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4-Azabicyclo[5,2,2]undeca-8,10-dien-3-ones. Photochemical Formations and Novel Rearrangements

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Water soluble novel compounds, 4-azabicyclo[5,2,2]undeca-8,10-dien-3-ones were synthesized on the photolysis of N-chloroacetyl derivatives of *para* methoxyphenethylamines (I and II). Some reactions of 4-azabicyclo[5,2,2]undeca-8,10-dien-3-ones (IV, VIII and IX) in acids were examined. Compounds IV and IX bearing one and two enol-ether groups respectively were rearranged by hydrogen chloride treatments into 4-azatricyclo[5,2,2,$0^{4,10}$]undeca-8-en-3-ones (XIII, XXVI, XXVII and XXVIII). On heating of IV or IX in acetic acid, a novel fragmentation reaction took place to yield a aromatized compound, X or XXIV. On the other hand, VIII having no enol-ether group was stable to acid treatments.

On the photolysis of N-chloroacetyl derivatives of 4-methoxy- and 3,4-dimethoxyphenethylamines (I and II), novel photocyclization products such as azaazulene, benzazepinones, tetracyclic compound and ten-membered lactam have been synthesized.[2)] Recently we isolated a novel water soluble product, 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5,2,2]-undeca-8,10-dien-3-one (IV) on the photolysis of N-chloroacetylmescaline (III) in good yield.[3)]

The present work was undertaken to see if N-chloroacetyl-4-methoxyphenethylamine (I) and N-chloroacetyl-3,4-dimethoxyphenethylamine (II), which had a *para* methoxy group each, could be converted to the products with the same type of IV, and to examine some chemical properties of the photo-products.

When an aqueous ethanol solution of I was irradiated with 100 watt high pressure mercury lamp, 7-formyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-*a*]azepin-3-one (V)[2a),b)] and 8-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI) (6.1%) were isolated from the ethyl acetate soluble fraction. The spectral data of VI were quite similar to that of 7-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one in the preceding paper,[4)] however the mixed mp was clearly depressed. The structure was also confirmed by the conversion to the corresponding amino acid (VII).

The aqueous layer gave 16.7 % of 1-methoxy-7-hydroxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (VIII), whose structure was established as follows. No λ_{max} above 210 nm was observed in the ultraviolet (UV) spectrum and the composition was determined by the elementary analysis and the mass spectrum as $C_{11}H_{15}O_3N$, which differs from the starting material in the change from chlorine to hydroxy group. In the infrared (IR) spectrum a hydroxy (3340 cm^{-1}) and an amide group (3230 and 1642 cm^{-1}) were easily assigned and four vinyl protons in the nuclear magnetic resonance (NMR) spectrum appeared around δ 6 ppm. By

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2) *a*) O. Yonemitsu, B. Witkop and I.L. Karle, *J. Am. Chem. Soc.*, **89**, 1039 (1967); *b*) O. Yonemitsu, T. Tokuyama, M. Chaykovsky and B. Witkop, *ibid.*, **90**, 776 (1968); *c*) O. Yonemitsu, Y. Okuno, Y. Kanaoka and B. Witkop, *ibid.*, **90**, 6522 (1968); **92**, 5686 (1970).

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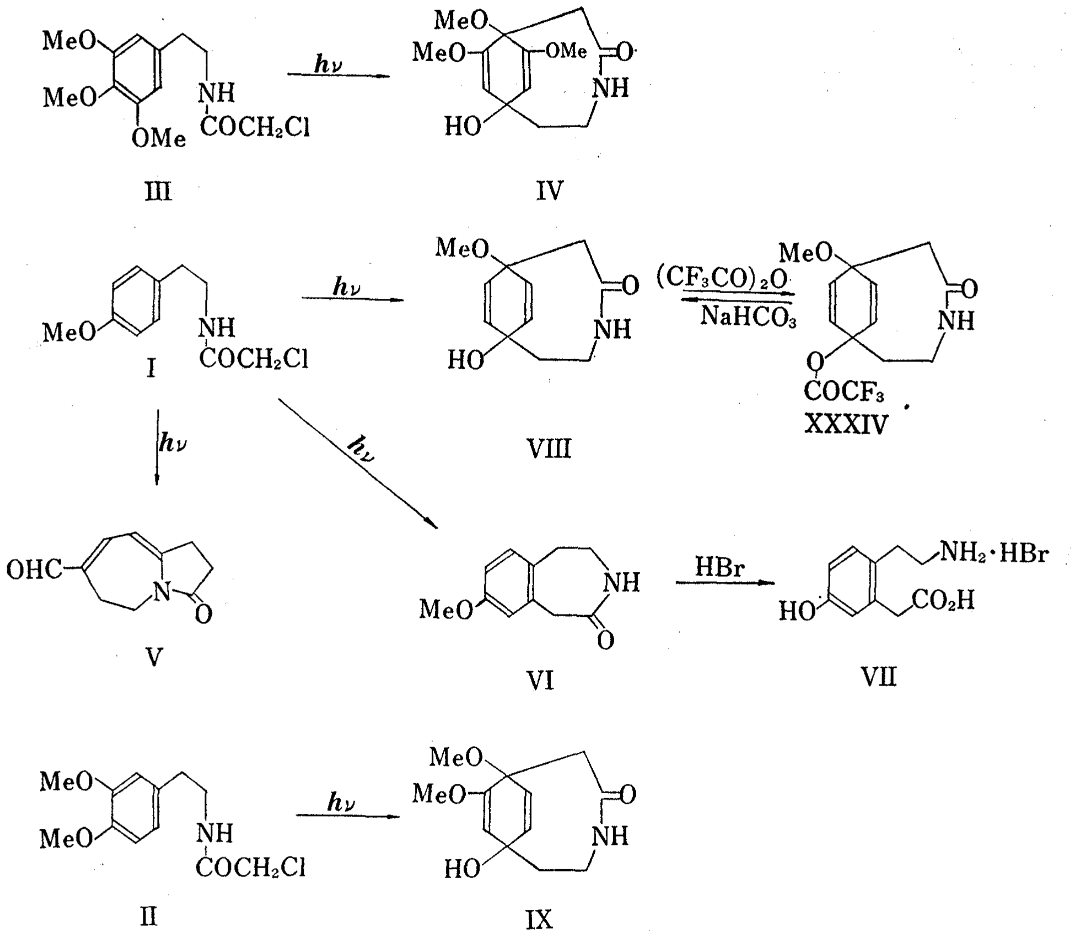

Chart 1

the brief treatment with trifluoroacetic anhydride, compound VIII was converted to the O-trifluoroacetate (XXXIV), which returned to VIII with aqueous sodium bicarbonate.

An aqueous ethanol solution of N-chloroacetyl-3,4-dimethoxyphenethylamine (II) was also irradiated under the same condition to afford a crystalline product in 5.4% yield from the aqueous layer. On the basis of its spectral data this compound was formulated as 1, 9-dimethoxy-7-hydroxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (IX).

4-Azabicyclo[5,2,2]undeca-8,10-dien-3-ones (IV, VIII and IX) have some properties of interest. They have a quinolic hydroxy group each, especially in IV and IX activated with enol-ethers, sensitive to acids. According to the X-ray analysis for IV,³⁾ the amide group in the nine-membered lactam ring lies so close to one of the enol-ethers in the six-membered ring that transannular reactions might be expected. The total line shape analysis⁵⁾ for the NMR spectra of IV and IX explains the slow ring-inversion of the nine-membered lactam caused by the hindered twisting of the C–N bond in the amide group because of its double bond character.⁶⁾ In fact, it has previously been reported³⁾ that IV was converted to X and XI by acetic acid treatment, and on treatment with hydrochloric acid in methanol IV rearranged deeply to XII.

The present paper reports on another transannular cyclization reaction, the effect of the methoxy groups for these conversion reactions, and some further reactions of the transannular reaction products.

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When IV was treated with hydrochloric acid in methanol at room temperature overnight, XII-hydrochloride was easily isolated in 71% yield, and as a minor product colorless prisms (XIII) was newly isolated in 22.4% yield. No λ_{max} above 210 nm in the UV spectrum was observed. In the IR spectrum OH and NH groups disappeared and the amide group in IV varied to a five-membered lactam (1705 cm^{-1}). The composition was determined by the mass spectrometry and the elemental analysis as $C_{14}H_{21}O_5N$, corresponded with the change from a hydroxy group to a methoxy group. In fact, four methoxy groups three methylene groups and only one vinyl proton in the NMR spectrum could be easily assigned. Therefore the structure of XIII was established as 1,7,9,10-tetramethoxy-4-azatricyclo[5,2,2,$0^{4,10}$]-undeca-8-en-3-one.

The tricyclic compound XIII reverted to the bicyclic compound XIV by the treatment of acetic acid containing a small amount of water. The composition $C_{13}H_{19}O_5N$ was identical with that of the starting material XIII. The IR and NMR spectra supported the structure of XIV, namely a ketone and a secondary amide in the IR spectrum, and three methoxy

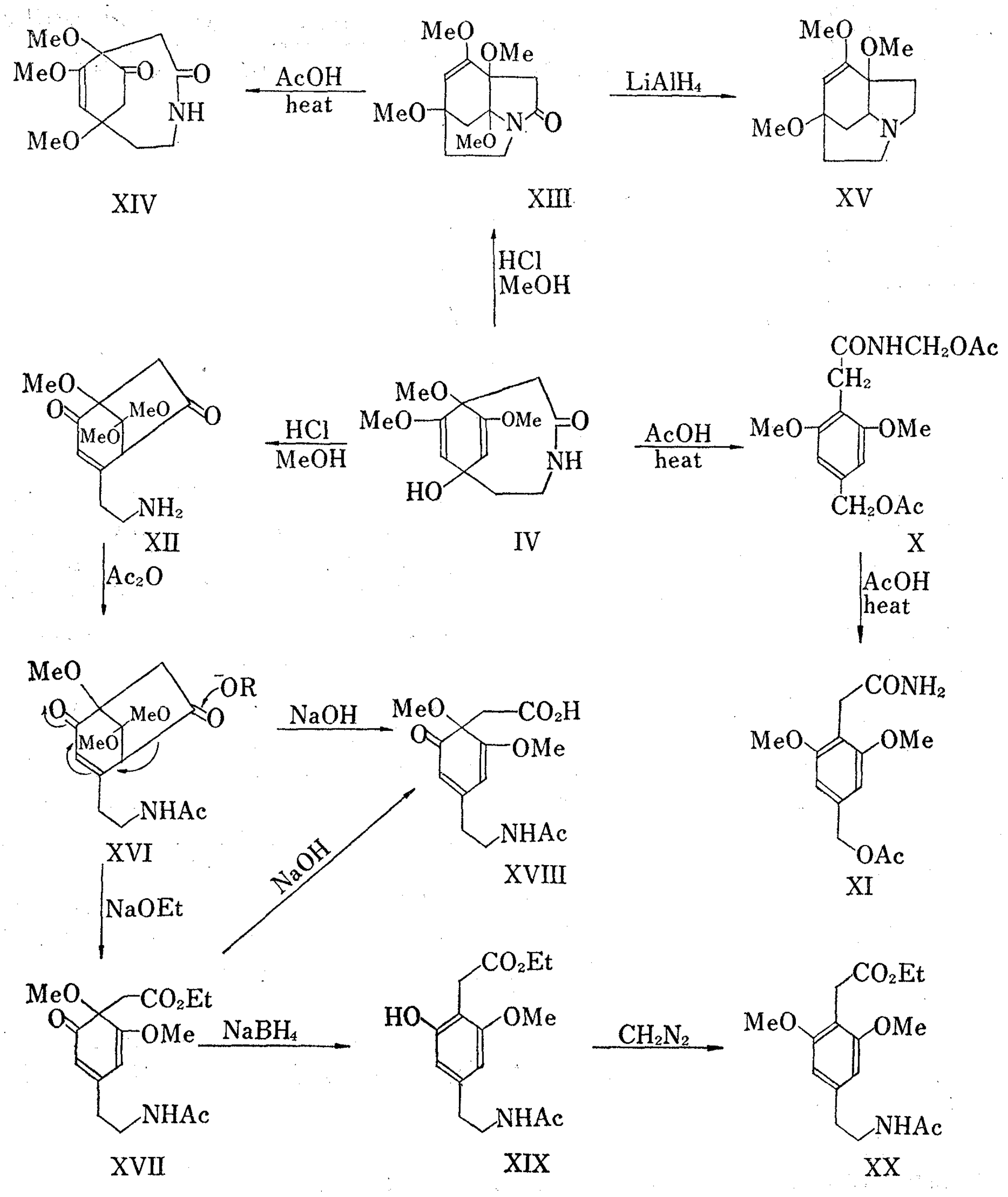


Chart 2

groups and a vinyl proton in the NMR spectrum could be assigned. Lithium aluminium hydride reduced the methoxy group in the α-methoxyamine moiety as well as the amide group to yield XV.

Compound XII is fairly unstable to alkali though stable to acid. When the acetate of XII (XVI) was treated for only 10 min with sodium methoxide the ring opening reaction took place to yield ethyl 1,6-dimethoxy-4-(2-acetylaminoethyl)-2-oxo-1,2-dihydrophenylacetate (XVII) as a yellow oil. The structure was established by the spectral data and the mechanistic consideration. Compound XVII was easily hydrolyzed with dilute aqueous sodium hydroxide to the corresponding acid XVIII, which was also obtained directly by the treatment with aqeuous sodium hydroxide. Reduction of the carbonyl group in XVII caused loss of methanol and aromatization to a phenolic compound XIX, whose UV λ_{max} appeared at 279 nm and shifted to 293 nm by the addition of sodium hydroxide. The treatment of XIX with excess of diazomethane overnight gave the corresponding methoxy compound XX. The structure of XVII, XVIII, XIX, and XX were also confirmed by the mass spectrometry.

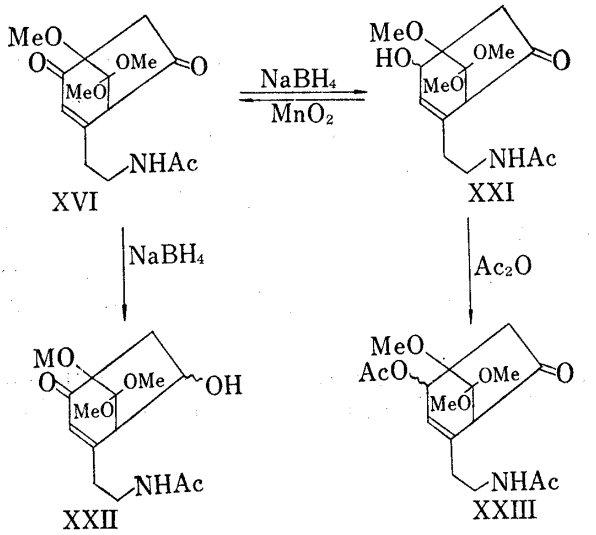
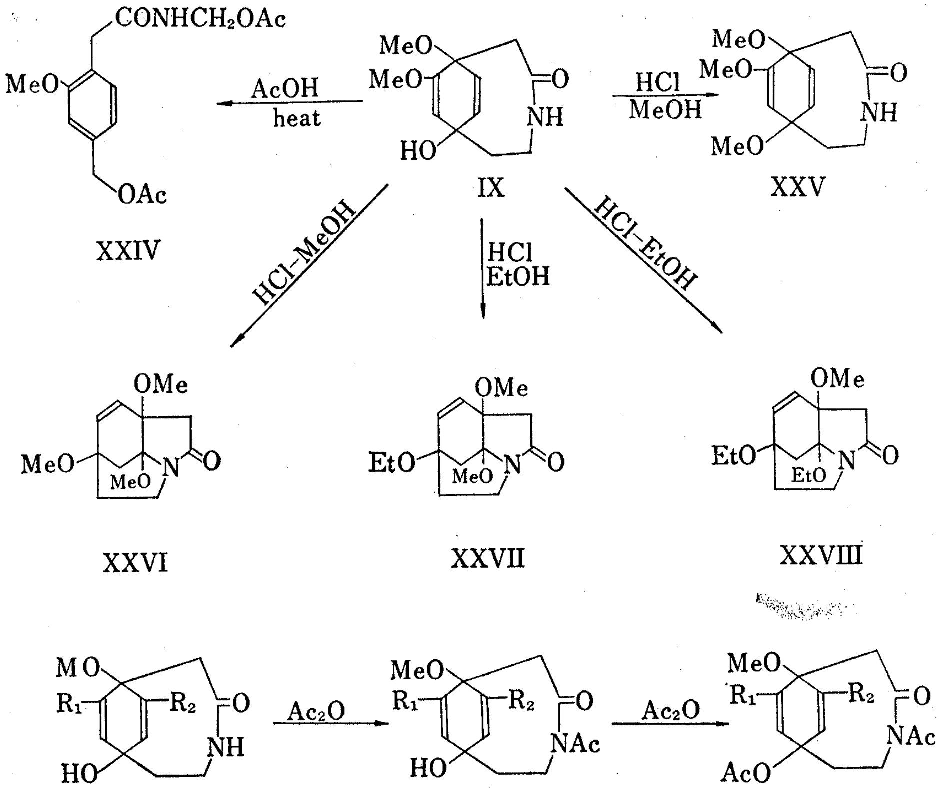


Chart 3



VIII : $R_1=R_2=H$
IX : $R_1=OMe$, $R_2=H$
IV : $R_1=R_2=OMe$

XXIX : $R_1=R_2=H$
XXX : $R_1=OMe$, $R_2=H$
XXXI : $R_1=R_2=OMe$

XXXII : $R_1=R_2=H$
XXXIII : $R_1=OMe$, $R_2=H$

Chart 4

The sodium borohydride reduction of XVI was also of interest. Both carbonyl groups at the 2 and 6 positions could be reduced to XXI and XXII, though the former, the reduction product of the α,β-unsaturated carbonyl group was isolated in much more higher yield than the latter. The compound XXI was easily converted to O-acetate XXIII, and returned to XVI by the mild oxidation with active manganese dioxide.

The photoproduct VIII containing no enol-ether group was expectedly stable to acids. On the treatment with acetic acid or hydrochloric acid in methanol, VIII was recovered unchanged almost quantitatively. On the other hand, the photoproduct IX containing one enol-ether group was fairly unstable to acids. When IX in acetic acid was heated under reflux, in analogy with IV, the novel fragmentation reaction took place to yield an aromatized product XXIV, whose fragmentation pattern in the mass spectrum was very similar to that of X. On the treatment of IX with hydrochloric acid in methanol, 7-methoxy compound XXV and the transannular reaction product XXVI were isolated. The structures of XXV and XXVI were determined by their NMR and mass spectra. Similarly, the treatment with hydrochloric acid in ethanol gave 7-ethoxy compound XXVII and a diethoxy compound as a minor product, the structure of the latter is presumably 1-methoxy-7,10-diethoxy-4-azatricyclo[5,2,2,$0^{4,10}$]undeca-8-en-3-one (XXVIII).

Finally, on heating with acetic anhydride, all three photoproducts (IV, VIII, and IX) were interestingly converted first to N-acetates (XXIX, XXX, and XXXI) and then N,-O-diacetates (XXXII and XXXIII).

Experimental

Photocyclization of N-Chloroacetyl-4-methoxyphenethylamine (I)——A solution of 559 mg (2.46 mmole) of N-chloroacetyl-4-methoxyphenethylamine (I) in 50 ml of ethanol and 450 ml of water was irradiated with 100 watt high pressure mercury lamp under nitrogen for 2 hr. The solution was stirred with 700 mg of silver carbonate for 15 min to remove chloride ion and the silver salts were then removed by filtration over Celite. The filtrate was concentrated to *ca.* 50 ml *in vacuo* and nine batches totaling a volume of 450 ml were combined and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated to give 991 mg of a brown oil, which was chromatographed on 10 g of silica gel column. Elution with ethyl acetate gave 370 mg of crude 7-formyl-1,2,5,6-tetrahydro-3H-pyrrolo-[1,2-*a*]azepin-3-one (V) and 260 mg (6.1%) of 8-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI). The crude VI was recrystallized from ethyl acetate–*n*-hexane to give colorless needles, mp 163—164°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.34; H, 6.93; N, 7.43. IR ν_{max}^{Nujol} cm^{-1}: 3310, 1633. UV λ_{max}^{EtOH} nm (ε): 279 (1980). Mass Spectrum *m/e*: 191 (M^+), 162, 135, 134. NMR $\delta_{max}^{CDCl_3}$: 7.07—6.62 (4H, m, 1H was disappeared by the addition of D_2O), 3.75 (5H, s), 3.63—3.35 (2H), 3.09—2.88 (2H).

The aqueous layer on evaporation *in vacuo* left 3.95 g of a brown oil, which was chromatographed on a column containing 32 g of silica gel. Elution with ethyl acetate gave a yellow solid, which was recrystallized from methanol to give 775 mg (16.7%) of colorless prisms of 1-methoxy-7-hydroxy-4-azabicyclo[5,2,2]-undeca-8,10-dien-3-one (VIII), mp 217—218°. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.12; H, 7.20; N, 6.80. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3230, 1642. UV: no λ_{max}^{EtOH} above 210 nm. Mass Spectrum *m/e*. 209 (M^+), 194, 150 (base peak). NMR δ^{D_2O}: 6.4—5.78 (4H), 3.29 (3H, s), 3.4—3.15 (2H), 3.24 (1H, d, $J=14$ Hz), 2.55 (1H, d, $J=14$ Hz), 2.1—1.8 (2H).

7-Trifluoroacetoxy-1-methoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXXIV)——Compound VIII was dissolved in large excess of trifluoroacetic anhydride at room temperature, and after 10 min the solution was evaporated *in vacuo* to leave an oil, which was crystallized by the addition of a drop of ethyl acetate. Recrystallization from ethyl acetate–*n*-hexane gave colorless needles (92%), mp 162—163° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}O_4NF_3$: C, 51.15; H, 4.62; N, 4.59. Found: C, 51.48; H, 4.53; N, 4.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1788, 1658. Mass Spectrum *m/e*: 192 [$M^+(305)-CF_3CO_2(113)$], 191, 149 (base peak). NMR $\delta_{max}^{CDCl_3}$: 1.7—2.5 (2H, m), 2.74 (1H, d, $J=13$ Hz), 2.96 (1H, d, $J=13$ Hz), 3.23 (3H, s), 3.1—3.6 (2H, m), 5.9—6.4 (4H), 6.2—6.7 (1H, broad).

A methanol solution (2 ml) of 30 mg of XXXIV was treated excess saturated aqueous sodium bicarbonate solution (*ca.* 1 ml) at room temperature for 20 min. The solution was evaporated *in vacuo* to dryness and the residue was extracted with methanol. After evaporation of methanol the residue was recrystallized from methanol–ether to give 16.1 mg (78.5%) of colorless prisms of VIII, mp 214—215°.

2-(2-Aminoethyl)-5-hydroxyphenylacetic Acid (VII)——To 121 mg (0.633 mmole) of VI was added 5 ml of 48% hydrobromic acid and the mixture was heated under reflux at 140° (bath temp.) for 1.5 hr. The hydrobromic acid was evaporated to dryness *in vacuo* to leave a brown solid, which was washed a small amount of absolute acetone and kept in an alkaline desiccator overnight. Recrystallization from ethanol–ether gave 107 mg (61.2%) of VII-hydrobromide as colorless plates, mp 192—193°. *Anal.* Calcd. for $C_{10}H_{14}O_3NBr$: C, 43.50; H, 5.11; N, 5.11; Br, 28.94. Found: C, 43.62; H, 5.27; N, 5.55; Br, 28.87. IR ν^{Nujol} cm^{-1}: 3400, 3280—3000, 1700. UV $\lambda_{max}^{H_2O}$ nm (ε): 277 (1650). NMR δ^{D_2O}: 2.8—3.4 (4H), 3.74 (2H, s), 6.78—7.29 (3H).

1,9-Dimethoxy-7-hydroxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (IX)——A solution of 1.48 g of N-chloroacetyl-3,4-dimethoxyphenethylamine (II) in 50 ml of ethanol and 240 ml of water was irradiated with 100 watt high pressure mercury lamp under nitrogen for 1.5 hr. The solution was stirred with excess silver carbonate, and the silver salts were removed by filtration. The filtrate was concentrated to *ca.* 50 ml and two batches totaling a volume of 100 ml were combined and extracted with methylene chloride. The extract was dried and evaporated to leave 2.055 g of a pale yellow solid, which contained 7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one, 8,9-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one and 1,2,5a,7b-tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3 *gh*]pyrrolizin-4(5H)-one as described in the previous paper.[2c)]

The aqueous layer was evaporated *in vacuo* to leave 279 mg of a pale brown oil, which was chromatographed on a silica gel column (6 g). Elution with ethyl acetate–ether (5:1) gave 148 mg (5.4%) of a colorless crystalline powder of 1,9-dimethoxy-7-hydroxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (IX) which was recrystallized from methanol–ether three times to give colorless prisms, mp 210—213°. *Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.16; H, 7.35; N, 5.73. IR ν^{Nujol} cm^{-1}: 3340, 3270, 1625. UV: no λ_{max} above 210 nm. Mass Spectrum *m/e*: 239 (M^+), 224, 180, 167, 156, 139, 137. NMR δ^{D_2O}: 1.5—2.1 (2H, m), 2.25—2.7 (2H, m), 3.18 (3H, s), 3.1—3.4 (2H, m), 3.59 and 3.77 (3H),[6)] 5.0—5.1 (1H), 5.68—6.25 (2H).

1,7,9,10-Tetramethoxy-4-azatricyclo[5,2,2,$0^{4,10}$]undeca-8-en-3-one (XIII)——To a ice-cooled methanol solution (15 ml) of 1.0 g (3.72 mmole) of 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (IV) was added 15 ml of 4N hydrochloric acid in methanol, and the solution was allowed to stand in a refrigerator overnight. After evaporation of methanol the residue was recrystallized from methanol–ether to give 805 mg (71%) of 1,8,8-trimethoxy-2,6-dioxo-4-(2-aminoethyl)-bicyclo[3,2,1]oct-3-ene (XII) hydrochloride, mp 122—124°. The filtrate was chromatographed on a silica gel column (25 g), elution with ethyl acetate, and recrystallization from ethyl acetate–*n*-hexane gave 235 mg (22.4%) of 1,7,9,10-tetramethoxy-4-azatricyclo[5,2,2,$0^{4,10}$]undeca-8-en-3-one (XIII) as colorless prisms, mp 135—136°. *Anal.* Calcd. for $C_{14}H_{21}O_5N$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.12; H, 7.59; N, 4.96. UV: no λ_{max} above 210 nm. IR ν^{Nujol} cm^{-1}: 1705, 1650. Mass Spectrum *m/e*: 283 (M^+), 268 (base peak), 252, 236, 221. NMR δ^{CDCl_3}: 1.61—1.94 (2H, m), 2.16 (2H, s), 2.51 (1H, d, $J=15$ Hz), 2.93 (1H, d, $J=15$ Hz), 2.9—3.2 (1H, m), 3.25 (3H, s), 3.37 (3H, s), 3.44 (3H, s), 3.59 (3H, s), 4.04—4.45 (1H, m), 4.91 (1H, s).

1,7,9-Trimethoxy-4-azabicyclo[5,2,2]undeca-8-en-3,10-dione (XIV)——A solution of 82 mg of XIII in 2 ml of acetic acid containing 1 drop of water was heated under reflux for 5 hr. Evaporation of acetic acid left a colorless solid, which was recrystallized from ethyl acetate–*n*-hexane to give 58 mg (88%) of colorless leaflets of 1,7,9-trimethoxy-4-azabicyclo[5,2,2]undeca-8-en-3,10-dione (XIV), mp 152—153°. *Anal.* Calcd. for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.67; H, 6.80; N, 5.28. UV: no λ_{max} above 210 nm. IR ν^{Nujol} cm^{-1}: 3400, 1680, 1655, 1645. Mass Spectrum *m/e*: 269 (M^+), 254 (base peak), 238, 222. NMR δ^{CDCl_3}: 1.6—1.89 (2H, m), 2.01 (1H, d, $J=12$ Hz), 2.22 (1H, d, $J=12$ Hz), 2.59 (1H, d, $J=15$ Hz), 2.85 (1H, d, $J=15$ Hz), 3.0—3.25 (1H, m), 3.25 (3H, s), 3.50 (3H, s), 3.60 (3H, s), 3.85—4.3 (2H, m; add D_2O, 1H, m), 4.91 (1H, s).

1,7,9-Trimethoxy-4-azatricyclo[5,2,2,$0^{4,10}$]undeca-8-ene (XV)——A tetrahydrofuran solution (30 ml) of 61 mg of XIII and 30 mg of lithium aluminium hydride was heated under gentle reflux for 3 hr. After addition of 130 mg of water the precipitated salts were removed by filtration and the filtrate was evaporated to leave an oil, which was chromatographed on a alumina column (5 g) eluting with ethyl acetate to give a colorless solid. Recrystallization from ethyl acetate–*n*-hexane gave 21 mg of colorless needles of 1,7,9-trimethoxy-4-azatricylo[5,2,2,$0^{4,10}$]undeca-8-ene (XV), mp 89—90°; picrate, mp 170—172° (ethyl acetate–*n*-hexane). Mass Spectrum *m/e*: 239 (M^+), 224 (base peak), 208, 194. NMR δ^{CDCl_3}: 1.5—2.1 (6H, m), 2.6—2.95 (4H, m), 3.28 (3H, s), 3.32 (3H, s), 3.3—3.5 (1H), 3.64 (3H, s), 4.73 (1H, s).

1,8,8-Trimethoxy-2,6-dioxo-4-(2-acetylaminoethyl)-bicyclo[3,2,1]oct-3-ene (XVI)——i) To 306 mg (1 mmole) of 1,8,8-trimethoxy-2,6-dioxo-4-(2-aminoethyl)bicyclo[3,2,1]oct-3-ene (XII) hydrochloride and 83 mg (1.01 mmole) of anhydrous sodium acetate were added 3 ml of acetic anhydride and 5 ml of benzene, and the mixture was heated at 60° for 1 hr. After evaporation of the acetic anhydride, the residue was dissolved in ethyl acetate, washed with water, dried, and the solvent was evaporated to leave a pale yellow solid. Recrystallization from ethyl acetate–ether gave colorless prisms (269 mg, 86.5%) of 1,8,8-trimethoxy-2,6-dioxo-4-(2-acetylaminoethyl)-bicyclo[3,2,1]oct-3-ene (XVI), mp 119—120°. *Anal.* Calcd. for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50. Found: C, 58.03; H, 6.80; N, 4.39. IR ν^{Nujol} cm^{-1}: 3325, 1755, 1686, 1644, 1624, 1555. Mass Spectrum *m/e*: 311 (M^+), 296, 279, 237, 222 (base peak), 2.5, 193. NMR δ^{CDCl_3}: 2.8—3.4 (4H, m), 3.22 (3H, s), 3.42 (1H, s), 3.53 (3H, s), 3.2—3.6 (2H), 3.64 (3H, s), 6.01 (1H, s).

ii) A chloroform solution (1.5 ml) of 7 mg of 1,8,8-trimethoxy-2-hydroxy-6-oxo-4-(2-acetylaminoethyl)-bicyclo[3,2,1]oct-3-ene (XXI) was stirred with 70 mg of active manganese dioxide at room temperature for 20 hr. After removal of manganese dioxide by filtration, the filtrate was concentrated to leave an oil, which was chromatographed on a preparative alumina thin-layer chromatography (TLC) developing with ethyl acetate to yield 4.7 mg of XVI, mp 119°, identical with the preceding product XVI with regard to the IR, UV and mass spectra.

Ethyl 1,6-Dimethoxy-4-(2-acetylaminoethyl)-2-oxo-1,2-dihydrophenylacetate (XVII)——A sodium ethoxide solution (20 mg of sodium in 1 ml of ethanol) was added to a solution of 50 mg (0.162 mmole) of XVI in 4 ml of ethanol. After 10 min, the solution was concentrated *in vacuo* and chromatographed on silica gel preparative TLC eluting with ethyl acetate–ethanol (10:1) to give 48 mg (92%) of ethyl 1,6-dimethoxy-4-(2-acetylaminoethyl)-2-oxo-1,2-dihydrophenylacetate (XVII) as a yellow oil. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 356 (2100); $\lambda_{\max}^{96\%\,\mathrm{H_2SO_4}}$ nm: 268, 470. IR ν cm^{-1}: 3340, 1741, 1669, 1635, 1560. Mass Spectrum *m/e*: 325 (M$^+$), 294, 247 (base peak), 205. NMR $\delta^{\mathrm{CDCl_3}}$: 1.18 (3H, t, $J=7$ Hz), 1.92 (3H, s), 2.53 (2H, t, $J=7$ Hz), 3.09 (5H, s), 3.25—3.7 (2H, m,), 3.78 (3H, s), 4.00 (2H, q, $J=7$ Hz), 5.45 (1H, s), 5.84 (1H, s), 6.29 (1H, broad).

1,6-Dimethoxy-4-(2-acetylaminoethyl)-2-oxo-1,2-dihydrophenylacetic Acid (XVIII)——i) A solution of 50 mg (0.162 mmole) of XVI in 1.5 ml of methanol was treated with 1.5 ml of 1N aqueous sodium hydroxide at room temperature for 1 hr. The solution was neutralized by the addition of Amberite IR-120, and the filtrate was concentrated *in vacuo* to leave 46 mg of a yellow solid. Recrystallization from ethanol–ether gave yellow prisms (39 mg, 81.7%) of 1,6-dimethoxy-4-(2-acetylaminoethyl)-2-oxo-1,2-dihydrophenylacetic acid (XVIII), mp 140° (deccmp.). *Anal.* Calcd. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.50; H, 6.51; N, 4.76. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 357 (2300). IR $^{\mathrm{Nujol}}$ cm^{-1}: 3350, 2720—2500, 1720, 1669, 1619, 1559. NMR $\delta^{\mathrm{DMSO\text{-}d_6}}$: 2.26—2.50 (2H, m), 2.78 (2H, s), 2.88 (3H, s), 3.05—3.38 (2H, m), 3.63(3H, s), 5.58 (1H, s), 5.65 (1H, s), 7.70 (1H, broad).

ii) A ethanol solution (1 ml) of 45 mg (0.137 mmole) of XVII was treated with 0.3 ml of 1N sodium hydroxide at room temperature for 1.5 hr. The solution was neutralized with Amberite IR-120, and the filtrate was evaporated to yield a yellow solid, which was recrystallized from ethanol–ether to give 35 ml (85.2%) of yellow prisms, mp 138—140° (decomp.).

Ethyl 4-(2-Acetylaminoethyl)-2-hydroxy-6-methoxyphenylacetate (XIX)——A solution of 20 mg (0.0616 mmole) of XVII in 2 ml of ethanol containing 5 mg of sodium borohydride was stirred at room temperature for 10 min. The solution was acidified by the addition of acetic acid and concentrated *in vacuo*. The residue was chromatographed on a preparative silica gel TLC eluting with ethyl acetate to give a colorless solid, which was recrystallized from chloroform to afford 7 mg (38.8%) of colorless needles, mp 151—152°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 279; $\lambda_{\max}^{\mathrm{NaOH\text{-}EtOH}}$ nm: 293. Mass Spectrum *m/e*: 295 (M$^+$), 249, 190 (base peak), 177, 162.

Ethyl 4-(2-Acetylaminoethyl)-2,6-dimethoxyphenylacetate (XX)——To a solution of 3 mg of XIX in 0.2 ml of ethanol was added excess diazomethane solution in ether, and the mixture was allowed to stand at room temperature overnight. After evaporation of solvents, the residue was chromatographed on a preparative alumina TLC eluting with ethyl acetate to give 2 mg of a colorless oil. Mass Spectrum *m/e*: 309 (M$^+$), 250, 236, 176 (base peak), 163. IR $\nu^{\mathrm{CHCl_3}}$ cm^{-1}: 3380, 1728, 1660.

1,8,8-Trimethoxy-2-hydroxy-6-oxo-4(2-acetylaminoethyl)-bicyclo[3,2,1]oct-3-ene (XXI)——A methanol solution (4 ml) of 99 mg of XVI and 11 mg of sodium borohydride was stirred under ice-cooling for 1 hr. After the addition of acetic acid to decompose excess sodium borohydride, the solvent was evaporated to leave a colorless oil, which was chromatographed on a alumina column (15 g). Elution with ethyl acetate–ethanol (20:1) gave 71 mg of 1,8,8-trimethoxy-2-hydroxy-6-oxo-4(2-acetylaminoethyl)-bicyclo[3,2,1]oct-3-ene (XXI) as a colorless oil, which was crystallization by trituration. Recrystallization from ethyl acetate–*n*-hexane gave colorless prisms, mp 153—154°. *Anal.* Calcd. for $C_{15}H_{23}O_6N$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.36; H, 7.45; N, 4.30. UV: no $\lambda_{\max}$ above 210 nm. IR ν^{Nujol} cm^{-1}: 3580, 3330, 1760, 1655. Mass Spectrum *m/e*: 313 (M$^+$), 295, 282, 263, 250, 240, 222. NMR $\delta^{\mathrm{CDCl_3}}$: 1.95 (3H, s), 2.20—2.80 (4H, m), 3.00 (1H, s), 3.06 (1H, s), 3.27 (3H, s), 3.49 (3H, s), 3.52 (3H, s), 3.06—3.27 (2H, m), 4.30 (1H, d, $J=5$ Hz), 5.80 (1H, d, $J=5$ Hz), 6.05 (1H, broad).

1,8,8-Trimethoxy-6-hydroxy-2-oxo-4-(2-acetylaminoethyl)bicyclo[3,2,1]oct-3-ene (XXII)——Further elution with ethyl acetate–ethanol (20:1) gave 24 mg of 1,8,8-trimethoxy-6-hydroxy-2-oxo-4-(2-acetylaminoethyl)bicyclo[3,2,1]oct-3-ene as a colorless oil. UV λ^{EtOH} nm: 242. IR ν cm^{-1}: 3560, 3400, 1690 (shoulder), 1670, 1515. Mass Spectrum *m/e*: 313 (M$^+$), 295, 280, 263, 233, 221, 206.

1,8,8-Trimethoxy-2-acetoxy-6-oxo-4-(2-acetylaminoethyl)bicyclo[3,2,1]oct-3-ene (XXIII)——A solution of 65 mg of XXI in 1 ml of acetic anhydride was heated at 100° for 1 hr. After evaporation of acetic anhydride, the residue was purified on a preparative alumina TLC to yield 47 mg of a colorless solid, which was recrystallized from ether to give colorless prisms, mp 82—85°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3480, 3400, 1760, 1740, 1670, 1515. Mass Spectrum *m/e*: 355 (M$^+$), 323, 295, 282, 280, 264, 250, 246, 223, 222, 205 (base peak).

N-Acetoxymethyl-2-methoxy-4-acetoxymethylphenylacetamide (XXIV)——Compound IX in acetic acid was heated under reflux for 1 hr. After evaporation of the acetic acid, the residue was chromatographed on a preparative silica gel TLC. Elution with ethyl acetate–methylene chloride (3:2) gave three spots. One of them (*Rf=ca.* 0.7) was examined by mass spectrometry, *m/e*: 309 (M$^+$), 281 (w), 249, 220, 193 (base peak), 165. The fragmentation pattern is quite similar to that of X.[3]

1,7,9-Trimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXV)——To a solution of 155 mg of IX in 3 ml of methanol was added 6 ml of 2N hydrogen chloride in methanol, and the solution was allowed to stand overnight at room temperature. After evaporation of the solvent, the residue was recrystallized from methanol–ether to afford 70 mg (42.7%) of 1,7,9-trimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXV), mp 218—222°. *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.36; H, 7.60; N, 5.44. IR ν^{Nujol} cm^{-1}: 3280, 1640. Mass Spectrum *m/e* 253 (M^+), 238, 222, 194, 181 (base peak), 168, 153, 151. NMR $\delta^{\mathrm{CDCl_3}}$: 3.19 (3H, s), 3.38 (3H, s), 3.59 and 3.27 (3H).6)

1,7,9-Trimethoxy-4-azatricyclo[5,2,2,0^{4,10}]undeca-8-en-3-one (XXVI)——The filtrate on evaporation gave 118 mg of an oil, which was chromatographed on a silica gel column (15 g) and elution with ethyl acetate gave 58 mg (35.4%) of XXVI as a colorless oil. IR ν cm^{-1}: 1715. Mass Spectrum *m/e*: 253 (M^+), 238 (base peak), 222, 206. NMR $\delta^{\mathrm{CDBl_3}}$: 1.55—1.9 (2H, m), 2.15 (2H, s), 2.13 (1H, d, $J=14$ Hz), 2.95 (1H, d, $J=14$ Hz), 2.9—3.3 (1H), 3.21 (3H, s), 3.34 (3H, s), 3.40 (3H, s), 4.0—4.4 (1H,) 5.49 (1H, d, $J=11$ Hz), 5.94 (1H, d, $J=11$ Hz).

1,10-Dimethoxy-7-ethoxy-4-azatricyclo[5,2,2,0^{4,10}]undeca-8-en-3-one (XXVII) and 1-Methoxy-7,10-diethoxy-4-azatricyclo[5,2,2,0^{4,10}]undeca-8-en-3-one (XXVIII)——A solution of 192 mg of IX in 15 ml of 2N hydrochloric acid in ethanol was allowed to stand overnight at room temperature. After evaporation of the solvent, the residue was recrystallized from ethanol–ether to afford 28 mg of the starting material. The filtrate (187 mg) after evaporation was chromatographed on a silica gel column, and elution with ethyl acetate gave an oil (12 mg) of 1-methoxy-7,10-diethoxy-4-azatricyclo[5,2,2,0^{4,10}]undeca-8-en-3-one (XXVIII). IR ν cm^{-1}: 1718. Mass Spectrum *m/e*: 281 (M^+), 252, 238, 149 (base peak).

The second fraction gave 24 mg of 1,10-dimethoxy-7-ethoxy-4-azatricyclo[5,2,2,0^{4,10}]undeca-8-en-3-one (XXVII) as an oil. IR ν cm^{-1}: 1718. Mass Spectrum *m/e*: 267 (M^+), 252, 238, 149 (base peak). NMR $\delta^{\mathrm{CDCl_3}}$: 1.18 (3H, t, $J=7$ Hz), 1.6—1.9 (2H), 2.16 (1H, d, $J=14$ Hz), 2.22 (2H, s), 3.00 (1H, d, $J=14$ Hz), 2.8—3.3 (1H, m), 3.49 (2H, q, $J=7$ Hz), 3.8—4.6 (1H, m), 3.40 (3H, s), 3.46 (3H, s), 5.42 (1H, d, $J=9$ Hz), 6.00 (1H, d, $J=9$ Hz).

N-Acetyl-7-hydroxy-1-methoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXIX)——A solution of 105 mg (0.5 mmole) of VIII in 5 ml of acetic anhydride was heated at 130° for 15 min. After evaporation of the acetic anhydride, the oil was separated with a preparative silica gel TLC (methylene chloride, acetic acid, 1:1). Fraction A (*Rf*=0.6) gave 72 mg (57%) of N-acetyl-7-hydroxy-1-methoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXIX), which was recrystallized from ether–*n*-hexane to afford colorless prisms, mp 71—72°. *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.63; H, 6.80; N, 5.57. IR ν^{Nujol} cm^{-1}: 3520, 1693. Mass Spectrum *m/e*: 234 (M^+-17), 209, 192, 164, 150 (base peak), 137, 124. NMR $\delta^{\mathrm{CDCl_3}}$: 1.99 (2H, m), 2.33 (3H, s), 2.39 (1H, s), 3.10 (2H, s), 3.18 (3H, s), 3.62 (2H, m), 5.97 (4H, s).

N-Acetyl-7-acetoxy-1-methoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXXII)——i) Fraction B (*Rf*=0.8) gave 23 mg (15.6%) of N-acetyl-7-acetoxy-1-methoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (XXXII), which was recrystallized from ether–*n*-hexane to afford colorless prisms, mp 73.5—74.5°. *Anal.* Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.59; H, 6.57; N, 4.77. IR ν^{Nujol} cm^{-1}: 1745, 1694. Mass Spectrum *m/e*: 251 (M^+-42), 236, 208, 192, 150 (base peak), 137, 124. NMR $\delta^{\mathrm{CDCl_3}}$: 1.99 (3H, s), 2.09 (2H, m), 2.37 (3H, s), 3.11 (2H, s), 3.23 (3H, m), 3.65 (2H, m), 5.99 (4H, s).

ii) Twenty mg of XXIX in 1 ml of acetic anhydride was heated at 130° for 2 hr and treated as described above to give 18 mg (77.2%) of XXXII.