PHOTOCYCLIZATION OF N-CHLOROACETYL-2-METHOXY- AND 2,4-DIMETHOXY-PHENETHYLAMINES TO 4-AZABICYCLO[5.3.1]UNDECA-9-ENE-3,8-DIONES

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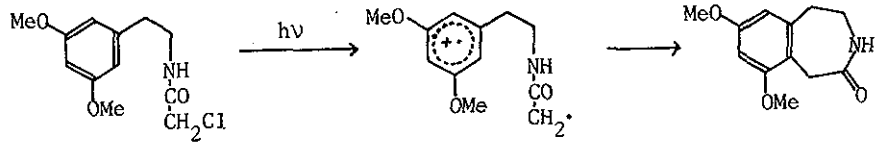
When N-chloroacetyl-2,4-dimethoxyphenethylamine (3) was irradiated, photocyclization occurred to form a transient cation intermediate (i), which was immediately attacked by a hydroxide ion to yield 11-hydroxy-10-methoxy-4-azabicyclo[5.3.1]-undeca-9-ene-3,8-dione (5). Similarly, on irradiation, N-chloro-acetyl-2-methoxyphenethylamine (8) gave the same type compound, 11-hydroxy-4-azabicyclo[5.3.1]undeca-9-ene-3,8-dione (9). Mechanistic consideration was also presented.

Mechanistic studies on the photocyclizations of N-chloroacetylphenethyl-amines have revealed a following common feature in their mechanisms:[1] Intramolecular electron transfer from the excited singlet state of an electron-rich aromatic chromophore to an electron-deficient chloroacetyl moiety leads to the cleavage of the C-Cl bond. The resultant methylene radical couples readily with the aromatic radical cation portion to form cyclization products. The cyclizations usually occur at the positions having high odd electron density, and therefore ortho-para directing sub-stituents such as MeO, OH and NMe_2 for electrophilic aromatic substitution



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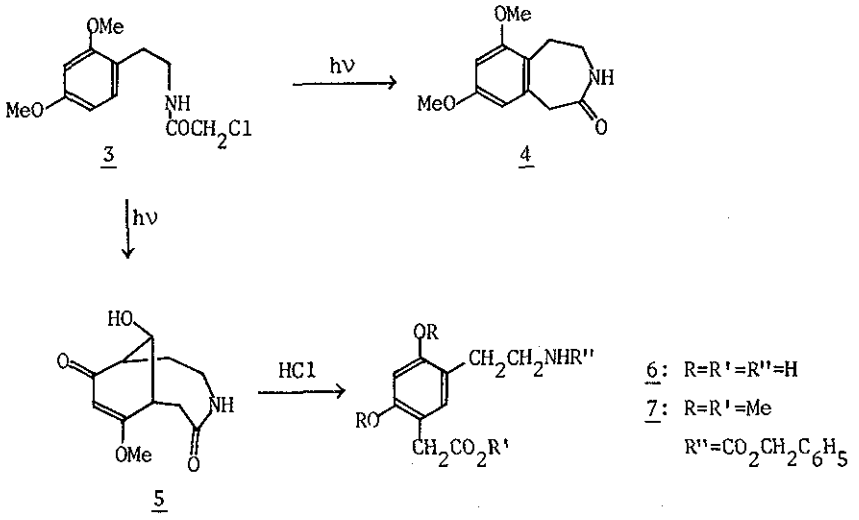
in ground state molecules also act in these photocyclizations. Thus N-chloroacetyl-3-methoxy- or 3,5-dimethoxyphenethylamine (1) gave quite easily benzazepinone derivatives (2).[2]

In this communication, we report photocyclization of 2-methoxy- and 2,4-dimethoxy compounds, which have electron-donative methoxy groups at the positions not suitable for the formation of azepinone derivatives.

When a 10 mM solution of N-chloroacetyl-2,4-dimethoxyphenethylamine (3) in 20% aqueous ethanol was irradiated with a 200 W high pressure mercury lamp under nitrogen for 5 hr, only a trace of an azepinone derivative (4; mp 190-192°, from ether) was isolated, but a 4-azabicyclo[5.3.1]undecane derivative (5; mp 210-215°, dec, from ethanol) was formed in fair yield (26%). The structure of 4 was easily established by analogy with that of 2 by spectroscopy[2] [λ_{max} (EtOH) 283 nm (ε, 2100); ν (Nujol) 3200, 1670 cm^{-1}; m/e 221 (M^+), 192, 164; δ ($CDCl_3$) 2.91 (2H, t, J = 6 Hz), 3.53 (2H, t, J = 6 Hz), 3.79 (8H, s), 6.29 (1H, d, J = 2Hz), 6.34 (1H, d, J = 2 Hz), 6.35 (1H, broad)].

The structure assignment of 5 rests also on its spectral data [ν (Nujol) 3300, 3260, 1645, 1620, 1590 cm^{-1}; λ_{max} (EtOH) 254 nm (ε, 13700); m/e 225 (M^+), 210, 193, 166, 141, 111; δ (D_2O) 2.1-3.5 (8H, m), 3.82 (3H, s), 4.38 (1H, d, J = 2.5 Hz), 5.59 (1H, s)]. The ir spectrum shows that 5 has a hydroxy and a conjugated carbonyl group. A strong absorption band in the uv



spectrum can be assigned to an enone chromophore (R-CO-CH=C$<^{R'}_{OMe}$, Calcd 257 nm). In the ^{1}H-nmr spectrum, only one vinyl proton appears at 5.59 ppm as a singlet. Finally, the signals in the ^{13}C-nmr spectra are nicely assigned as shown in Fig 1.

In order to confirm the structure, 5 was heated under reflux in 6 N HCl to give an aromatic amino acid (6) [66%; mp 184-185°, dec; λ_{max} (H_2O) 282 nm (ε, 3300); λ_{max} (H_2O-NaOH) 297 nm (ε, 4600); λ_{max} (H_2O-HCl) 277 nm (ε, 3200);

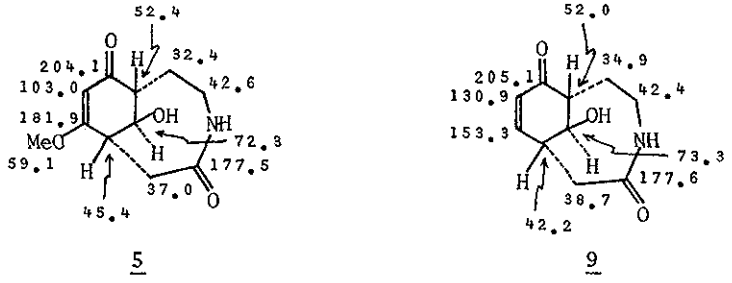
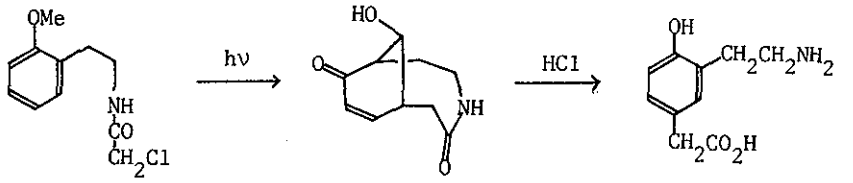


Fig 1. Chemical Shifts in the ^{13}C-NMR Spectra of 5 and 9.

δ (D_2O) 3.00 (2H, t, J = 6 Hz), 3.35 (2H, t, J = 6 Hz), 3.58 (2H, s), 6.61 (1H, s), 7.04 (1H, s)], which was converted to a carbobenzyloxy derivative (7) [91%; mp 65-67°; m/e 387 (M^+), 328, 323; δ ($CDCl_3$) 2.72 (2H, t, J = 7 Hz), 3.31 (2H, t, J = 7 Hz), 3.51 (2H, s), 3.64 (3H, s), 3.80 (6H, s), 5.08 (2H, s), 6.41 (1H, s), 6.87 (1H, s), 7.31 (5H, s)].

Similarly, N-chloroacetyl-2-methoxyphenethylamine (8) was irradiated to yield 11-hydroxy-4-azabicyclo[5.3.1]undeca-9-ene-3,8-dione (9) as an only isolable product in 23% yield. The structure of 9 was established by its spectral data [mp 191-193.5°; λ_{max} (EtOH) 226 nm (ε, 10600) (Calcd 227 nm); ν (Nujol) 3160, 1640 cm^{-1}; m/e 195 (M^+), 136; δ (D_2O) 2.1-3.4 (8H, m), 4.45 (1H, s), 6.28 (1H, d, J = 10 Hz), 7.17 (1H, o, J = 10, 6 and 2.5 Hz)]. On acid hydrolysis with HCl, 9 also gave an amino acid (10) [50%; mp 261-263°, dec; λ_{max} (H_2O) 277.5 nm (ε, 1900); λ_{max} (H_2O-NaOH) 296 nm (ε, 3300); λ_{max} (H_2O-HCl) 276 nm (ε, 1900); δ (D_2O) 2.98 (2H, t, J = 5.5 Hz), 3.29 (2H, t, J = 5.5 Hz), 3.58 (2H, s), 6.88 (1H, d, J = 9 Hz), 7.10 (1H, q, J = 9 and 2 Hz), 7.12 (1H, d, J = 2 Hz)].



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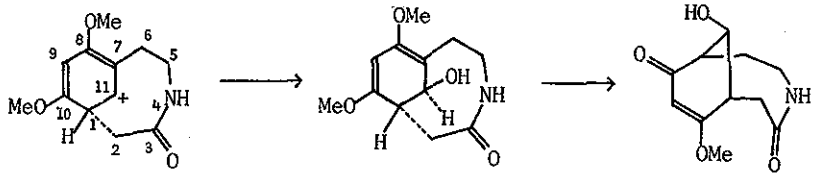
Intramolecular ortho-para cyclization of 3 gives a strained cation (i), which must be a transient intermediate for the formation of 5. This type of intermediates (iii, v, vii) has been proposed in the photocyclizations of N-chloroacetyl derivatives of 3,4-dimethoxyphenethylamine (11)[3] and 2,5-dimethoxyphenethylamine (12),[4] however, a subsequent step changed from the transannular cyclization for the formation of pyrroloindoles to the



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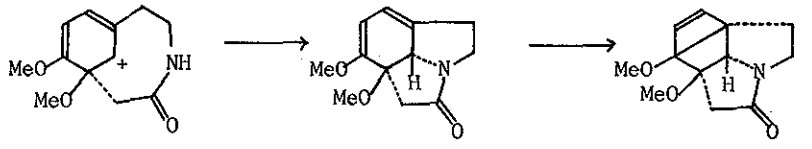

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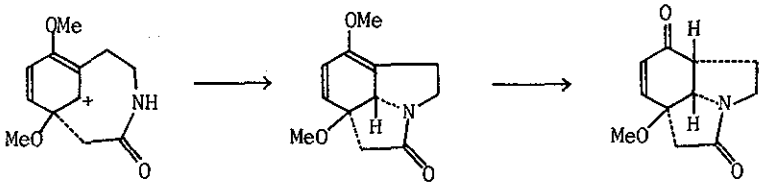

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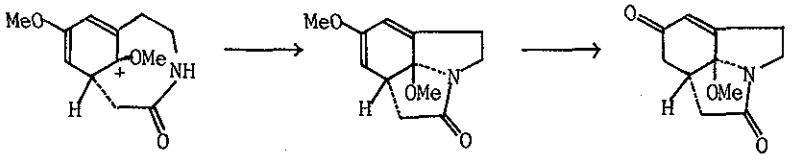

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hydroxylation to form ii.

Inspection of models indicates that compared with the hydroxylation, the transannular cyclization may be an unfavorable process because of the formation of highly strained molecules (iv, vi, viii). A β-methoxy group at positions 1 and 11 in iii, v and vii, however, may hinder sterically the β-side attack of a hydroxide ion, and hence the transannular cyclization becomes an actual process. The intermediate (i) without a methoxy group at positions 1 and 11 is naturally attacked by a hydroxide ion to form ii, *followed by hydrolysis to* 5.[5]

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3 O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, J. Am. Chem. Soc., 1970, 92, 5686.

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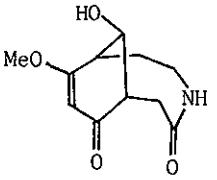
5. As pointed out by a referee, we cannot completely rule out another possible structure (5a) for the photoproduct (5). The structure (5) is nevertheless favored because two double bonds in the strained intermediate (ii) are not coplanar and therefore hydrolysis of one of two enol-ethers takes place in a 1,2 fashion rather than in a 1,4 fashion.



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