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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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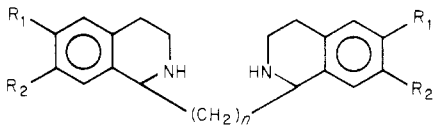
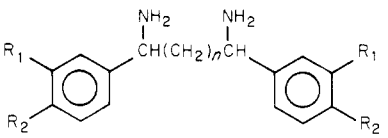
Since the previously investigated bis(tetrahydroisoquinolines) 1 and bis(benzylamines) 2 may be classified as 1,ω-diaryl-1,ω-alkanediamines, it appeared worthwhile to examine this structural concept as a guideline for predicting significant fibrinolytic activity. The prototype bis compounds **7**, **14**, **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.

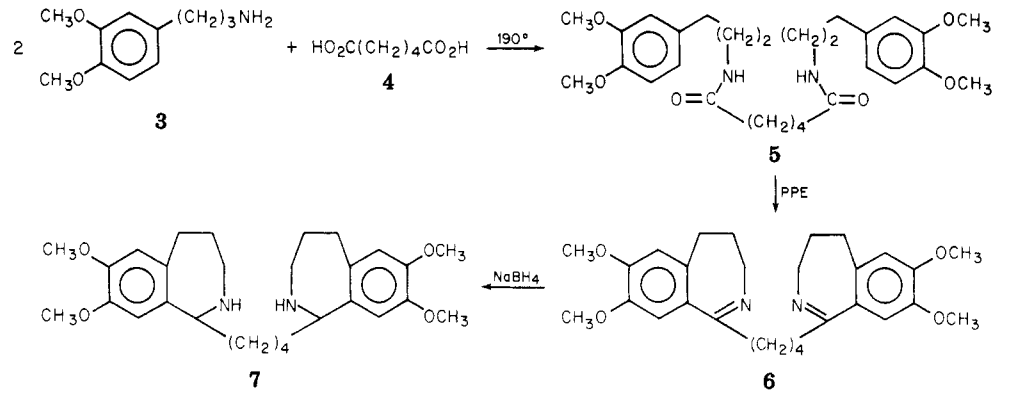
Chemistry. The three-step synthetic sequence (Scheme I) leading to the bis(tetrahydrobenzazepine) **7** is similar to that utilized in the preparation of the bis(tetrahydroisoquinolines) **1**,[2a] and both the condensation and reduction steps leading to **5** and **7**, respectively, proceeded in good 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 $NaBH_4$.

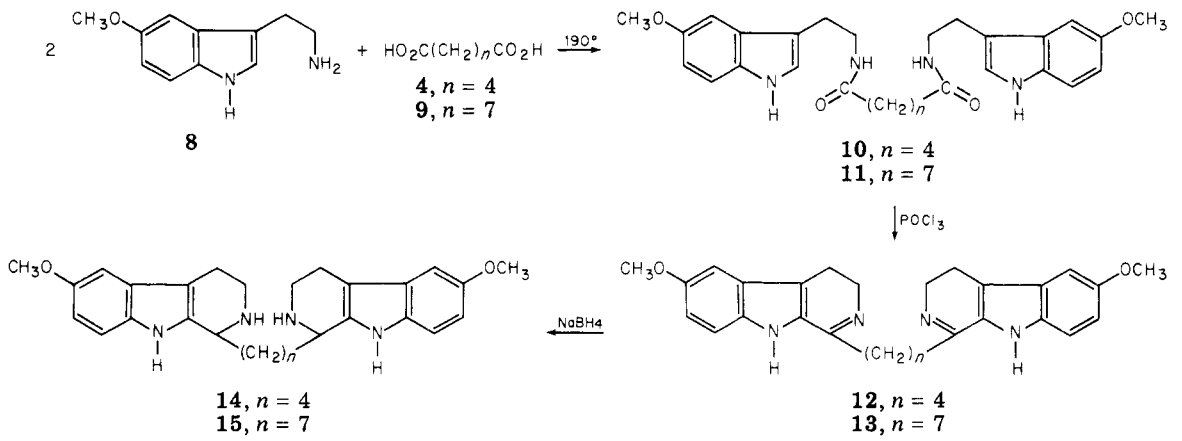
Compounds **29–31** (Scheme III) were variations of particular interest since they combine in one structure both the tetrahydroisoquinoline and benzylamine moieties. The ω-aroylaliphatic acids **17–19** required for condensation with **16** were prepared by the general procedure of Papa et al.[6a] Bischler–Napieralski 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

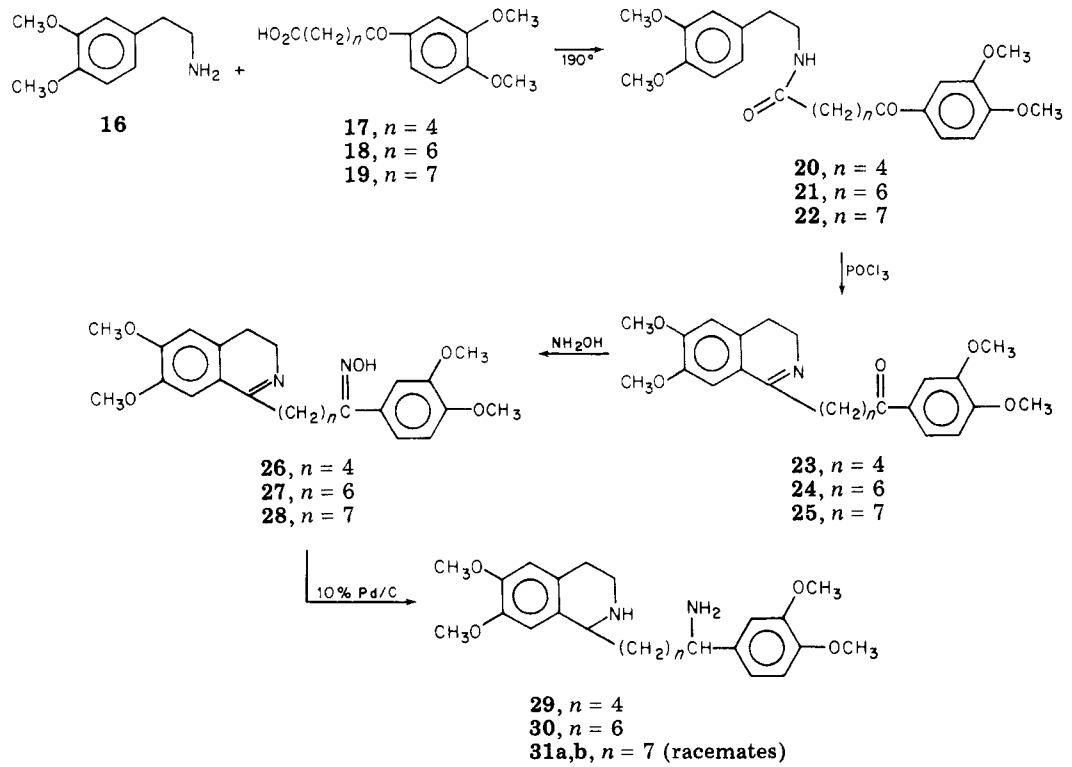
Scheme I



Scheme II



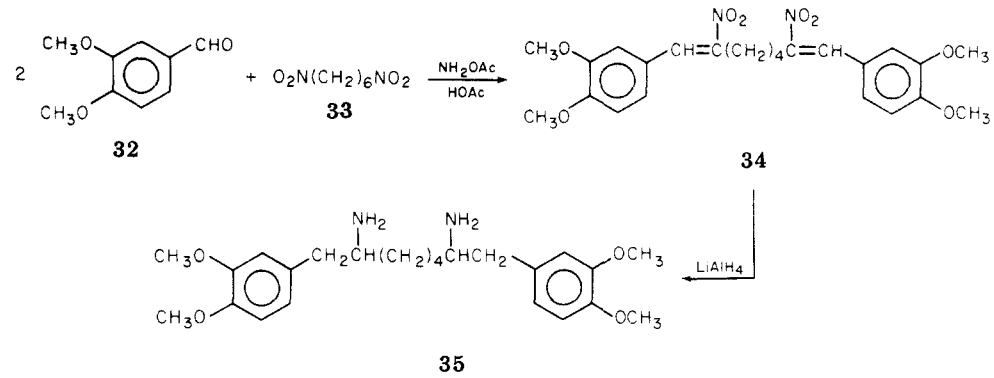
Scheme III



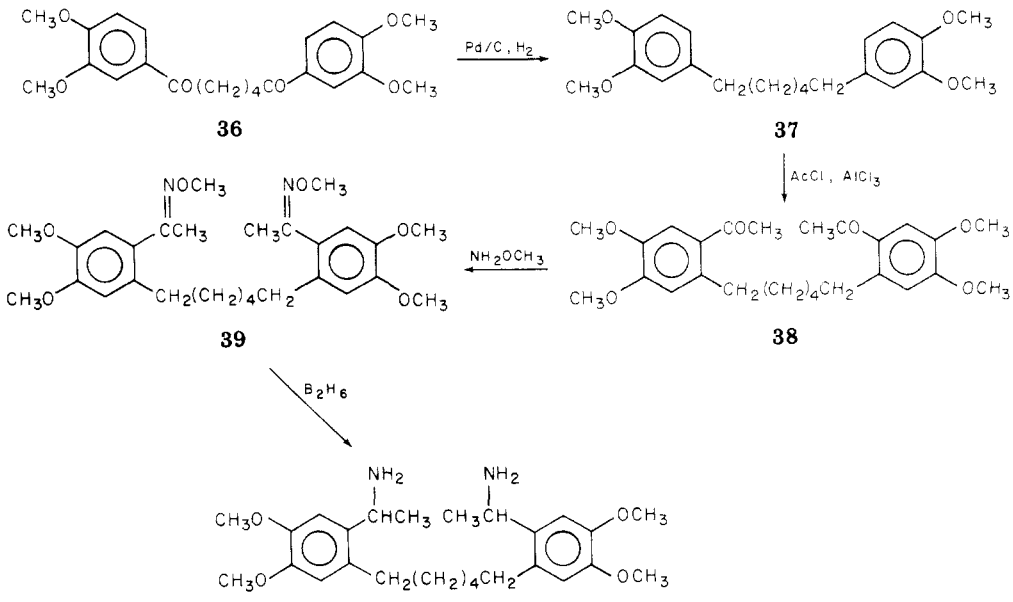
in the literature and the use of 2 equiv of NH_4OAc rather than one in the reaction (cf. **34**) seems to provide higher yields of the bis(ω-nitrostyrenes).[7] Further reduction of the latter compounds to the corresponding bis(phenethylamines) apparently has not been reported previously, and, as expected, $LiAlH_4$ readily converted **34** to **35**.

The final molecular modification which was examined is represented by **40**, a structural isomer of compounds of type **2**. Condensation and reduction methods used in the synthesis of the latter compounds[2b] were applied to the

Scheme IV



Scheme V



synthesis of **40** (Scheme V).

Since no stereospecificity should be operative in the above reductive methods, compounds **7**, **14**, **15**, **35**, and **40** which have two identical chiral centers exist as meso, D, and L modifications. In addition, two racemates are possible for compounds **29–31** with two different chiral centers. Only in the case of **31** were the two racemates, **31a** and **31b**, separated and characterized. In each of the other cases, the crude mixture of isomers resulting from the reduction step was treated as a homogeneous entity and purified by recrystallization of the dihydrochloride salts from suitable solvents. This procedure sometimes produced low recoveries of the less soluble isomers, although crude yields of the mixed isomers were generally good (>70%). Also, as expected, the melting points of the crude and recrystallized dihydrochloride salts frequently showed wide separation.

Biological Evaluation. For testing purposes the crude mixture of isomeric dihydrochloride salts was recrystallized once or twice as described above. Therefore, except in the case of **31** in which the two racemates were separated, the ED_{50} values reported in Table I are for compounds whose isomeric composition will vary between equal populations of all possible isomers and 100% of the less soluble isomer. Previous work in the area of the bis(tetrahydroisoquinolines) has shown, in two cases, that the potencies of the pure meso and pure DL forms do not differ significantly.[2a]

The testing protocol was identical with that described in previous articles.[2a,8] A minimum of three rats was used for each ip dose. The animals were bled 0.75 hr after administration of the compound and dilute whole blood clots were formed. The ED_{50} (mg/kg) represents that dose which causes 50% of the clot to lyse in a standard period (4 hr) at 37°. Baseline fibrinolytic activity was determined by injection of vehicle in place of test compounds. Serotonin was used as the standard for synthetic agents.[8]

Structure–Activity Relationships. The compounds described in the present work were designed to provide information on additional structural parameters essential for predicting significant fibrinolytic activity.

Compounds **29–31** were obvious candidates for investigation and indeed it was found that these unsymmetrical hybrids of structures **1** and **2** possess potencies comparable but not superior to the more active members of the latter series.[2] Stereochemical factors again appeared to exert little effect on fibrinolytic activity since the two racemic forms of **31**, like the meso and DL isomers of **1a**, showed no significant difference in potency.

When the nitrogen-containing rings of series **1** compounds were expanded a moderate decrease in potency was observed (cf. **7** and **1a**, Table I).

The potencies of the bis(methoxytetrahydropyridoindoles), **14** and **15**, indicate moderate fibrinolytic activity. However, the ED_{50} values (2–6 mg/kg) fall within the same range found for the bis(monomethoxytetrahydroisoquinolines), **1b** and **1c**, and suggest the equivalence of indole and benzene as aryl moieties. It would be of interest

Table I. Comparative Fibrinolytic Potencies (Rat)

Compd no.[a]	ED_{50}, mg/kg ip[b,c]	Compd no.[a]	ED_{50}, mg/kg ip[b,c]
1a	0.3–0.4	29	0.9
1b	2	30	~1
1c	6	31a	0.7
2a	0.4	31b	0.5
7	0.7	35	15
14	6	40	4
15	2	Serotonin	1

[a] Dihydrochloride salts. [b] See Biological Evaluation section. [c] Fiducial limits are ±20%.

to test the less accessible 6,7-dimethoxy analogs of **14** and **15** to determine whether this aromatic substitution pattern, as in the case of series **1** and **2**, leads to significantly more potent compounds.

Comparison of the ED_{50} values of the bis(benzylamine) **2a** with the bis(phenethylamine) **35** establishes the strong deactivating effect attendant upon formal insertion of a methylene group between the aryl and carbinylamine functions. Similarly, a shift of the alkylene chain from the α-benzylamine position of series **2** compounds to an ortho position leads to a compound (**40**) of moderate activity.

In summary, molecular modification applied to the general 1,ω-diaryl-1,ω-alkanediamine system can serve as a useful guideline for the design of new indirect activators of the fibrinolytic system.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. Boiling points are uncorrected. Ir spectra of solids (Nujol mulls) and liquids (neat) were measured on a Perkin-Elmer Model 137 spectrometer. Uv spectra were determined in MeOH using a Cary recording spectrophotometer. Solutions were dried over anhydrous K_2CO_3 (amines) or Na_2SO_4 (nonbasic products) and evaporated to dryness under reduced pressure on a rotary evaporator. EtOH refers to a commercial 2B grade of absolute EtOH. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

N,N'-Bis[3-(3,4-dimethoxyphenyl)propyl]hexanediamide (5). A mixture of 19.5 g (0.1 mol) of **3**[9] and 7.3 g (0.05 mol) of **4** was placed in an oil bath preheated to 190° and heating maintained at 185–195° for 3 hr under a slow stream of N_2. After cooling, the residue was recrystallized from MeOH to yield 21.3 g (85%) of colorless needles: mp 133–134°; ir 3330 (NH), 1640 (C=O), 1600 (aromatic), 1540 (amide II), and 1517 cm^{-1} (aromatic). Anal. ($C_{28}H_{40}N_2O_6$) C, H, N.

1,1'-Tetramethylenebis(4,5-dihydro-7,8-dimethoxy-3H-2-benzazepine) (6). A mixture of 5.0 g (0.01 mol) of **5** and 50 g of polyphosphate ester[4] contained in a 200-ml flask was heated (foaming) in an oil bath at 120° for 5 hr. The dark red-brown solution was poured into 250 ml of ice–water and the resulting cloudy solution washed with CH_2Cl_2 (2 × 10 ml). The aqueous layer was made basic with 10 *N* NaOH, and the oil which separated was extracted with PhH. The combined extracts were washed with H_2O, dried, and evaporated. Trituration of the oily residue under cyclohexane gave 2.0 g of a tan powder, which was recrystallized from cyclohexane (Norit) to yield 0.70 g (15%) of off-white crystals: mp 133–135°; ir 1621 (C=N) and 1608, 1580, 1513 cm^{-1} (aromatic); uv max 295 nm (ε 10100) and 262 (11000). Anal. ($C_{28}H_{36}N_2O_4$) C, H, N.

1,1'-Tetramethylenebis(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-2-benzazepine) (7) Dihydrochloride. A solution of 2.0 g (4.3 mmol) of **6** in 50 ml of EtOH was stirred and treated with 0.66 g (17.5 mmol) of $NaBH_4$. After refluxing for 4 hr, the mixture was poured into H_2O and extracted with $CHCl_3$. The combined extracts were dried and evaporated, and the residual free base was converted to its dihydrochloride salt with ethanolic HCl–EtOAc. On standing for 48 hr, 2.0 g of crystals was deposited: mp 257–258°. Recrystallization (95% EtOH–EtOAc) gave 1.6 g (69%) of white solid: mp 258–259°; ir 2400–2700 (NH_2^+) and 1613, 1580, 1513 cm^{-1} (aromatic); uv max 237 nm (ε 15800) and 283 (5640). Anal. ($C_{28}H_{42}Cl_2N_2O_4$) C, H, N.

N,N'-Bis[2-(5-methoxy-1H-indol-3-yl)ethyl]hexanediamide (10). Fusion of 7.00 g (0.0368 mol) of **8**[10] and 2.66 g (0.0182 mol) of **4** at 200° for 2 hr under a slow stream of N_2 gave, on cooling, 8.5 g (96%) of a light yellow glass which failed to crystallize: ir 3436 and 3310 (indole and amide NH) and 1647 cm^{-1} (amide C=O).

N,N'-Bis[2-(5-methoxy-1H-indol-3-yl)ethyl]nonanediamide (11). Fusion of 9.90 g (0.0521 mol) of **8**[10] and 4.90 g (0.0261 mol) of nonanedioic acid (**9**) as described for **10** gave 14 g (>100%) of **11** as a noncrystallizable light yellow glass.

1,1'-Tetramethylenebis(4,9-dihydro-6-methoxy-3H-pyrido[3,4-b]indole) (12) Dihydrochloride. A mixture of 8.50 g (0.0173 mol) of **10** and 64 ml of $POCl_3$ was refluxed with stirring for 15 min. On cooling and scratching, the red solution deposited a yellow solid (7.2 g) which was filtered, washed with PhH and a small amount of Me_2CO, and recrystallized from MeOH (90 ml) to yield 5.0 g (50%) of the dihydrochloride salt of **12**: mp 266–268°; ir 3400–3175 (solvate OH and indole NH), 2725–2415 (=NH^+), and 1555 cm^{-1} (C=N^+). Anal. ($C_{28}H_{32}Cl_2N_4O_2 \cdot 3H_2O$) C, H, N.

1,1'-Heptamethylenebis(4,9-dihydro-6-methoxy-3H-pyrido[3,4-b]indole) (13). A mixture of 12.0 g (0.0225 mol) of **11** and 96 ml of $POCl_3$ was refluxed for 15 min. The precipitate (11.0 g) which formed on cooling was filtered, washed with PhH and a small amount of Me_2CO, and recrystallized from *i*-PrOH–H_2O to yield 10.5 g of yellow crystals of the dihydrochloride salt of **13**. The free base was obtained by dissolving the salt in 500 ml of hot H_2O and adding 1 *N* NaOH. The precipitate was recrystallized from EtOH–H_2O to yield 5.5 g (49%) of a yellow solid: mp 242–243°; ir 1545 cm^{-1} (C=N); uv max 211 nm (ε 58800), 230 infl (27100), 326 (32400), and 360 infl (15600). Anal. ($C_{31}H_{36}N_4O_2$) C, H, N.

1,1'-Tetramethylenebis(2,3,4,9-tetrahydro-6-methoxy-1H-pyrido[3,4-b]indole) (14) Dihydrochloride. To a suspension of 6.50 g (0.0112 mol) of the above dihydrochloride salt of **12** in 500 ml of hot (70°) EtOH, H_2O (total ca. 50 ml) was added in portions until the solid dissolved. The heat source was removed and $NaBH_4$ (4.65 g, 0.123 mol) was added in portions over several minutes. After refluxing for 2 hr, solvents were evaporated and the residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted further with $CHCl_3$ and the combined extracts were washed with H_2O, dried, and evaporated. The residual oily free base gave 5.5 g of crude **14**·2HCl on treatment with ethanolic HCl. On further recrystallization from H_2O–EtOH, 4.0 g (67%) of yellow solid was obtained: mp 277–279°; ir 3270 (indole NH), 2760–2460 (NH_2^+), and 1605 cm^{-1} (NH_2^+ and/or aromatic). Anal. ($C_{28}H_{36}Cl_2N_4O_2$) C, H, N.

1,1'-Heptamethylenebis(2,3,4,9-tetrahydro-6-methoxy-1H-pyrido[3,4-b]indole) (15) Dihydrochloride. $NaBH_4$ (0.91 g, 0.024 mol) was added in portions to a warm solution of 3.0 g (0.006 mol) of **13** in 400 ml of EtOH. After refluxing for 3 hr, the EtOH was evaporated and the residue diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried, and evaporated to yield the crude free base as an amorphous yellow solid. A sample was dried further under high vacuum (0.01 mm): uv max 224 nm (ε 43500), 276 (14400), 293 infl (11600), and 305 infl (7510). On treatment with ethanolic HCl followed by digestion on the steam bath, the initially formed gel crystallized to give 3.0 g of crude dihydrochloride salt. Recrystallization from H_2O–EtOH yielded 2.5 g (68%) of fine yellow needles: mp 220–224°; ir 3480 (solvate OH), 3320 (indole NH), 2750–2460 (NH_2^+), and 1610 cm^{-1} (NH_2^+ and/or aromatic); uv max 221 nm (ε 54300), 275 (17800), 288 (infl (14100), and 307 infl (8450). Anal. ($C_{31}H_{42}Cl_2N_4O_2 \cdot 2H_2O$) C, H, N.

3,4-Dimethoxy-ε-oxobenzenehexanoic Acid (17). A solution of 190 g (1.38 mol) of 1,2-dimethoxybenzene and 1 l. of dry 1,1,2,2-tetrachloroethane was cooled to ca. −10° (ice–salt bath) and, with stirring, 333.0 g (2.50 mol) of $AlCl_3$ was added in portions during ca. 1 hr so that the internal temperature was <0°. With stirring and cooling at 0–3°, 223.8 g (1.25 mol) of freshly distilled 6-chloro-6-oxohexanoic acid methyl ester[11] was then added dropwise during 2.5 hr. After storing overnight in the refrigerator

(2°), the red mixture was poured slowly onto a mixture of 2 kg of crushed ice and 250 ml of concentrated HCl. During the addition, a further 1.5 kg of crushed ice was added in portions to keep the temperature <0°. After stirring for an additional 15 min at <0°, the mixture was warmed to room temperature, and the aqueous layer was separated and further extracted with $CHCl_3$ (2 × 500 ml). The combined organic extracts were washed with H_2O (5 × 500 ml) and dried. The $CHCl_3$ was evaporated and the residue distilled through a 6-in. Vigreux column to give, as the main fraction, 287.0 g (82%) of the methyl ester of **17**: bp 175–176° (0.1 mm); mp 65–66°; ir 1740 (ester C=O) and 1672 cm^{-1} (aromatic C=O).

Without further purification, a mixture of 280.0 g (1.0 mol) of the methyl ester and 550 ml of 10% aqueous NaOH was stirred and heated on the steam bath for 1.5 hr. The clear solution was diluted with 500 ml of H_2O, cooled (ice bath), and acidified with 10% aqueous HCl. The precipitate was washed and air-dried to give 261 g (98%) of white solid: mp 124–125° (partial melting and resolidification at ca. 117–119°). After recrystallization from 1:1 H_2O–EtOH (1300 ml) and drying in vacuo over P_2O_5, the product (235 g, 90% recovery) had mp 127–128° (partial melting and resolidification at 122–123°) (lit.[12] mp 123°); ir 1740 (carboxyl C=O) and 1675 cm^{-1} (aromatic C=O). Anal. ($C_{14}H_{18}O_5$) C, H.

3,4-Dimethoxy-η-oxobenzeneoctanoic Acid (18). By the procedure described above, a mixture of 216 g (1.56 mol) of 1,2-dimethoxybenzene, 1 l. of dry 1,1,2,2-tetrachloroethane, 378 g (2.84 mol) of $AlCl_3$, and 313 g (1.42 mol) of 8-chloro-8-oxooctanoic acid ethyl ester[13] gave, on distillation through a 6-in. Vigreux column, 353 g (77%) of the ethyl ester of **18**: bp 192–193° (0.05 mm). GLC analysis [3.8% UCW-98 on 80–100 mesh Chromosorb W (HP-AW-DMCS), 4-ft glass column × 4 mm i.d.] indicated a purity of ca. 80%. Redistillation under the same conditions failed to affect the composition and the compound was purified further by recrystallization from anhydrous Et_2O (−70°, 1 g/5 ml) to yield 268 g (59%) of white solid: mp 40–43°; GLC ca. 95% pure.

Saponification of 264 g (0.82 mol) of the ethyl ester with 452 ml of 10% aqueous NaOH was carried out as described for **17**. The yield of crude, air-dried product was 247 g (>100%): mp 74–83°. Recrystallization from EtOH (1200 ml)–H_2O (500 ml) (Norite) gave 213 g (88%) of white solid: mp 77–84°; ir 1710 (carboxyl C=O) and 1678 cm^{-1} (aromatic C=O). For analysis a sample was dried in vacuo over P_2O_5, 24 hr, 0.05 mm, 60°: mp 94–95°. Anal. ($C_{16}H_{22}O_5$) C, H.

3,4-Dimethoxy-θ-oxobenzenenonanoic Acid (19). The reaction of 152 g (1.10 mol) of 1,2-dimethoxybenzene, 650 ml of dry 1,1,2,2-tetrachloroethane, 266 g (2.0 mol) of $AlCl_3$, and 235 g (1.0 mol) of 9-chloro-9-oxononanoic acid ethyl ester[13] was carried out as described above. In this case, the combined $CHCl_3$–$Cl_2CHCHCl_2$ extracts were washed with H_2O (2 × 1 l.), 5% K_2CO_3 (3 × 1 l.), and H_2O (2 × 1 l.) and dried as usual. Distillation through a 6-in. Vigreux column gave 229 g (68%) of the ethyl ester of **19**: bp 195–197° (0.1 mm); GLC analysis [3.8% OV-17 on 100–120 mesh Gas Chrom Q, 6-ft glass column × 4 mm i.d.] shows 95% purity; ir 1733 (ester C=O) and 1675 cm^{-1} (aromatic C=O).

Saponification of 229 g (0.68 mol) of the ethyl ester with 375 ml of 10% aqueous NaOH was carried out as described above. The crude product was recrystallized twice from 2:1 EtOH–H_2O to yield 165 g (79%) of **19**: mp 73–76°. The analytical sample was recrystallized again (mp 75–76°) and dried in vacuo over P_2O_5, 24 hr, 0.02 mm, 60°: mp 93–94°; ir 1712 and 1701 (shoulder) (carboxyl C=O) and 1669 cm^{-1} (aromatic C=O). Anal. ($C_{17}H_{24}O_5$) C, H.

3,4-Dimethoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-ε-oxobenzenehexanamide (20). A mixture of 186 g (0.70 mol) of **17** and 133.0 g (0.735 mol) of **16** was placed in an oil bath preheated to 190° and heating maintained at 185–195°, with magnetic stirring, for 5 hr under a slow stream of N_2. The orange glass which formed on cooling was dissolved in 2 l. of $CHCl_3$ and the solution washed with 10% HCl (3 × 300 ml), 10% K_2CO_3 (5 × 300 ml), H_2O (3 × 300 ml), and dried. The $CHCl_3$ was evaporated and the residual orange oil triturated under Et_2O. The solid which gradually formed was filtered, washed with Et_2O, and air-dried to give 255 g (85%) of a cream colored, amorphous solid: mp 57–60°; ir 3344 (NH), 1666 (aromatic C=O), 1639 (amide C=O), 1587 (aromatic), 1546 (amide II), and 1511 cm^{-1} (aromatic). Two recrystallizations from EtOAc yielded, after thorough air-drying, 225 g (75%) of a white solid: mp 58–60°; ir, similar to above, with C=O of EtOAc at 1745 cm^{-1}. The product retained EtOAc tenaciously and satisfactory analytical data could not be obtained even after drying under high vacuum.

3,4-Dimethoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-η-oxobenzeneoctanamide (21). A mixture of 210 g (0.714 mol) of **18** and 142 g (0.785 mol) of **16** was heated and worked up as described for **20**. The solid which formed on trituration under Et_2O amounted to 261 g (80%): mp 76–77°. Two recrystallizations from EtOAc–Et_2O (Norite) gave 169 g (52%) of product: mp 80–81°; ir 3322 (NH), 1669 (aromatic C=O), 1645 (amide C=O), 1587 (aromatic), 1555 (amide II), and 1513 cm^{-1} (aromatic). Anal. ($C_{26}H_{35}NO_6$) C, H, N.

3,4-Dimethoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-θ-oxobenzenenonanamide (22). A mixture of 162 g (0.526 mol) of **19** and 105 g (0.580 mol) of **16** was heated and worked up as described for **20**. The solid which formed on Et_2O trituration amounted to 191 g (77%): mp 90–93°. Two recrystallizations from EtOAc–Et_2O (Norite) yielded 114 g (38%): mp 95–97°. One additional recrystallization from PhH–cyclohexane gave 102 g (34%) of pure product: mp 107–109°; ir 3356 (NH), 1681 (aromatic C=O), 1650 (amide C=O), 1592 (aromatic), 1538 (amide II), and 1515 cm^{-1} (aromatic). Anal. ($C_{27}H_{37}NO_6$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1-[5-(3,4-dimethoxyphenyl)-5-oxopentyl]isoquinoline (23). A solution of 68.2 g (0.16 mol) of **20** in 340 ml of $POCl_3$ was stirred at room temperature for 4 hr with protection from moisture. Excess $POCl_3$ was evaporated (<40°) and the residual viscous, dark brown oil mixed with 500 ml of H_2O. The temperature rose rapidly to 90° and cooling was applied to keep the temperature at 80–90°. After 15 min the exothermic reaction was complete and the hot mixture was poured into 1.5 l. of H_2O and cooled, and the turbid solution was washed with PhH to remove some insoluble, red oil. Addition of excess concentrated NH_4OH to the aqueous layer caused separation of an oil which was extracted with PhH. The combined extracts were washed with H_2O, dried, and concentrated to 400 ml. Elution through 300 g of neutral Al_2O_3 (activity I), followed by evaporation, and trituration of the residue under Et_2O provided 16.1 g (24%) of a light orange-tan solid: mp 98–99°. The melting point was unchanged on recrystallization from 1:1 PhH–cyclohexane (14.2 g, 22%, pale tan solid). For analysis the product was recrystallized twice (Norite) to give colorless rods: mp 98–99°; ir 1669 (aromatic C=O), 1631 (C=N), and 1595, 1580, 1513 cm^{-1} (aromatic). Anal. ($C_{24}H_{29}NO_5$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1-[7-(3,4-dimethoxyphenyl)-7-oxoheptyl]isoquinoline (24) Hydrochloride. A stirred mixture of 132 g (0.29 mol) of **21** and 536 ml of dry PhH was treated cautiously, in portions, with 189 ml of $POCl_3$. After refluxing for 2 hr with protection from moisture, the solution was evaporated to dryness and the residue cautiously mixed with 3 l. of ice and H_2O. When the exothermic reaction was complete, the mixture was heated on the steam bath until complete solution occurred. While still hot, the solution was made basic with excess 10 *N* NaOH and cooled, and the product was extracted with PhH (3 × 500 ml). The combined extracts were washed with H_2O, dried, decolorized with 7 g of Norite, and evaporated. Since treatment of the residue with *i*-PrOH–HCl failed to yield solid product, the *i*-PrOH was evaporated and replaced with EtOAc. Trituration provided 83 g (58%) of crude hydrochloride salt: mp 115–117°. Two recrystallizations from *i*-PrOH gave 63 g (44%) of product: mp 119–121°; ir 3520 (solvate OH), 2785 (=NH^+), 1667 (aromatic C=O), 1650 (C=N^+), and aromatic bands at 1608, 1590, 1565, and 1513 cm^{-1}. Anal. ($C_{26}H_{34}ClNO_5 \cdot H_2O$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1-[8-(3,4-dimethoxyphenyl)-8-oxooctyl]isoquinoline (25). A mixture of 99 g (0.21 mol) of **22**, 388 ml of dry PhH, and 137 ml of $POCl_3$ was refluxed for 2 hr with protection from moisture. After work-up as described above for **24**, the dried and charcoaled PhH extracts were evaporated to yield a brown oil (99 g) which was triturated under 1 l. of anhydrous Et_2O until solid. The resulting cream powder (74 g, 78% yield, mp 76–79°) was dissolved in 250 ml of PhH and placed on a column of 900 g of neutral Al_2O_3 (activity I). Elution with 1:1 PhH–$CHCl_3$ and evaporation left 62 g (65%) of solid: mp 79–80°. Recrystallization from 700 ml of PhH–cyclohexane (1:4) gave 51 g (54%) of **25**: mp 80–81°; ir 1675 (aromatic C=O), 1623 (C=N), and aromatic bands at 1597, 1587, 1570, and 1508

cm^{-1}. Anal. ($C_{27}H_{35}NO_5$) C, H, N.

Oxime 26. Solutions of 8.80 g (0.0214 mol) of **23** in 60 ml of EtOH, 3.51 g (0.0428 mol) of NaOAc in 24 ml of H_2O, and 2.97 g (0.0427 mol) of NH_2OH·HCl in 12 ml of H_2O were combined and refluxed for 15 hr. The EtOH was evaporated and the residue diluted with H_2O. The solution was washed with PhH (3 × 40 ml), made basic with concentrated NH_4OH, and extracted with $CHCl_3$ (2 × 50 ml). After washing (H_2O) and drying the combined extracts, the $CHCl_3$ was evaporated and the residue triturated under anhydrous Et_2O. The crude product (8.5 g, 93%, mp 165–169°) was recrystallized from 95% EtOH to give 7.4 g (81%) of pale yellow crystalline solid: mp 167–170°. Anal. ($C_{24}H_{30}N_2O_5$) C, H; N: calcd, 6.57; found, 7.13.

Oxime 27. Solutions of 55.0 g (0.11 mol) of **24**·HCl·H_2O in 300 ml of EtOH, 16.0 g (0.23 mol) of NH_2OH·HCl in 50 ml of H_2O, and 28.3 g (0.345 mol) of NaOAc in 50 ml of H_2O were combined and refluxed for 15 hr. The residue remaining after evaporation of the EtOH was dissolved in 2 l. of H_2O and made basic with 10 *N* NaOH. After extracting the oily product with $CHCl_3$ (2 × 600 ml), the combined extracts were washed with H_2O, dried, and evaporated to leave an orange oil which solidified on trituration with Et_2O. The crude product (44 g, 85%, mp 113–117°) was recrystallized from EtOH (Norite) to yield 37.5 g (75%) of **27**: mp 117–118°. Anal. ($C_{26}H_{34}N_2O_5$) C, H, N.

Oxime 28. By the procedure described for **27**, 47.5 g (0.105 mol) of **25** gave 39.0 g (79%) of **28**: mp 127–129° (EtOH). Anal. ($C_{27}H_{36}N_2O_5$) C, H, N.

1-[5-Amino-5-(3,4-dimethoxyphenyl)pentyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (29) Dihydrochloride. A solution of 9.37 g (0.022 mol) of **26** in 225 ml of glacial HOAc and 3.75 g of 10% Pd/C was hydrogenated (Parr apparatus, 50 psig) at room temperature until the absorption of H_2 ceased (ca. 18 hr). The catalyst was filtered, and the colorless filtrate evaporated to dryness after adding 10 ml of concentrated HCl. A solution of the residue in 70 ml of H_2O containing 10 ml of concentrated HCl was filtered from slight insolubles, made basic with 10 *N* NaOH, and extracted with PhH (3 × 75 ml). The combined extracts were washed with saturated NaCl, dried, and evaporated. Treatment of the residual oil with ethanolic HCl provided 9.5 g (89%) of a mixture of the diastereoisomeric dihydrochloride salts of **29** as a cream powder: mp 191–196°. Recrystallization was best effected (65% recovery) by dissolving the product in boiling EtOH (1g/25 ml) and boiling to one-third volume. Three such recrystallizations gave mp 210–212°; ir 2730–2480 (NH_3^+ and NH_2^+), 2040 (NH_3^+), 1618 and 1600 (NH_3^+, NH_2^+, and aromatic), and 1517 cm^{-1} (aromatic). Anal. ($C_{24}H_{36}Cl_2N_2O_4$) C, H, N.

1-[7-Amino-7-(3,4-dimethoxyphenyl)heptyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (30) Dihydrochloride. Hydrogenation of 17.5 g (0.0385 mol) of **27** in glacial HOAc with 7 g of 10% Pd/C was carried out as described for **29**. Since no solid separated on treatment of the oily free base with ethanolic HCl, the EtOH was evaporated and the residue triturated with EtOAc to give 19.5 g (ca. 98%) of an amorphous mixture of the diastereoisomeric dihydrochloride salts of **30**. Recrystallization from *i*-PrOH–Et_2O (Norite) yielded 9.0 g of an off-white solvate: mp 110–113°. Two additional recrystallizations as above and drying under high vacuum gave solvated product of the same melting point and ir: ir 3450 (solvate OH), 2650–2450 (NH_3^+ and NH_2^+), 2020 (NH_3^+), 1603 and 1585 (NH_3^+, NH_2^+, and aromatic), and 1513 cm^{-1} (aromatic). Anal. ($C_{26}H_{40}Cl_2N_2O_4$·1.5H_2O) C, H, N.

1-[8-Amino-8-(3,4-dimethoxyphenyl)octyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (31a,b) Dihydrochlorides. Hydrogenation of 37.0 g (0.079 mol) of **28** in glacial HOAc with 14.8 g of 10% Pd/C was carried out as described for **29**. An amorphous mixture (43 g, >100%) of the racemic dihydrochloride salts, **31a** and **31b**, was obtained by treating the free base with EtOH–HCl, evaporating, and triturating the residue with EtOAc. Separation was effected by digesting the crude mixture with 1.4 l. of boiling *i*-PrOH and filtering. The insoluble fraction (7 g) was recrystallized by dissolving in 150 ml of boiling EtOH (Norite) and concentrating to one-half volume. Cooling gave 5.5 g (ca. 13%) of white **31a**·2HCl: mp 232–233°. The melting point was unchanged after an additional recrystallization: ir 3520 (solvate OH), 2730–2470 (NH_3^+ and NH_2^+), 2030 (NH_3^+), 1616 and 1600 (NH_3^+, NH_2^+, and aromatic), and 1515 cm^{-1} (aromatic). Anal. ($C_{27}H_{42}Cl_2N_2O_4$·H_2O) C, H, N.

The filtrate containing the second racemate was concentrated to one-third volume and treated with Et_2O to the cloud point. The precipitate (12 g) was recrystallized twice from *i*-PrOH to give 10.5 g (ca. 25%) of white **31b**·2HCl: mp 112–115°. A sample for analysis was dried in vacuo (P_2O_5, 78°, 0.02 mm, 24 hr): mp 111–112°; ir 3415 (solvate OH), 2740–2475 (NH_3^+ and NH_2^+), 2060 (NH_3^+), 1618 and 1600 (NH_3^+, NH_2^+, and aromatic), and 1520 cm^{-1} (aromatic). Anal. ($C_{27}H_{42}Cl_2N_2O_4$·H_2O) H, N; C: calcd, 59.23; found, 59.63.

1,8-Bis(3,4-dimethoxyphenyl)-2,7-dinitro-1,7-octadiene (34). A solution of 24.9 g (0.150 mol) of 3,4-dimethoxybenzaldehyde (**32**), 13.2 g (0.075 mol) of 1,6-dinitrohexane (**33**), and 5.78 g (0.075 mol) of NH_4OAc in 20 ml of glacial HOAc was refluxed for 2 hr. After cooling, the precipitate was filtered and washed with a small amount of EtOH to give 8.5 g (24%) of a yellow powder, mp 184–185°, unchanged on recrystallization from glacial HOAc. Anal. ($C_{24}H_{28}N_2O_8$) C, H, N.

1,6-Bis[(3,4-dimethoxyphenyl)methyl]-1,6-hexanediamine (35). A suspension of 12.5 g (0.330 mol) of $LiAlH_4$ in 500 ml of dry THF was stirred and refluxed under N_2 for 4 days while 13.0 g (0.028 mol) of **34** was washed into the mixture using a Soxhlet extractor. After cooling and carefully decomposing the mixture with H_2O, the precipitate was filtered and washed with 250 ml of boiling THF. The combined filtrate and washings were dried and evaporated leaving a yellow oil which on treatment with ethereal HCl gave 7.5 g of an amorphous solid. When the latter was dissolved in 50 ml of *i*-PrOH and cooled, 3.0 g (22%) of crystalline product was obtained: mp 248–250°. Recrystallization from *i*-PrOH–EtOAc provided 2.5 g: mp 265–267°; ir 2780–2400 (NH_3^+), 2020 (NH_3^+), 1607 and 1590 (NH_3^+ and aromatic), and 1517 cm^{-1} (aromatic). Anal. ($C_{24}H_{38}Cl_2N_2O_4$) C, H, N.

1,6-Bis(3,4-dimethoxyphenyl)hexane (37). A suspension of 40.0 g (0.104 mol) of **36**[2b] and 4.0 g of 10% Pd/C in 250 ml of glacial HOAc was hydrogenated in a Parr apparatus (50 psig, room temperature, 2–3 hr). After evaporation of the HOAc, recrystallization (EtOH) of the residue gave 31.0 g (83%) of white solid: mp 77–78° (lit.[14] mp 76.5–77.5°); ir no C=O, aromatic bands at 1613, 1595, and 1517 cm^{-1}.

1,6-Bis(2-acetyl-4,5-dimethoxyphenyl)hexane (38). A stirred solution of 69.2 g (0.520 mol) of $AlCl_3$ in 800 ml of dry 1,1,2,2-tetrachloroethane was maintained at 0–3° while adding dropwise 37.6 g (0.48 mol) of AcCl (15 min) followed by a solution of 57.2 g (0.160 mol) of **37** in 250 ml of dry tetrachloroethane (2 hr). The thick mixture was stirred for 2 hr at 0–3°, stored in the refrigerator (2–4°) for 2 days, and then decomposed by pouring onto a mixture of 1.5 kg of ice and 200 ml of concentrated HCl. Sufficient $CHCl_3$ was added, if necessary, to give two clear layers, and the organic phase was separated, washed with H_2O and 10% K_2CO_3, and dried. Evaporation left an oil which was dissolved in 200 ml of anhydrous Et_2O and cooled at −30° to give 22.0 g (31%) of a white solid: mp 104–108°. Recrystallization (EtOH) yielded 18.0 g (25%) of colorless crystals: mp 112–114°; ir 1681 (C=O) and 1610, 1570, 1517 cm^{-1} (aromatic). Anal. ($C_{26}H_{34}O_6$) C, H.

The bis(oxime) derivative was prepared by refluxing a mixture of the bis(ketone) (0.1 mol) and NH_2OH·HCl (0.4 mol) in 100 ml of pyridine–EtOH (2:1 by volume) for 3 hr. Evaporation and trituration of the residue with H_2O gave a white solid which was recrystallized from *i*-PrOH to yield 3.0 g (64%) of crystals: mp 143–148°. Anal. ($C_{26}H_{36}N_2O_6$) H, N; C: calcd, 66.08; found, 65.64.

The bis(methoxime) derivative **39** [71% yield, mp 74–75° (EtOH)] was prepared from CH_3ONH_2·HCl in a similar manner and, without further characterization, reduced with diborane as described below.

α,α'-Dimethyl-2,2'-hexamethylenebis(4,5-dimethoxybenzenemethanamine) (40) Dihydrochloride. Under N_2, a stirred solution of 10.0 g (0.020 mol) of **39** (see above) in 100 ml of dry THF was treated dropwise during 1.5 hr at 0–2° with 120 ml of a commercial 1 *M* borane–THF solution. After stirring for 1 hr at 0–3° and then overnight at room temperature, the mixture was cooled and carefully decomposed with 30 ml of H_2O. Evaporation left a colorless glass which was refluxed for 1 hr with 200 ml of 10% KOH. The suspension was cooled and filtered, and the insoluble white solid was added in portions to 250 ml of

boiling 10% HCl (foaming). After refluxing for 1 hr, the solution was cooled, diluted with 100 ml of H_2O, and filtered hot. The oil which separated on addition of excess 10 *N* NaOH to the cold filtrate was extracted with PhH, and the combined extracts were washed with H_2O, dried, and evaporated. Treatment of the oily residue with ethanolic HCl gave, after 2 days, 9.0 g (87%) of crystalline product: mp 217–220°. Recrystallization from 95% EtOH–Et_2O provided 5.0 g (48%): mp 225–228°. Constant melting material was obtained by two additional recrystallizations: mp 234–235°; ir 2780–2550 (NH_3^+), 2100 (NH_3^+), 1613 and 1563 (NH_3^+ and aromatic), and 1517 cm^{-1} (aromatic). Anal. ($C_{26}H_{42}Cl_2N_2O_4$) C, H, N.

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Basic Derivatives of 6,7-Dihydroindolo[1,7-*ab*][1]benzazepine and 6*H*-Indolo[7,1-*cd*][1,5]benzoxazepine as Potential Antidepressant Agents

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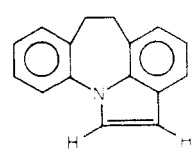
Basic derivatives of 6,7-dihydroindolo[1,7-*ab*][1]benzazepine and 6*H*-indolo[7,1-*cd*][1,5]benzoxazepine incorporating the imipramine basic side chain were synthesized and screened for antidepressant activity in mice. With few exceptions, the compounds unsubstituted at C-2 antagonized reserpine-induced ptosis and hypothermia showing negligible anticholinergic and antihistaminic properties. The compound 1-[2-(*N*-methyl-*N*-benzylamino)ethyl]-6,7-dihydroindolo[1,7-*ab*][1]benzazepine had the highest toxicity–activity ratio.

In studies of imipramine-like antidepressants, some compounds incorporating the main structural features of imipramine were investigated.[1] The imipramine basic side chain was also incorporated into 6,7-dihydroindolo[1,7-*ab*][1]benzazepine (I), but the resulting compounds all substituted at C-2 did not show imipramine-like activity in the usual pharmacological tests.[2] Continuing along this line, 3-methyl-1,2,3,4,8,9-hexahydropyrido[4',3':2,3]-indolo[1,7-*ab*][1]benzazepine (II) was also synthesized[3] and was claimed to have powerful antiserotonin activity but was devoid of antidepressant activity. It occurred to us that the alkyl substituents at C-2 could be responsible for the absence of activity, either by steric hindrance in drug–receptor interaction or by preventing the formation of some active metabolites. Therefore, novel N-substituted 1-(2-aminoethyl)-6,7-dihydroindolo[1,7-*ab*]-[1]benzazepines (Table IV, **28–31**), unsubstituted at C-2, were synthesized and evaluated for antidepressant activity. Since the initial pharmacological results were positive, we have synthesized several other compounds including some basic derivatives of 6*H*-indolo[7,1-*cd*][1,5]benzoxazepine



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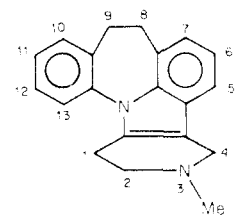

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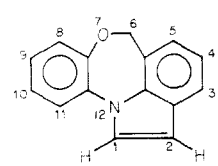

III

(III), in order to gain further insight into the structure–activity relationships.

Chemistry. The synthesis of all the compounds reported in Table IV begins with the preparation of **5–13** as