A Novel Synthesis of Aromatic Methoxy and Methylenedioxy Substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines

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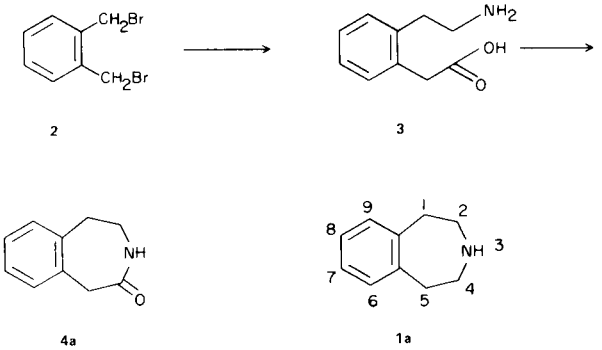
A new synthesis of aromatic methoxy and methylenedioxy substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines is described. Suitably substituted phenethylamines and their α-methyl homologs in the form of their *N*-acetyl derivatives are chloromethylated, the resulting benzyl chlorides are reacted with cyanide and hydrolysis of the latter yields 2-(2-aminoethyl)phenylacetic acid derivatives. Thermal cyclization yields the corresponding lactams. Hydride reduction of these lactams furnishes the substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines which may be methylated on nitrogen by formaldehyde and hydrogen. By this sequence a number of previously undescribed compounds have been prepared.

The 2,3,4,5-tetrahydro-1*H*-3-benzazepines (1), exemplified by structures **1a**, **b** occur as part of the basic skeleton of rheadan alkaloids (2) and simple benzazepines have been reported to exhibit a variety of interesting pharmacological properties (3,4). Since the reported methods, reviewed in Scheme I, for synthesizing aromatic substituted benzazepines are limited with respect to scope and efficiency, better synthetic procedures for preparing these substances are clearly desirable. We now report a new, versatile synthesis of oxygenated aromatic benzazepines.

Historically, the first synthesis of the unsubstituted benzazepine **1a** was reported by von Braun and Reich (5). In a lengthy sequence summarized below, **1a** was prepared from *o*-xylylene dibromide (**2**) *via* 2-(2-aminoethyl)-phenylacetic acid (**3**) and its lactam **4**.

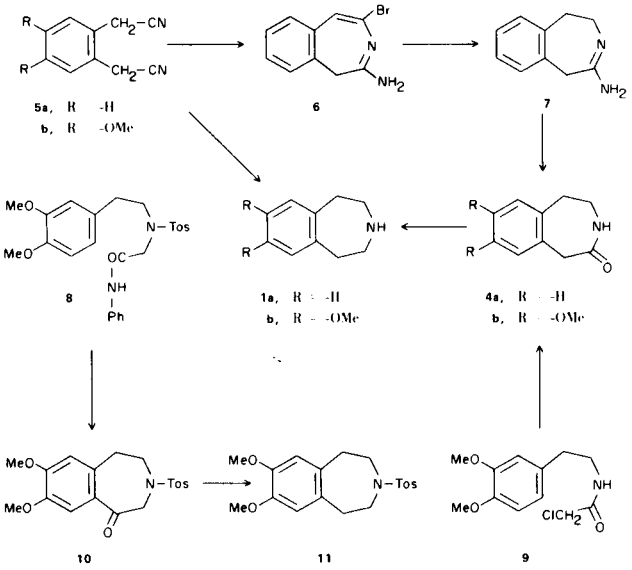


2 3 4a 1a

Subsequently, several other methods, summarized in Scheme I, have been reported for the synthesis of this ring system.

SCHEME I

(Tos = 4-$CH_3C_6H_4SO_2$-)



Most of these syntheses of **1a** or 7,8-dimethoxybenzazepine (**1b**) start with the dinitriles **5a**, **b** or the substituted phenethylamines **8** or **9**. Catalytic hydrogenation of **5a**, **b** yielded **1a** (6), **b** (7), directly. Reaction of **5a** with hydrogen bromide (8,9) led to **4a** *via* the intermediates **6** and **7**. Hydride reduction (10) of **4a** gave **1a**. Recently lactams of the type **4b** and **20a**, **e** (Scheme II) have been obtained by irradiation of *N*-(phenethyl)-2-chloroacetamides such as **9** with a high pressure mercury arc (**11a**, **b**).

The cyclization of derivatives of homoveratrylamine such as **8** has been described (12) and the resulting *N*-

tosylketone **10** was reduced to the tosyl amine **11**. However, clean elimination of the tosyl group has not been achieved.

We now report a new and facile synthesis of **1a, b** and related substituted benzazepines. This approach has greater flexibility than the previously reported methods and it can be extended to the preparation of homologous ring systems (13).

Our new synthesis starts with suitabily aromatic substituted (14) phenethylamines in the form of their acetyl derivatives **12** (Scheme II). These are chloromethylated with hydrochloric acid and formaldehyde to give the benzyl chlorides **13**. Reaction with cyanide, preferably in dimethylsulfoxide, yields the nitriles **14**. The latter afford eventually, *via* the esters **15** and the acids **16**, the amino acids **17** in the form of their zwitterions. The succeeding steps follow the pattern used in previous studies (15,16) to finally yield the benzazepines **1b**, **22a-d, e**. Thus the present work constitutes a refinement of the original von Braun-Reich (5) synthesis.

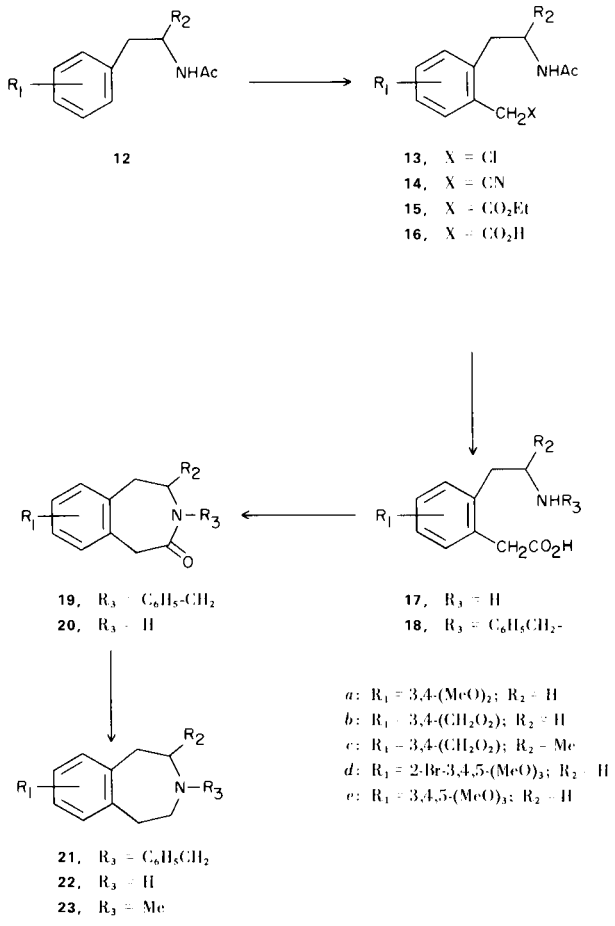
Reductive methylation of the secondary amines with formaldehyde yields the tertiary amines corresponding to the general formula **23**. As shown in Scheme II, the presence of an α-methyl group in the starting *N*-(phenethyl)acetamides **12c** does not effect the sequence and furnishes a benzazepine with a methyl (17) group in the hetero ring, a type of compound unavailable by the previously described procedures.

The lactone **20e** (11a,b) was obtained by the same procedures from *N*-(2-bromo-3,4,5-trimethoxyphenethyl)-acetamide (**12d**) *via* the sequence **13** → **14** → **15** → **16** → **17**. In this case, **17** was cyclized (18) directly to the bromolactone **20d**. Debromination with hydrogen and a palladium catalyst furnished the desired lactone **20e** identical with that described by Yonemitsu (11a,b,19). Subsequent reduction of **20e** with diborane gave the trimethoxybenzazepine **22e**.

To the reaction sequence shown in Scheme II, the following remarks may be added. In several instances the chloromethylated products formed stable hydrochlorides that were isolated and fully characterized by analyses and spectra. In other instances, the hydrogen chloride was not so firmly held and precise analyses were not obtained but the spectra and the derived products support the assigned structures. The preferred route to the amino acids **18** is *via* the acid catalyzed ethanolysis of the nitriles **15** to **16** and subsequent hydrolysis through **17** to **18**.

It has already been shown (15,16) that lactam formation from amino acids proceeds more readily with secondary than with primary amines. Accordingly, the amino acids **17** were converted to their benzyl derivatives prior to cyclization (18). Reduction of the lactams **19** was accomplished with lithium aluminum hydride or preferably diborane.

SCHEME II



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Ir spectra were determined on a Beckman IR-5 recording spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer (TMS) and are reported in ppm (δ). Vapor phase chromatography was performed with 4% polyethylene glycol (molecular weight 4000) monostearate on Chromosorb W columns, unless otherwise stated. The instruments used were either the Beckman GC2A with Thermotrac or the F & M-810, R 13N.

All compounds described herein were examined for homogeneity by thin layer chromatography on Silica G plates using a solution consisting of 90 parts of ethanol, 10 parts of ether, and 2 parts by volume of ammonium hydroxide for development, unless otherwise stated. The developed chromatograms were visualized under ultraviolet light or by means of the Dragendorff reagent.

N-(2-Chloromethyl-4,5-methylenedioxyphenethyl)acetamide (**13b**).

In a 100 ml. round-bottom flask provided with a stirrer, thermometer, gas inlet tube, and a condenser were placed 4.12 g. (0.02 mole) of *N*-(3,4-methylenedioxyphenethyl)acetamide (**12b**),

(20), 2.1 g. of 37% formaldehyde solution, and 50 ml. of ethylene chloride. The mixture was cooled to 3° and hydrogen chloride passed into the stirred mixture. After about 10 minutes, a precipitate appeared, and in another 5 minutes a thick paste of crystals had formed. At this point, another 2.1 g. of 37% formaldehyde was added, whereupon the mixture thinned out considerably. After another 25 minutes, practically all of the solid had dissolved, whereupon the reaction mixture was poured into ice water, the lower ethylene chloride layer was separated and washed three times with water, then dried. On filtration, approximately 0.5 g. of a solid separated. The clear ethylene chloride filtrate was freed of solvent in a rotary evaporator, leaving 4.1 g. of a crystalline solid. After recrystallization from acetone, the solid melted at 116.5-122°.

Recrystallization of this material from ethyl acetate gave crystals of m.p. 138-142° dec. that analyzed slightly low for chlorine. However, the molecular weight of the "base" (obtained from the mass spectrum) and the preparation of the derivatives **14b**-**18b** confirmed the assigned structure.

Anal. Calcd. for $C_{12}H_{14}ClNO_3$·HCl: C, 49.33; H, 5.17; N, 4.79; Cl, 24.27. Found: C, 49.52; H, 5.42; N, 4.69; Cl, 23.18. M.W. from low resolution mass spectrum: 255; Calcd. for $C_{12}H_{14}ClNO_3$:255.

N-(2-Cyanomethyl-4,5-methylenedioxyphenethyl)acetamide (**14b**).

From another chloromethylation experiment carried out as above, 4.7 g. of solid was obtained after evaporation of the ethylene chloride solution. It was dissolved in 10 ml. of DMSO and 1.32 g. (0.028 mole) of sodium cyanide was added to the stirred solution; within a few minutes, the temperature rose from 25 to 32°. After 1.5 hours at ambient temperature the mixture was poured into ice and water. The suspension was extracted with three 50-ml. portions of benzene. The benzene layers were washed 6 times with saturated brine, then with water, the solution was dried, and the solvent distilled in a rotary evaporator leaving 4.1 g. of a crystalline solid. Two recrystallizations from ethanol gave 3.46 g. of m.p. 153.5-155.5°; yield 70%.

The ir spectrum (chloroform) showed bands at 3450 (NH), 3025, 2910, 2255 (CN), 1690 (CONH), 1510 and 1500 cm^{-1}. The nmr spectrum (DMSO-d_6) showed: δ = 1.83 (3H, s, CH_3CO), (4H, s, CH_2CH_2), 3.92 (2H, m, CH_2CN), 6.00 (2H, s, OCH_2O) and 6.83 (J = 0.8 2H, d, CH-3, CH-6).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.56; H, 5.96; N, 10.89.

Ethyl Ester of 6-(2-Acetamidoethyl)-3,4-methylenedioxyphenylacetic Acid (21) (**15b**).

The above cyanomethyl compound **14b**, 2.58 g. (0.0104 mole), was dissolved in 30 ml. of ethanol saturated with hydrogen chloride. After 6 hours at 25°, the mixture was poured into ice and water. The ester was collected by extraction with three 25-ml. portions of benzene, the benzene extracts washed successively with water, saturated bicarbonate solution, water then dried. Distillation of the solvent gave a mass of long prismatic needles which were recrystallized from a mixture of ethanol and petroleum ether (b.p. 60-90°), m.p. 123-125°.

The ir spectrum (potassium bromide) showed bands at 3300 (NH), 3100 (aromatic), 2995, 2900, 1720, and 1600 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.20; H, 6.52; N, 4.80.

6-(2-Acetamidoethyl)-3,4-methylenedioxyphenylacetic Acid (22) (**16b**).

A small sample of the above ester was warmed on a steam bath in alcoholic solution with excess sodium hydroxide. The solution was brought to *p*H 9, a flocculent precipitate was removed by filtration, and the clear filtrate acidified to *p*H 3. After standing overnight, clusters of crystals had separated. The crystals were recovered by filtration, washed with a little cold water, then recrystallized from a minimum of hot water, m.p. 188-190.5°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.91; H, 5.60; N, 5.20.

6-(2-Aminoethyl)-3,4-methylenedioxyphenylacetic Acid Hydrochloride (23) (**17b**·HCl).

One g. of acetamido derivative **16b** was refluxed with 20 ml. of 4 *N* hydrochloric acid for 10 hours. The excess acid was removed on a rotary evaporator leaving a solid residue which was recrystallized from a mixture of 2-propanol and ethyl acetate. The white crystals of the amino acid hydrochloride thus obtained melted at 210-212°.

Anal. Calcd. for $C_{11}H_{13}NO_4$·HCl: C, 50.88; H, 5.43; N, 5.39; Cl, 13.65. Found: C, 50.88; H, 5.49; N, 5.07; Cl, 13.69.

6-(2-Benzylaminoethyl)-3,4-methylenedioxyphenylacetic Acid (24) (**18b**).

To a solution of 26 g. (0.1 mole) of **17b** hydrochloride in 80 ml. of water, was added 8.4 g. (0.21 mole) of sodium hydroxide in 42 ml. of water, followed by 11.7 g. (0.11 mole) of benzaldehyde. The initially turbid mixture cleared on swirling. After 1 hour, the mixture was evaporated to a thick syrup on a rotary evaporator, the syrup dissolved in 75 ml. of ethanol, and the evaporation to syrup repeated. The residue was dissolved in 500 ml. of ethanol and 6.5 g. (0.17 mole) of sodium borohydride was added in several portions. After stirring for 1.5 hours, the solvent was removed on a rotary evaporator, leaving a grayish solid. This residue was dissolved in 200 ml. of water and 10% hydrochloric acid added to *p*H 7. The precipitate which formed was collected by filtration, washed with water, and dried; yield 24.7 g., m.p. 217-218° dec. By concentrating the filtrate and chilling, another 1.4 g. of solid, m.p. 205-207° was obtained; total yield 26.1 g. or 84%.

A sample of this product was recrystallized from aqueous ethanol and obtained as shiny white crystals, m.p. 218.5-219° dec.

The ir spectrum (potassium bromide) showed bands at 2300-2050 (salt bands), 1625, 1535 cm^{-1}. The nmr spectrum (TFA): δ = 3.23-3.52 (4H, m, CH_2CH_2), 3.80 (2H, s, CH_2CO), 5.70 (2H, s, CH_2N), 5.97 (2H, s, OCH_2O), 6.76 (2H, CH-2, CH-5, J = 0.5) and 7.45 (5H, s, aromatic).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.12; H, 6.11; N, 4.49.

3-Benzyl-7,8-methylenedioxy-1,3,4,5-tetrahydro-2*H*-3-benzazepine-2-one (25) (**19b**).

Compound **18b** (24.7 g.) was refluxed with 500 ml. of xylene under a Dean-Stark trap for 7 hours. During this period, water was steadily collected and the solid gradually dissolved. The clear solution was distilled in a rotary evaporator leaving a crystalline residue, m.p. 141-142°. This was recrystallized from 2-propanol and 20.0 g. (89%) of slightly off-white crystals were obtained, m.p. 141-142°. Recrystallization of a sample gave dense white rhombs of m.p. 141-142°.

The ir spectrum (chloroform) showed bands at 3000 and 2915, 1650, 1505, and 1493 cm^{-1}. The nmr spectrum (deuteriochloroform) showed δ = 2.67-3.58 (4H, m, CH_2CH_2); 3.83 (2H, s, CH_2CO), 4.60 (2H, s, aryl-CH_2-N), 5.87 (2H, s, OCH_2O), 6.55 (2H, d, CH-6, CH-9, J = 0.6), and 7.25 (5H, s, aromatic).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.50; H, 6.13; N, 4.55.

3-Benzyl-7,8-methylenedioxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (26) (**21b**).

Compound **19b** (14.8 g., 0.05 mole) was dissolved in 150 ml. of tetrahydrofuran under nitrogen, and to the stirred solution 150 ml. of 1 *M* diborane in tetrahydrofuran was added at 0-5° over a period of 30 minutes. The mixture was then refluxed for 2 hours, cooled in an ice bath, and 150 ml. of 1 *N* hydrochloric acid cautiously added. (The first few ml. of acid react with considerable vigor). After all the acid had been added, the tetrahydrofuran was distilled with simultaneous replacement by water until the vapor temperature reached 100°. The solution was cooled, made strongly alkaline with sodium hydroxide, and the resulting suspension was extracted once with 100 ml. of benzene and then twice with 200-ml. portions of benzene. The combined benzene extracts were dried over anhydrous potassium carbonate and the solvent distilled in a rotary evaporator leaving a yellow oil that rapidly crystallized. One g. of these crystals was recrystallized from 10-12 ml. of ethanol yielding 0.54 g. of long prismatic needles, m.p. 98-100°.

The nmr spectrum (deuteriochloroform) showed δ = 2.68 (8H, m, $4CH_2$), 3.58 (2H, s, CH_2N), 5.82 (2H, s, CH_2O_2), 6.53 (2H, s, CH-6 and CH-9), and 7.27 (5H, m, C_6H_5).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.54; H, 6.81; N, 4.92.

The hydrochloride **21b**·HCl was prepared by dissolving the above remaining solid in warm ethanol and acidifying to *p*H 4 with dilute ethanolic hydrochloric acid. After distilling the solvent in a rotary evaporator and repeating the distillation after the addition of 2-propanol a crystalline residue was obtained. This was recrystallized from 2-propanol containing a little water; there was obtained 11.8 g. of white crystals, m.p. 242-244° dec.

Anal. Calcd. for $C_{18}H_{19}NO_2 \cdot HCl$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.97; H, 6.07; N, 4.39.

7,8-Methylenedioxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (27) (**22b**·HCl).

Ten g. (0.0315 mole) of **21b**·HCl was dissolved in 220 ml. of acetic acid and the solution shaken under 40 lbs. of hydrogen pressure in the presence of 1 g. of 10% Pd/C catalyst at 45-50°. Hydrogen uptake ceased after 3.5 hours. The catalyst was removed by filtration and the solvent distilled from the filtrate in a rotary evaporator. The crystalline residue was digested in boiling 2-propanol for 30 minutes, filtered and dried; yield 6.85 g. of m.p. 287-287.5° dec.

The nmr spectrum (DMSO-d_6) showed δ = 3.13 (8H, m, $4CH_2$), 6.01 (2H, s, CH_2O_2), 6.16 (2H, s, CH-6 and CH-9), and a very broad diffuse band from 8.3-10 (2H, $\overset{+}{N}H_2$).

Anal. Calcd. for $C_{11}H_{13}NO_2 \cdot HCl$: C, 58.02; H, 6.20; N, 6.15; Cl, 15.57. Found: C, 58.22; H, 6.05; N, 5.89; Cl, 15.49.

Free Base (**22b**).

A sample of the hydrochloride was dissolved in water and the free base liberated by the addition of concentrated ammonium hydroxide. The cloudy emulsion soon deposited crystals that were recovered by filtration, washed with water, and dried. After recrystallization from 60-90° petroleum ether, the base melted at 82-84°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.30; H, 6.83; N, 7.56.

3-Methyl-7,8-methylenedioxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (28) (**23b**·HCl).

To 19.1 g. (0.1 mole) of the base (**22b**) in 100 ml. of methanol was added 12 ml. of 37% formaldehyde (0.15 mole) and 5 g. of methanol-washed Raney nickel. The suspension was shaken under 50 lbs. of hydrogen pressure for about 1 hour after which hydrogen uptake ceased. The catalyst was removed by filtration and the solvent distilled in a rotary evaporator. The residual oil was dissolved in 100 ml. of benzene, the solution washed four times with water to remove excess formaldehyde, dried, and the solvent distilled leaving 20.55 g. of colorless oil. This oil was distilled from a small Claisen flask, and the fraction boiling at 166-167°/13 mm. 15.2 g., was taken as the pure product.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.25; H, 7.42; N, 6.85.

The hydrochloride was prepared in the usual way and after recrystallization from 2-propanol it melted at 277° dec.

The nmr spectrum (deuterium oxide) showed δ = 3.10 (3H, s, CH_3-N), 2.9-4.0 (8H, broad s, 4 CH_2), 6.05 (2H, s, CH_2O_2), and 6.85 (2H, s, CH-6 and CH-9).

Anal. Calcd. for $C_{12}H_{15}NO_2 \cdot HCl$: C, 59.63; H, 6.67; Cl, 14.67. Found: C, 60.25; H, 6.80; Cl, 14.96.

Rac. *N*-(6-Chloromethyl-α-methyl-3,4-methylenedioxyphenethyl)-acetamide (**13c**).

A mixture of 2.21 g. (0.01 mole) of *N*-(α-methyl-3,4-methylenedioxyphenethyl)acetamide (29) (**12c**), 6.1 (0.075 mole) of 37% formaldehyde and 20 ml. of ethylene chloride was stirred at 0-3° while a stream of hydrogen chloride was introduced. After 25 minutes, the flask was filled with a mass of white crystals which were recovered by filtration and washed with ethylene chloride. The solid was slurried with several portions of hot acetone to give 2.0 g. of white *amide hydrochloride,* m.p. 163.5-164.5°. The ir spectrum (potassium bromide) showed bands at 3250, 3130, 3050-2550, 2410, 1699, 1560, and 1500 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 1.08 (3H, d, CH_3-CH); 1.85 (3H, s, CH_3-CO), 2.58-2.88 (2H, m, CH_2-), 3.94 (1H, m, -CH), 4.93 (2H, s, CH_2-Cl), 6.00 (2H, s, O-CH_2-O), and 6.95 (2H, s, CH-2, CH-5) and 9.0-9.1 (2H, broad, NH_2+).

Anal. Calcd. for $C_{13}H_{16}ClNO_3 \cdot HCl$: C, 50.99; H, 5.60; N, 4.58; Cl, 23.16. Found: C, 51.29; H, 5.79; N, 4.65; Cl, 22.53.

Alternately the crystalline mass obtained by filtration of the chloromethylation mixture was resuspended in ethylene chloride and sufficient sodium bicarbonate solution added to neutralize the acidity; two homogeneous phases resulted. The organic layer was washed with water, dried, and the solvent was distilled. The resulting solid residue was recrystallized from 2-propanol to yield a crystalline solid, the hydrochloric acid-free amide, *i.e.,* the "free base," m.p. 132-133°.

The ir spectrum (potassium bromide) of the "free base" showed bands at 3315, 3095, 2980, 2910, 1630, 1560, and 1500 cm^{-1}. The nmr spectrum (DMSO-d_6) showed δ = 1.13 (3H, d, CH_3-CH), 1.92 (3H, s, $CH_3\overset{O}{\overset{\|}{C}}$), 2.33-2.81 (2H, m, CH_2-CH), 4.15 (1H, m, -CH), 4.67 (2H, s, CH_2Cl), 5.93 (2H, s, OCH_2O), 6.73 (2H, d, CH-2, CH-5, J = 0.3).

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; N, 5.91. Found: C, 57.76; H, 6.24; N, 4.91.

Rac. *N*-(6-Cyanomethyl-α-methyl-3,4-methylenedioxyphenethyl)-acetamide (**14c**).

Amide hydrochloride **13c** (26.5 g., 0.087 mole) was added to 265 ml. of DMSO containing 25.6 g. (0.52 mole) of sodium

cyanide. The temperature of the stirred mixture rose from 24 to 40°, where it was maintained for 3 hours. The suspension was poured into 1.5 l. of ice water and the resulting mixture extracted with three 500-ml. portions of chloroform. The combined extracts were washed with saturated brine, water, then dried (magnesium sulfate), and distilled on a rotary evaporator, leaving 20 g. of a solid. This solid was first slurried in a 1:1 mixture of ethyl acetate and petroleum ether (b.p. 60-90°) and then recrystallized from 200 ml. of toluene to give 15.5 g. of crystalline nitrile, m.p. 134-135.5°.

The ir spectrum (chloroform) showed bands at 3490, (NH), 3000, 2880, 2755, 2250, (CN), 1670 (amide), and 1510.

The nmr spectrum (deuteriochloroform) showed δ = 1.12 (3H, d, CH_3); 1.92 (3H, s, CH_3CO), 2.80 (2H, m, CH_2-CH), 3.82 (2H, s, CH_2-CN), 4.16 (1H, m, -CH), 5.92 (2H, O-CH_2-O), and 6.75 (2H, s, CH-2, CH-5).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.67; H, 6.17; N, 10.93.

Rac. 2-[6-(2-Acetamidopropyl)-3,4-methylenedioxyphenyl]acetic Acid (**16c**).

A mixture of 202 ml. of ethanol saturated with hydrogen chloride and 20.2 g. (0.078 mole) of the nitrile **14c** was stirred at room temperature for 1 hour then refluxed for 4.5 hours. The ammonium chloride was removed by filtration and the solvent distilled from the filtrate in a rotary evaporator. The syrupy yellow residue was then refluxed with a solution of 18.8 g. (0.408 mole) of sodium hydroxide in 468 ml. of 50% aqueous ethanol for 48 hours. After distilling the bulk of the ethanol, the residual solution was acidified to *p*H 3, whereupon the crystalline acid separated. The solid was collected by filtration, washed and dried; yield 10 g., m.p. 195-197°. Recrystallization from aqueous ethanol gave crystals of m.p. 197-198°.

The ir spectrum (potassium bromide) showed bands at 3350, 3250, 2900-3000, 2755, 2250-2650 (broad and diffuse), 1990 (broad), 1700, 1620, 1600, 1510, and 1500 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 1.00 (3H, d, CH_3), 1.77 (3H, s, CH_3-CO), 2.25-2.94 (2H, m, CH_2-CH), 3.60 (2H, s, CH_2-aryl) 3.84 (1H, m, -CH), 5.95 (2H, s, O-CH_2O), 6.88 (2H, s, CH-2, CH-5), 7.74 (1H, broad, NH), and at about 12.0 (1H, broad, diffuse, CO_2H). Evidently complete ester hydrolysis occurred but only partial deacetylation took place.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.44; H, 6.16; N, 4.98.

The hydrolytic mother liquor also contained the deacetylated amino acid, **17c** which precipitated when the *p*H of the filtrate was adjusted to 7 and the solution chilled. However, a satisfactory analytical sample of this amino acid was not obtained.

Rac. 4-Methyl-7,8-methylenedioxy-1,3,4,5-tetrahydro-2*H*-3-benzazepine-2-one (30) (**20c**).

The aforementioned crude amino acid **16c** together with the residue that remained on complete evaporation of the mother liquor described in the preceeding paragraph was refluxed in 450 ml. of tetralin under a Dean-Stark trap for 45 minutes and the hot solution filtered from insoluble material. On cooling, the filtrate deposited crystals and an equal volume of petroleum ether (b.p. 30-60°) was added to complete the crystallization. Filtration gave a creamy white crystalline product which was washed with petroleum ether and dried; yield 5.0 g., m.p. 177-178°. Recrystallization from ethyl acetate gave white cottony needles, m.p. 175-175.5°.

The ir spectrum (potassium bromide) showed bands at 3210 (sh, at 3300), 3100, 2900-2975, 1695, 1510, and 1495 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 1.15 (3H, s, CH_3), 2.94 (2H, d, CH_2-CH), 3.5-4.0 (3H, m, -CH and CH_2), 5.97 (2H, s, OCH_2O), 6.74 (2H, s, CH-6, CH-9), and 7.3 (1H, broad, NH).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.89; H, 6.01; N, 6.41.

Rac. 2-Methyl-7,8-methylenedioxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (31) Hydrochloride (**22c**·HCl).

The lactam **20c** (4.4 g., 0.02 mole) in 60 ml. of tetrahydrofuran was treated with 60 ml. of 1 *M* diborane in tetrahydrofuran at 0°. The solid dissolved and the solution was refluxed for 3 hours after which 100 ml. of 3 *N* hydrochloric acid was added cautiously and the solution heated on a steam bath until the tetrahydrofuran had been distilled out. The cooled solution was extracted with two 50-ml. portions of chloroform to remove unreacted lactam, the aqueous layer then made alkaline, and the base was extracted with three 50-ml. portions of 1:1 benzene-ether. The extract was washed with water, dried (potassium carbonate), and the solvent was distilled, leaving 3.0 g. of a very pale amber oil. This was dissolved in a mixture of 2-propanol-ether and an excess of ethereal hydrogen chloride added. The resulting creamy white solid was collected, washed and dried; yield 3.1 g., m.p. 266-268° dec. Upon recrystallization from water, 1.8 g. of the crystalline hydrochloride was obtained, m.p. 271.5-272.5° dec.

The ir spectrum (potassium bromide) showed a weak band at 3190, further bands near 2975, a broad complex from 2475 to 2850, 1600, and 1500 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 1.28 (3H, s, CH_3), 2.55-3.45 (7H, m, N-CH-CH_2- and -CH_2-CH_2-N), 5.94 (2H, s, OCH_2O), and 6.77 (2H, s, CH-6, CH-9). The low resolution mass spectrum showed a peak at 205 corresponding to the molecular ion of the free base.

Anal. Calcd. for $C_{12}H_{15}NO_2$·HCl: C, 59.63; H, 6.67; N, 5.80; Cl, 14.67. Found: C, 59.56; H, 6.71; N, 5.50; Cl, 14.56.

N-(2-Chloromethyl-4,5-dimethoxyphenethyl)acetamide (**13a**).

Forty-four and six-tenths g. (0.2 mole) of **12a**, 124 ml. of 37% formaldehyde, and 400 ml. of chloroform were mixed and cooled to -15°. Hydrogen chloride was passed into the stirred suspension at -15°. As the mixture neared saturation with hydrogen chloride, crystals began to form and suddenly, after about 1.7 hours, the reaction vessel was filled with a mass of crystals. The crystals were transferred to a sintered glass funnel and as much liquid as possible removed by suction; the filter cake was washed twice with chloroform and then transferred to a vacuum dessicator, (20 mm., calcium chloride and sodium hydroxide flakes) where it was brought to constant weight, 50 g., m.p. 139-143°.

A sample was recrystallized from ethyl acetate and obtained as clusters of sword-shaped crystals, m.p. 151-153° dec. with evolution of hydrogen chloride. This substance is the hydrochloride of **13a**.

The ir spectrum showed two weak bands at 3250, 3125, a strong band at 2925-3000, a broad salt band from 2625 to 2000, and others at 1680, 1605, and 1520 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 1.87 (3H, s, CH_3CO), 2.6 to 3.2 (4H, m, CH_2-CH_2), 3.75, 3.77 (6H, d, 2 CH_3O), 4.77 (2H, s, CH_2Cl), and 6.92 (2H, d, CH-3, CH-6, J = 0.3).

Anal. Calcd. for $C_{13}H_{18}NO_3$·HCl: C, 50.66; H, 6.21; N, 4.55; Cl, 23.00. Found: C, 50.66; H, 6.10; N, 4.47; Cl, 22.71.

N-(2-Cyanomethyl-4,5-dimethoxyphenethyl)acetamide (**14a**).

Fifty g. of **13a** hydrochloride, was added to a stirred suspension

of 20 g. of sodium cyanide in 500 ml. of DMSO. The temperature of the stirred mixture spontaneously rose to 44° during the course of 30 minutes and then fell. After 1 hour the mixture was poured into 1.5 l. of ice water and extracted with five 200-ml. portions of chloroform. The chloroform extracts were washed four times with saturated brine, dried (magnesium sulfate), and finally distilled in a rotary evaporator, leaving 49 g. of a cream-colored solid, m.p. 134-136°. Recrystallization of this solid from ethyl acetate gave 27.9 g. of the crystalline nitrile, m.p. 138-140°. Two g. of a second crop, m.p. 136-137°, was obtained from the filtrate.

The ir spectrum (chloroform) showed bands at 3450, 3025, 2950, 2250 (CN), 1680, 1605, 1515, and 1500 cm^{-1}.

The nmr spectrum (deuteriochloroform) showed δ = 1.95 (3H, s, CH_3CO), 2.75 (2H, t, CH_2 aryl), 3.38 (2H, t, CH_2N), 3.85 (6H, s, 2 CH_3O), 6.06 (1H, broad, NH), and 6.77 (2H, s, CH-3, CH-6).

In the mass spectrum, the molecular ion was observed at 262.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.91; N, 10.68. Found: C, 64.32; H, 7.03; N, 10.40.

2-[2-(2-Aminoethyl)-4,5-dimethoxyphenyl]acetic Acid (**17a**).

Ten g. of nitrile **14a** was stirred for 1 hour with 150 ml. of ethanol saturated with hydrogen chloride, then refluxed for 4 hours. When cool, the ammonium chloride was removed by filtration and the solvents distilled from the filtrate leaving 11.7 g. of a pale amber oil. The oil was not characterized, but was refluxed with 8.64 g. of sodium hydroxide and 180 ml. of 50% aqueous ethanol for 48 hours. This solution was evaporated to dryness in a rotary evaporator, then dissolved in 50 ml. of water and the resulting solution passed over a column of 290 ml. of DOWEX®-50 (H form; 100-200 mesh) which retained the amino acid. After washing the column free of salts with approximately 1 l. of water, the amino acid was eluted with 1.25 l. of a 10% pyridine solution. Distillation of the pyridine-water eluate in a rotary evaporator yielded 7.46 g. of crystalline solid. One g. of this solid was recrystallized from 5 ml. of water (32). The buff plates that separated melted at 221-223° dec.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.32; H, 7.06; N, 5.81.

2-[2-(2-Benzylaminoethyl)-4,5-dimethoxyphenyl]acetic Acid (**18a**).

Ten g. of the nitrile **14a** was esterified and hydrolyzed as described above. Following distillation of the alcohol, the residual solid was dissolved in 50 ml. of water and the *p*H adjusted to 7.0. To this solution, 1.6 g. (0.04 mole) of sodium hydroxide in 8 ml. of water was added, followed by 4.24 g. (0.04 mole) of benzaldehyde. After stirring for 15 minutes, the solution was distilled to a semi-solid in the rotary evaporator. 2-Propanol (50 ml.) was added to the residue and the process repeated. The residue was dissolved in 200 ml. of methanol, 2.3 g. (0.060 mole) of sodium borohydride was added in several portions, then the mixture stirred for 30 minutes. The methanol was distilled in a rotary evaporator, 60 ml. of water added to the residue and the *p*H was adjusted to 7.0 by the addition of 10% hydrochloric acid. After chilling in ice for 30 minutes, the white precipitate that had formed was collected. It weighed 8.0 g., m.p. 208-210°. Recrystallization from aqueous ethanol gave 4.1 g. of the benzylamino acid, m.p. 213-213.5°.

The ir spectrum (potassium bromide) showed bands at 3450, 3050, 2950-2975, a broad diffuse complex at 2050-2950, 1720, and 1540 cm^{-1}.

The nmr spectrum (TFA) showed δ = 3.17-3.67 (2H, m, CH_2-N), 3.88 (2H, s, CH_2-CO_2H), 3.90 and 3.95 (6H, d, 2 CH_3O), 4.43 (2H, t, CH_2-aryl), 6.89 (2H, d, CH-3, CH-6), and 7.47 (5H, m, phenyl).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.03; H, 6.89; N, 4.11.

3-Benzyl-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepine-2-one (**19a**).

A stirred suspension of 4.1 g. of **18a** was refluxed in 75 ml. of xylene under a Dean-Stark trap for 24 hours, at the end of which time a clear solution had resulted. Distillation of the xylene *in vacuo* left 4.0 g. of shining white plates, m.p. 141-142°. A sample recrystallized from toluene melted at 141-142°.

The ir spectrum of this product (potassium bromide) showed bands at 3050, 2925-2975, 2840, 1650, 1605, 1530, and 1495 cm^{-1}.

The nmr spectrum (DMSO-d_6) showed δ = 2.89 (2H, t, CH_2-1), 3.70 (4H, s, CH_2-4 and CH_2-5), 3.73, 3.77 (6H, d, 2 CH_3O), 3.89 (2H, s, CH_2CO), 4.58 (2H, s, N-CH_2-aryl), 6.72 (2H, s, CH-6 and CH-9), 7.32 (5H, s, phenyl).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.50; H, 6.85; N, 4.69.

3-Benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**21a**).

Three and eleven hundreths g. (0.01 mole) of **19a** was reduced with 20 ml. of a 1 *M* solution of diborane in THF, as described for **19c**. The yield of **21a**, m.p. 69-71° after recrystallization from aqueous ethanol, was practically quantitative.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 76.73; H, 7,80; N, 4.71. Found: C, 77.00; H, 7.99; N, 4.62.

The Hydrochloride (**21a**·HCl).

The above base was converted to the hydrochloride as described for **21c**. After repeated recrystallization from 2-propanol containing a little water the m.p. was 228-229.5° dec.; however, the carbon analyses were consistently low as shown by the average of four determinations.

Anal. Calcd. for $C_{19}H_{23}NO_2$·HCl: C, 68.36; H, 7.25; N, 4.20; Cl, 10.62. Found: C, 67.40; H, 7.43; N, 4.09; Cl, 10.50.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (**22a**·HCl).

This compound was obtained by catalytic debenzylation of **21a**·HCl. The salt was recrystallized from 2-propanol, m.p. 242-242.5° dec. (Lit. (7) 243-245° dec.).

7,8-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (**23a**·HCl).

Methylation of base **22a** was carried out on 4.5 g. (0.022 mole) as described for **23c**. The crude base was treated with ethereal hydrogen chloride and the resulting salt recrystallized twice from 2-propanol, m.p. 262-263° dec. (Lit. (7,33) 359-361° dec.).

The nmr spectrum (DMSO-d_6): δ = 2.76 (3H, s, CH_3N), 3.22 (8H, broad s, 4 CH_2), 3.75 (6H, s, 2 CH_3O), 6.88 (2H, s, CH-6 and CH-9), and 11.9 (1H, broad diffuse s, $\overset{+}{N}H$).

Anal. Calcd. for $C_{13}H_{19}NO_2$·HCl: C, 60.58; H, 7.82; Cl, 13.75. Found: C, 60.38; H, 8.00; Cl, 13.78.

N-(2-Bromo-3,4,5-trimethoxyphenethyl)acetamide (**12d**).

Fifty g. (0.2 mole) of 3,4,5-trimethoxyphenethylamine hydrochloride was dissolved in 250 ml. of water and to the stirred solution, 29.1 g. (0.182 mole) of bromine in 200 ml. of acetic acid was added over a period of 2.5 hours while maintaining the temperature below 5°. After standing overnight at 23°, the mixture was poured into 500 ml. of water and made alkaline (*p*H 10)

with 30% sodium hydroxide. The dark oil that separated was collected by 3 extractions with 200-ml. portions of benzene, the combined extracts were dried over anhydrous potassium carbonate and the dried solution distilled in a rotary evaporator leaving 57 g. of a dark oil that was distilled at reduced pressure (simple Claisen apparatus). A colorless oil, 9 g. was collected up to 130.5°/0.2 mm. and the 2-bromo-3,4,5-trimethoxyphenethylamine distilled at 130.5-134°/0.2 mm., yield 34.5 g. (59%).

Anal. Calcd. for $C_{11}H_{16}BrNO_3$: Br, 27.54. Found: Br, 26.29.

The above base, 34.3 g., (0.12 mole) was refluxed with 25 g. of acetic anhydride in 200 ml. of toluene for 2 hours after which the toluene, acetic acid, and anhydride were distilled in a rotary evaporator. The residual oil that solidified was dissolved in a hot mixture of 200 ml. of ethyl acetate and 300 ml. of 60-90° petroleum ether. On cooling a dense crystalline solid separated; yield 31.7 g., m.p. 87-88.5°.

The nmr spectrum (deuteriochloroform) δ = 1.97 (3H, s, CH_3CO), 2.95 (2H, t, CH_2-aryl), 3.50 (2H, t, CH_2N), 3.83, 3.85, 3.87 (9H, 3s, 3 CH_3O), 6.02 (1H, s, NH), and 6.63 (1H, s, CH-6). A peak at 6.42 indicated the presence of approximately 10% of some impurity, probably unbrominated starting material.

Anal. Calcd. for $C_{13}H_{18}BrNO_4$: C, 47.28; H, 5.56; N, 4.16; Br, 23.97. Found: C, 47.00; H, 5.46; N, 4.22; Br, 24.05.

N-(2-Bromo-6-chloromethyl-3,4,5-trimethoxyphenethyl)acetamide (**13d**).

Compound **12d** was dissolved in 100 ml. of chloroform. Twenty ml. of concentrated hydrochloric acid and 6.75 g. (0.225 mole) of paraformaldehyde were added and a slow stream of hydrogen chloride was passed into the vigorously stirred mixture (creased flask) at 0° for 8 hours, then allowed to stand overnight at 0°. The mixture was diluted with 300 ml. of ice water, the chloroform layer removed, and the aqueous layer was extracted with two 100-ml. portions of chloroform. After washing the combined chloroform extract once with cold water, it was dried and the chloroform was distilled in a rotary evaporator leaving 12.7 g. of a white solid. This solid was broken up, washed with five 100-ml. portions of 60-90° petroleum ether, and dried; yield 10.8 g., m.p. 138-145°. After one recrystallization from ethyl acetate, the m.p. was 145-147°. Another recrystallization from ethyl acetate raised the m.p. to 150-152.5°.

Anal. Calcd. for $C_{14}H_{19}BrClNO_4$: C, 44.17; H, 5.03; N, 3.68; Br, 20.99; Cl, 9.31. Found: C, 44.39; H, 5.09; N, 3.63; Br, 20.90; Cl, 9.27.

N-(2-Bromo-6-cyanomethyl-3,4,5-trimethoxyphenethyl)acetamide (**14d**).

This compound was prepared in the same manner as described for other nitriles. Despite repeated recrystallization a satisfactory analysis could not be obtained for this substance. A typical analysis follows:

Anal. Calcd. for $C_{15}H_{19}BrN_2O_4$: C, 48.53; N, 5.16; N, 7.54; Br, 21.53. Found: C, 51.56; H, 5.38; N, 7.33; Br, 19.50.

Ethyl Ester of 2-(2-Acetamidoethyl-3-bromo-4,5,6-trimethoxyphenyl)acetic Acid (**15d**).

Three and fifty-five hundredth g. (0.00957 mole) of **14d** was converted to the ester as described for **15b** yielding 3.55 g. of crude product. A sample of this material was recrystallized twice from ether and obtained as prismatic needles of m.p. 118-122°.

Anal. Calcd. for $C_{17}H_{24}BrNO_6$: C, 48.82; H, 5.78; N, 3.34; Br, 19.10. Found: C, 49.13; H, 5.81; N, 3.32; Br, 18.96.

2-(2-Aminoethyl-3-bromo-4,5,6-trimethoxyphenyl)acetic Acid (**17d**).

The crude ethyl ester, **15d**, was refluxed with 1.2 g. of sodium hydroxide in 12 ml. of water and 12 ml. of ethanol for 5.5 hours. The pale amber solution was extracted with three 20-ml. portions of chloroform, then distilled in a rotary evaporator to remove ethanol. The *p*H of the remaining aqueous solution was adjusted to 7.0 with hydrochloric acid whereupon a copious off-white precipitate formed. The solid was collected by filtration (34), washed, and dried; yield, 1.55 g., m.p. 216.5-218°. After one recrystallization from water, the m.p. was 218-219.5°.

The nmr spectrum (DMSO-d_6 + TFA) δ 2.95 (4H, broad s, CH_2CH_2), 3.65 (2H, s, CH_2CO), 3.75, 3.78, 3.80 (9H, 3s, 3 CH_3O), and 7.92 (3H, broad s, $\overset{+}{N}H_3$).

6-Bromo-1,3,4,5-tetrahydro-7,8,9-trimethoxy-2*H*-3-benzazepine-2-one (**20d**).

Zwitterion **17d** (1.55 g.) was refluxed under a Dean-Stark trap in 100 ml. of xylene for 14.5 hours at which time a clear solution had resulted. The cooled solution was extracted with two 10-ml. portions of saturated sodium bicarbonate solution, dried, and the solvent distilled in a rotary evaporator leaving 1.28 g. of a creamy yellow solid. This was recrystallized from 50 ml. of ethyl acetate and obtained as white prismatic needles of m.p. 188-190.5°, yield 0.94 g.

Anal. Calcd. for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24; Br, 24.20. Found: C, 47.01; H, 4.24; N, 4.12; Br, 24.50.

1,3,4,5-Tetrahydro-7,8,9-trimethoxy-2*H*-3-benzazepine-4-one (**20e**).

Compound **20d** (0.94 g., 0.00205 mole) was shaken under 50 lbs. of hydrogen pressure in 200 ml. of acetic acid together with 0.235 g. of sodium acetate and 0.25 g. of 10% Pd/C catalyst; hydrogen uptake ceased after about one hour. The catalyst was removed by filtration, and the filtrate distilled to dryness in a rotary evaporator. The residue was dissolved in 40 ml. of chloroform and 40 ml. of water, the water was separated and the chloroform solution washed with three 10-ml. portions of water. After drying over magnesium sulfate, the chloroform was distilled in a rotary evaporator and the residue, 0.7 g. of m.p. 162-164°, recrystallized from 30 ml. of ethyl acetate. The product, 0.59 g. formed white prismatic needles of m.p. 166-168° (Lit. (11b) 164.5-166.5°).

The nmr spectrum (deuteriochloroform) δ = 3.02 (2H, t, CH_2-1), 3.50 (2H, m, CH_2-2), 3.80 (2H, s, CH_2-5), 3.81 (9H, s, 3 CH_3O), 6.42 (1H, s, CH-9), and 6.78 (1H, s, NH).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.26; H, 6.87; N, 5.51.

2,3,4,5-Tetrahydro-6,7,8-trimethoxy-1*H*-3-benzazepine **22e** and its Hydrochloride.

This base was prepared by a procedure similar to that used for **21c**. It was obtained as a crystalline solid of m.p. 64-66° by recrystallization from 30-60° petroleum ether.

The nmr spectrum (deuteriochloroform) δ = 1.97 (1H, s, NH), 2.93 (4H, m, 4 CH_2), 3.80, 3.83, 3.82 (9H, 3s, 3 CH_3O) and 6.48 (1H, s, CH-9).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.80; H, 8.07; N, 5.97.

The hydrochloride of **22e**, was prepared in the usual manner and after recrystallization for 2-propanol-ethyl acetate, it melted at 191-192° dec.

The ir spectrum (potassium bromide) showed bands at 2975, 2850, 2775, and a series of salt bands to 2475, 1610, 1600, and 1505 cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}NO_3 \cdot HCl$: C, 57.04; H, 7.36; N, 5.12; Cl, 12.95. Found: C, 57.10; H, 7.54; N, 5.12; Cl, 13.04.

Acknowledgment.

Thanks are due to Dr. F. Scheidl and his staff for the microanalyses. The ir spectra were obtained by Mr. S. Traiman and the nmr spectra by Dr. T. Williams of our Physical Chemistry Department.

REFERENCES

(1) For brevity the term benzazepine will hereafter be used instead of 2,3,4,5-tetrahydro-1*H*-3-benzazepine.

(2a) F. Sǎntavý, J. L. Kaal, L. Hruban, L. Dolejš, V. Hanuš, K. Bláha, and A. D. Cross, *Collect. Czech. Commun.*, **30**, 3479 (1965). (b) W. Klötzer, S. Teitel, J. F. Blount, and A. Brossi, *J. Am. Chem. Soc.*, **93**, 4321 (1971).

(3) In Netherlands Patent Application, NE 68,02257, Derwent 33521, 7-chlorobenzazepine is claimed to have anorectic properties.

(4) In U. S. Patent 3,393,192 a variety of substituted benzazepines are claimed to exhibit anti-bacterial, anti-depressant, antihypertensive, and analgesic activity.

(5) J. von Braun and H. Reich, *Ann. Chem.*, **445**, 225 (1925).

(6) P. Ruggli, B. B. Bussemaker, W. Müller, and A. Staub, *Helv. Chim. Acta*, **18**, 1388 (1935).

(7) J. H. Wood, M. A. Perry, and C. C. Tung, *J. Am. Chem. Soc.*, **73**, 4689 (1951).

(8) J. H. Osborn, *Dissertation Abstr.*, **19**, 2475 (1959).

(9) F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.*, 2, 26-36 (1965).

(10) J. O. Halford and B. Weissmann, *J. Org. Chem.*, 17, 1646 (1952).

(11a) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Am. Chem. Soc.*, **90**, 776 (1968); (b) O. Yonemitsu, *et al.*, *ibid.*, **92**, 5686, 5691 (1970).

(12) *Cf.* G. Hazebroucq, *Ann. Chim.*, 1 [14], 221 (1966) for a summary of the attempts to prepare this ketone **11**.

(13) B. Pecherer, R. C. Sunbury, F. Humiec, and A. Brossi, *XXIII IUPAC Congress* in Boston, Mass., July 26-30, 1971. Paper No. 155, p. 63.

(14) Suitably-substituted phenethylamines are those in which the aromatic ring contains electron-releasing substituents that will direct an incoming substituent to a position that is ortho to the acetamidoalkyl side chain.

(15) B. Pecherer, J. Stumpf, and A. Brossi, *Helv. Chim. Acta*, 53, 763 (1970).

(16) B. Pecherer, F. Humiec, and A. Brossi, *ibid.*, **54**, 743 (1971).

(17) Quite likely higher alkyl groups would have no effect on the sequence. Unpublished work has shown that the chloromethylation is feasible in the presence of an α-aryl group.

(18) It has been noted that in many cases 3-benzazepinones can be prepared directly from primary amino acids. By contrast, 3-benzazocinones, do not form so readily under the same conditions and it is, therefore, expeditious to convert the primary amine to a secondary amine to facilitate the cyclization.

(19) We thank Dr. B. Witkop (NIH) for a sample of this lactone.

(20) E. Späth and N. Polgar, *Monatsh. Chem.*, **51**, 190 (1929).

(21) Chemical Abstracts nomenclature: ethyl ester of 6-(2-acetamidoethyl)-1,3-benzodioxole-5-acetic acid.

(22) Chemical Abstracts nomenclature: 6-(2-acetamidoethyl)-1,3-benzodioxole-5-acetic acid.

(23) Chemical Abstracts nomenclature: 6-(2-aminoethyl)-1,3-benzodioxole-5-acetic acid hydrochloride.

(24) Chemical Abstracts nomenclature: 6-(2-benzylaminoethyl)-1,3-benzodioxole-5-acetic acid.

(25) Chemical Abstracts nomenclature: 7-benzyl-5,7,8,9-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*][3]benzazepin-6-one.

(26) Chemical Abstracts nomenclature: 7-benzyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxolo[4,5-*h*]benzazepine.

(27) Chemical Abstracts nomenclature: 6,7,8,9-tetrahydro-5*H*-1,3-dioxolo[4,5-*h*]benzazepine.

(28) Chemical Abstracts nomenclature: 6,7,8,9-tetrahydro-7-methyl-5*H*-1,3-dioxolo[4,5-*h*][3]benzazepine hydrochloride.

(29) Prepared by refluxing α-methylhomopiperonyl amine with acetic anhydride in toluene for 4.5 hours followed by distillation of the reaction mixture. Compound **12c** distilled at 138-142°/0.2 mm. as a colorless viscous oil which set to a mass of white crystals when rubbed under petroleum ether (b.p. 60-90°), m.p. 94-95° after recrystallization from petroleum ether-ethyl acetate.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.4; H, 6.83; N, 6.33. Found: C, 64.84; H, 6.90; N, 6.06.

(30) Rac. 8-methyl-5,7,8,9-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*][3]-benzazepin-6-one.

(31) Rac. 6-methyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxolo[4,5-*h*]-[3]benzazepine hydrochloride.

(32) The amino acid will not crystallize from concentrated solutions containing salts.

(33) The literature value may be a misprint in the first digit; or perhaps a higher melting polymorph was encountered. In any event the structure of **24a**·HCl is secured by analysis and nmr spectrum.

(34) This mixture was extremely difficult to filter. In another preparation the solid was more conveniently collected by centrifugation.