Synthesis of 2,3,4,5-Tetrahydro-7,8-dimethoxy-1*H*-2-benzazepines

Raymond R. Wittekind and Sam Lazarus (1)

Department of Organic Chemistry, Warner-Lambert Research Institute
Morris Plain, N. J. 07950

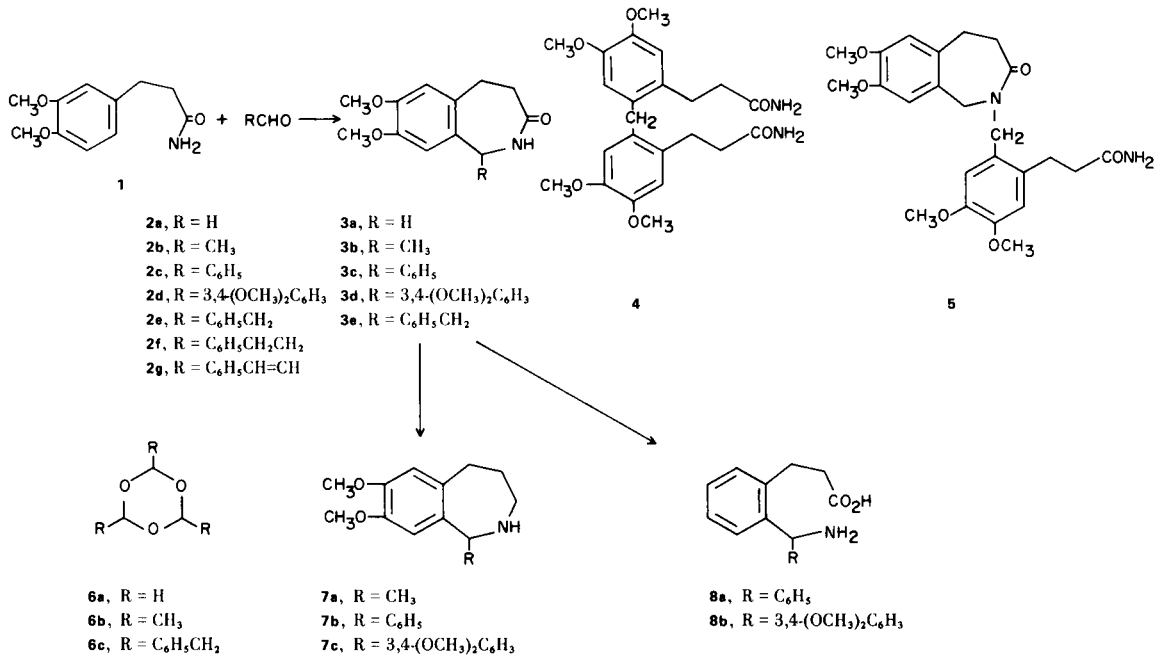
Received February 1, 1971

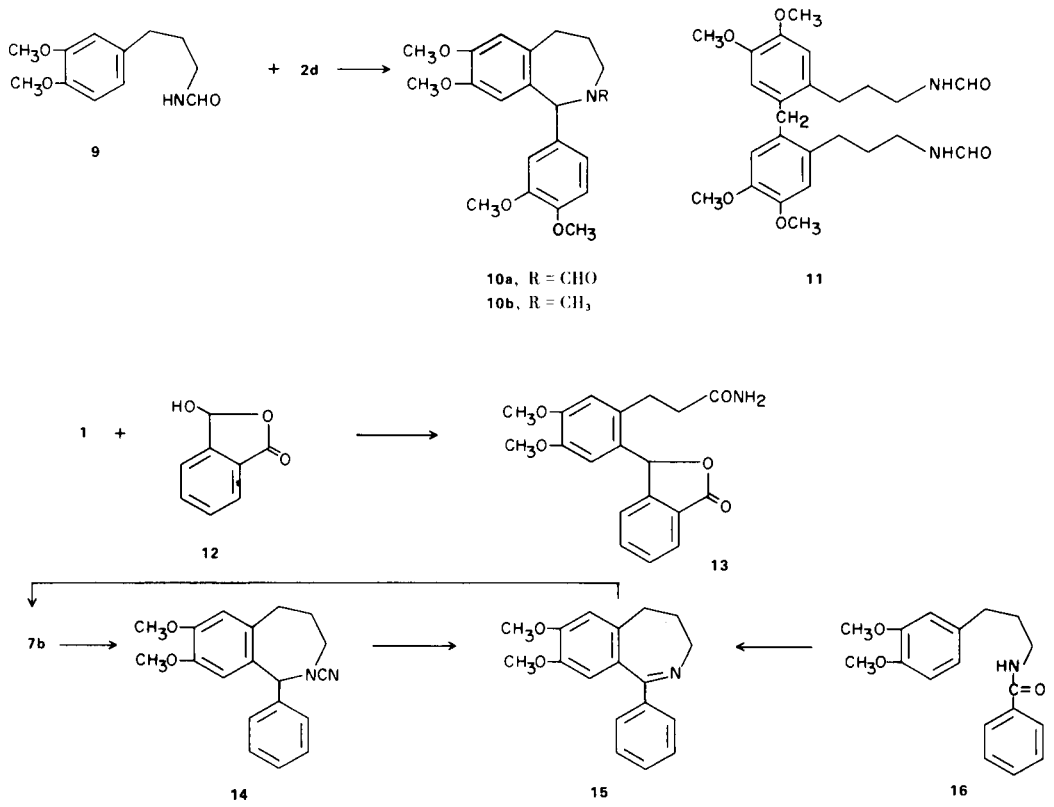
The continuing interest in the synthesis and properties of 2,3,4,5-tetrahydro-1*H*-2-benzazepines (2a-k), due, in part, to the presence of this ring system in the Amaryllidaceae alkaloids, galanthamine, lycoramine and crinine (3), and, in part, to the potential cardiovascular activity associated with this functional group (4), prompts us to record the results of our studies in this area.

Treatment of 3-(3,4-dimethoxyphenyl)propionamide (**1**) (5) with benzaldehyde (**2c**) in polyphosphoric acid-glacial acetic acid (6) afforded the benzazepinone **3c** (7) in 64% yield (8). Alkaline hydrolysis of **3c** gave the amino acid **8a** and lithium aluminum hydride reduction furnished the benzazepine **7b**, identical to a sample subsequently prepared by Konaoka, *et al.* (2e) by the polyphosphate ester induced cyclodehydration of the *N*-benzoylpropylamine **16** to the dihydrobenzazepine **15** followed by sodium borohydride reduction. Similarly, **1** and 3,4-dimethoxybenzaldehyde (**2d**) gave **3d** which was converted **8b** and **7c**.

In order to ascertain the scope of this new cyclodehydration reaction, the propionamide **1** was treated with several aliphatic aldehydes in polyphosphoric acid-glacial acetic acid. At room temperature, phenylacetaldehyde (**2e**) and **1** gave resinous material and unchanged **1** as the only identifiable product. At 100°, in addition to intractable tars and unchanged **1**, 2-phenylnaphthalene, the self-condensation product of **2e** (9), was obtained in moderate yield. Similarly, 3-phenylpropionaldehyde (**2f**), cinnamaldehyde (**2g**), acetaldehyde (**2b**) (as well as the corresponding diethylacetal) and formaldehyde (**2a**) gave resinous products when treated with **1** in polyphosphoric acid-galcial acetic acid at 25 and 100°.

However, when propionamide **1** was treated with *s*-trioxane (**6a**) in polyphosphoric acid-glacial acetic acid at room temperature, the benzazepinone **3a** was obtained in 36% yield. In addition to **3a**, the diphenylmethane **4** was isolated in 17% yield. The initial structural assignment of the latter was based on the well-documented formation





of this type of compound under chloromethylation conditions (10) and was supported by infrared and nuclear magnetic resonance spectral data. Essentially the same results were obtained in the absence of glacial acetic acid. In an attempt to suppress the formation of the *bis*-condensation product **4**, a dilute solution of **1**, **6a** and trifluoroacetic acid was allowed to stand at room temperature for two days. In addition to **3a** (8%), the *N*-benzyl derivative **5** (3%) of **3a** was obtained by chromatography.

When the propionamide **1** was treated with paraldehyde (**6b**) in trifluoroacetic acid under essentially the same conditions used for the preparation of **3a**, the 1-methylbenzazepinone **3b** was isolated in 49% yield. Lithium aluminum hydride reduction of **3b** afforded the known 1-methylbenzazepine **7a** (2e). Application of the *s*-trioxane-trifluoroacetic acid process for the synthesis of the desired 1-benzylbenzazepinone **3e** was unsuccessful. Reaction of the hydrocinnamamide **1** with *cis,cis,cis*-2,4,6-tribenzyl-*s*-trioxane (**6c**) (11) gave only unchanged **1** and an intractable viscous oil.

Phthalaldehydic acid, which exists in the hydroxylactone form (**12**), and propionamide **1** in polyphosphoric acid furnished the amidolactone **13** (12).

A related approach (13) was investigated as a possible route to 2-alkylbenzazepines. Treatment of *N*-[3-(3,4-dimethoxyphenylpropyl)]formamide (**9**) with veratraldehyde (**2d**) in polyphosphoric acid-glacial acetic acid afforded the *N*-formylbenzazepine **10a** in 84% yield. Reduction of **10a** with lithium aluminum hydride in boiling tetrahydrofuran gave the *N*-methylbenzazepine **10b**. Under similar conditions, **9** and *s*-trioxane (**6a**) afforded bisformamide **11** (14) in excellent yield. Like the corresponding diphenylmethane **4**, **11** exhibited spectral properties consistent with the assigned structure.

A novel dehydrocyanation was observed during the course of this work. Treatment of the cyanamide **14**, prepared from the benzazepine **7b** and cyanogen bromide, with sodium amide in liquid ammonia gave dihydrobenzazepine **15**. Catalytic hydrogenation of **15** returned **7b** (15).

EXPERIMENTAL (16)

1,2,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepin-3-one (**3c**).

3-(3,4-Dimethoxyphenyl)propionamide (**1**) (300 g., 1.44 moles) and freshly distilled benzaldehyde (**2c**) (167 g., 1.58 moles) were added, with stirring, under a nitrogen atmosphere, to a solution of phosphorous pentoxide (2.10 kg.), 85% phosphoric acid (1.25 l.) and glacial acetic acid (3.00 l.), cooled in an ice-bath. The solution was stirred at room temperature for three days. The reaction mixture was poured onto ice-water (*ca.* 10 l.). The precipitate was collected on a filter, washed with water, dried *in vacuo* and recrystallized from acetonitrile; yield 275 g. (64%) of the lactam

3c, m.p. 191-192°; γ max (chloroform) 3400 (NH), 2840 (OCH_3), 1660, 1640 (C=O), 1613, 1519 (aromatic) cm^{-1}; λ max 283 mμ (ε, 3,800), λ inf 287 mμ (ε, 3,400); δ (deuteriochloroform) 2.69 (A_2B_2, 4H, $-CH_2CH_2-$), 3.80 (singlet, 3H, $-OCH_3$), 3.89 (singlet, 3H, $-OCH_3$), 5.50 (doublet, J = 7 cps, 1H, ArArCHN-), 6.61 (singlet, 1H, aromatic), 6.71 (singlet, 1H, aromatic), 7.28 (singlet, 5H, aromatic), 7.86 (doublet, J = 7 cps, 1H, -NH-) ppm.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.47; H, 6.65; N, 4.70.

Alkaline Hydrolysis of 1,2,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepine-3-one (**3c**).

A solution of the lactam **3c** (7.00 g., 0.0234 mole), 20% potassium hydroxide solution (70 ml.) and absolute ethanol (70 ml.) was heated under reflux for two hours. The reaction mixture was cooled in an ice-bath, neutralized with glacial acetic acid and evaporated under reduced pressure. The residue was triturated with water and then recrystallized from 50% ethanol-water; yield 3.80 g. (51%) of 2-(α-aminobenzyl)-4,5-dimethoxyhydrocinnamic acid (**8a**), m.p. 188-189°; ν max (nujol) typical amino-acid spectrum; λ max 236 mμ (ε, 9,960), 282 (3,160), λ inf 286 mμ (ε, 3,000).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.53; H, 6.54; N, 4.56.

2,3,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-2-benzazepine (**7b**). A. Chemical Reduction of 1,2,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepine-3-one (**3c**).

The lactam **3c** (25.0 g., 0.0840 mole) was reduced with lithium aluminum hydride (9.50 g., 0.252 mole) in dry tetrahydrofuran (750 ml.) by the Soxhlet technique. The reaction mixture was heated under reflux for 24 hours after complete dissolution and allowed to stand at room temperature overnight. Water (30 ml.) was added, with stirring, to the reaction mixture cooled in an ice-bath. After three hours, the solid was collected, washed with tetrahydrofuran and boiling benzene and the combined filtrates were concentrated. The residue was dissolved in ether (*ca.* 2 l.), filtered and washed with 2*N* hydrochloric acid and with saturated sodium chloride solution. The aqueous extracts were cooled in an ice-bath, basified with potassium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with saturated sodium chloride solution, dried (magnesium sulfate), filtered and concentrated. Recrystallization of the residue from cyclohexane (Norit A) gave 15.6 g. (71%) of the benzazepine **7b**, m.p. 114-115°.

An analytical sample, obtained by repeated recrystallization from 2-propanol, had m.p. 116-118°; ν max (CH_2Cl_2) 2850 (OCH_3), 1607, 1590, 1514 (aromatic) cm^{-1}; λ max (CH_2Cl_2) 1.545 μ; λ max 236 mμ (ε, 7,820), 283 (3,030); δ (deuteriochloroform) 3.57 (singlet, 3H, $-OCH_3$), 3.83 (singlet, 3H, $-OCH_3$), 5.10 (singlet, 1H, ArAr'CHN-), 6.19 (singlet, 1H, aromatic), 6.70 (singlet, 1H, aromatic), 7.32 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.24; H, 7.66; N, 4.89.

The hydrochloride of **7b** had m.p. 247-249° dec., ν max (nujol) 2850 (OCH_3), 2800, 2740, 2610, 2540 ($\overset{+}{N}H_2$), 1610, 1576 (aromatic), 1545 ($\overset{+}{N}H_2$), 1518, 1492 (aromatic) cm^{-1}; λ max 286 mμ (ε, 2,400).

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.93; N, 4.38. Found: C, 67.78; H, 7.10; N, 4.39.

B. Catalytic Hydrogenation of 4,5-Dihydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepine (**15**).

A mixture of the dihydrobenzazepine **15** (0.250 g., 0.889 mmole), 10% palladium-on-carbon (*ca.* 10 mg.) and 95% ethanol (10 ml.) was hydrogenated in a semi-micro hydrogenation apparatus at room temperature and atmospheric pressure. After eight hours, the theoretical volume of hydrogen was absorbed and there was no further uptake. The catalyst was collected, washed with absolute ethanol and the filtrate was concentrated. Trituration of the residual oil gave 0.100 g. (40%) of **7b**, m.p. 116-117°, alone or admixed with an authentic sample prepared by method A and a sample (m.p. 114-115°) supplied by Professor Y. Ban (15). The infrared spectra and paper partition electrophoretograms of the benzazepines prepared by methods A and B and a sample supplied by Professor Y. Ban (15) were identical.

1-(3,4-Dimethoxyphenyl)-1,2,4,5-tetrahydro-7,8-dimethoxy-3*H*-2-benzazepin-3-one (**3d**).

A solution of 3-(3,4-dimethoxyphenyl)propionamide (**1**) (100 g., 0.480 mole), freshly distilled 3,4-dimethoxybenzaldehyde (**2d**) (87.0 g., 0.526 mole), phosphorous pentoxide (700 g.), 85% phosphoric acid (700 g.) and glacial acetic acid (1 l.) was stirred at room temperature for 48 hours. The reaction mixture was poured onto ice (*ca.* 1 kg.), neutralized (*p*H 6) with 50% sodium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with saturated sodium sulfate solution, dried (magnesium sulfate), filtered and evaporated. Recrystallization from ethyl acetate gave 140 g. (82%) of the lactam **3d**, m.p. 183-184°; γ max (chloroform) 3390 (NH), 2840 (OCH_3), 1660, 1640 (C=O), 1612, 1597, 1513 (aromatic) cm^{-1}; λ max 282 mμ (ε, 7,200); δ (deuteriochloroform) 2.75 (multiplet, 4H, $-CH_2CH_2-$), 3.78 (singlet, 6H, $-OCH_3$), 3.88 (singlet, 6H, $-OCH_3$), 5.50 (doublet, J = 5 cps, 1H, ArAr'CHN-), 6.55 (singlet, 1H, aromatic), 6.70 (singlet, 1H, aromatic), 6.78 (singlet, 3H, aromatic), 7.59 ppm (doublet, J = 5 cps, 1H, -NH-).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.48; N, 3.92. Found: C, 67.40; H, 6.63; N, 3.92.

1-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-2-benzazepine (**7c**).

A suspension of the lactam **3d** (10.0 g., 0.0280 mole), lithium aluminum hydride (3.18 g., 0.0841 mole) and dry tetrahydrofuran (2 l.) was heated under reflux, with stirring, for ten hours and allowed to stand overnight. Water (16 ml.) was added, with stirring, to the reaction mixture, cooled in an ice-bath and after three hours, the solid was collected, washed thoroughly with boiling benzene and the combined filtrates were evaporated. The residual oil was dissolved in benzene and the benzene solution was washed with 4*N* hydrochloric acid, saturated sodium sulfate solution, dried (magnesium sulfate), filtered and concentrated. The combined aqueous phases were cooled in an ice-bath, basified with 50% sodium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with saturated sodium sulfate solution, dried (magnesium sulfate), filtered and evaporated. Distillation of the residual oil from an oil-jacketed flask gave 6.42 g. (67%) of the azepine **7c** as a yellow oil, b.p. 200-205° (bath temperature, 0.1 mm.); γ max (carbon tetrachloride) 2850 (OCH_3), 1618, 1595, 1514 (aromatics) cm^{-1}; λ max (carbon tetrachloride) 1.536 μ; λ max 232 mμ (ε, 16,200), 280 (6,650); λ inf 284 mμ (ε, 6,300).

The hydrobromide, obtained in 92% yield, had m.p. 220-221° dec., ν max (nujol) 2760, 2700, 2580, 2530 ($\overset{+}{N}H_2$), 1611, 1594, 1520 (aromatics), 1580 ($\overset{+}{N}H_2$) cm^{-1}; λ max 284 mμ (ε, 6,090).

Anal. Calcd. for $C_{20}H_{26}BrNO_4$: C, 56.61; H, 6.18; Br, 18.83; N, 3.30. Found: C, 56.70; H, 6.37; Br, 18.82; N, 3.08.

The fumarate had m.p. 171-172°; γ max (nujol) 2700-2400 ($^{+}NH_2$, OH), 1700 (CO_2H), 1634 (C=C), 1611 (aromatic), 1580 (CO_2-), 1528 (aromatic) cm^{-1}; λ max 235 mμ (ε, 17,960), 280 (6,600).

Anal. Calcd. for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.86; H, 6.43; N, 2.98.

Alkaline Hydrolysis of 1-(3,4-Dimethoxyphenyl)-1,2,4,5-tetrahydro-7,8-dimethoxy-3*H*-2-benzazepin-3-one (**3d**).

A mixture of the lactam **3d** (10.0 g., 0.0280 mole) and 25% potassium hydroxide solution (60 ml.) was heated under reflux for six hours and allowed to stand at room temperature for approximately 70 hours. A trace of insoluble material was removed by filtration. The filtrate was cooled in an ice-bath and neutralized with glacial acetic acid. The resulting precipitate was collected, washed with water, dried and recrystallized from methanol; yield 8.72 g. (83%) of 2-(α-aminoveratryl)-4,5-dimethoxyhydrocinnamic acid (**8b**), m.p. 170-171°; γ max (nujol) typical amino acid spectrum; λ max 280 mμ (ε, 6,440), 235 (16,900).

Anal. Calcd. for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 64.10; H, 6.85; N, 3.74.

Condensation of 3-(3,4-Dimethoxyphenyl)propionamide (**1**) with Phthalaldehydic Acid (**12**).

A mixture of the amide **1** (10.0 g., 0.0479 mole), phthalaldehydic acid (**12**) (7.08 g., 0.0470 mole), phosphorous pentoxide (70 g.) and 85% phosphoric acid (70 g.) was stirred at room temperature for 17 hours. The reaction mixture was poured onto ice-water and extracted with methylene chloride. The organic extracts were washed with 5% sodium bicarbonate solution, saturated sodium sulfate solution, dried (magnesium sulfate), filtered and concentrated. Trituration of the residue with ethyl acetate followed by recrystallization from ethyl acetate-ethanol gave 9.32 g. (57%) of 4,5-dimethoxy-2-phthalidylhydrocinnamamide (**13**), m.p. 184-185°; γ max (chloroform) 3490, 3390, 3180 (NH_2), 2850 (OCH_3), 1753 (lactone C=O), 1670 (amide C=O), 1609, 1597, 1593, 1515 (aromatic) cm^{-1}; λ max 230 mμ (ε, 18,700), 281 (4,400); λ inf 287 mμ (ε, 3,320); δ (deuteriochloroform) 2.30-3.34 (A_2B_2, 4H, $-CH_2CH_2-$), 3.61 (singlet, 3H, $-OCH_3$), 3.87 (singlet, 3H, $-OCH_3$), 5.70-6.00 (multiplet, 2H, $-NH_2$), 6.26 (singlet, 1H, ArAr'CHO-), 6.75, 6.84 (singlets, 2H, aromatic), 7.20-8.10 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.79; H, 5.84; N, 3.86.

Reaction of 3-(3,4-Dimethoxyphenyl)propionamide (**1**) with *s*-Trioxane (**6a**). A. In the Presence of Polyphosphoric Acid-Glacial Acetic Acid.

A solution of the amide **1** (5.00 g., 0.0239 mole), *s*-trioxane (**6a**) (0.72 g., 0.0080 mole), phosphorus pentoxide (35.0 g.), 85% phosphoric acid (35.0 g.) and glacial acetic acid (120 ml.) was allowed to stand at room temperature for 24 hours. The reaction mixture was poured onto ice, neutralized (*p*H 6) with 50% sodium hydroxide solution and extracted with methylene chloride. The combined organic extracts were washed with saturated sodium sulfate solution, dried (magnesium sulfate) and filtered. Evaporation of the solvent *in vacuo* gave 4.71 g. of a tan solid, m.p. 127-142.0°. The crude product was triturated with methylene chloride and the insoluble material was collected and recrystallized from absolute ethanol; yield 0.87 g. (17%) of the diphenylmethane **4**, m.p. 206-207°; γ max (nujol) 3440, 3360, 3350, 3220, 3190 (NH_2), 1693, 1660 (C=O), 1617 (NH_2), 1520 (aromatic) cm^{-1}; λ max 232 mμ (ε, 18,400), 284 (6,680), λ inf 288 mμ (ε, 6,160), δ (DMSO-d_6) 3.59, 3.74, 3.89 (singlets, 14H, $-OCH_3$, $-CH_2-$), 6.49, 6.84 (singlets, 4H, aromatic), 7.3 (multiplet, 4H, $-NH_2$) ppm.

Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; mol. wt. 430. Found: C, 63.94; H, 6.81; N, 6.55; mol. wt. (mass spectrometry) 430.

Recrystallization of the residual crystalline solid (3.63 g.), obtained by evaporation of the methylene chloride filtrate, from ethyl acetate-absolute ethanol, 2-propanol and methanol (twice) gave 1.89 g. (36%) of the lactam **3a**, m.p. 170-171°; γ max (deuteriochloroform) 3400, 3280, 3200 (NH), 3850 (OCH_3), 1665, 1640 (C=O), 1613, 1519 (aromatic) cm^{-1}; λ max 283 mμ (ε, 3,130), λ inf 286 mμ (ε, 2,750); δ (deuteriochloroform) 2.88 (multiplet, 4H, $-CH_2CH_2-$), 3.85 (singlet, 6H, $-OCH_3$), 4.26 (doublet, J = 5 cps, 2H, $ArCH_2N-$), 6.60, 6.66 (singlets, 2H, aromatic), 7.88 (multiplet, 1H, -NH-) ppm.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.31; H, 6.96; N, 6.00.

B. In the Presence of Trifluoroacetic Acid.

A solution of the propionamide **1** (20.0 g., 0.0967 mole), *s*-trioxane (**6a**) (3.37 g., 0.0374 mole) and trifluoroacetic acid (2 l.) was allowed to stand at room temperature for two days. The reaction mixture was poured onto ice-water, neutralized with 85% potassium hydroxide and extracted with methylene chloride. The combined organic extract was washed with saturated sodium chloride solution, dried (magnesium sulfate), filtered and evaporated. The residue was dissolved in methylene chloride and chromatographed on Woelm neutral alumina (activity I, 500 g.). Evaporation of the ethyl acetate (4 l.) eluant gave 0.609 g.(3.1%) of 2-[(2,3,4,5-tetrahydro-7,8-dimethoxy-3-oxo-1*H*-2-benzazepine-2-yl)methyl]-4,5-dimethoxy hydrocinnamamide (**5**), m.p. 282-284°.

An analytical sample, obtained by recrystallization from ethanol had m.p. 284-285°; ν max (potassium bromide) 3300 (NH_2), 2850 (OCH_3), 1655 (C=O), 1610, 1510 (aromatic) cm^{-1}; γ max 231 mμ (ε, 18,000), 285 (6,520); δ (DMSO-d_6) 2.1-3.0 (multiplet, 8H, $-CH_2CH_2-$), 3.57, 3.77 (singlets, 14H, $-OCH_3$, $-CH_2-$), 4.27 (multiplet, 2H, $-CH_2-$), 6.33, 6.89 (singlets, 2H, aromatic), 8.55 (multiplet, 2H, $-NH_2$) ppm.

Anal. Calcd. for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33; O, 21.69; mol. wt. 442. Found: C, 65.33; H, 7.00; N, 6.43; O, 21.50; mol. wt. (mass spectrometry) 442.

Evaporation of subsequent ethyl acetate eluants followed by recrystallization from ethanol gave 1.63 g. (7.7%) of the benzazepinone **3a**, m.p. 166-168°, the infrared and proton magnetic resonance spectra of which were identical to those of a sample prepared by method A.

1,2,4,5-Tetrahydro-7,8-dimethoxy-1-methyl-3*H*-2-benzazepin-3-one (**3b**).

A solution of the propionamide **1** (5.00 g., 0.0239 mole), paraldehyde (1.16 g., 0.00875 mole) and freshly distilled trifluoroacetic acid (150 ml.) was allowed to stand at room temperature for 23 hours. The reaction mixture was poured onto ice-water and extracted with methylene chloride. The organic extracts were washed with 1*M* sodium carbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), filtered and concentrated. Recrystallization of the residue from ethyl acetate gave 2.76 g. (49%) of the benzazepinone **3b**, m.p. 165-166°; γ max (chloroform) 3400 (NH), 1640 (C=O), 1595 (aromatic) cm^{-1}; λ max 231 mμ (ε, 7,050), 282 (3,480); γ inf 285 mμ (ε, 3,130); δ ($CDCl_3$) 1.63 (doublet, J = 7 cps, 3H, CH_3-), 2.3-3.5 (multiplet, 4H, $-CH_2CH_2-$), 3.91 (singlet, 6H, CH_3O-), 4.6-5.1 (multiplet, 1H, -CH-), 5.79, 5.88 (singlets, 2H, aromatic), 7.3 (1H, -NH-) ppm.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; O, 20.40. Found: C, 66.14; H, 7.28; N, 6.15; O, 20.48.

2,3,4,5-Tetrahydro-7,8-dimethoxy-1-methyl-1*H*-2-benzazepine (**7a**).

1,2,4,5-Tetrahydro-7,8-dimethoxy-1-methyl-3*H*-2-benzazepin-3-one (**3b**) (9.04 g., 0.0384 mole) was reduced with lithium aluminum hydride (4.5 g., 0.12 mole) in boiling tetrahydrofuran (900 ml.) by the Soxhlet technique. After four days, ether (900 ml.) and water (21 ml.) were added cautiously to the reaction mixture and the suspension was stirred overnight. The alumina was collected and washed with ether. The filtrate was dried (sodium sulfate), filtered and evaporated. Distillation of the residue from an oil-jacketed flask at 0.005 mm. gave 5.79 g. (68%) of the benzazepine **7a**, b.p. 95-100° (bath temp.) (lit. (**2e**) b.p. 115-120° (3 mm.)) as a viscous yellow oil.

The hydrobromide, prepared in 48% yield, had m.p. 195-196°; ν max (chloroform) 2400-2800 ($\overset{+}{N}H_2$), 1610, 1570, 1510 (aromatic) cm^{-1}; γ max 235 mμ (ϵ, 8,310), 280 (2,950); γ inf 285 mμ (ϵ, 2,620); δ (deuterium oxide) 1.5-3.5 (multiplet, 6H, $-CH_2CH_2CH_2-$), 1.82 (doublet, J = 8 cps, 3H, $-CH_3$), 3.89 (singlet, 6H, $-OCH_3$), 5.6-5.9 (multiplet, 1H, $-\overset{+}{C}H-$), 6.98, 7.05 (singlets, 2H, aromatic) ppm.

Anal. Calcd. for $C_{13}H_{20}BrNO_2$: C, 51.67; H, 6.67; Br, 26.44; N, 4.63; O, 10.59. Found: C, 51.81; H, 6.76; Br, 26.57; N, 4.34; O, 10.72.

N-[3-(3,4-Dimethoxyphenylpropyl)]formamide (**9**).

A solution of 3-(3,4-dimethoxyphenyl)propylamine (25.0 g., 0.128 mole) and 90% formic acid (10.0 g., 0.196 mole) was heated under reflux for five hours and allowed to stand overnight. Benzene was added to the reaction mixture and the solution was concentrated. The residue was distilled at 0.05 mm.; yield 25.2 g. of a colorless oil, b.p. 180-183°, which solidified slowly on standing. Recrystallization from benzene-ether gave 21.7 g. (76%) of the formamide **9**, m.p. 58-60°; γ max (chloroform) 3440, 3350 (NH) 2860 (OCH_3), 1688 (C=O), 1608, 1594, 1513 (aromatic), 1545 (NH) cm^{-1}; λ max 229 mμ (ϵ, 8,720), 280 (3,050); λ inf 284 mμ (ϵ, 2,590); δ (deuteriochloroform) 1.6-3.5 (multiplet, 6H, $-CH_2CH_2CH_2-$), 3.72 (singlet, 6H, $-OCH_3$), 6.8-7.2 (multiplet, 3H, aromatic, -NH-), 8.13 (singlet, 1H, -CHO) ppm.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.37; H, 7.76; N, 6.14.

Reaction of *N*-[3-(3,4-Dimethoxyphenylpropyl)]formamide (**9**) with Paraformaldehyde in the Presence of Polyphosphoric Acid-Glacial Acetic Acid.

A solution of the formamide **9** (25.0 g., 0.112 mole), *s*-trioxane (**6a**) (3.35 g., 0.0372 mole), phosphorous pentoxide (175 g.), 85% phosphoric acid (175 g.) and glacial acetic acid (500 ml.) was stirred at room temperature for 24 hours. The reaction mixture was poured onto ice-water, neutralized with sodium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with saturated sodium sulfate solution, 5% sodium bicarbonate solution, saturated sodium sulfate solution, dried (magnesium sulfate) and filtered. Evaporation of the filtrate under reduced pressure followed by recrystallization from ethyl acetate gave 20.0 g. (78%) of 2,2′-methylenebis[[*N*-[3-(4,5-dimethoxyl)propyl]]]formamide **11**, m.p. 128-129°; γ max (methylene chloride) 3470, 3350 (NH), 1790, 1780 (C=O), 1610, 1515 (aromatic) cm^{-1}; γ max 231 mμ (ϵ, 18,800), 285 (7,180); γ inf 289 mμ (ϵ, 6,250); δ (DMSO-d_6) 1.2-3.4 (multiplet, 12H, $-CH_2CH_2CH_2-$), 3.60, 3.77, 3.87 (singlets, 14H, $-OCH_3$, $-CH_2-$), 6.52, 6.85 (singlets, 4H, aromatic), 7.5-8.1 (multiplet, 4H, -NH-, -CHO) ppm.

Anal. Calcd. for $C_{25}H_{34}N_2O_6$: C, 65.48; H, 7.47; N, 6.11; mol. wt. 458. Found: C, 65.78; H, 7.64; N, 5.95; mol. wt. (mass spectrometry) 458.

1-(3,4-Dimethoxyphenyl-2-methyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-2-bnezazepine (**10b**).

A solution of the formamide **9** (15.0 g., 0.0672 mole), freshly distilled 3,4-dimethoxybenzaldehyde (12.3 g., 0.0740 mole), phosphorus pentoxide (105 g.), 85% phosphoric acid (105 g.) and glacial acetic acid (300 ml.) was stirred at room temperature for 24 hours. The reaction mixture was poured onto ice (*ca.* 300 g.), neutralized with 50% potassium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with saturated sodium sulfate solution, 5% potassium hydroxide solution, saturated sodium sulfate solution, dried (magnesium sulfate) and filtered. Distillation of the residual oil, obtained by concentration under reduced pressure, from an oil-jacketed flask gave 21.0 g. (84%) of 1-(3,4-dimethoxyphenyl)-2-formyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-2-benzazepine **10a**, as a pale yellow oil, b.p. 235-245° (bath temp., 0.05 mm.), which solidified to a glass; γ max (chloroform) 2850 (OCH_3), 1670 (C=O), 1618, 1593, 1514 (aromatic) cm^{-1}; λ max 282 mμ (ϵ, 6,980); λ inf 285 mμ (ϵ, 6,550).

A solution of the azepine **10a** (7.00 g., 0.0188 mole) and dry tetrahydrofuran (100 ml.) was added dropwise over one-half hour to a stirred suspension of lithium aluminum hydride (2.45 g., 0.0648 mole) and dry tetrahydrofuran (200 ml.). After the addition was complete, the reaction mixture was heated under reflux for four hours and allowed to stand overnight. Water (8 ml.) was added and the mixture was stirred for two hours. The insoluble material was collected on a filter and the filter cake was washed thoroughly with tetrahydrofuran and hot benzene. The filtrate was evaporated and the residue was dissolved in methylene chloride, dried (magnesium sulfate) and filtered. Concentration of the filtrate followed by distillation from an oil-jacketed flask afforded 6.20 g. (92%) of 1-(3,4-dimethoxyphenyl)-2-methyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-2-benzazepine (**10b**) as a pale yellow oil, b.p. 185-195° (bath temp., 0.05 mm.), γ max (chloroform) 2850 (OCH_3), 2800 (NCH_3), 1608, 1595, 1515 (aromatic) cm^{-1}; λ max 281 mμ (ϵ, 6,400); λ inf 284 (ϵ, 6,350).

The hydrochloride, prepared in 74% yield, had m.p. 210-211° dec.; γ max (chloroform) 2850 (OCH_3), 220-2800 ($\overset{+}{N}H$), 1611, 1596, 1521 (aromatic) cm^{-1}; λ max 238 mμ (ϵ, 14,500), 282 (6,720); γ inf 285 mμ (ϵ, 6,520).

Anal. Calcd. for $C_{21}H_{28}ClNO_4$: C, 64.03; H, 7.16; Cl, 9.00; N, 3.56. Found: C, 64.24; H, 7.35; Cl, 9.28; N, 3.52.

2,3,4,5-Tetrahydro-2-cyano-7,8-dimethoxy-1-phenyl-1*H*-2-benzazepine (**14**).

To a solution of freshly sublimed cyanogen bromide (17.0 g., 0.160 mole) and dry benzene (250 ml.) cooled in an ice-bath to 6° was added, dropwise, with stirring, a solution of the benzazepine **7b** (15.0 g., 0.0530 mole), triethylamine (16.2 g., 0.0159 mole) and dry benzene (200 ml.) at a rate such that the temperature of the reaction did not exceed 10°. After the addition was complete, the reaction mixture was stirred for two hours at room temperature and then washed with water, dried (magnesium sulfate) and filtered. Trituration of the residue, obtained by evaporation of the filtrate with cyclohexane followed by recrystallization from *t*-butyl alcohol gave 9.00 g. (55%) of the cyanamide **14**, m.p. 114-115°; γ max (chloroform) 2850 (OCH_3), 2260 (C≡N), 1610, 1490, 1516, 1495 (aromatic) cm^{-1}; λ max 237 mμ (ϵ, 7,680), 284 (3,140); λ inf 287 mμ (ϵ, 2,900); δ (deuteriochloroform) 1.5-3.6 (multiplet, $-CH_2CH_2CH_2-$), 3.74, 3.87 (singlets, 6H,

-OCH_3), 5.61 (singlet, 1H, $ArAr'\overset{+}{C}HN$-), 6.60, 6.75 (singlets, 2H, aromatic), 7.30 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.79; H, 6.67; N, 8.95.

4,5-Dihydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepine (**15**).

The cyanamide **14** (30.0 g., 0.0972 mole) was added in one-portion, with stirring, to a solution of sodium amide and liquid ammonia, prepared from sodium (22.5 g., 0.0978 mole), liquid ammonia (500 ml.) and hydrated ferric chloride (*ca.* 20 mg.). The reaction mixture was stirred under reflux for five hours and the ammonia was allowed to evaporate. Methylene chloride (300 ml.) and ice-water (50 ml.) were added to the residue and the resulting two-phase system was stirred for two and one-half hours and then passed through a filter. The layers of the filtrate were separated and the organic phase was washed with water and evaporated. Benzene was added to the residue and the solution was washed with 5% hydrochloric acid and water. The combined aqueous extracts were cooled in an ice-bath, basified with 50% potassium hydroxide solution and extracted with benzene. The organic extracts were washed with water, dried (potassium carbonate) and evaporated. Distillation of the residue from an oil-jacketed flask at 0.1-0.2 mm. gave 13.1 g. of a viscous oil, b.p. 180-200° (bath temp.). Trituration with Skelly B followed by recrystallization from Skelly B gave 8.80 g. (32%) of 4,5-dihydro-7,8-dimethoxy-1-phenyl-3*H*-2-benzazepine (**15**), m.p. 81.0-84.5°.

An analytical sample, prepared by repeated recrystallization from Skelly B, had m.p. 84.5-85.5°; γ max (chloroform) 2850 (OCH_3), 1604 (aromatic), 1570 (C=N), 1511, 1489 (aromatics) cm^{-1}; λ max 237 mμ (ϵ, 22,600), 301 (5,800); δ (deuteriochloroform) 2.0-3.1 (multiplet, 6H, $-CH_2CH_2CH_2-$), 3.72, 3.93 (singlets, 6H, $-OCH_3$), 6.63, 6.81 (singlets, 2H, aromatic), 7.1-7.8 (multiplet, 5H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.83; H, 6.81; N, 4.98. Found: C, 77.12; H, 6.93; N, 5.16.

The hydrobromide had m.p. 210-212°; γ max (chloroform) 2400-2900 ($C=\overset{+}{N}H$), 1611, 1597 (aromatic), 1560 ($C=\overset{+}{N}H$), 1520, 1495 (aromatic) cm^{-1}; λ max 241 mμ (ϵ, 10,200), 268 (12,580), 370 (5,860); γ inf 305 mμ (ϵ, 6,120); δ (deuteriochloroform) 2.6-3.7 (multiplet, 6H, $-CH_2CH_2CH_2-$), 4.07 (singlet, 6H, $-OCH_3$), 6.73, 7.19 (singlets, 2H, aromatic), 7.8 (multiplet, 5H, aromatic), 13.8 (multiplet, 1H, $-\overset{+}{N}H-$) ppm.

Anal. Calcd. for $C_{18}H_{20}BrNO_2$: C, 59.68; H, 5.56; Br, 22.06; N, 3.87. Found: C, 59.52; H, 5.86; Br, 22.06; N, 3.74.

The picrate had m.p. 257-259° (lit. (2e) m.p. 246-247°); γ max (chloroform) 1630 ($C=\overset{+}{N}H$), 1565, 1460 (aromatic) cm^{-1}; λ max 236 mμ (ϵ, 19,600), 363 (18,800); γ inf 252 (ϵ, 16,600).

Anal. Calcd. for $C_{24}H_{22}N_4O_9$: C, 56.47; H, 4.31; N, 10.91. Found: C, 56.58; H, 4.57; N, 11.09.

cis,cis,cis-2,4,6-Tribenzyl-*s*-trioxane (**6c**).

A solution of freshly distilled phenylacetaldehyde (**2e**) (36.3 g., 0.303 mole), freshly distilled boron trifluoride etherate (0.05 ml.) and anhydrous ether (30 ml.) was allowed to stand at room temperature for two days. The precipitate was collected and washed with ether; yield 9.32 g. (26%) of the trioxane **6c**, m.p. 154-156° (lit. (11) m.p. 154-156°); ν max (dichloromethane) 1605, 1595 (aromatic), 1130 (ether) cm^{-1}; γ max 257 mμ (ϵ, 570); δ (deuteriochloroform) 2.98 (doublet, J = 5 cps, 6H, $-CH_2-$), 4.95 (triplet, J = 5 cps, 3H, $-\overset{+}{C}H-$), 7.20 (singlet, 15H, aromatic) ppm.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71; O, 13.38. Found: C, 79.96; H, 6.79; O, 13.38.

Acknowledgment.

The authors are grateful to Mrs. U. Zeek for microanalyses and Dr. R. C. Greenough and Mr. R. Puchalski for spectral determinations. We also thank Mr. W. Cetenko, Mr. S. Fahey and Mr. C. Weissman for technical assistance and Dr. R. I. Meltzer for advice and encouragement.

REFERENCES

(1) Present address: Photoproducts Department, E. I. Du Pont, De Memours and Co., Inc., Parlin, New Jersey, 08859.

(2a) I. M. Goldman, J. K. Larson, J. R. Tretter and E. G. Andrews, *J. Am. Chem. Soc.*, **91**, 4941 (1969); (b) J. R. Brooks and D. N. Harcourt, *J. Chem. Soc.*, 625 (1969); (c) F. Caesar and A. Mondon, *Chem. Ber.*, **101**, 990 (1969); (d) S. Akaboshi and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **14**, 622 (1966); (e) Y. Konaoka, E. Sato, O. Yonemitsu and Y. Ban, *Tetrahedron Letters*, 2419 (1964); (f) N. S. Hjelte and T. Agaback, *Acta. Chem. Scand.*, **18**, 191 (1964); (g) M. Tomita and S. Minami, *Yakugaku Zasshi*, **83**, 1022 (1963); (h) A. Rieche and E. Hoeft, *J. Prakt. Chem.*, **17**, 293 (1962); (i) B. Belleau, *J. Med. Pharm. Chem.*, **1**, 343 (1959); (j) H. J. Schmid, A. Hunger and K. Hoffmann, *Helv. Chim. Acta.*, **39**, 607 (1956); (k) J. v. Braun and F. Zobel, *Ber.*, **56**, 695 (1923).

(3) W. C. Wildman in "The Alkaloids", R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chapter 9.

(4) H. Ozawa and I. Otruki, *Chem. Pharm. Bull.* (Tokyo), **15**, 1875 (1967).

(5) J. S. Buck and W. H. Perkin, Jr., *J. Chem. Soc.*, 1657 (1924).

(6) This process was patterned after Belleau's scheme for the elaboration of the erythrinane skeleton from 2-(3,4-dimethoxyphenyl)-*N*-[2-(2-oxocyclohexyl)ethyl]acetamide: B. Belleau, *Can. J. Chem.*, **35**, 651 (1957).

(7) The proton magnetic resonance spectrum of **3c** which exhibited two one-proton singlets at δ 6.6 and 6.7 ppm, characteristic of a 1,2,4,5-tetrasubstituted benzene moiety, established the direction of cyclization: J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance", McGraw-Hill Book Company, Inc., New York, N. Y., 1959, p. 259.

(8) In the absence of the diluent, glacial acetic acid, the yield of **3c** was 30%.

(9) J. Volhard, *Ann. Chem.*, **296**, 1 (1897).

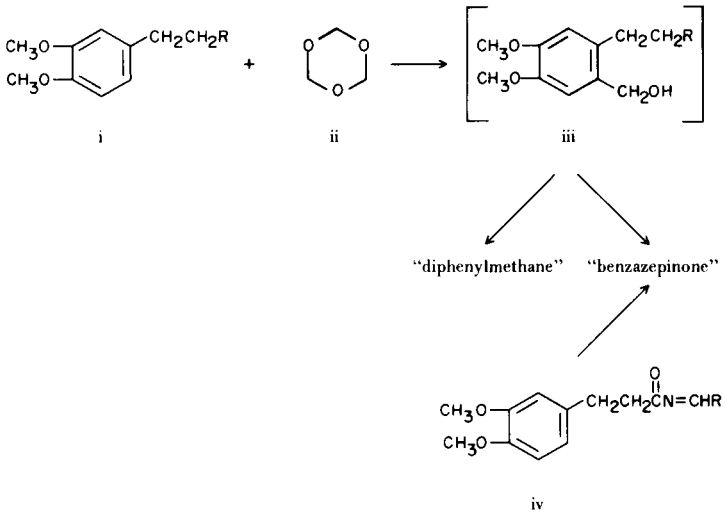
(10) R. C. Fuson and C. H. McKeever, "Organic Reactions", Vol. 1, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 63.

(11) *cis,cis,cis*-2,4,6-Tribenzyl-*s*-trioxane (**6c**) was prepared by a modification of the method of Young (D. C. Young, U. S. Patent 2,649,462 (1953); *Chem. Abstr.*, **48**, 8261 (1954)) as described in the Experimental. The nuclear magnetic resonance spectrum of **6c** exhibited a six-proton doublet at 2.98 and a three-proton triplet at 4.95 ppm and thus confirmed the anticipated all *cis*-stereochemistry of the alkyl substituents. A lower melting (119.0-121.0°) isomeric (elemental analysis) product, which rapidly changed to **6c** on standing or dissolution in organic solvents, was obtained by collection of the initial precipitate. This substance may be the thermodynamically less stable *cis,cis,trans*-isomer.

(12) *Cf.*, for example, the formation of 3-(*p*-methoxyphenyl) phthalide by the acid-catalyzed condensation of phthalaldehydic acid with anisole: V. W. Floutz, *J. Org. Chem.*, **26**, 2584 (1961).

(13) This process was patterned after Mondon's scheme for the synthesis of erythrina alkaloids: A. Mondon, *Chem. Ber.*, **92**, 1461 (1959).

(14) The intermediacy of the carbinols iii (R = $-CONH_2$ and $-CH_2NHCHO$) was established by the isolation of the diphenylmethanes **4** and **11**. These carbinols may also be involved in the formation of the benzazepinones. The involvement of the eneamide iv as an intermediate in the formation of the benzazepinones can not be excluded, however.



i ii iii iv

(15) We thank Professor Y. Ban, Hokkaido University, Sapporo, Japan, for a sample of the 1-phenylbenzazepine **7b**.

(16) Melting Points were determined in open capillary tubes on a Thomas-Hoover Unimelt. The ultraviolet spectra were measured in 95% ethanol with a Beckman DK-1 spectrophotometer. The infrared spectra were determined on a Baird Model 455 spectrophotometer. The nuclear magnetic resonance spectra were measured on a Varian A-60 spectrometer with tetramethylsilane as the internal standard. The mass spectra were determined on a Consolidated Electronics Corp. Model 21-103C spectrograph. All analytical samples were thin-layer chromatographically homogeneous.