.34 (2H, CH_2, s), 6.8-7.6 (8H, ArH, m).

Anal. Calcd. for $C_{21}H_{28}ClN_3O_5$: C, 57.60; H, 6.44; N, 9.60. Found: C, 57.78; H, 6.19; N, 9.81.

N-(7,8-Dimethoxy-1*H*-3-benzazepin-2-yl)-*N'*-phenylurea (**18**).

Procedure A.

To 3.06 g (7 mmoles) of crude **17** in 10 ml of glacial acetic acid at room temperature was added 1.47 g (15 mmoles) of methanesulfonic acid. The mixture was stirred overnight at room temperature resulting in a thick slurry. The slurry was poured into ice water and the precipitated solid was filtered and washed with water to give 1.41 g of crude product, mp 160-180°. Slurrying the crude product in 1*N* sodium hydroxide/ethanol and filtration gave 1.02 g (43%) of **18**, mp 183-185°. Recrystallization from ethanol/chloroform (1:1) gave the analytical sample, mp 198-199°; ^{1}H-nmr (DMSO-d_6): δ 3.38 (2H, CH_2, s), 3.78 (3H, CH_3, s), 3.82 (3H, CH_3, s), 6.56 (1H, CH=, d, J = 8), 6.8-7.5 (8H, ArH and CH=, m), 9.96 (1H, NH, s), 11.86 (1H, NH, s); ms: electron impact, m/e 337, 218 (100%).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.50; H, 5.72; N, 12.28.

Procedure B.

To a suspension of 2.18 g (10 mmoles) of **1a** as the free base in 20 ml of dry dimethoxyethane at room temperature was added 1.19 g (10 mmoles) of phenylisocyanate. After refluxing for 2 hours, the suspension was cooled and filtered to give 2.8 g (53%) of **18**, mp 195-196°, identical by tlc (72:24:4 chloroform/methanol/acetic acid), nmr, ms, and ir to **18** prepared by procedure A.

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