Formation of Dibenzo[*b,f*]azecines by the Reaction of 1-Halogeno-phenethyl-1*H*-2-benzazepines with Dimsylsodium¹⁾

SHINZO KANO, TSUTOMU YOKOMATSU, and SHIROSHI SHIBUYA

Tokyo College of Pharmacy²⁾

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Treatment of 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-2-methyl-1*H*-2-benzazepine (7a) with dimsylsodium afforded 5,6,7,8,13,14-hexahydro-*trans*-13,14-methano-2,3,10,11-tetramethoxy-5-methyldibenzo[*b,f*]azecine (8) and its *cis*-isomer (9). The structure of the former was confirmed by direct comparison with the authentic sample prepared by the Simmons-Smith reaction of the 13,14-*trans*-5,6,7,8-tetrahydrodibenzo[*b,f*]azecine (11). 5,6,7,8,13,14-Hexahydro-11-hydroxy-*cis*-13,14-methano-2,3,10-trimethoxy-5-methyldibenzo[*b,f*]azecine (15) was obtained by the reaction of 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-8-hydroxy-7-methoxy-2-methyl-1*H*-2-benzazepine (7d) with dimsylsodium. The same reaction by the use of 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-2-methyl-1*H*-2-benzazepine (7e) afforded the 13-(methylsulfinyl)methyl-5*H*-dibenzo[*b,g*]azacycloundecine (16).

Keywords—benzyne reaction; ring expansion; dibenzo[*b,f*]azecine; dibenzo[*b,g*]azacycloazaundecine; Simmons-Smith reaction

In continuation of our study focussed on the benzyne reaction of 1-halogenophenethyl-isoquinolines (1) using dimsylsodium³⁾ as a base, we found a novel ring expansion of 1-substituted isoquinolines leading to dibenzo[*b,g*]azecine system (3)^{4,5)} (Chart 1). Apparently, 3 was formed through the cleavage of the C-N bond of the intermediate (2) by dimsyl anion. We successively investigated the reaction of a series of 1-halogenophenethyl-1*H*-2-benzazepines, which were homologous of isoquinolines, with dimsylsodium as an extension of the previous works in order to examine whether the similar ring expansion occurred or not. These results were described in this paper.

Chart 1

Firstly, a series of 1-halogenophenethyl-2,3,4,5-tetrahydro-2-methyl-1*H*-2-benzazepines were synthesized as follows. The Bischler-Napieralski type cyclization of the amide (4a),

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2) Location: 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.

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prepared from 3,4-dimethoxyphenylpropylamine⁶⁾ and 2-bromo-4,5-dimethoxyphenylpropionic acid yielded the 4,5-dihydro-3*H*-2-benzazepine (**5a**). Methylation of **5a** with methyl iodide, followed by reduction of the methiodide (**6a**) with sodium borohydride afforded 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-2-methyl-1*H*-2-benzazepine (**7a**). Similarly, 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-8-hydroxy-7-methoxy-2-methyl-1*H*-2-benzazepine (**7d**) and 1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-2-methyl-1*H*-2-benzazepine (**7e**) were synthesized from the corresponding amides (**4b**) and (**4c**), respectively, by the usual manner, as shown in Chart 2 and described in the experimental section, (**4b**→**5b**→**6b**→**7b**→**7d**; **4c**→**5c**→**6c**→**7c**→**7e**).

Chart 2

The 1*H*-2-benzazepine (**7a**), thus obtained, was treated with dimsylsodium in dimethyl sulfoxide (DMSO) to give three products, which were separated by column chromatography on silica gel. The first product, $C_{23}H_{29}NO_4$ (MS m/e : M^+ , 383), obtained from the benzene fraction, was assigned to 5,6,7,8,13,14-hexahydro-*trans*-13,14-methano-5-methyldibenzo- $[b,f]$ -azecine (**8**) by direct comparison with the authentic sample prepared by the Simmons-Smith reaction of the 13,14-*trans*-5,6,7,8-tetrahydrodibenzo- $[b,f]$ azecine (**11**)⁷⁾. The nuclear magnetic resonance (NMR) spectrum of **8** exhibited NCH_3 signal at δ 2.76 and four aromatic signals at δ 6.46, 6.53, 6.70 and 6.85 as singlets, respectively. Its ^{13}C -NMR spectrum⁸⁾ showed a methylene signal at δ 14.37 and two methine signals at δ 20.53 and 27.81, due to the *trans*-diphenylcyclopropane moiety, and three methylene signals were observed at δ 27.48, 30.60 and 52.85. Successively, the chloroform fraction afforded the second product (**9**). Its molecular formula was confirmed by elemental and mass spectral analysis (M^+ , m/e 383) as $C_{23}H_{29}NO_4$. Its NMR spectrum showed NCH_3 signal at δ 2.58 and four aromatic signals at δ 6.38, 6.43, 6.47, and 6.57 as singlets, respectively. Its ^{13}C -NMR spectrum exhibited an extremely high methylene signal at δ 7.88 and two methine signal at δ 21.85 and 22.25, indicating a presence of *cis*-diphenylcyclopropane system as a partial structure, and three methylene signals at δ 25.75, 28.61 and 54.37. On the basis of these facts, the second product was assigned to 5,6,7,8,13,14-hexahydro-*cis*-13,14-methano-2,3,10,11-tetramethoxy-5-methyldibenzo- $[b,f]$ -azecine (**9**), *cis*-isomer of **8**. In addition to **8** and **9**, 2,3,4,5-tetrahydro-1-(2-hydroxy-3-methylthio-4,5-dimethoxyphenethyl)-7,8-dimethoxy-2-methyl-1*H*-2-benzazepine (**10**), formed by the reaction of dimsylsodium with benzyne intermediate, was obtained from 2% methanol-chloroform fraction. The 13,14-methanodibenzo- $[b,f]$ azecines (**8**) and (**9**) were also obtained by the reaction of the methiodide (**14**: $X^-=I^-$) with dimsylsodium. The methiodide (**14**:

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8) ^{13}C -NMR spectra were taken with a Varian NV-14 spectrometer in $CDCl_3$ using TMS as an internal standard operating at 15.1 MHz.

X⁻=I⁻) was prepared by methylation of the quino[2,1-*a*][2]benzazepine (**13**) obtained by cyclization of the tetrahydro-1*H*-2-benzazepine (**12**). This indicated that **8** and **9** were derived through the N-methyl quino[2,1-*a*][2]benzazepinium salt (**14**: X⁻=appropriate anion) as an intermediate from **7a**.

Chart 3

Similar reaction of the 2,3,4,5-tetrahydro-8-hydroxy-1*H*-2-benzazepine (**7d**) with dimethylsodium afforded the *cis*-13,14-methanodibenzo[*b,f*]azecine (**15**), in 35% yield. Its spectroscopic data were quite similar to those of **9**, and NCH₃ and four aromatic proton signals were observed at δ 2.58, 6.38, 6.43, 6.47 and 6.57 as singlets, respectively, in its NMR spectrum. Its ¹³C-NMR spectrum exhibited a methylene signal at δ 7.75 and two methine signals at δ 20.05 and 22.25, attributable to diphenylcyclopropane moiety, and three methylene signals at δ 25.83, 28.81 and 54.64. O-Methylation of **15** with diazomethane gave **9**. Thus, the product from **7d** was assigned to 5,6,7,8,13,14-hexahydro-11-hydroxy-*cis*-13,14-methano-2,3,10-trimethoxy-5-methyldibenzo[*b,f*]azecine (**15**). On the other hand, in contrast to these results, the reaction of **7e** with dimethylsodium gave the dibenzo[*b,g*]azacycloundecine (**16**). Deoxygenation of **16** with zinc amalgam afforded the 13-(methylthio)methyl derivative (**17**), the NMR spectrum of which showed singlets attributable to SCH₃ and NCH₃ at δ 1.84 and 2.03, respectively. Desulfurization of **17** with Raney Ni catalyst yielded the corresponding 13-methyl derivative (**18**). The signals due to 13-CH₃ were observed at δ 1.40 as a doublet (J = 6.5 Hz) in its NMR spectrum. The NCH₃ protons resonated at δ 2.03 as a singlet. These abnormally high aromatic NCH₃ signals in the NMR spectra of **17** and **18** would be caused by the anisotropy of the benzene-A ring. For a further proof of the structure of **16**, the reaction of the methiodide (**22**) of the quino[2,1-*a*][2]benzazepine (**21**) with dimethylsodium was

TABLE I. Elemental Analysis of 4, 5, and 7

Compound	Formula	Yield(%)	mp(°C)	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
4a	C ₂₂ H ₂₈ BrNO ₅	67	108—110 (Benzene-ether)	56.65	6.05	3.00	56.95	6.11	2.77
4b	C ₂₈ H ₃₂ BrNO ₅	65	119—120 (Benzene-ether)	61.99	5.95	2.58	62.28	5.92	2.30
4c	C ₂₈ H ₃₂ BrNO ₅	65	140—141 (Benzene-ether)	61.99	5.95	2.58	62.26	6.00	2.30
5a	C ₂₈ H ₂₉ BrN ₄ O ₁₁ ^{a)}	64	181—182 (EtOH)	49.64	4.31	8.27	49.58	4.43	8.07
5b	C ₂₈ H ₃₀ BrNO ₄	67	Oil ^{b)}						
5c	C ₃₄ H ₃₈ BrN ₄ O ₁₁ ^{a)}	67	207—208(dec.) (EtOH-ether)	54.19	4.41	7.44	54.32	4.55	7.21
7a	C ₂₃ H ₃₁ BrClNO ₄ ^{c)}	87	202—204 (MeOH-ether)	55.15	6.24	2.80	55.01	6.23	2.65
7b	C ₂₉ H ₃₅ BrClNO ₄ ^{c)}	85	214—216(dec.) (MeOH-ether)	60.36	6.11	2.43	60.13	6.20	2.22
7c	C ₂₈ H ₃₇ BrN ₄ O ₁₁ ^{a)}	85	100—101 (EtOH-ether)	54.84	4.47	7.31	54.64	4.62	7.03
7d	C ₂₈ H ₃₁ BrN ₄ O ₁₁ ^{a)}	72	179—180 (EtOH)	49.49	4.60	8.25	49.56	4.65	8.15
7e	C ₂₈ H ₃₁ BrN ₄ O ₁₁ ^{a)}	70	121—222 (EtOH)	49.49	4.60	8.25	49.13	4.80	8.09

a) Picrate.

b) Used for the following reaction because of difficulty of crystallization.

c) Hydrochloride.

TABLE II. Elemental Analysis of Reaction Products of 7a, d, e, 12, 14 (X⁻=I⁻), 19 and 22

Starting material	Product	Formula	mp (°C)	Yield (%)	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
7a	8 ^{a)}	C ₂₃ H ₂₉ NO ₄	138—140 (MeOH-ether)	19	72.03	7.62	3.65	72.08	7.63	3.26
	9 ^{b)}	C ₂₃ H ₂₉ NO ₄	129—130 (MeOH-ether)	34	72.03	7.62	3.65	72.06	7.59	3.36
	10 ^{c)}	C ₂₄ H ₃₃ NO ₅ S	130—131 (MeOH-ether)	2.9	64.40	7.43	3.13	64.57	7.47	3.04
12	13	C ₂₂ H ₂₇ NO ₄	117—118.5 (MeOH-ether)	60	71.52	7.37	3.79	71.55	7.57	3.84
14	8 ^{d)}	C ₂₃ H ₂₉ NO ₄	138—140 (MeOH-ether)	8.7						
	9 ^{d)}	C ₂₃ H ₂₉ NO ₄	129—130 (MeOH-ether)	17.5						
7d	15 ^{b)}	C ₂₂ H ₂₇ NO ₄	133—135 (MeOH)	35	71.52	7.37	3.79	71.63	7.35	3.70
7e	16 ^{e)}	C ₂₂ H ₃₃ NO ₅ S	Oil ^{e)}	46.8						
19	20	C ₂₈ H ₃₁ NO ₄	143—144 (MeOH-ether)	77	75.48	7.01	3.14	75.35	6.98	3.05
22	16 ^{f)}	C ₂₂ H ₃₃ NO ₅ S	Oil	52						

a) Obtained from the benzene fraction.

b) Obtained from the CHCl₃ fraction.c) Obtained from the 2% MeOH-CHCl₃ fraction.

d) Identical with the product obtained from 7a.

e) Used for the following reaction because of difficulty of crystallization.

f) Identical with the product obtained from 7e.

TABLE III. NMR Spectra of 5, 7, 8, 9, 10, 13, 15, and 20

No.	NMR (δ) in CDCl ₃
5a	3.82 (6H, s, 2 $\times$ OCH ₃), 3.85, 3.93 (6H, each s, 2 $\times$ OCH ₃), 6.70, 6.75, 6.80, 6.95 (4H, each s, 4 $\times$ Ar-H).
5b	3.80 (6H, s, 2 $\times$ OCH ₃), 3.88 (3H, s, OCH ₃), 5.07 (2H, s, PhCH ₂ O), 6.67 (2H, s, 2 $\times$ Ar-H), 6.78, 6.92 (2H, each s, 2 $\times$ Ar-H).
5c	3.77, 3.81, 3.85 (9H, each s, 3 $\times$ Ar-H), 5.10 (2H, s, PhCH ₂ O), 6.68, 6.72, 6.78, 6.91 (4H, each s, 4 $\times$ Ar-H).
7a	2.18 (3H, s, NCH ₃), 3.88 (12H, 4 $\times$ OCH ₃), 6.67 (2H, s, 2 $\times$ Ar-H), 6.77, 7.00 (2H, each s, 2 $\times$ Ar-H).
7b'	2.10 (3H, s, NCH ₃), 3.82 (6H, s, 2 $\times$ OCH ₃), 3.83 (3H, s, OCH ₃), 5.07 (2H, s, PhCH ₂ O), 6.65 (2H, s, 2 $\times$ Ar-H), 6.67, 6.95 (2H, each s, 2 $\times$ Ar-H).
7c	2.18 (3H, s, NCH ₃), 3.78, 3.83, 3.86 (9H, each s, 3 $\times$ OCH ₃), 5.04 (2H, s, PhCH ₂ O), 6.68 (2H, s, 2 $\times$ Ar-H), 6.73, 6.94 (2H, each s, 2 $\times$ Ar-H).
7d	2.13 (3H, s, NCH ₃), 3.82 (9H, s, 3 $\times$ OCH ₃), 6.58 (1H, s, Ar-H), 6.70 (2H, s, 2 $\times$ Ar-H), 6.93 (1H, s, Ar-H).
7e	2.16 (3H, s, NCH ₃), 3.84 (9H, s, 3 $\times$ OCH ₃), 6.57, 6.63, 6.69, 6.93 (4H, each s, 4 $\times$ Ar-H).
8	2.76 (3H, s, NCH ₃), 3.88 (12H, s, 4 $\times$ OCH ₃), 6.48, 6.53, 6.70, 6.85 (4H, each s, 4 $\times$ Ar-H).
9	2.58 (3H, s, NCH ₃), 3.67, 3.73, 3.77, 3.78 (12H, each s, 4 $\times$ OCH ₃), 6.30, 6.40, 6.52, 6.60 (4H, each s, 4 $\times$ Ar-H).
10	2.23 (3H, NCH ₃), 2.43 (3H, s, SCH ₃), 6.50, 6.63, 6.67 (3H, each s, 3 $\times$ Ar-H).
13	3.80 (3H, s, OCH ₃), 3.90 (9H, s, 3 $\times$ OCH ₃), 6.27 (1H, s, Ar-H), 6.20 (2H, s, 2 $\times$ Ar-H), 6.70 (1H, s, Ar-H).
15	2.58 (3H, s, NCH ₃), 6.38, 6.43, 6.47, 6.57 (4H, each s, 4 $\times$ Ar-H).
20	3.78 (3H, s, OCH ₃), 3.87 (6H, s, 2 $\times$ OCH ₃), 5.09 (2H, s, PhCH ₂ O), 6.25, 6.58, 6.63, 6.71 (4H, each s, 4 $\times$ Ar-H).

1-(2-Bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-1H-2-benzazepine (12)—To a stirred solution of 5 g of the hydrochloride of 5a in 150 ml of MeOH was added 2.5 g of NaBH₄ under ice-cooling. After the mixture was refluxed for 0.5 hr, the solvent was evaporated and the resulting residue was suspended in H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄ and evaporated to leave 4 g of 12 as a colorless oil, picrate, mp 222–224° (MeOH–ether). *Anal.* Calcd. for C₂₈H₃₁BrN₄O₁₁: C, 49.49; H, 4.60; N, 8.25. Found: C, 49.69; H, 4.64; N, 7.97.

N-Methyl Quino[2,1-a][2]benzazepinium Iodide (14)—Treatment of 13 with CH₃I as usual afforded 14 (X[−] = I[−]), mp 227–228° (dec.) (MeOH). *Anal.* Calcd. for C₂₃H₃₀INO₄: C, 54.01; H, 5.91; N, 2.74. Found: C, 53.75; H, 5.81; N, 2.37.

The Simmons-Smith Reaction of 11—To a stirred solution of 0.4 g of 11 in 50 ml of dry dioxane was added 1.5 ml of 25% Et₂Zn hexane solution and 1.2 g of CH₂I₂. The mixture was warmed at 80° for 4 hr under stirring. The mixture was decomposed with excess NH₄Cl and H₂O, and extracted with CHCl₃. The extract was washed with CHCl₃, dried over Na₂SO₄ and evaporated. The resulting residue was chromatographed on 5 g of silica gel. Elution with CHCl₃ (20 ml) afforded 80 mg of colorless needles, which was identical with 8 in all respect.

6,7,8,13,14,15-Hexahydro-10-hydroxy-2,3,11-trimethoxy-5-methyl-13-(methylthio)methyl-5H-dibenzo-[b,g]azacycloundecine (17)—A mixture of 1.4 g of 16, 40 ml of 50% AcOH–conc. HCl (1:1) and Zn–Hg (prepared from 5 g of Zn and 0.5 g of HgCl₂) was heated on a water bath for 1 hr. After removal of inorganic substance, the mixture was made basic with 28% NH₄OH and extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄ and evaporated to leave 1.1 g of 17 as colorless needles, mp 100–102° (ether–hexane). *MS* *m/e*: (M⁺), NMR (CDCl₃) δ : 1.84 (3H, s, SCH₃), 2.03 (3H, s, NCH₃), 3.83 (6H, s, 2 $\times$ OCH₃), 3.86 (3H, s, OCH₃), 6.55, 6.62, 6.68, 6.75 (4H, each s, 4 $\times$ Ar-H). *Anal.* Calcd. for C₂₂H₃₃NO₄S: C, 66.79; H, 7.71; N, 3.25. Found: C, 67.02; H, 7.92; N, 3.16.

6,7,8,13,14,15-Hexahydro-10-hydroxy-2,3,11-trimethoxy-5,13-dimethyl-5H-dibenzo[b,g]azacycloundecine (18)—A solution of 1 g of 17 in 100 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 10 hr. After removal of catalyst, the solvent was evaporated to give 0.5 g of 18 as a colorless oil. *MS* *m/e*: 385 (M⁺), NMR (CDCl₃) δ : 1.40 (3H, d, *J* = 6.5 Hz, 13-CH₃), 2.03 (3H, s, NCH₃), 3.85 (6H, s, 2 $\times$ OCH₃), 3.87 (3H, s, OCH₃), 6.55, 6.62, 6.68, 6.75 (4H, each s, 4 $\times$ Ar-H), picrate, mp 193–194° (EtOH). *Anal.* Calcd. for C₂₉H₃₄N₄O₁₁: C, 56.67; H, 5.68; N, 9.12. Found: C, 56.52; H, 5.67; N, 9.12.

7-Benzoyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-2,3,4,5-tetrahydro-8-methyl-1H-2-benzazepine (19)—To a solution of 4 g of the hydrochloride of 20 in 150 ml of MeOH was added 3 g of NaBH₄ and

the mixture was worked up as usual to give 3.5 g of **19** as a colorless oil. NMR (CDCl_3) δ : 3.83 (9H, s, $3 \times \text{OCH}_3$), 5.06 (2H, s, PhCH_2O), 6.67 (1H, s, Ar-H), 6.72 (2H, s, $2 \times \text{Ar-H}$), 6.95 (1H, s, Ar-H), picrate, mp 100—102° (MeOH-ether). *Anal.* Calcd. for $\text{C}_{34}\text{H}_{35}\text{BrN}_4\text{O}_{11}$: C, 54.04; H, 4.67; N, 7.42. Found: C, 53.84; H, 4.85; N, 7.21.

Quino[2,1-*a*][2]benzazepine (21)—A mixture of 2 g of **20**, 9 ml of EtOH and 9 ml of conc. HCl was refluxed for 0.5 hr. The solvent was evaporated and the remaining residue was made basic with 28% NH_4OH and extracted with CHCl_3 . The extract was washed with H_2O , dried over Na_2SO_4 and evaporated to leave 1.5 g of **21** as a pale brownish oil. MS m/e : 355 (M^+); this was characterized as the methiodide (**22**), since it was unstable and difficult to crystallize, mp 195—197° (MeOH). *Anal.* Calcd. for $\text{C}_{28}\text{H}_{28}\text{INO}_4$: C, 53.12; H, 5.67; N, 2.82. Found: C, 53.05; H, 5.95; N, 2.63.

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