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Photocyclization of N-Chloroacetyl-3-methoxyphenethylamine and N-Chloroacetyl-3,5-dimethoxyphenethylamine

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On irradiation of N-chloroacetyl derivatives of 3-methoxyphenethylamine (VII) and 3,5-dimethoxyphenethylamine (XV) in 10% aqueous ethanol, 1,2,4,5-tetrahydro-3H-3-benzazepin-2-ones (VIII, IX, and XVI) were synthesized in good yield, whereas in ethanol novel ten-membered lactams (XIII and XVII) were main products. The photo-reaction of N-chloroacetylphenethylamine (XXI) in the presence or absence of veratrol (XXV) gave the intermolecular reaction product (XXVI) or the radical reaction products (XXII and XXIV), which may support the proposed dualistic mechanism.

In the course of our extensive study on the photochemistry of pharmacodynamic amines,[2] N-chloroacetyl-3,4-dimethoxyphenethylamine (I) afforded benzazepinones (II, III), tetracyclic compound (IV), novel ten-membered lactam (V) and N-acetyl compound (VI).[3] The product distribution shows some dependence on the solvent, namely, on the photolysis in aqueous solution, II, III, and IV were mainly isolated, whereas in organic solvents, V and VI were main products. Among them benzazepinones (II, III) were produced by the photocyclization at the *para* and *ortho* positions to the methoxy group, whereas the ten-membered lactam (V) was formed by the cyclization on the *meta* methoxy group.

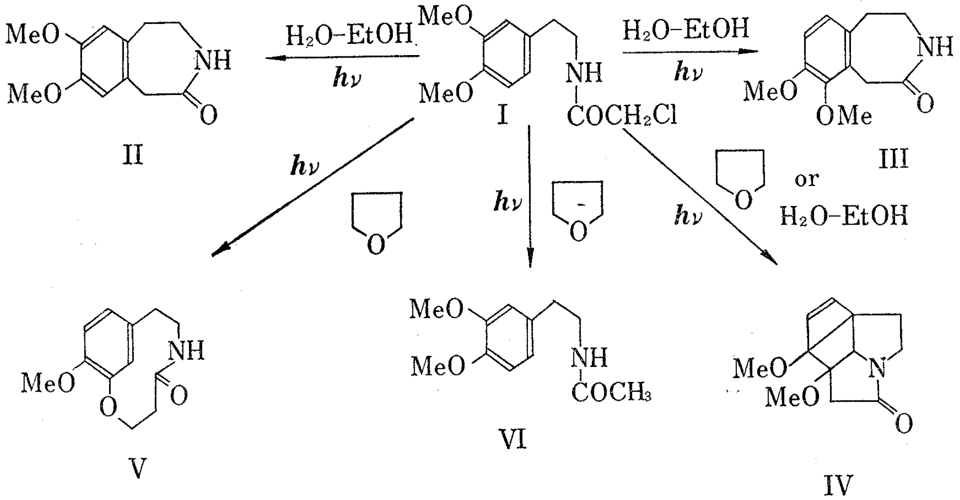

Chart 1

In the present paper, we chose N-chloroacetyl deivatives of 3-methoxyphenethylamine (VII) and 3,5-dimethoxyphenethylamine (XV) as better substrates for these photocyclization reactions.

When a 10 mM solution of N-chloroacetyl-3-methoxyphenethylamine (VII) in ethanol–water was irradiated with 100 W high pressure mercury lamp for 2 hr, two benzazepinones

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[1] Location: *Kita-12, Nishi-6, Sapporo.*
[2] O. Yonemitsu, H. Nakai, Y. Kanaoka, I.L. Karle and B. Witkop, *J. Am. Chem. Soc.*, **92**, 5691 (1970), and references cited therein.
[3] O. Yonemitsu, Y. Okuno, Y. Kanaoka and B. Witkop, *J. Am. Chem. Soc.*, **90**, 6522 (1968); *idem, inid.*, **92**, 5686 (1970).

(VIII, 27% and IX, 30%) were isolated by the column chromatography over silica gel. The elemental analyses and the spectral data (infrared (IR), ultraviolet (UV) and mass of VIII and IX are almost same, however in the nuclear magnetic resonance (NMR) spectra the aromatic protons of each compounds show different patterns. Benzazepinon VIII gives a typical pattern of 1,2,4-trisubstituted benzene (*ortho* coupling constant=9 Hz, *meta*=2 Hz, *para*=0), though IX gives a poorly separated multiplet. In order to confirm these structures, VIII and IX were heated with 48% hydrobromic acid to yield an amino acid (X) (IR: 1710 cm^{-1}) and a five-membered lactone (XI) (IR: 1800 cm^{-1}) respectively.

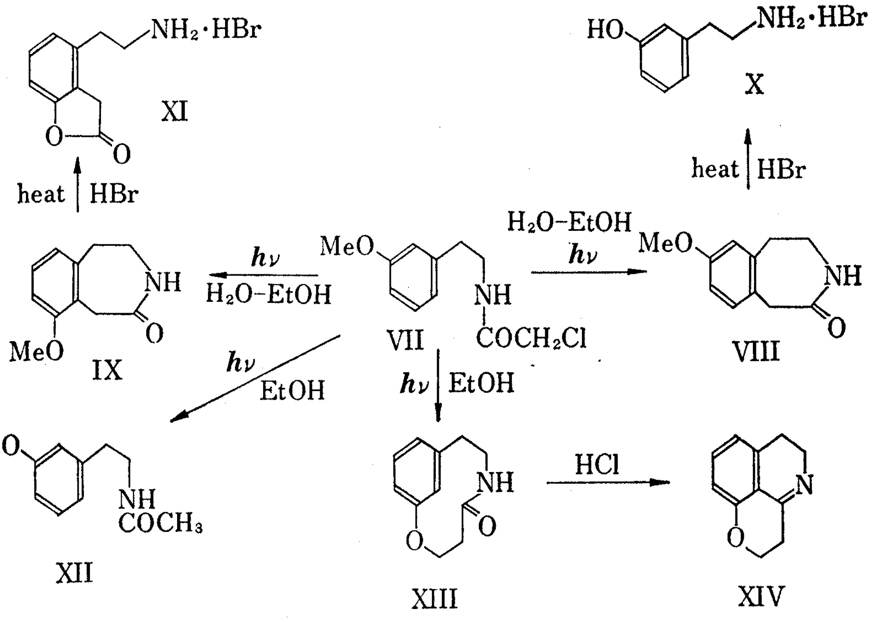

Chart 2

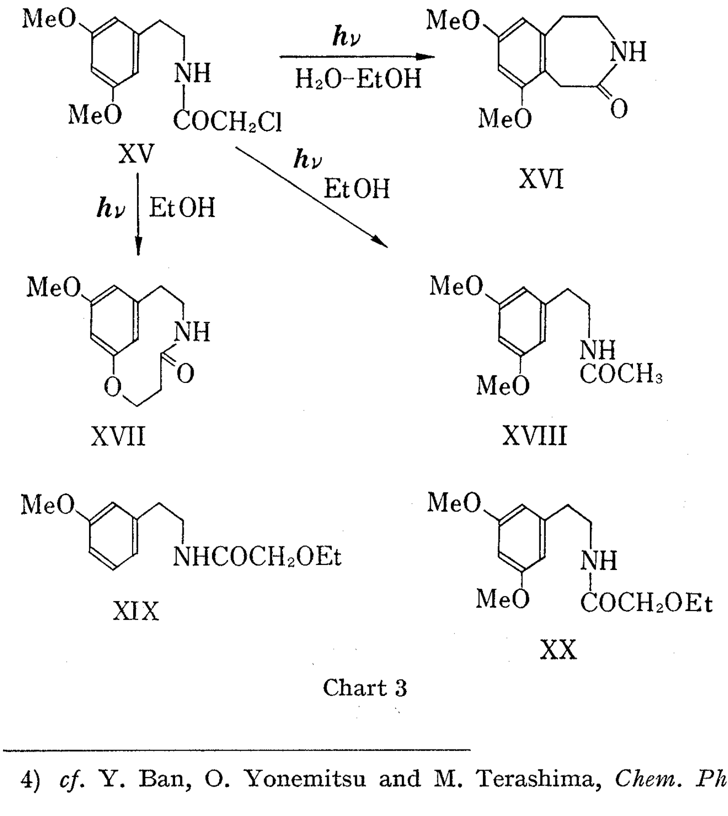

Chart 3

On irradiation of VII in ethanol, N-acetyl-3-methoxyphenethylamine (XII) produced by the photoreduction of C-Cl bond with the hydrogen donating solvent was mainly isolated, and a small amount of a novel ten-membered lactam (XIII) was also yielded. In the NMR spectrum four aromatic protons remain unchanged, though the methoxy group disappears. This NMR data indicates that the photocyclization has occured at the methoxy group. In analogy with the confirmation of V,[3] XIII was heated with hydrochloric acid in methanol to give a dihydroisoquinoline compound (XIV), whose chromophore, $\lambda_{max}=318$ and 340 (shoulder) nm, is easily assigned in the UV spectrum.[4]

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[4] *cf.* Y. Ban, O. Yonemitsu and M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **8**, 198 (1960).

In the case of N-chloroacetyl-3,5-dimethoxyphenethylamine (XV) on irradiation in ethanol–water, a benzazepinone (XVI) was isolated in high yield (70%) as a single product. In ethanol, a ten-membered lactam (XVII) was given in 7.6% yield.

On the photolysis in ethanol, VII and XV gave trace amounts of another products, which may be O-ethyl compounds XIX and XX respectively based on the mass spectra.

On the basis of fluorescence quenching,[5] solvent effect,[6] oxygen effect[6] and flash-photolysis,[7] we proposed recently the mechanism in which the benzazepinone was formed by *electron transfer* from the excited aromatic chromophore and the cage reaction *via energy transfer* afforded the ten-membered lactam.[6]

One of supporting data for the dualistic mechanism, electron transfer and energy transfer,[6] was provided by the photolysis of N-chloroacetylphenethylamine (XXI) with or without veratrol (XXIV).

When a 20 mM solution of N-chloroacetylphenethylamine (XXI) in ethanol–water was irradiated, the photoreaction proceeded very slowly and over one-third of the starting material was recovered. The main product was a reduction product, N-acetylphenethylamine (XXII), accompanied with a benzazepinone (XXIII) and a trace of a dimer, N,N-diphenethylsuccinamide (XXIV), whose structures were confirmed by the NMR and mass spectra and by the comparison with the authentic samples.[8,9] On the other hand, in the presence of equimolar veratrol (XXV), instead of the formation of XXIII and XXIV, the acetamide group was introduced to the *para* position to the methoxy group of XXV by the *intermolecular* reaction of the chloroamide group and the electron-rich aromatic nucleus to yield N-phenethyl-3,4-dimethoxyphenylacetamide (XXVI). The structure of XXVI was confirmed by the comparison with the authentic sample *via* a usual method from 3,4-dimethoxyphenylacetic acid and phenethylamine.

Compounds XXII and XXIV must have been formed by a typical radical process *via* the energy transfer from the excited benzene ring. However the originally inefficient intermolecular formation of XXVI must have occured *via* a different mechanism. Since XXV

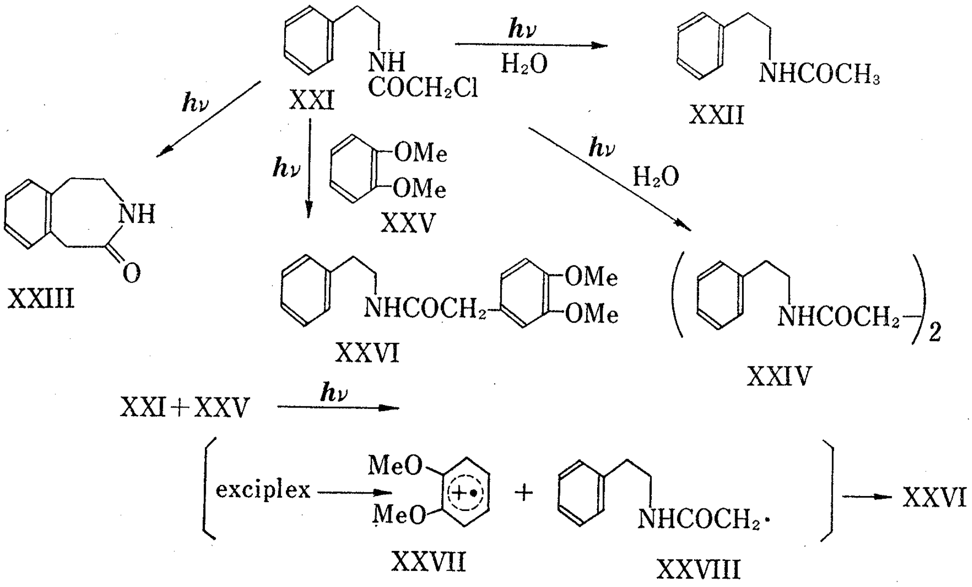

Chart 4

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[5] T. McCall, G.S. Hammond, O. Yonemitsu and B. Witkop, *J. Am. Chem. Soc.*, **92**, 6991 (1970).

[6] O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi and B. Witkop, *Photochem. Photobiol.*, **15**, 509 (1972).

[7] S. Naruto, O. Yonemitsu, N. Kanamaru and K. Kimura, *J. Am. Chem. Soc.*, **93**, 4053 (1971).

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

[9] R. Child and F.L. Pyman, *J. Chem. Soc.*, 2010 (1929).

has a lower ionization potential, the excited XXV released an electron to cleave the C-Cl bond of XXI *via* the intermolecular exciplex of XXI and XXV, followed by the radical reaction of probable intermediates (XXVII and XXVIII) to yield XXVI.

The solvent effect in the photolysis of VII and XV is considered to be as follows: in ethanol (dielectric constant, 24.3)[10] the photoexcitation of the aromatic chromophore being insufficient to the ionization causes mainly the radical process *via* the energy transfer, on the other hand in water with the highest dielectric constant (78.6)[10] the ionization potential of methoxybenzene is lowered to cause the electron-transfer process.

Experimental

Photocyclization of N-Chloroacetyl-3-methoxyphenethylamine (VII). A. In Water-Ethanol. 7-Methoxy- and 9-Methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VIII and IX)——A solution of 685 mg (3 mmole) of N-chloroacetyl-3-methoxyphenethylamine (VII) in 300 ml of 10% aqueous ethanol was irradiated for 2 hr with a high pressure mercury lamp (100 W Eikosha type) under nitrogen. Excess silver carbonate (500 mg) was added to the slightly yellow solution and the precipitated salts were then removed by filtration over Celite. The filtrate was concentrated to *ca.* 70 ml *in vacuo* at room temperature and extracted with ethyl acetate several times. The extract was dried over sodium sulfate and evaporated *in vacuo* to leave 550 mg of a pale yellow solid, which was taken up in 5 ml of ethyl acetate and placed on a chromatography column (1.5×29 cm) containing 27 g of silica gel. Ethyl acetate was passed through the column to elute the products, and the three fractions were obtained.

The first fraction was 15 mg (2%) of the starting material, and the pale yellow solid of the second was recrystallized from ethyl acetate to give 172 mg (30%) of 9-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (IX) as colorless leaflets, mp 163—164.5°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.86; H, 6.85; N, 7.04. Mass Spectrum m/e: 191 (M^+), 176, 162, 147, 135, 134, 117, 105, 104, 103, 91, 77. IR ν^{Nujol} cm^{-1}: 3240 (m), 3100 (w), 1665 (s). UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 277.5 (1630). NMR δ^{CDCl_3}: 3.05 (2H, t, $J=6$ Hz), 3.45 (2H, t, $J=6$ Hz), 3.78 (3H, s), 3.92 (2H, s), 6.45—6.95 (3H).

After recrystallization from ethyl acetate, the third fraction gave 155 mg (27%) of 7-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VIII) as colorless needles, mp 156—157.5°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.06; H, 6.81; N, 7.33. Mass Spectrum m/e: 191 (M^+), 147, 135, 134, 121, 117, 105, 104, 103, 91. IR ν^{Nujol} cm^{-1}: 3230 (m), 3100 (w), 1660 (s). UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 279.5 (1720). NMR δ^{CDCl_3}: 2.99 (2H, t, $J=6$ Hz), 3.48 (2H, t, $J=6$ Hz), 3.77 (5H, s), 6.58 (1H, d, $J=2$ Hz), 6.66 (1H, q, $J=2$ Hz and 9 Hz), 7.00 (1H, d, $J=9$ Hz).

B. In Ethanol. 2-Oxa-6-azabicyclo[7,3,1]trideca-1(13),9,11-trien-5-one (XIII)——A solution of 728 mg of VII in 320 ml of ethanol was irradiated with 10 W low pressure mercury lamp (Osawa Co.) for 2.5 hr in a steady stream of purified nitrogen.[11] The reaction mixture was treated as described above and 680 mg of a brown oil afforded from ethyl acetate extract was chromatographed on a alumina column (1.5×27 cm) to give 22 mg (3.6%) of 2-oxa-6-azabicyclo[7,3,1]trideca-1(13),9,11-trien-5-one (XIII). Recrystallization from ethanol-ether gave 16 mg (2.6%) of colorless needles, mp 245—246°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.99; H, 6.96; N, 7.35. IR ν^{Nujol} cm^{-1}: 3400, 3150, 1655. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 273 (710), $\lambda_{\max}^{\text{EtOH-HCl}}$ nm: 290, 356. Mass Spectrum m/e: 191 (M^+), 162, 134, 120. NMR δ^{CDCl_3}: 2.3—2.9 (4H), 3.1—3.3 (2H), 4.2—4.45 (2H), 6.85—7.1 (4H).

Other fractions were 50 mg (6.9%) of the starting material, 24 mg (3.9%) of IX, 35 mg (5.7%) of VIII and 264 mg (43%) of N-acetyl-3-methoxyphenethylamine (XII). IR ν^{Nujol} cm^{-1}: 3300, 1650, 1550. Mass Spectrum m/e: 193 (M^+), 134. A trace of N-ethoxyacetyl-3-methoxyphenethylamine (XIX) was also detected by the mass spectrum m/e: 237 (M^+), 149, 134.

Hydrobromic Acid Treatment of VIII and IX. 4-(2′-Aminoethyl)-2,3-dihydrobenzofuran-2-one (XI) Compound IX (*ca.* 40 mg) in 48% hydrobromic acid (*ca.* 8 ml) was heated under reflux for 1 hr. The yellow solution was then evaporated *in vacuo* at 100° and the brown residue was dried in an alkaline desiccator overnight. To the residue a small amount of 60% perchloric acid was added and a precipitated perchlorate was then collected by filtration and washed with cold water three times to remove excess acid. Recrystallization from water gave slightly yellow needles of XI, mp 226—228° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_6NCl$: C, 43.26; H, 4.36; N, 5.04. Found: C, 42.99; H, 4.11; N, 4.98. IR ν^{Nujol} cm^{-1}: 1800 (five-membered lactone).

Compound VIII was also treated with hydrobromic acid as described above to give an amino acid (X). IR ν^{Nujol} cm^{-1}: 1710.

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[10] *cf.* C. Reichardt, *Angew. Chem.*, 77, 30 (1965).

[11] L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, 1967, p. 393.

Photocyclization of N-Chloroacetyl-3,5-dimethoxyphenethylamine (XV). A. In Water-Ethanol. 7,9-Dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (XVI)——A solution of 621 mg (2.4 mmole) of N-chloroacetyl-3,5-dimethoxyphenethylamine (XV) in 240 ml of 10% aqueous ethanol was irradiated with 10 W mercury lamp for 40 min, and the reaction mixture was treated as described above. The ethyl acetate extract was chromatographed on a column (1×24 cm) of silica gel to give 410 mg (77%) of a colorless solid. Recrystallization from ethanol gave 370 mg (70%) of 7,9-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (XVI) as colorless needles, mp 183—184.5°. *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.76; N, 6.19. IR ν^{Nujol} cm^{-1}: 3240, 1675. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 279 (shoulder, 2200), 285 (2260). Mass Spectrum *m/e*: 221 (M^+), 206, 192, 177, 164, NMR δ^{CDCl_3}: 3.02 (2H), 3.45 (2H), 3.76 (6H, s), 3.83 (2H, s), 6.23 (1H, d, $J=3$ Hz), 6.30 (1H, d, $J=3$ Hz).

B. In Ethanol——A solution of 773 mg (3 mmole) of XV in 260 ml of ethanol containing 510 mg (1.8 mmole) of powdered silver carbonate was stirred under nitrogen and irradiated with 10 W lamp for 5 hr. The reaction mixture was filtered over Celite and the filtrate was evaporated *in vacuo* to leave an oil, which was taken up in *ca.* 150 ml of dichloromethane and washed with water. Evaporation of the solvent gave 700 mg of a viscous oil, which was chromatographed on alumina column to give four fractions.

The first fraction was 125 mg (16%) of the starting material and the second was 86 mg of a colorless solid, which was recrystallized from benzene–*n*-hexane to give 65 mg (9.7%) of N-acetyl-3,5-dimethoxyphenethylamine (XVIII) as colorless needles, mp 84—85°. *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.41; H, 7.64; N, 6.02. IR ν^{Nujol} cm^{-1}: 3320, 1630. Mass Spectrum *m/e*: 223 (M^+), 164. NMR δ^{CDCl_3}: 1.93 (3H, s), 2.86 (2H, t, $J=6$ Hz), 3.55 (2H, t, $J=6$ Hz), 3.80 (6H, s), 5.7 (1H, broad), 6.29 (3H, s).

The third fraction was crude crystal of 11-methoxy-2-oxa-6-azabicyclo[7,3,1]trideca-1(13),9,11-trien-5-one (XVII), which was recrystallized from ethanol–ether to give 50 mg (7.6%) of colorless needles, mp 206—209°. *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.00; H, 7.07; N, 6.41. IR ν^{Nujol} cm^{-1}: 3320, 1645. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 279.5 (1020), $\lambda_{\text{max}}^{\text{EtOH-HCl}}$ nm: 240, 247, 318, 340 (shoulder). Mass Spectrum *m/e*: 221 (M^+), 202, 192, 164. NMR δ^{CDCl_3}: 2.3—3.5 (6H), 3.75 (3H, s), 4.2—4.4 (2H), 6.25—6.55 (3H).

The final fraction was recrystallized from ethanol to give 50 mg (7.6%) of XVI. Between the first and second fractions a trace of N-ethoxyacetyl-3,5-dimethoxyphenethylamine (XX) was detected by the mass spectrum, *m/e*: 267 (M^+), 164.

Photolysis of N-Chloroacetylphenethylamine (XXI)——A solution of 1.191 g of N-chloroacetylphenethylamine (XXI) in 60 ml of ethanol and 240 ml of water was irradiated with 100 W high pressure mercury lamp under nitrogen for 6 hr. After the chloride ion was removed with the aid of silver carbonate, the solution was concentrated *in vacuo* at 40° to *ca.* 100 ml and extracted with methylene chloride. The extract was dried and evaporated to leave 972 mg of a pale yellow oil, which was chromatographed on four plates of preparative alumina TLC (20×20 cm) using methylene chloride as a solvent to separate three fractions, A, B and C from the top of plates. Fraction A was 410 mg (34.5%) of the starting material, which was recrystallized from benzene–*n*-hexane, mp 64—65°. Fraction B was 71 mg (7.2%) of N-acetylphenethylamine (XXII), which was identical with the authentic sample. The fraction C was 144 mg of a yellow solid, which was combined with the water soluble fraction (106 mg) and chromatographed on a silica-gel column (30 g). Elution with ethyl acetate–methylene chloride (1:1) gave 72 mg (7.4%) of crude 1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (XXIII), which was recrystallized from acetone to afford colorless needles, mp 158—159°.[8] *Anal.* Calcd. for $C_{10}H_{11}ON$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.83; H, 7.24; N, 8.49. Mass Spectrum *m/e*: 161 (M^+), 132, 117, 105, 104. IR ν^{Nujol} cm^{-1}: 3200, 1690. NMR δ^{CDCl_3}: 3.08 (2H, t, $J=6$ Hz), 3.50 (2H, t, $J=6$ Hz), 3.82 (2H, s), 6.6—7.0 (1H), 7.12 (5H, s).

Further elution with the same solvent, a trace of N,N-diphenethylsuccinamide (XXIV) was isolated. The mass spectrum of XXIV, *m/e*: 324 (M^+), 220, 204 (base peak), 105, 104, was completely identical with that of the authentic sample.[9]

Photolysis of N-Chloroacetylphenethylamine (XXI) in the Presence of Veratrol (XXV)——A solution of 1.204 g (6.1 mmole) of N-chloroacetylphenethylamine (XXI) and 0.85 g (6.1 mmole) of veratrol (XXV) in 60 ml of ethanol and 240 ml of water was irradiated for 1.5 hr as described above. The methylene chloride extract on evaporation left 1.091 g of a pale yellow oil, which was chromatographed on a silica-gel column (60 g). Elution with methylene chloride gave 529 mg (44%) of the recovered starting material and 468 mg of a brown oil. The oil was separated into two fractions A and B by preparative TLC with alumina using methylene chloride as a solvent.

Fraction A was 85 mg (7%) of the second crop of the starting material. To the fraction B ether was added, the ether soluble fraction gave 44 mg (4.4%) of N-acetylphenethylamine (XXII) and from the ether insoluble fraction 57 mg (3.2%) of N-phenethyl-3,4-dimethoxyphenylacetamide (XXVI) was isolated,which was recrystallized from benzene–*n*-hexane to afford colorless needles, mp 103—105°. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.10; H, 7.32; N, 4.46. IR ν^{Nujol} cm^{-1}: 3350, 1640. NMR δ^{CDCl_3}: 2.72 (2H, t, $J=6$ Hz), 3.46 (2H, s), 3.45 (2H), 3.91 (3H, s), 3.87 (3H, s), 5.50 (1H, broad), 6.5—7.4 (8H).

N-Phenethyl-3,4-dimethoxyphenylacetamide (XXVI)——A solution of 196 mg (1 mmole) of 3,4-dimethoxyphenylacetic acid and 115 mg (1.15 mmole) of triethylamine in 8 ml of tetrahydrofuran was cooled with an ice–bath and 120 mg (1.1 mmole) of ethyl chloroformate was added with stirring. After 10 min a solution of 121 mg (1 mmole) of phenethylamine in 1 ml of tetrahydrofuran was added dropwise, the mixture was stirred for 2 hr and then allowed to stand in a refrigerator overnight. The residue was dissolved in 20 ml of benzene and washed successively with diluted hydrochloric acid, 10% aqueous potassium carbonate and water, and dried over anhydrous sodium sulfate. The filtrate was evaporated to leave 296 mg (99%) of crude XXVI as pale yellow crystals, which were recrystallized from benzene–*n*-hexane to give colorless needles, mp 102—104°, mixed mp with the photoproduct, 103—105°.

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