Photocyclization of Pharmacodynamic Amines. IV. Novel Heterocycles from N-Chloroacetyl-3,4-dimethoxyphenethylamine[1]

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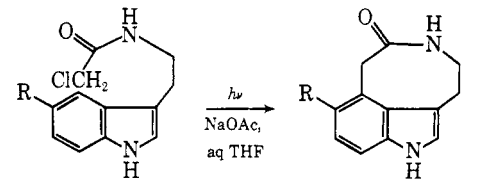
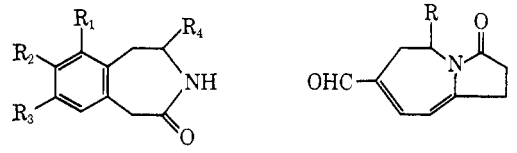
Abstract: Irradiation of N-chloroacetyl-3,4-dimethoxyphenethylamine in aqueous ethanol with a high-pressure mercury lamp gave 7,8- and 8,9-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (yields 27 and 6%, respectively), of which the latter was hydrolyzed and lactonized by 48% HBr to 4-(β-aminoethyl)-7-hydroxy-2,3-dihydrobenzofuran-2-one, the former to 2-(β-aminoethyl)-4,5-dihydroxyphenylacetic acid, characterized as the ethyl ester. In addition a deep-seated photorearrangement gave 11% 1,2,5a,7b-tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3-*gh*]pyrrolizin-4(5H)-one which easily aromatized on warming with Al_2O_3 in toluene to the tricyclic lactam of 6-methoxy-2,3-dihydroindole-7-acetic acid and on esterification opened up to form methyl 4,5-dimethoxy-7-azatricyclo[4.3.0.0^{1,4}]non-2-ene-5-acetate, reconvertible to starting material by base. Photolysis in tetrahydrofuran gave the ten-membered lactam (11% yield), 12-methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),-9,11-trien-5-one which with 6.0 *N* HCl at 20° underwent an unusually facile transannular Bischler–Napieralski reaction to yield 9-methoxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline. These unusual photocyclizations are discussed in terms of intramolecular transfer of energy from an excited aromatic singlet state to the C–Cl bond.

On irradiation with a high-pressure mercury lamp, N-chloroacetyl-L-tryptamines (I) are easily cyclized to tricyclic lactams (II).[3] This photocyclization, which has been extended to N-chloroacetyl derivatives of aromatic amino acids and pharmacodynamic amines, has led to tricyclic indoles (II),[3] benzazepinones (III),[4] and azaazulenes (IV).[4,5]



I, R = H or CH_3O II, R = H or CH_3O



III, $R_1 = R_2 = R_3 = H, OH$; $R_4 = H, CO_2H$ IV, R = H, CO_2H

N-Chloroacetyl-3,4-dimethoxyphenethylamine (V), derived from the catatonigenic compound erroneously implied as a metabolite in schizophrenia,[6] has now been selected as starting material for several novel photocyclizations.

When a 10 mmol/l. solution of N-chloroacetyl-3,4-dimethoxyphenethylamine (V) in ethanol–water solution was irradiated with a 100-W high-pressure mercury lamp for 1.5 hr, two benzazepinones (VI and VII) and a novel tetracyclic compound (VIII) were isolated by recrystallization and column chromatography over silica gel (Scheme I).

The structural assignments of VI and VII, in analogy to the photocyclization products of N-chloroacetyldopamine,[4] rest on the nmr and uv spectra. On the basis of mass spectra, both VI and VII have the composition $C_{12}H_{15}NO_3$ (mol wt 221). In the nmr spectrum of VI, the main product of photocyclization, the two aromatic protons in positions 6 and 9 are distinct singlets at 6.63 and 6.65 ppm with no sign of *ortho* coupling. However, the two aromatic protons in the cyclization product VII happen to be in the same position at 6.87 ppm.

An unambiguous chemical proof is based on lactonization of VII by heating with 48% hydrobromic acid. The structure of the resulting five-membered lactone was easily recognized by its ir spectrum (1795 cm^{-1}). By contrast, VI was opened by 48% HBr to an amino acid IX, which was isolated and crystallized as the methyl ester IXa.

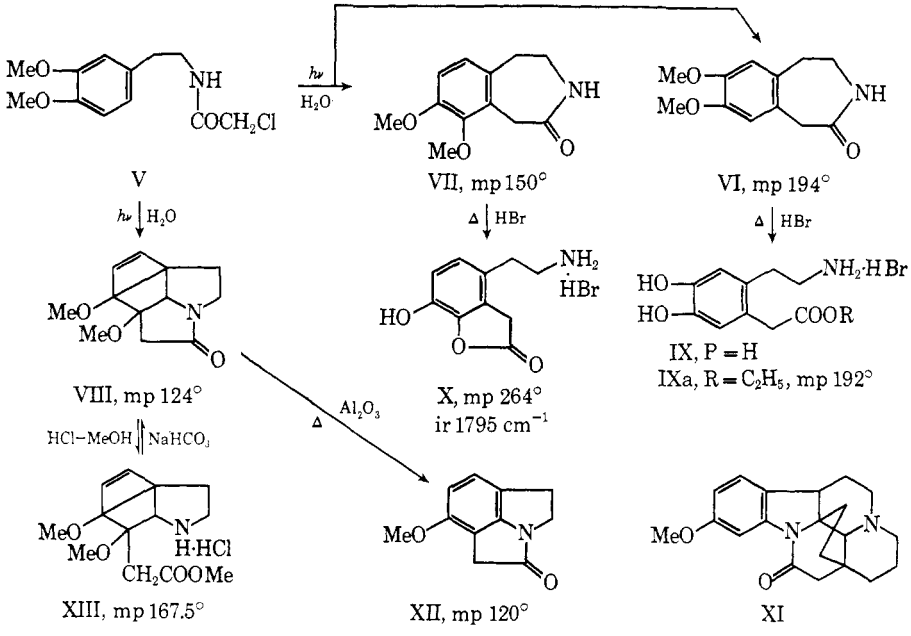
In addition a deep-seated photorearrangement gave the tetracycle VIII, which has only uv end absorption and no NH group in the ir spectrum. The composition of VIII was determined by mass spectrometry as $C_{12}H_{15}NO_3$, isomeric with VI and VII. The base peak at *m/e* 190, equivalent to $C_{11}H_{12}NO_2$, results from loss of one of the two methoxy groups of VIII.

More information about VIII was obtained from the nmr spectrum. The two vinyl protons appear in the same position at 6.45 ppm. The separate singlets at 3.35 and 3.42 ppm indicate that two methoxy groups must be on saturated carbons.

The complete structure of VIII was established by X-ray analysis as 1,2,5a,7b-tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3-*gh*] pyrrolizin-4 (5H)-one.[7] Bond lengths and angles of VIII are illustrated in Figure 1. While this highly strained polycyclic molecule VIII is stable to X-ray radiation over a total

(1) *Cf. J. Amer. Chem. Soc.*, **90**, 6522 (1968).
(2) (a) Hokkaido University; (b) to whom correspondence should be addressed at the National Institutes of Health.
(3) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3491 (1966); T. Kobayashi, T. F. Spande, H. Aoyagi, and B. Witkop, *J. Med. Chem.*, **12**, 636 (1969).
(4) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 776 (1968).
(5) O. Yonemitsu, B. Witkop, and I. L. Karle, *ibid.*, **89**, 1039 (1967).
(6) *Cf.* C. R. Creveling and J. W. Daly, *Nature*, **216**, 190 (1967).
(7) I. L. Karle, J. W. Gibson, and J. Karle, *Acta Cryst.*, **B25**, 2034 (1969).

Scheme I



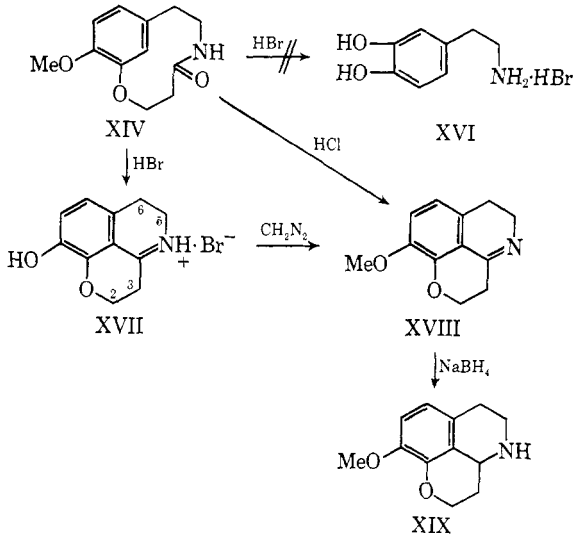
of 300 hr, mild chemical conditions suffice to bring about aromatization with relief of strain. Upon heating with alumina in toluene, VIII rearranges to a compound with λ_{max} 301, 254, and 219 mμ, practically identical with that of the indole alkaloid schizogalin (XI,[8] λ_{max} (ϵ) 301 (6250), 254 (8100), 219 mμ (18,550)).[9] This aromatization proceeds with loss of methanol to yield the tricyclic lactam XII of 6-methoxy-2,3-dihydroindole-7-acetic acid.

This structure of 2-keto-8-methoxy-1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]indole (XII) was confirmed by mass and nmr spectra. The parent peak at *m/e* 189 corresponds to $C_{11}H_{11}NO_2$. Two aromatic protons are well-separated doublets at 6.40 and 6.94 ppm split because of *ortho* coupling (J = 8.0 Hz).

Under the condition of esterification with hydrogen chloride in anhydrous methanol, the tetracyclic VIII opened to the hydrochloride of the methyl ester of the tricyclic dihydroindole XIII which, on standing overnight at room temperature, easily recyclized to VIII.

Irradiation of N-chloroacetyl-3,4-dimethoxyphenethylamine (V) in tetrahydrofuran solution under the conditions described above gave a novel ten-membered lactam (XIV) as a major product, in addition to VI, VII, VIII, N-acetyl-3,4-dimethoxyphenethylamine (XV), and recovered V in the ratios shown in Table I.

Lactam XIV (12-methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one) had a chromophore, λ_{max} 285.5 nm, identical with that of the starting material V. The nmr spectrum showed the three



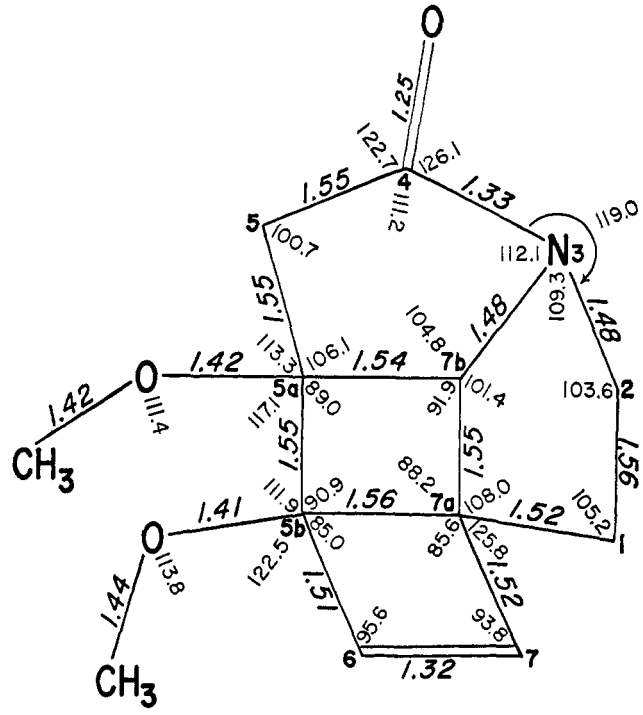


Figure 1. Bond distances and angles of compound VIII. Additional angles about atoms 5a, 5b, and 7a are as follows: 6–5b–5a, 114.6; O–5b–7a, 126.0; 5b–5a–5, 116.1; O–5a–7b, 111.9; 1–7a–5b, 127.0; 7–7a–7b, 115.9.

(8) U. Renner and P. Kernweisz, *Experientia*, **19**, 244 (1963).

(9) N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids," Volume II, The Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind., Dec 1963.

Table I. Effect of Solvent on Yield and Topography of Photocyclization

	Irradiation in aqueous ethanol, yield, %	Irradiation in tetrahydrofuran, yield, %	Topography of photocyclization
7,8-Dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI)	32.5	5.5	*para* cyclization } with reference to
8,9-Dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VII)	9	4	*ortho* cyclization } 3-OMe group
1,2,5a,7b-Tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta-1,4-cyclobuta[1,2,3-*gh*]pyrrolizin-4(5H)-one (VIII)	11	10	*meta* cyclization (with reference to side chain)
12-Methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (XIV)		13	*meta* O-methyl cyclization
N-Acetyl-3,4-dimethoxyphenethylamine (XV)		4	Reductive photolysis
N-Chloroacetyl-3,4-dimethoxyphenethylamine (V)	4.5	10	Recovered starting material

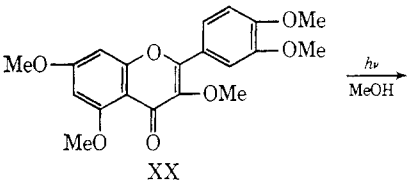
aromatic protons in the same position at 6.88 ppm, only one methoxy group at 3.88 ppm and four methylene groups as multiplets centered at 2.53, 3.24, and 4.29 ppm (4 H, 2 H, and 2 H, respectively). On the basis of these data, photocyclization must have involved one of the two methoxy groups.

In order to confirm the above structure, XIV was heated in 48% hydrobromic acid at 140° for 2 hr. Unexpectedly, XIV was not converted to dopamine (XVI), but to a yellow compound, which on the basis of the uv spectrum must be the dihydroisoquinoline XVII.[10] The nmr spectrum confirms that the two aromatic protons of XVII are well-separated doublets at 6.85 and 7.18 ppm split by *ortho* coupling (J = 8.2 Hz). Methylation with diazomethane in methanol–ether gave the O-methyl ether XVIII, which was also obtained from XIV under milder cyclization conditions with 1.0 N hydrochloric acid under reflux or with 6.0 N hydrochloric acid at room temperature for a few minutes. Transformations of XIV to XVII and XVIII provide examples of an unusually facile *transannular Bischler–Napieralski reaction* and support the structure of the ten-membered lactam XIV.

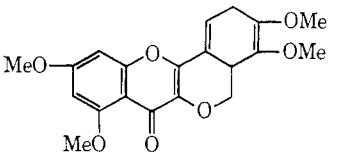
The O-methyl ether XVIII was readily reduced with sodium borohydride in ethanol at room temperature to yield the tricyclic tetrahydroisoquinoline XIX,[11] which has a chromophore of the veratrole type.

A precedent for the participation of an aromatic methoxy substituent is the photocyclization of quercetin pentamethyl ether (XX) to lumimethyl quercetin (XXI).[12] That the unfavorable ten-membered lactam XIV formed without recourse to high dilution technique in tetrahydrofuran strongly suggests that a new reaction mechanism may be involved.

In the absence of further detailed studies, speculations on the mechanism of these photocyclizations are unwarranted. The results presented here point to a common precursor, probably an excited aromatic singlet state in which there exists strong coupling with the carbon–chlorine bond. The intramolecular energy transfer[13] from the aromatic chromophore, rather than



XX



XXI

direct absorption of energy by the amide carbonyl group of V, may assist homolytic or heterolytic cleavage of the C–Cl bond (Scheme II).

Benzazepinones VI and VII may be obtained through substitution of the benzene ring by the common precursor XXII to yield XXIII *via* A, and XXIV *via* B, followed by elimination of hydrogen. The unstable eight-membered lactam XXV (*via* C) undergoes transannular addition to the benzpyrrolizidine (XXVI), in which the diene forms two four-membered rings by a disrotatory photocyclization process.[14] The ten-membered lactam XIV may arise *via* the species XXVII. If XXVII were a ketocarbonium ion, loss of a proton to a carbene could occur, which could either cyclize to XIV or rearrange to a ketene which could add solvent. The

$$\mathrm{RNHCO{-}\ddot{C}H \longrightarrow RNHCH{=}C{=}O}$$

absence of products of the structure $\mathrm{R \cdot NHCH_2COOR}$ militates against the carbene hypothesis. The detailed mechanisms of these unusual reactions are currently under investigation.

Experimental Section

Methods. All melting points are uncorrected. The light source for photocyclizations was a 100-W high-pressure mercury lamp (Eikosha, Type PIH-100 from Eikosha Co., Osaka). Proton magnetic resonance spectra were measured with the Hitachi, H-60 high-resolution nmr spectrometer. Mass spectra were determined with the Hitachi, RMU-6E double-focusing mass spectrometer.

(10) *Cf.* Y. Ban, O. Yonemitsu, and M. Terashima, *Chem. Pharm. Bull. Jap.*, **8**, 198 (1960).

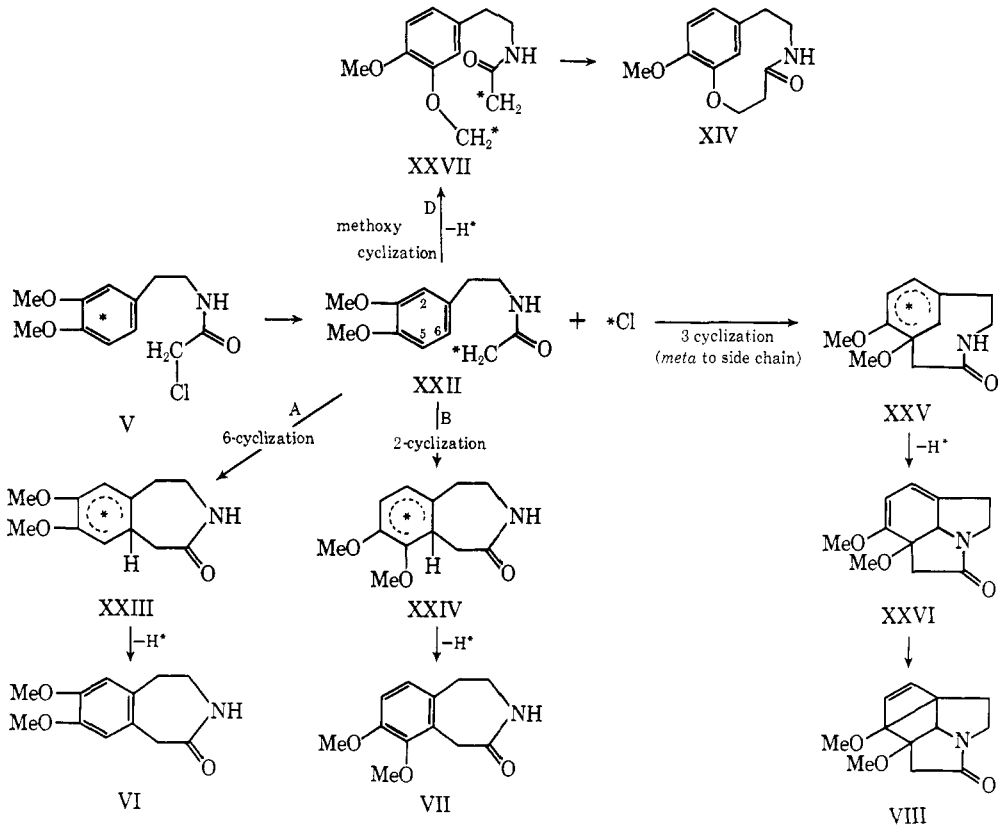
(11) *Cf.* B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, **75**, 4474 (1953); W. M. Whaley and C. N. Robinson, *ibid.*, **75**, 2008 (1953).

(12) A. C. Waiss, Jr., R. E. Lundin, A. Lee, and J. Corse, *ibid.*, **89**, 6213 (1967).

(13) *Cf.* G. S. Hammond, H. Gotthardt, L. M. Coyne, M. Axelrod, D. R. Rayner, and K. Mislow, *ibid.*, **87**, 4959 (1965); H. Morrison and R. Peiffer, *ibid.*, **90**, 3428 (1968). We are indebted for advice and discussions to Dr. George S. Hammond, in whose laboratory Mr. Thomas McCall observed fluorescence quenching in the "loosely bound exciplexes" between irradiated aromatics and chloroacetamide or methyl chloroacetate. Such quenching effects should be even more informative when the energy transfer becomes intramolecular; *cf.* M. T. McCall, G. S. Hammond, B. Witkop, and O. Yonemitsu, *ibid.*, **92**, in press.

(14) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

Scheme II. Breakdown of the Common Hypothetical Photoexcited Intermediate XXII into All of the Five Observed Products[a]



[a] The asterisks leave open the question of radical or ionic pathways.

Photocyclization of N-Chloroacetyl-3,4-dimethoxyphenethylamine (V) in Ethanol–Water. A solution of 772.5 mg (3 mmol) of N-chloroacetyl-3,4-dimethoxyphenethylamine (V)[15] in 240 ml of water and 60 ml of ethanol was irradiated under nitrogen at room temperature for 1.5 hr. The pale yellow solution was adjusted to pH 7.0 by addition of 2.0 *N* sodium hydroxide solution, concentrated *in vacuo* to 100 ml, and extracted with ethyl acetate. The extract on evaporation left 550 mg of slightly yellow powder which was recrystallized from ethanol to give 177 mg (26.6%) of crude 7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI) as fine colorless needles, mp 191.5–193.5°. The ethanolic mother liquor on evaporation left 336 mg of a pale yellow oil, which was chromatographed on a column of silica gel (1.7 × 20 cm). Elution with dichloromethane and ethyl acetate (1:1) gave fractions A and B. Fraction C was obtained by elution with ethyl acetate.

Fraction A (125 mg) was rechromatographed. Elution with dichloromethane gave 35 mg of starting material (V) and 72 mg (10.8%) of crystals of **1,2,5a,7b-tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3-*gh*]pyrrolizin-4(5H)-one (VIII);** this was recrystallized from ethanol to give 47 mg (7.1%) of small colorless prisms: mp 122–123.5°; uv end absorption; ir (Nujol) 1704 (CO), 786 (C=CH) cm^{-1}, no NH; mass spectrum *m/e* 221 (M^+), 190 (M^+ − MeO), 162; nmr ($DCCl_3$) δ 1.7–2.5 (m, 2 H), 2.90 (s, 2 H), 3.05 (m, 1 H), 3.35 (s, 3 H), 3.42 (s, 3 H), 3.78 (s, 1 H), 6.45 (s, 2 H). Permanganate in acetone and tetranitromethane in $CHCl_3$ were both consumed.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.85; N, 6.53.

Fraction B weighed 58 mg (8.7%) and consisted of **8,9-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VII),** which was recrystallized from water to give 37 mg (5.5%) of colorless leaflets: mp 148–150°; uv max (EtOH) 278 nm (ε 1250), 282 (1240); ir (Nujol) 3230 (NH), 1649 (CO) cm^{-1}; mass spectrum *m/e* 221 (M^+), 164, 149; nmr ($DCCl_3$) δ 3.14 (2 HO), 3.61 (2 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 3.99 (s, 2 H), 6.87 (s, 2 H).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.21; H, 6.77; N, 6.40.

Fraction C was the second crop of VI, 40 mg (6.0%). The combined **7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI)** was recrystallized from ethanol to afford 206 mg (31%) of fine colorless needles: mp 192–194°; ir ν^{Nujol} cm^{-1} 3260 (NH), 1673 (CO); nmr δ^{DCCl_3} 3.07 (2 H, t, J = 6 Hz), 3.59 (2 H, t, J = 6 Hz), 3.80 (2 H, s), 3.87 (6 H, s), 6.63 (1 H, s), 6.65 (1 H, s); mass *m/e* 221 (M^+), 165, 164, 149.

Photocyclization of N-Chloroacetyl-3,4-dimethoxyphenethylamine (V) in Tetrahydrofuran. A solution of 1.545 g of V in 300 ml of anhydrous tetrahydrofuran was irradiated as described at room temperature for 1.5 hr. Three batches, with a total volume of 900 ml, were evaporated *in vacuo* at 35–40°. The residual pale brown oil was dissolved in 600 ml of ethyl acetate and washed with water saturated with sodium chloride. The ethyl acetate layer was dried over anhydrous sodium sulfate, and evaporated to leave 5.676 g of a pale brown oil. Recrystallization from ethanol gave 315 mg (8%) of the ten-membered lactam, **12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (XIV),** mp 247–250°. The ethanolic mother liquor was concentrated and chromatographed on a column of silica gel (2.2 × 38 cm). Elution with ethyl acetate–dichloromethane (1:1) gave four fractions.

The first fraction was 1.1 g of a mixture of VIII and recovered starting material. Rechromatography on silica gel column (2.2 × 26 cm) and elution with dichloromethane gave 482 mg of starting material (V) and 409 mg (10.2%) of VIII which was recrystallized from ethanol to give small colorless prisms, mp 122–123.5°.

The second fraction (165 mg, 4.2%) consisted of the benzazepinone VII which was recrystallized from ethanol to form colorless leaflets, mp 148.5–150°.

The third fraction was rechromatographed on a column of silica gel (2.2 × 26.5 cm). Elution with ethyl acetate–dichloromethane (1:1) gave 590 mg of a mixture of XIV and N-acetyl-3,4-dimethoxyphenethylamine (XV). Recrystallization from ethanol gave 170 mg (4.3%) of XIV, mp 247–250°. The mother liquor was evaporated and recrystallized from dichloromethane–ether to give 150 mg (3.8%) of XV, mp 95–96°, which was identical with an authentic specimen[16] with regard to ir spectra.

The lactam XIV was recrystallized from ethanol to afford colorless needles: mp 248–250°; uv λ_{max}^{EtOH} nm (ε) 285.5 (1530); ir

(15) R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931); C. Viel, J.-M. Arnaud, R. Dorme, A. Cheutin, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 431 (1967).

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

ν^{Nujol} cm^{-1} 3350, 1645 (NH–CO); mass *m/e* 221 (M^+), 192, 164, 149, 137; nmr (100 Mc) in $DCCl_3$ showed a singlet at 3.88 (3 H), multiplets centered at 2.53, 3.24, 4.29, and 5.22 (4 H, 2 H, 2 H, and 1 H, respectively), and a singlet at 6.88 (3 H).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.13; H, 6.83; N, 6.14.

The final fraction consisted of 217 mg (5.5%) of the benzazepinone VI which was recrystallized from ethanol to give colorless needles, mp 191–193°.

4,5-Dimethoxy-5-methoxycarbonylmethyl-7-azatricyclo[4.3.0.0^{1,4}]-non-2-ene (XIII). A 70-mg sample of VIII was dissolved in 1.2 *N* hydrochloric acid in anhydrous methanol and allowed to stand overnight at room temperature. The colorless solution was evaporated to give a quantitative yield of 4,5-dimethoxy-5-methoxycarbonylmethyl-7-azatricyclo[4.3.0.0^{1,4}]non-2-ene (XIII) hydrochloride. Recrystallization from methanol–ether gave fine colorless needles: mp 166–167.5°; uv no λ_{max} above 213 nm; ir ν^{Nujol} cm^{-1} 1748 (CO); nmr in D_2O showed three methoxy groups at δ 3.41, 3.59, and 3.90.

Anal. Calcd for $C_{13}H_{20}NO_4Cl$: C, 53.89; H, 6.96; N, 4.83. Found: C, 54.16; H, 6.97; N, 5.40.

Recyclization of XIII to VIII. To the solution of 34 mg of XIII HCl in 2 ml of water was added excess sodium bicarbonate. The free base (XIII) was extracted with ethyl acetate, dried over sodium sulfate, and evaporated *in vacuo* to leave a colorless oil: ir (Nujol) 1730 (CO) cm^{-1}.

It was allowed to stand overnight at room temperature to give a solid which was recrystallized from water to afford colorless small prisms of VIII, mp 123.5°, identical with the photoproduct VIII with regard to mixture melting point, tlc, ir, and mass spectra.

2-Oxo-8-methoxy-1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]indole (XII). To a solution of 55 mg of VIII in 5 ml of toluene was added 600 mg of active alumina (Merck, Activity II–III), and the mixture refluxed for 1.5 hr. After evaporation to dryness *in vacuo*, extraction with hot ethyl acetate, drying over anhydrous sodium sulfate, and removal of solvent, a pale yellow oil was obtained which was purified by chromatography on a column (1.7 × 20 cm) of silica gel. Elution with dichloromethane gave 21 mg (44%) of 2-oxo-8-methoxy-1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]indole (XII). Recrystallization from water gave fine colorless feathers: mp 118–120°; uv λ_{max}^{EtOH} nm (ϵ) 219 (20,500), 254 (6030), 301 (4630); mass *m/e* 189 (M^+), 160, 145, 129; nmr δ^{DCCl_3} 3.55 (2 H), 3.85 (2 H, s), 3.88 (3 H, s), 4.08 (2 H), 6.40 (1 H, d, J = 8.0 Hz), 6.94 (1 H, d, J = 8.0 Hz); XII was also obtained from VIII by heating with active alumina at 150° for 5 min or by refluxing in xylene with alumina for 30 min.

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.96; H, 5.96; N, 7.36.

9-Hydroxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline (XVII). A 100-mg sample of XIV was dissolved in 1 g of 48% hydrobromic acid and heated at 140° for 2 hr. The resulting yellow solution was evaporated to dryness to afford a yellow solid, which was recrystallized from ethanol to give 85 mg of fine needles of 9-hydroxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline (XVII) hydrobromide: mp 225–228° dec; uv λ_{max}^{EtOH} nm (ϵ) 218 (13,550), 238 (sh 7370), 304 (9200), 394 (1900); $\lambda_{max}^{0.01\ N\ NaOH-EtOH}$ nm (ϵ) 251.5 (15,750), 284 (sh 6300), 368 (2810); ir ν^{Nujol} cm^{-1} 3290 (OH), 1660 (C=N$^+$); nmr δ^{D_2O} 3.10 (2 H, t, J = 8 Hz), 4.57 (2 H, s), 6.76 (1 H, d, J = 7.8 Hz), 7.09 (1 H, d, J = 7.8 Hz).

Anal. Calcd for $C_{11}H_{12}NO_2Br$: C, 48.93; H, 4.48; N, 5.19. Found: C, 48.63; H, 4.61; N, 5.23.

9-Methoxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline (XVIII). Method A. A 100-mg sample of XIV was dissolved in 10 ml of 6.0 *N* hydrochloric acid and allowed to stand at room temperature for 10 min. The yellow solution was evaporated *in vacuo* to give fine yellow needles of 9-methoxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]-isoquinoline (XVIII) hydrochloride in a quantitative yield. Recrystallization from ethanol–ether gave fine needles: mp 204°; uv λ_{max}^{EtOH} nm (ϵ) 221 (13,350), 300 (9000), 385 (2190); $\lambda_{max}^{0.01\ N\ NaOH-EtOH}$ nm (ϵ) 265.5 (8450), 327.5 (3370); ir ν^{Nujol} cm^{-1} 1670 (C=N$^+$); nmr δ^{D_2O} 3.02 (2 H, t, J = 7.5 Hz), 3.72 (3 H, s), 3.82 (2 H, t, J = 7.5 Hz), 4.48 (2 H), 6.85 (1 H, d, J = 8.2 Hz), 7.18 (1 H, d, J = 8.2 Hz).

Method B. To the solution of 30 mg of XVII·HBr in 1 ml of methanol was added excess diazomethane in ether, and the mixture was allowed to stand at room temperature for 2 days. After evaporation of solvent the residual oil was dissolved in 1.2 *N* hydrochloric acid in methanol, and evaporated to dryness. The residual yellow solid was recrystallized from ethanol to afford XVIII·HCl, which was identical with XVIII·HCl prepared from XIV by the hydrochloric acid procedure with regard to mixture melting point, ir, and uv spectra. The free dihydroisoquinoline base XVIII was prepared by the addition of powdered sodium carbonate to a cold solution of 35 mg of XVIII·HCl in 1 ml of water. The yellow oil which precipitated was extracted with ethyl acetate, the extract was dried over anhydrous sodium sulfate and evaporated *in vacuo* to leave 28 mg of XVIII as a red oil; uv λ_{max}^{EtOH} nm 266, 328; ir ν^{Nujol} cm^{-1} 1641 (C=N); nmr δ^{DCCl_3} 2.70 (2 H, t, J = 7.5 Hz), 2.84 (2 H, t, J = 6.0 Hz), 3.83 (2 H, t, J = 7.5 Hz), 3.89 (3 H, s), 4.55 (2 H, t, J = 6.0 Hz), 6.66 (1 H, d, J = 8.2 Hz), 6.85 (1 H, d, J = 8.2 Hz).

9-Methoxy-2,3,3a,4,5,6-hexahydropyrano[2,3,4-*ij*]isoquinoline (XIX). To a solution of 170 mg of XVIII·HCl in 10 ml of ethanol, 80 mg of sodium borohydride was added at room temperature. The yellow color of the solution was immediately discharged. After 5 min the solution was evaporated *in vacuo;* 8 ml of water added; and the mixture extracted five times with chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent, addition of methanolic hydrochloric acid, and renewed evaporation gave 160 mg of 9-methoxy-2,3,3a,4,5,6-hexahydropyrano[2,3,4-*ij*]isoquinoline (XIX) hydrochloride; this was recrystallized from ethanol to afford a colorless crystalline powder: mp 262–263°; uv λ_{max}^{EtOH} nm (ϵ) 287 (2400); ir no absorption band for C=N; nmr (100 Mc) δ^{D_2O} 2.30 (2 H, m), 3.11 (2 H), 3.85 (3 H, s), 4.40 (3 H, m), 6.86 (1 H, d, J = 8.0 Hz), 7.02 (1 H, d, J = 8.0 Hz).

Anal. Calcd for $C_{12}H_{16}NO_2Cl$: C, 59.62; H, 6.67; N, 5.79. Found: C, 59.61; H, 6.62; N, 5.80.

The free base XIX was prepared by addition of 1 drop of 10% sodium carbonate solution to a cold aqueous solution of 15 mg of the hydrochloride. The colorless powder (XIX) which precipitated was collected by filtration: uv λ_{max}^{EtOH} mμ 287; mass *m/e* 205 (M^+), 204, 177, 176, 161, 148.

4-(β-Aminoethyl)-7-hydroxy-2,3-dihydrobenzofuran-2-one (X). A suspension of 23.2 mg of VII in 3.5 ml of 48% hydrobromic acid was refluxed for 1 hr (bath temperature, 140°). The pale yellow solution was allowed to stand at room temperature overnight, and evaporated *in vacuo* at 50°. The crude solid of X·HBr was dried in a desiccator over NaOH pellets for 2 days. Two recrystallizations from methanol–ether gave 15 mg of colorless prisms: mp 263–264° dec; ir ν^{Nujol} cm^{-1} 1795 (γ-lactone (CO)).

Anal. Calcd for $C_{10}H_{12}NO_3Br$: C, 43.83; H, 4.41; N, 5.11. Found: C, 44.00; H, 4.62; N, 5.33.

Ethyl 2-(β-Aminoethyl)-4,5-dihydroxyphenylacetate (IXa). A 100-mg sample of 7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI) in 4 ml of 48% hydrobromic acid was heated under reflux at 104° for 2 hr. After evaporation of hydrobromic acid *in vacuo*, the residue was dissolved in water and reevaporated to dryness several times. The residual pale brown solid (115 mg) was dried in an alkaline desiccator for 2 days. On paper electrophoresis at pH 6.5 IX moves like an amino acid, ir (KBr) 1720 cm^{-1} (CO). A 15-mg sample of the above IX·HBr in water was stirred with excess silver carbonate for 30 min. After removal of silver salts by filtration, the filtrate was evaporated to dryness to give the amino acid as a pale brown solid, ir ν (KBr) 1590 cm^{-1} (COO^-). A 40-mg sample of VI in 5 ml of 48% hydrobromic acid was heated under reflux for 1 hr. After evaporation of hydrobromic acid *in vacuo*, the residue was dissolved in ethanol, and ethanol was reevaporated several times. The residual pale brown solid was dried in an alkaline desiccator for 2 days. Repeated recrystallization from ethanol–ether gave colorless prisms: mp 191–192°; ir ν (Nujol) 1693 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{18}NO_4Br$: C, 45.04; H, 5.67; N, 4.38. Found: C, 44.78; H, 5.65; N, 4.29.