ABNORMAL PHOTOLYSIS OF N-BENZYL-8-PHENETHYLMINE DERIVATIVES HAVING BROMINE AND IODINE ATOMS

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Abstract - Abnormal photolysis of N-benzyl-8-phenethylamines (3a, 3c and 4c) having bromine and iodine atoms provided 4-iodo-5,6,7,8-tetrahydrodibenz[\(\sigma,\varepsilon\)azocine (1c), and 4-iodo-1,2-methyleneoxy- and 9-iodo-11,12-methylenedioxy-5,6,7,8-tetrahydrodibenz[\(\sigma,\varepsilon\)]azocines (5a and 6a), respectively.

As a continuation of studies on the syntheses of apogalanthamine analogs\(^2\) as \(\alpha\)-adrenergic blocking agents,\(^3\) we have synthesized\(^4\) 4- and 9-bromo-5,6,7,8-tetrahydrodibenz[\(\sigma,\varepsilon\)]azocines (1a and 2a) and their methylenedioxy derivatives (1b and 2b) by photochemical cyclization of 2-halo-N-(2-halobenzyl)-8-phenethylamines (3a, 4a and 3b, 4b).

This paper describes the photochemical cyclization of the 8-phenethylamines (3a, 3c and 4c) having bromine and iodine atoms to the halogen-exchange compounds 4-iodo-5,6,7,8-tetrahydrodibenz[\(\sigma,\varepsilon\)]azocine (1c) and 4-iodo-1,2-methyleneoxy- and 9-iodo-11,12-methylenedioxy-5,6,7,8-tetrahydrodibenz[\(\sigma,\varepsilon\)]azocines (5a and 6a). Previously we reported\(^4\) that irradiation of the hydrochlorides of 3a,b and 4a,b gave the desired 4-bromoazocines 1a,b and 9-bromoazocines 2a,b, respectively. In the case of photolysis of 3a, an unexpected compound A was also obtained with the desired azocine 1a. Photolysis of the hydrochlorides of 3c and 4c gave no desired bromoazocines 5b and 6b, but unexpected compounds B and C.

The structures of these unexpected compounds A-C were determined from spectral data as follows. The mass (MS) spectrum of compound A showed an M\(^+\) at m/z 335, indicating the molecular formula \(\text{C}_{15}\text{H}_{14}\text{IN}\). Fragments of \([\text{M-CH}_2\text{CH}_2]^{+}\) and \([\text{M-CH}_2\text{NH}_2]^{+}\) suggested the presence of an azocine ring in compound A. The \(^1\text{H NMR}\) spectrum of compound A showed AB-type doublets at 5.40 and 3.27 (each 1H, J=14Hz),
which were assigned as characteristic C-5 methylene protons in dibenz[α,α]azocine
derivatives. From these findings and the structure of the starting material 3a,
compound A was temporarily thought to be 9-iodo-5,6,7,8-tetrahydrodibenz[α,α]-
azocine (2c). However, its signal (δ 4.10) of 5-H (lower) showed a downfield shift
from those (δ 3.88 ± 0.07) of dibenz[α,α]azocines, because of the anisotropic
effects of the iodine atom at C-4. Thus, compound A was concluded to be 4-iodo-
azocine (1c) and this conclusion was confirmed by its direct comparison with
authentic 4-iodoazocine (1c). The formation of 1c seems to be explained by
exchange of the bromine atom in the normal product 1a for an iodine atom during
photolysis of 3a, as described below.

The high resolution MS spectra of compounds B and C showed the same molecular ion
peaks (m/z 379: C_{16}H_{14}NO_{2}) and the same fragments ([M-CH=CH]^{+} and
[M-CH_{2}NH]^{+}) as those of 1c. In the ^1H NMR spectra of compounds B and C, the signals at δ 4.10
and 3.21, and 3.96 and 3.26, respectively, were due to AB-type doublets of C-5
methylene protons. The peak (δ 4.10) of 5-H (lower) in compound was similar to that
of the above 4-iodoazocine (1c), but the peak (δ 3.96) of 5-H (lower) in compound C
showed the usual chemical shift (δ 3.88 ± 0.07) of dibenz[α,α]azocines containing
9-iodoazocine 2c and 9-bromoazocine 2a. These data suggest that compounds B
and C are methylenedioxy derivatives of 4-iodoazocine 1c and 9-iodoazocine 2c,
respectively. The location of the methylenedioxy groups in compounds B and C were
determined as follows. The signals for methylenedioxy protons at positions 2 and
3, and 10 and 11 in the dibenz[α,α]azocine derivatives were all singlets. However,
each proton of the methylenedioxy groups in compounds B and C showed
AB-type doublets (J = 1 Hz) at δ 6.01 and 5.88, and 6.01 and 5.89, respectively. These
chemical shift differences of the doublets seemed to be due to magnetic unequi-
valence of the each proton by the second benzene and azocine rings and suggested
that the methylenedioxy groups were located ortho to the central bond of the
biphenyl system, namely at C-1 and C-2 in compound B and at C-11 and C-12 in compound
C. Thus, compounds B and C were concluded to be 4-iodo-1,2-methylenedioxyazocine
(5a) and 9-iodo-11,12-methylenedioxyazocine (6a). This assignment was supported by
the singlets at δ 7.36 (3-H) in 5a and at δ 7.41 (10-H) in 6a, indicating that the
iodine atom and the methylenedioxy group were in the same benzene ring.

There are many reports about the exchange reactions of an iodine atom with
chlorine and bromine atoms on photolysis of iodoarenes. On the contrary, we found
that the bromine atoms in 3a, c and 4c were displaced by iodine atoms during
photolysis to give the unexpected azocines 1c, 5a and 6a. The formations of 1c, 5a and 6a may be explained as follows: displacement of the bromine atoms in the cyclohexadienyl radicals D, E and F (which are intermediates in the photolysis of 3a, c and 4c) by the iodo radicals (generated from 3a, c and 4c) should give cyclohexadienyl radicals G, H and I, which afford 1c, 5a and 6a.

Photolysis of 3c gave not only compound B(5a) but also 9-iodo-2,3-methylenedioxyazocine(2d) and 2,3-methylenedioxyazocine(2e). The structures of 2d,e were determined by elemental analysis of their styphnates and by 1H NMR spectral measurements (see "Experimental") of their free bases.

EXPERIMENTAL
All melting points are uncorrected. The spectrophotometers used were a JEOL model JMS-D 300 for mass spectra, and a JEOL model JMS-PS-100 for 1H NMR spectra. Irradiation was carried out with a RIKO UVL-400H apparatus. The plates used for preparative thin-layer chromatography (PLC) were coated with silica gel (Kieselgel, PF254, Merck).

2-Iodo-N-(2-bromo-4,5-methylenedioxybenzyl)-6-phenethylamine (3c) ------ A mixture of 1.20 g of 7a and 1.04 g of 8a was heated in a sealed tube at 110°C for 1 h. To a solution of the reaction mixture in 50 ml of CHCl3-MeOH(3:2) was added 1.04 g of NaBH4 gradually with stirring at room temperature for 3 h. The solvent was evaporated in vacuo. The residue was mixed with 10 ml of H2O and extracted with CHCl3. The extract was mixed with 15% HCl and the CHCl3 extract was concentrated to give the hydrochloride(674 mg, 32.3%) of 3c as colorless needles, mp 149-150°C (from acetone-MeOH). Anal. Calcd for C16H15BrINO2·HCl: C, 38.70; H, 3.25; N, 2.82. Found: C, 38.54; H, 3.30; N, 2.80. 1H NMR(CDC13)6 (free base): 7.92 (1H, d, J=8, 2 Hz, 3-H in phenethyl group), 6.96 and 6.88 (each 1H, s, 3-H and 6-H in benzyl group), 5.92 (2H, s, OCH2O), 3.87 (2H, br s, Ar-CH2-N), 2.88 (4H, br s, Ar-CH2CH2-N), 1.63 (1H, s, NH).

2-Bromo-4,5-methylenedioxy-N-(2-iodobenzyl)-6-phenethylamine (4c) ------ The hydrochloride of 4c was prepared from 7b(0.35 g), 8b(0.26 g), and NaBH4(0.35 g) in the same way as above as colorless needles(265 mg, 50.2%), mp 222-227°C (from acetone-MeOH). Anal. Calcd for C16H15BrINO2·HCl: C, 38.70; H, 3.25; N, 2.82. Found: C, 38.45; H, 3.29; N, 2.73. 1H NMR(CDC13)6 (free base): 6.96 and 6.72 (each 1H, s, 3-H and 6-H in phenethyl group), 7.81 (1H, d, J=8, 2 Hz, 3-H in benzyl group), 5.90 (2H, s, OCH2O), 3.80 (2H, br s, Ar-CH2-N), 2.84 (4H, br s, Ar-CH2CH2-N), 1.59 (1H, s, NH).

Photolysis of the Hydrochloride of 3c ------ A solution of the hydrochloride(610 mg)
of 3c in H_2O (1000 ml) was irradiated under N_2 with stirring at room temperature for 70 min. The reaction mixture was adjusted to pH 10 with Na_2CO_3 and extracted with CHCl_3. The extract was washed with H_2O, dried and evaporated to afford an oil (406 mg), which was subjected to PLC on SiO_2 in CHCl_3-MeOH (10:1). Four fractions (I-IV) were separated and extracted with CHCl_3-MeOH (1:1). Fraction I (Rf 0.24-0.30) gave a crude oil (15.6 mg), which was purified by PLC on SiO_2 in benzene-diethylamine (10:1) to give an oil (8.2 mg, 2.6%) of 2e. \^1H NMR (CDCl_3) δ: 6.76 and 6.89 (each 1H, s, 1-H and 4-H), 5.95 (2H, s, OCH_2O), 3.85 and 3.08 (each 1H, d, J=14 Hz, AB-type of 5-H_2), 1.96 (1H, s, NH). This oil 2e was converted to yellow needles as its acidic styphnate, mp 217.5-223°C (from acetone). Anal. Calcd for C_{16}H_{15}N_2O_2.C_6H_3N_3O_8: C, 53.02; H, 3.64; N, 11.24. Found: C, 53.27; H, 3.81; N, 10.80. The oily product (25.8 mg) obtained from fraction II (Rf 0.42-0.52) was further purified by PLC on SiO_2 in benzene-diethylamine (10:1) to give an oil (15.0 mg, 3.2%) of 3d. \^1H NMR (CDCl_3) δ: 6.69 and 6.81 (each 1H, s, 1-H and 4-H), 7.87 (1H, dd, J=8, 2Hz, 10-H), 6.86 (1H, dd, J=8, 8Hz, 11-H), 5.93 (2H, s, OCH_2O), 3.79 and 3.03 (each 1H, d, J=14 Hz, AB-type of 5-H_2), 2.50 (1H, br s, NH). The oil of 3d was crystallized as yellow needles (9 mg) of its neutral styphnate, mp 228-230.5°C (from acetone). Anal. Calcd for C_{16}H_{14}N_2O_2: C, 45.48; H, 3.11; N, 6.98. Found: C, 45.48; H, 3.26; N, 6.60. Fraction III (Rf 0.56-0.65) gave the crude product (15.1 mg), which was purified by PLC on SiO_2 in benzene-diethylamine (10:1) to give an oil (15.1 mg, 1.8%) of 3e. \^1H NMR (CDCl_3) δ: 7.36 (1H, s, 3-H), 6.01 and 5.88 (each 1H, d, J=1Hz, AB-type of OCH_2O), 4.10 and 3.21 (each 1H, d, J=14 Hz, AB-type of 5-H_2). MS m/z: 379 (M^+); (High MS m/z 379.0048. C_{16}H_{14}NO_2 requires 379.0066), 364, 351 (M^+CH_2=CH_2); (High MS m/z 350.9704. C_{16}H_{10}NO_2 requires 350.9754), 350, 349 (M^+CH_2=NH); (High MS m/z 348.9697. C_{15}H_{10}O_2 requires 348.9722), 335, 252, 224, 223, 222, 194, 193, 165. The oil of 3e was converted to colorless needles as its perchlorate, mp 279-282°C (from ether-MeOH). Anal. Calcd for C_{16}H_{14}NO_2.HClO_4: C, 39.32; H, 3.30; N, 2.87. Found: C, 39.46; H, 2.99; N, 2.81. The starting material 3c (167 mg, 29.5%) was recovered from fraction IV (Rf 0.78-0.98).

Photolysis of the hydrochloride of 4c ---- A solution of the hydrochloride (257 mg) of 4c in H_2O (500 ml) was irradiated for 1.5 h and worked up in the same way as for 3c to give an oil (97 mg). This oil was subjected to PLC on SiO_2 in CHCl_3-MeOH (7:1). Extraction of fraction I (Rf 0.49-0.58) with CHCl_3-MeOH (1:1) gave an oil (3 mg, 1.5%) of compound C (6a). \^1H NMR (CDCl_3) δ: 7.41 (1H, s, 10-H), 6.01 and 5.89 (each 1H, d, J=1Hz, AB-type of OCH_2O), 3.96 and 3.26 (each 1H, d, J=14 Hz, AB-type of 5-H_2), 2.64 (1H, br s, NH).
MS m/z: 379 (M⁺) (High MS m/z 379.0017. C₁₆H₁₄INO₂ requires 379.0067), 364, 351 (M⁺-CH₂=CH₂) (High MS m/z 350.9743. C₁₄H₁₀INO₂ requires 350.9754), 350, 349 (M⁺-CH₂=NH₂) (High MS m/z 348.9708. C₁₅H₁₀O₂ requires 348.9723), 335, 252, 224, 223, 222, 194, 193, 165. Extraction of fraction II (Rf 0.84-0.91) gave an oil (45.3 mg, 19.0%) of the starting material 4c.

4-Iodo-5,6,7,8-tetrahydrodibenz[a,e]azocine (1c): Compound A

1H NMR (CDCl₃) δ: 7.92 (1H, dd, J=8, 2Hz, 3-H), 6.98 (1H, dd, J=8, 8Hz, 2-H), 4.10 and 3.27 (each 1H, d, J=14Hz, AB-type of 5-H₂), 1.86 (1H, br s, NH). MS m/z: 335 (M⁺) (High MS m/z 335.0147. C₁₅H₁₄INO requires 335.0170), 320, 307 (M⁺-CH₂=CH₂) (High MS m/z 306.9862. C₁₃H₁₀INO₂ requires 306.9860), 306, 305 (M⁺-CH₂=NH₂), 291, 208, 180, 179.

REFERENCES

1) Part IX in the series "Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents ". For part VIII, see ref. 4.


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