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ABNORMAL PHOTOLYSIS OF N-BENZYL-β-PHENETHYLAMINE DERIVATIVES HAVING BROMINE AND IODINE ATOMS[1]

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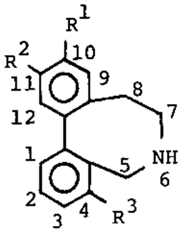
Abstract - Abnormal photolysis of N-benzyl-β-phenethylamines (3a, 3c and 4c) having bromine and iodine atoms provided 4-iodo-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine(1c), and 4-iodo-1,2-methylenedioxy- and 9-iodo-11,12-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines(5a and 6a), respectively.

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

This paper describes the photochemical cyclization of the β-phenethylamines(3a,3c and 4c) having bromine and iodine atoms to the halogen-exchange compounds 4-iodo-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine(1c) and 4-iodo-1,2-methylenedioxy- and 9-iodo-11,12-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]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.

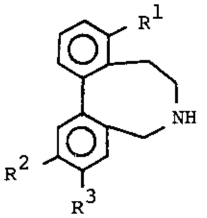
The structures of these unexpected compounds A-C were determined from spectral data as follows. The mass(MS) spectrum of compound A showed an M^+ at m/z 335, indicating the molecular formula $C_{15}H_{14}NI$. Fragments of $[M-CH_2=CH_2]^+$ and $[M-CH_2=\overset{+}{N}H_2]^+$ suggested the presence of an azocine ring in compound A. The ^1H NMR spectrum of compound A showed AB-type doublets at δ4.10 and 3.27(each 1H, J=14Hz),



1a: $R^1=R^2=H, R^3=Br$

1b: $R^1, R^2=OCH_2O, R^3=Br$

1c: $R^1=R^2=H, R^3=I$



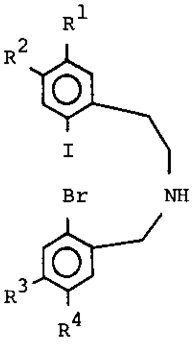
2a: $R^1=Br, R^2=R^3=H$

2b: $R^1=Br, R^2, R^3=OCH_2O$

2c: $R^1=I, R^2=R^3=H$

2d: $R^1=I, R^2, R^3=OCH_2O$

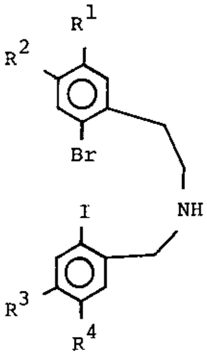
2e: $R^1=H, R^2, R^3=OCH_2O$



3a: $R^1=R^2=R^3=R^4=H$

3b: $R^1, R^2=OCH_2O$,
$R^3=R^4=H$

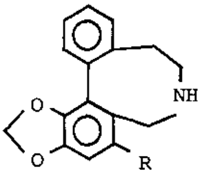
3c: $R^1=R^2=H$,
$R^3, R^4=OCH_2O$



4a: $R^1=R^2=R^3=R^4=H$

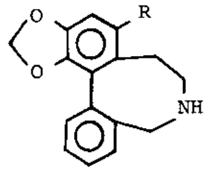
4b: $R^1=R^2=H$,
$R^3, R^4=OCH_2O$

4c: $R^1, R^2=OCH_2O$,
$R^3=R^4=H$



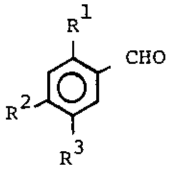
5a: R=I

5b: R=Br



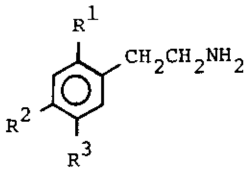
6a: R=I

6b: R=Br



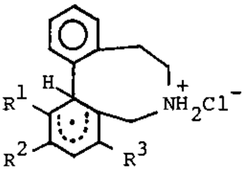
7a: $R^1=Br, R^2, R^3=OCH_2O$

7b: $R^1=I, R^2=R^3=H$

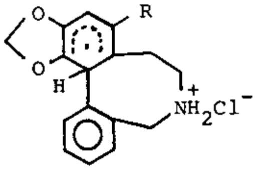


8a: $R^1=I, R^2=R^3=H$

8b: $R^1=Br$,
$R^2, R^3=OCH_2O$



D: $R^1=R^2=H, R^3=Br$
E: $R^1, R^2=OCH_2O$,
$R^3=Br$
G: $R^1=R^2=H, R^3=I$
H: $R^1, R^2=OCH_2O$,
$R^3=I$



F: R=Br
I: R=I

which were assigned as characteristic C-5 methylene protons in dibenz[*c*,*e*]azocine derivatives.[2] 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[*c*,*e*]-azocine(2c). However, its signal(δ4.10) of 5-H(lower) showed a downfield shift from those(δ3.88 ± 0.07)[2b] of dibenz[*c*,*e*]azocines, because of the anisotropic *effects*[5] *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).[2g] 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: $C_{16}H_{14}INO_2$) and the same fragments($[M-CH_2=CH_2]^+$ and $[M-CH_2=\overset{+}{N}H_2]^+$) as those of 1c. In the ^{1}H NMR spectra of compounds B and C, the signals at δ4.10 and 3.21, and 3.96 and 3.26, respectively, were due to AB-type doublets of C-5 methylene protons. The peak(δ4.10) of 5-H(lower) in compound was similar to that of the above 4-iodoazocine(1c), but the peak(δ3.96) of 5-H(lower) in compound C showed the usual chemical shift(δ3.88 ± 0.07)[2b] of dibenz[*c*,*e*]azocines containing *9-iodoazocine* 2c[2g] *and 9-bromoazocine* 2a.[4] *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[*c*,*e*]azocine derivatives were all singlets.[2,4] However, each proton of the methylenedioxy groups in compounds B and C showed AB-type doublets(J=1Hz)[6] at δ6.01 and 5.88, and 6.01 and 5.89, respectively. These *chemical shift differences* of the doublets seemed to be due to magnetic unequivalence[7] 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 δ7.36(3-H) in 5a and at δ7.41(10-H) in 6a, indicating that the iodine atom and the methylenedioxy group were in the same benzene ring.

There are many reports[8] 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[2f] 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, PF_{254}, Merck).

2-Iodo-N-(2-bromo-4,5-methylenedioxybenzyl)-β-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 $CHCl_3$-MeOH(3:2) was added 1.04 g of $NaBH_4$ gradually with stirring at room temperature for 3 h. The solvent was evaporated *in vacuo*. The residue was mixed with 10 ml of H_2O and extracted with $CHCl_3$. The extract was mixed with 15% HCl and the $CHCl_3$ 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 $C_{16}H_{15}BrINO_2\cdot HCl$:C,38.70;H,3.25;N,2.82. Found: C,38.54;H,3.30;N,2.80. ^1H NMR($CDCl_3$)δ(free base):7.92(1H,dd,J=8,2Hz,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,OCH_2O), 3.87(2H,br s,Ar-CH_2-N),2.88(4H,br s,Ar-CH_2CH_2-N),1.63(1H,s,NH).

2-Bromo-4,5-methylenedioxy-N-(2-iodobenzyl)-β-phenethylamine(4c) -----
The hydrochloride of 4c was prepared from 7b(0.35 g), 8b(0.26 g), and $NaBH_4$(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 $C_{16}H_{15}BrINO_2\cdot HCl$:C,38.70;H,3.25;N,2.82. Found: C,38.45;H,3.29;N,2.73. ^1H NMR($CDCl_3$)δ(free base):6.96 and 6.72(each 1H,s,3-H and 6-H in phenethyl group),7.81(1H,dd,J=8,2Hz,3-H in benzyl group),5.90(2H,s,OCH_2O), 3.80(2H,br s,Ar-CH_2-N),2.84(4H,br s,Ar-CH_2CH_2-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=14Hz,AB-type of 5-H_2), 1.96(1H,s,NH). This oil 2e was converted to yellow needles as its acidic styphnate,[2b] mp 217.5-223°C(from acetone). Anal.Calcd for $C_{16}H_{15}NO_2 \cdot C_6H_3N_3O_8$: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 2d. ^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=14Hz,AB-type of 5-H_2),2.50(1H,br s,NH). The oil of 2d was crystallized as yellow needles(9 mg) of its neutral styphnate, mp 228-230.5°C(from acetone). Anal.Calcd for $C_{16}H_{14}INO_2 \cdot 1/2C_6H_3N_3O_8$: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 compound B(5a) as an oil(7.2 mg,1.8%). ^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=14Hz,AB-type of 5-H_2). MS m/z:379(M^+)(High MS m/z 379.0048. $C_{16}H_{14}INO_2$ requires 379.0066), 364, 351(M^+-CH_2=CH_2)(High MS m/z 350.9704. $C_{14}H_{10}INO_2$ requires 350.9754), 350, 349(M^+-CH_2=$\overset{+}{N}H_2$)(High MS m/z 348.9697. $C_{15}H_{10}IO_2$ requires 348.9722), 335, 252, 224, 223, 222, 194, 193, 165. The oil of 5a was converted to colorless needles as its perchlorate, mp 279-282°C(from ether-MeOH). Anal. Calcd for $C_{16}H_{14}INO_2 \cdot HClO_4 \cdot 1/2H_2O$: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=14Hz,AB-type of 5-H_2),2.64(1H,br s,NH).

MS m/z:379(M^+)(High MS m/z 379.0017. $C_{16}H_{14}INO_2$ requires 379.0067), 364, 351 ($M^+-CH_2=CH_2$)(High MS m/z 350.9743. $C_{14}H_{10}INO_2$ requires 350.9754), 350, 349 ($M^+-CH_2=\overset{+}{N}H_2$)(High MS m/z 348.9708. $C_{15}H_{10}IO_2$ 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[*c*,*e*]azocine(**1c**): Compound A[4] -----

^{1}H NMR($CDCl_3$)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-H_2),1.86(1H,br s,NH). MS m/z:335(M^+)(High MS m/z 335.0147. $C_{15}H_{14}IN$ requires 335.0170), 320,307($M^+-CH_2=CH_2$)(High MS m/z 306.9862. $C_{13}H_{10}IN$ requires 306.9860), 306,305($M^+-CH_2=\overset{+}{N}H_2$),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.
2) a) S.Kobayashi,M.Kihara,K.Yamasaki,Y.Ishida,and K.Watanabe,Chem.Pharm.Bull., 23,3036(1975); b) S.Kobayashi,M.Kihara,S.Shizu,S.Katayama,H.Ikeda,K.Kitahiro, and H.Matsumoto,ibid.,25,3312(1977); c) M.Kihara and S.Kobayashi,ibid.,26, 155(1978); d) S.Kobayashi,M.Kihara,and S.Mineo,ibid.,26,635(1978);
   e) S.Kobayashi,M.Kihara,and H.Nakauchi,Yakugaku Zasshi,98,161(1978);
   f) S.Kobayashi,M.Kihara,and H.Matsumoto,ibid.,98,863(1978); g) S.Kobayashi, M.Kihara,and T.Shingu,ibid.,100,302(1980).
3) a) Y.Ishida,K.Watanabe,S.Kobayashi,and M.Kihara,Jpn.J.Pharmacol.,26,607(1976);
   b) Y.Ishida,K.Watanabe,S.Kobayashi,and M.Kihara,Chem.Pharm.Bull.,25,1851(1977);
   c) Y.Ishida,K.Kasahara,S.Kobayashi,and M.Kihara,ibid.,26,3603(1978);
   d) Y.Ishida,K.Sadamune,S.Kobayashi,and M.Kihara,J.Pharm.Dyn.,6,391(1983).
4) M.Kihara,Y.Miyake,M.Iitomi,and S.Kobayashi,Chem.Pharm.Bull., "in press".
5) L.M.Jackmann and S.Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry " 2nd ed., Pergamon Press, New York, N.Y.,1969.
6) B.Gozler and M.Shamma,J.Nat.Prod.,46,433(1983).
7) T.Goto and K.Tori, "Zikken Kagaku Koza, Zoku vol.12, Nuclear Magnetic Resonance Spectroscopy", ed. by Chemical Society of Japan,Maruzen,Tokyo,1967,pp.319-454.
8) a) R.K.Sharma and N.Kharasch,Angew.Chem.(Internal.Edit.),7,36(1968);
   b) J.Grimshaw and A.P. de Silva,Chem.Soc.Rev.,10,181(1981).

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