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PHOTOCYCLIZATION OF N-CHLOROACETYL DERIVATIVES OF 3,4-DIMETHOXYPHENYLBUTYLAMINE AND 3,4-DIMETHOXYPHENYLPENTYLAMINE TO BICYCLIC DIENOLS AND ACID-CATALYZED TRANSANNULAR CONVERSION TO AZEPINOINDOLES

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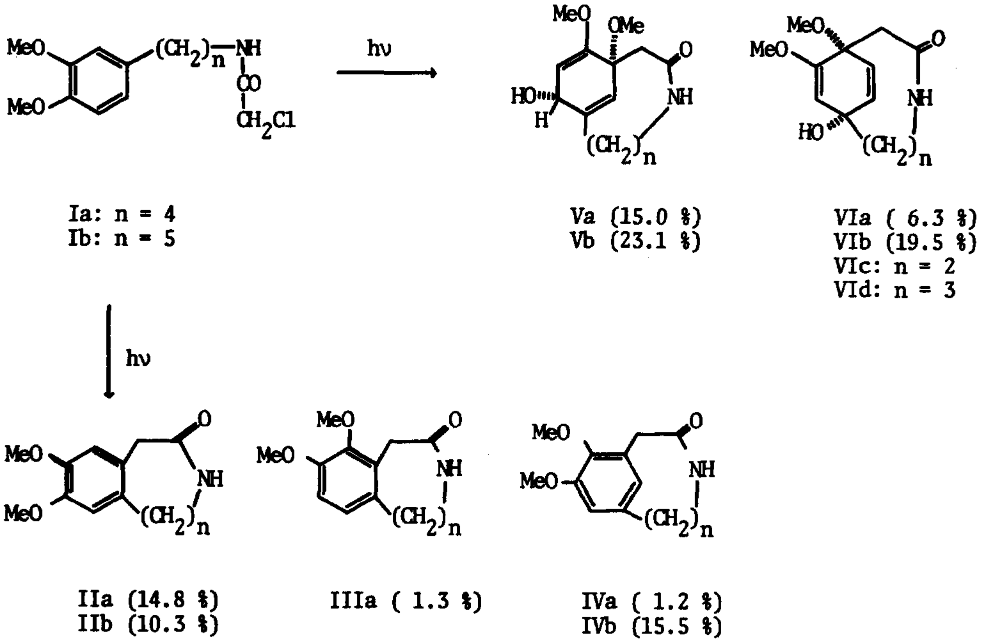
In contrast with the usual ionic reactions of methoxy and hydroxy substituted benzenes, the photocyclizations of N-chloroacetylphenethylamines occur at the positions substituted with methoxy and hydroxy groups as well as at the ortho and para positions with reference to these substituents.[1] On the basis of mechanistic studies, the reactivity of each position in the benzene rings, if steric factors can be disregarded, has been proposed to be proportional to the odd electron density in the intermediary aromatic radical cations and phenoxy radicals.[2] Calculated results indicate that the positions substituted with methoxy groups in the radical cation of 1,2-dimethoxybenzene are rather reactive than their ortho and para positions.[3] The reactivity-odd electron density relationship in the phenethylamine derivatives, however, is far from quantitative because of the geometrical limitaiton owing to too short distance between the aromatic rings and the chloroacetamide moiety.[5] In the present paper, we describe the photocyclizations of homologous compounds with longer side chains, N-chloroacetylphenylbutylamine (Ia) and pentylamine (Ib), which have shown a better reactivity-electron density relationship affording novel dienolic products.

A 50% aqueous acetonitrile solution of Ia containing sodium bicarbonate with a 100 W high pressure mercury lamp for 3 hr. The benzazoninone (IIa) [mp 174-175° (EtOH)][6] and small amounts of another benzazoninone (IIIa) [mp 147-148° (EtOAc-hexane)] and an aza[7]metacyclophane (IVa) [mp 117° (EtOAc-hexane)] were isolated by column chromatography from the fraction soluble in ethyl acetate. The mass, ir and uv spectra gave no distinct signals among these three products, but the nmr spectra have their characteristic signals of aromatic protons, respectively. Thus, the two aromatic protons in IIa are distinct singlets at 6.54 and 6.93 ppm. However, at 60° the



Ia: n = 4
Ib: n = 5

Va (15.0 %)
Vb (23.1 %)

VIa (6.3 %)
VIb (19.5 %)
VIc: n = 2
VId: n = 3

IIa (14.8 %)
IIb (10.3 %)

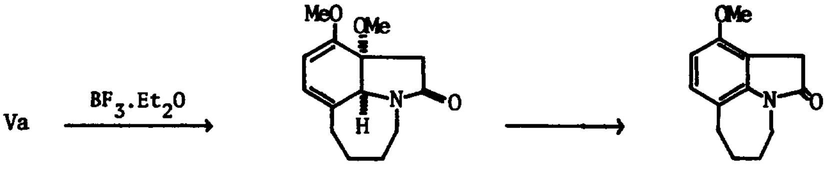
IIIa (1.3 %)

IVa (1.2 %)
IVb (15.5 %)

two aromatic protons in IIIa are well separated doublets at 6.72 and 6.84 ppm because of ortho coupling (J = 8 Hz), and in IVa similar doublets with meta coupling (J = 2 Hz) appear at 6.00 and 6.95 ppm.

From the aqueous layer two dienolic compounds Va [mp 152-153° (EtOH-EtOAc); δ (DMSO-d_6)^7 2.98 (3H, s), 3.54 (3H, s), 4.16 (1H, dd, J = 4, 7.5 Hz, $=CH-\overset{OH}{C\underline{H}}-$), 4.82 (1H, d, J = 7.5 Hz, O$\underline{H}$), 4.96 (1H, d, J = 4 Hz, $=C\underline{H}-\overset{OH}{CH}-$), 5.50 (1H, s, $-\overset{|}{C}=C\underline{H}-\underset{|}{C}-$), 7.55 (1H, broad s, N$\underline{H}$)] and VIa [mp 126-127°, dec (EtOH-EtOAc)]^8 were isolated. Both Va and VIa have only uv end absorption, the composition $C_{14}H_{21}NO_4$ determined by mass spectrometry and the base peak at m/e 218, equivalent to $C_{13}H_{16}NO_2$ (M^+-H_2O, MeO). The nmr data of Va shown in the above brackets revealed its structure, which was confirmed by <u>a facile acid-catalyzed transannular aromatization</u> to the azepinoindole (VIIIa).

When Va was treated with boron trifluoride etherate in tetrahydrofuran at room temperature for 20 hr, the transannular dehydration proceeded to yield a tricyclic dienol ether (VIIa) [mp 105-106° (EtOAc-hexane); ν 1685 cm^{-1}; δ 5.28 (1H, d, J = 7 Hz), 5.84 (1H, d, J = 7 Hz)]. Further treatment of VIIa with the same catalyst in acetonitrile brought about aromatization to give VIIIa [mp 90-91° (CH_2Cl_2-hexane)]. The structure of VIIIa was confirmed by mass and nmr spectra. The parent peak, also the base peak, at m/e 217 corresponds to $C_{13}H_{15}NO_2$. Two aromatic protons are well separated doublets at 6.54 and 7.00 ppm with ortho coupling (J = 9 Hz).

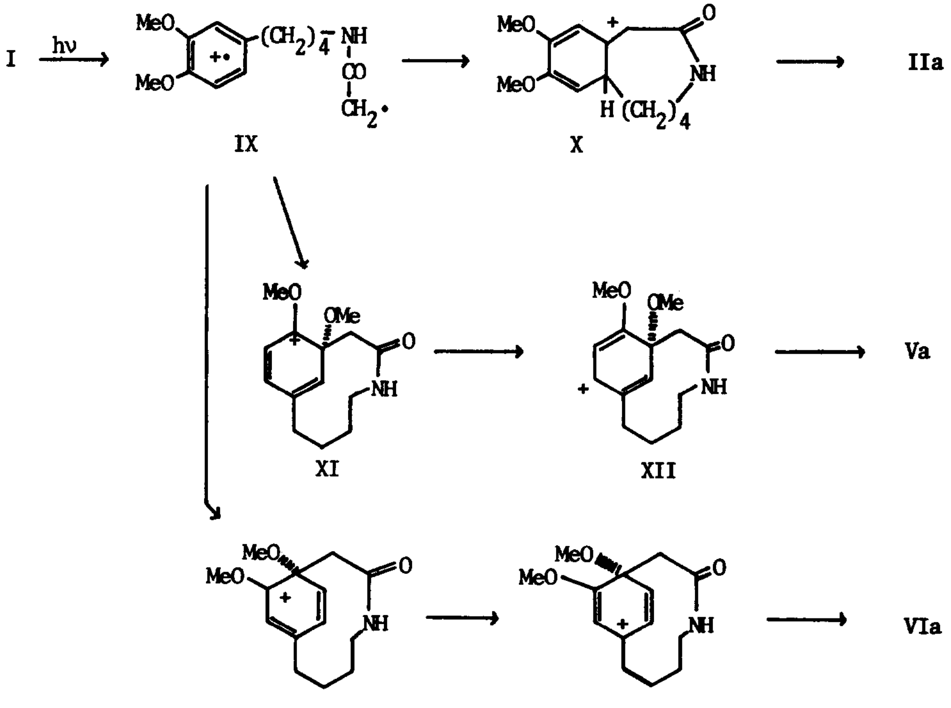


VIIa (75 %) VIIIa (89 %)

Another dienolic product VIa has spectral and chemical properties similar to those of the known analogous compound VIc.[5b,9]

The photolysis of Ib under similar conditions gave the same type of products, IIb [mp 158-159° (CH_2Cl_2-hexane); δ 6.65 (1H, s), 6.80 (1H, s)], IVb [mp 177-178° (CH_2Cl_2-hexane); δ 6.54 (1H, d, J = 2 Hz), 6.64 (1H, d, J = 2 Hz)], Vb [mp 129-130° (EtOH-EtOAc); δ (DMSO-d_6) 2.90 (3H, s), 3.52 (3H, s), 4.30 (1H, dd, J = 4, 7.5 Hz), 4.88 (1H, d, J = 7.5 Hz), 5.00 (1H, d, J = 4 Hz), 5.36 (1H, s)], and VIb [mp 138-140°, dec (EtOH-Et_2O)].[11]

In the photocyclizations presented here common transient intermediates may be described as IX. The cyclizations at unsubstituted positions in the benzene rings form cationic intermediates



IX X

XI XII

XIII XIV

(e.g., X), which deprotonate to yield the final products II, III and IV.[12] On the other hand, the cyclizations at the positions substituted with methoxy groups as predicted by the calculated electron densities occur rather efficiently and form intermediary cations (e.g., XI and XIII), which are attacked by water probably without aromatization[13] and transannular cyclizations.[1,5a] The hydroxylation occurs regio- and stereo-selectively in the least hindered manner.[15]

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(1) Y. Okuno, M. Kawamori, K. Hirao, and O. Yonemitsu, Chem. Pharm. Bull., 23 (1975), and references cited therein.

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(5) (a) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, J. Am. Chem. Soc., 92, 5686 (1970); (b) H. Nakai, K. Hemmi, T. Iwakuma, and O. Yonemitsu, Chem. Pharm. Bull., 20, 998 (1972).

(6) Y. Okuno, K. Hemmi, and O. Yonemitsu, Chem. Commun., 745 (1971).

(7) When D_2O was added, the signals changed as follows: 4.16 (1H, d, J = 4 Hz), 4.82 and 7.55 (disappeared).

(8) δ (DMSO-d_6) 1.1-1.6 (6H, m), 2.16 (1H, d, J = 12 Hz), 2.64 (1H, d, J = 12 Hz), 2.94 (3H, s), 3.54 (3H, s), 4.65 (1H, s), 4.81 (1H, d, J = 2 Hz), 5.46 (1H, d, J = 10 Hz), 5.74 (1H, dd, J = 10, 2 Hz), 6.68 (1H, broad s).

(9) In the spectrum of VIc at room temperature, the methyl signal of the enol ether portion splits into two peaks because of hindered ring inversion of a medium sized ring (nine-membered) caused by hindered twisting of amide.[10] The corresponding methyl signal in VIa, however, appears at 3.54 ppm as a singlet, indicating no effect of amide-twisting in a eleven-membered lactam.

(10) K. Hemmi, H. Nakai, S. Naruto, and O. Yonemitsu, J. C. S. Perkin II, 2252 (1972).

(11) δ (DMSO-d_6) 0.7-1.0 (2H, m), 1.2-1.6 (6H, m), 2.24 (1H, d, J = 12 Hz), 2.70 (1H, d, J = 12 Hz), 2.91 (3H, s), 3.52 (3H, s), 4.59 (1H, s), 4.76 (1H, d, J = 2 Hz), 5.41 (1H, d, J = 10 Hz), 5.73 (1H, dd, J = 10, 2 Hz), 7.28 (1H, broad s).

(12) The yield of IVa (ten-membered lactam) was negligibly poor, but IVb (eleven-membered lactam) was isolated in a fair yield. On irradiation of I (n = 2 and 3),[5,6] of course, no formation of IV was observed. These results may indicate the minimum ring-size in the cyclization forming this type of azametacyclophanes.

(13) The dienol-benzene rearrangement[14] via XIV to IVb cannot be completely ruled out because the yield of IVb was somewhat higher than that expected from the electron densities.

(14) H. Heimgartner, J. Zsindely, H. -J. Hansen, and H. Schmidt, Helv. Chim. Acta, 55, 1113 (1972).

(15) Cf. Y. Okuno and O. Yonemitsu, Heterocycles, 4, 1371 (1975).