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Syntheses of Dibenzo[*b,g*]azecines and Dibenzo[*b,f*]azonines

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The benzyne reaction of 1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (**13**) was examined by using sodium methylsulfinylmethanide and the dibenzo[*b,g*]azecine (**16**) was obtained. The 1-halogenophenethylisoquinoline (**14**) also yielded the corresponding dibenzo[*b,g*]azecine (**17**) under the similar conditions. The reductive deoxygenation of (**16**) and (**17**), followed by desulfurization of 14-(methylthio)methyl derivative (**18**) and (**19**) gave the corresponding 14-methyl derivative (**20**) and (**21**), respectively. The similar ring expansion occurred also in the case of 1-halogenobenzylisoquinoline (**15**) to give the dibenzo[*b,f*]azonine (**29**), which was converted to the 13-methyl derivative (**31**).

We previously examined the benzyne reaction of 1-halogenobenzylisoquinoline (**1**) by the use of sodium methylsulfinylmethanide and obtained 5,6,12,12a-tetrahydro-12a-methyldibenzo[*b,g*]indolizine (**2**).[2] The reaction of a series of 1-halogenophenethyl-3,4-dihydroisoquinolines with sodium methylsulfinylmethanide yielded 13a-(methylsulfinyl)methyldibenzo[*a,f*]quinolizine (**3**)[3] and this reagent was found to show an interesting behavior to the benzyne reaction of 1-halogenobenzyl- and 1-halogenophenethylisoquinolines.[2–4] We successively examined the reaction of 1-halogenophenethyl-1,2,3,4-tetrahydro-6-hydroxyisoquinolines with sodium methylsulfinylmethanide as an extention of the previous works. These results were reported in this paper.

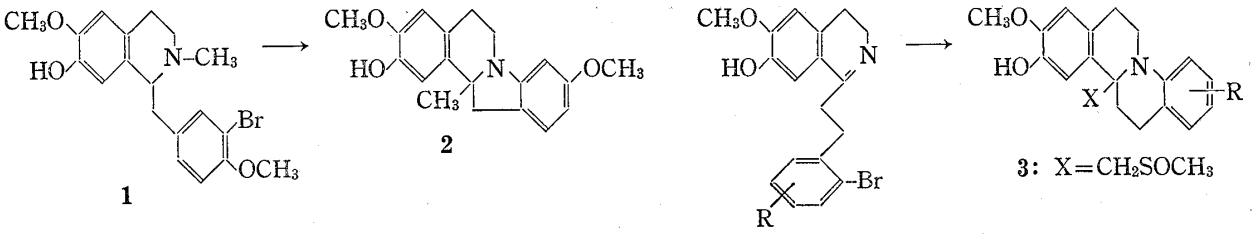
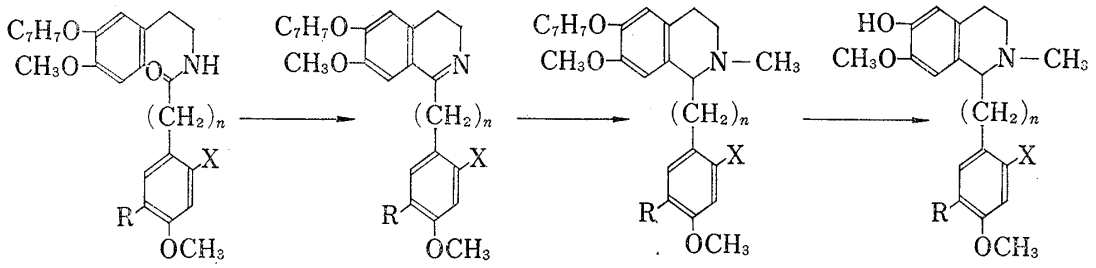


Chart 1

First, we examined the reaction of 1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (**13**) with sodium methylsulfinylmethanide. The isoquinoline (**13**) was prepared by debenzylation of the isoquinoline (**10**) obtained from the amide (**4**) in the usual way (**4**→**7**→**10**). The chromatographic separation of the crude product of the reaction of **13** with methylsulfinylmethanide afforded the dibenzo[*b,g*]azecine (**16**) possessing the methylsulfinylmethyl group at the 14-position. The molecular formula, $C_{23}H_{31}O_5NS$, was verified by microanalysis and mass spectrum (M^+, *m/e* 433). Its nuclear magnetic resonance (NMR) ($CDCl_3$) spectrum showed the product (**16**) to be a mixture of diastereoisomers. Attempts to separate each isomer were unsuccessful. The reductive

1) Location: *3–20–1, Kitashinjuku, Shinjuku-ku, Tokyo.*
2) S. Kano, T. Yokomatsu, N. Yamada, K. Matsumoto, S. Tokita, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **22**, 1607 (1974).
3) S. Kano, T. Yokomatsu, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **23**, 1098 (1975).
4) S. Kano, T. Ogawa, T. Yokomatsu, E. Komiyama, and S. Shibuya, *Tetrahedron Letters*, **1974**, 1063.

deoxygenation of **16** with amalgamated zinc gave 14-(methylthio)methyldibenzo[*b*,*g*]azecine (**18**), the NMR ($CDCl_3$) spectrum of which showed a singlet due to SCH_3 at 1.75 ppm. Its NCH_3 signal appeared at 2.38 ppm and four aromatic protons resonated at 6.65, 6.78, 6.80 and 6.87 ppm as singlets. The desulfurization of 18 with Raney Ni catalyst yielded the 14-methyl derivative (**20**), which exhibitted M^+ at *m*/*e* 371 in its mass spectrum. Its NMR ($CDCl_3$) spectrum showed a doublet (J=7 Hz) at 1.05 ppm and a singlet at 2.40 ppm due to 14-CH_3 and NCH_3, respectively. Previously, these structures (**16**), (**18**) and (**20**) were considered to be the dibenzo[*e*,*g*]azecine systems (**22**), (**23**) and (**24**), respectively, from their considerably high NCH_3 signals in their NMR ($CDCl_3$) spectra.[4] And we excluded the structures (**16**), (**18**) and (**20**) possessing aromatic NCH_3 group. The NCH_3 signal of **20** shifted to higher field than usual aromatic NCH_3 signal by the anisotropy of the benzene A ring. The final structural proof of **16** was accomplished by the direct comparison with the authentic specimen prepared by the reaction of the methiodide (**28**) of the dibenzo[*a*,*f*]quinolizine (**27**) with sodium methylsulfinylmethanide. The quinolizine (**27**) was synthesized by cyclization of the tetrahydroisoquinoline (**26**), prepared by debenzylation of the isoquinoline (**25**). Therefore, the product from the reaction of **13** with sodium methylsulfinylmethanide was proved to be the diastreoisomeric mixture of **16** and we wish to correct the previous structures (**22**), (**23**) and (**24**) to (**16**), (**18**) and (**20**), respectively.



4: n=2, R=OCH_3, X=Br
5: n=2, R=Br, X=H
6: n=1, R=OCH_3, X=Br
7: n=2, R=OCH_3, X=Br
8: n=2, R=Br, X=H
9: n=1, R=OCH_3, X=Br
10: n=2, R=OCH_3, X=Br
11: n=2, R=Br, X=H
12: n=1, R=OCH_3, X=Br
13: n=2, R=OCH_3, X=Br
14: n=2, R=Br, X=H
15: n=1, R=OCH_3, X=Br

Chart 2

It is of interest to investigate the similar reaction using the isoquinoline (**14**) in order to examine whether any difference was observed in this reaction between the position isomers according to the bromine atom. The isoquinoline (**14**) was prepared from the amide (**5**) through the usual method (**5**→**8**→**11**→**14**) as described in the experimental section. The molecular formula, $C_{22}H_{29}O_4NS$, of the product from the isoquinoline (**14**) was confirmed by mass spectrum (M^+, *m*/*e* 403) and microanalysis. The reductive deoxygenation of the product (**17**) with amalgamated zinc, followed by the desulfurization of the 14-(methylthio)methyldibenzo[*b*,*g*]azecine (**19**) gave the desired 14-methyl derivative (**21**). The 14-CH_3 protons resonated at 1.00 ppm as doublet (J=7 Hz), and NCH_3 signal appeared at 2.40 ppm in its NMR ($CDCl_3$) spectrum. The ^{13}CNMR ($CDCl_3$) spectrum of (**21**) also indicated that the product from the isoquinoline (**14**) had the dibenzo[*b*,*g*]azecine skeleton and $^{13}C_{14}$ resonated at 30.238 ppm.

Secondly, this ring transformation reaction was applied to the synthesis of the dibenzo[*b*,*f*]azonine system. The reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (**15**), prepared from the amide (**6**) through the usual method as above (**6**→**9**→**12**→**15**), with sodium methylsulfinylmethanide was investigated. The chromatographic separation of the crude product gave the 13-(methylsulfinyl)methyldibenzo[*b*,*f*]azonine (**29**) as a mixture of diastereoisomers. The molecular formula, $C_{22}H_{29}O_5NS$

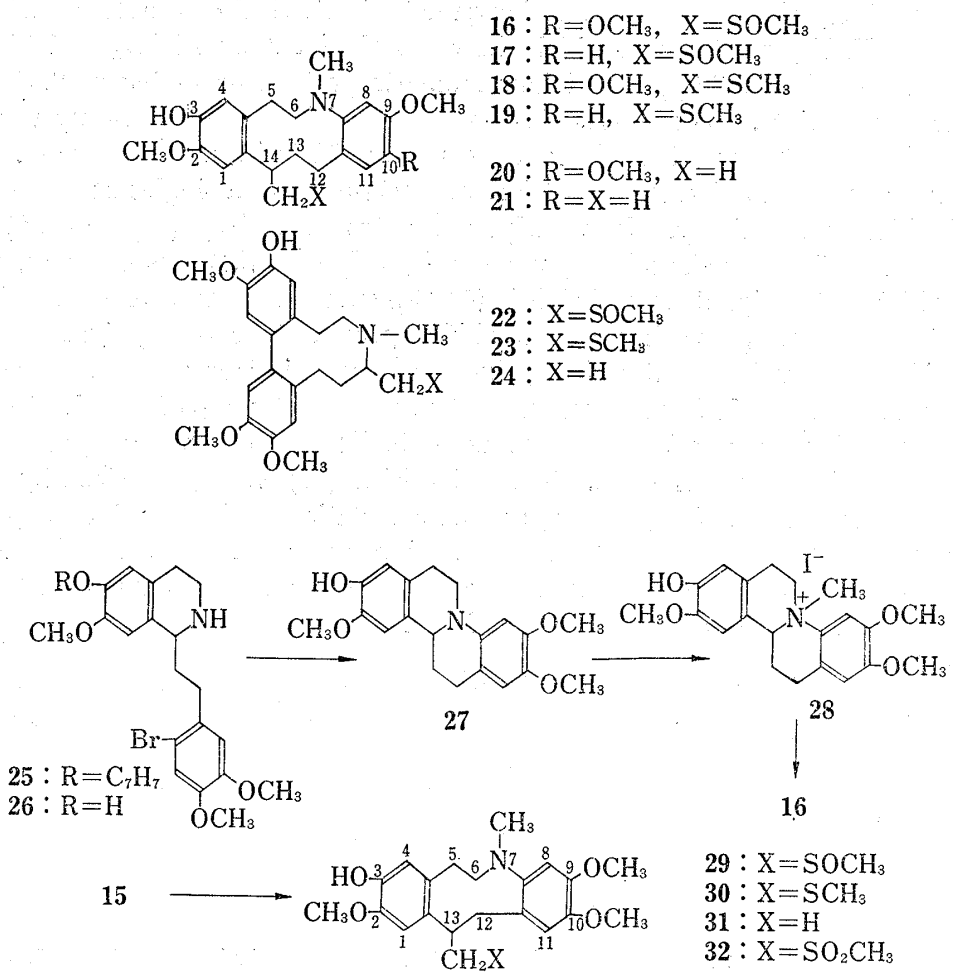


Chart 3

was verified by microanalysis and mass spectrum (M^+, *m/e* 419). Oxidation of **29** with hydrogen peroxide in ethanol afforded the corresponding methyl sulfone derivative (**32**). Deoxygenation of **29** followed by desulfurization of the 13-(methylthio)methyl derivative (**30**) gave the 13-methyldibenzo[*b*,*f*]azonine derivative (**31**). The ^{13}CNMR ($CDCl_3$) spectrum of 31 also supported the presence of the dibenzo[*b*,*f*]azonine system in **31** and the $^{13}C_{13}$ resonated at 36.985 ppm as shown in the Table.

Thus, one step synthesis of the dibenzo[*b*,*g*]azecine system has been achieved through the reaction of 1-halogenophenethylisoquinolines with sodium methysulfinylmethanide. The dibenzo[*b*,*f*]azonine system also synthesized from the 1-halogenobenzylisoquinoline. This ring transformation reaction would be applicable to the synthesis of medium ring system containing nitrogen.

Table. ^{13}CNMR ($CDCl_3$) Spectra of (**21**) and (**31**): ppm

21	24.608(14-CH_3), 22.045(C_{12}), 29.850(C_5), 30.238(C_{14}), 41.887(C_{13}), 47.857(NCH_3), 55.234(OCH_3), 55.817(OCH_3), 59.603(C_6), 107.460, 108.431, 111.440, 114.255, 129.933, 132.942, 133.913, 137.553, 143.280, 145.028, 152.502, 158.375
31	22.763(13-CH_3), 31.840(C_5), 36.985(C_{13}), 41.838(C_{12}), 46.158(NCH_3), 55.914(3OCH_3), 63.389(C_6), 106.734, 107.608, 111.976, 115.471, 132.898, 134.016, 137.992, 143.141, 144.694, 146.636, 147.894

Experimental[5]

N-(3-Benzyloxy-4-methoxyphenethyl)-2-(2-bromo-4,5-dimethoxyphenyl)propionamide (4)——A mixture of 7.0 g of 3-benzyloxy-4-methoxyphenethylamine and 7.8 g of 2-bromo-4,5-dimethoxyphenylpropionic acid was heated at 180° for 1 hr. After cooling, the mixture was recrystallized from MeOH–ether to give 9.8 g (68.4%) of **4** as colorless needles, mp 130—131°. *Anal.* Calcd. for $C_{27}H_{30}O_5NBr$: C, 61.35; H, 5.72; N, 2.65. Found: C, 61.57; H, 5.82; N, 2.57.

N-(3-Benzyloxy-4-methoxyphenethyl)-2-(3-bromo-4-methoxyphenyl)propionamide (5)——A mixture of 8.0 g of 3-benzyloxy-4-methoxyphenethylamine and 7.8 g of 3-bromo-4-methoxyphenylpropionic acid was heated at 180° for 1 hr. The mixture was worked-up as above to give 10.8 g of **5** as colorless needles, mp 143—144° (MeOH–ether). *Anal.* Calcd. for $C_{26}H_{28}O_4NBr$: C, 62.66; H, 5.66; N, 2.81. Found: C, 63.00; H, 5.78; N, 2.71.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-7-methoxyisoquinoline (7)——A solution of a mixture of 8.5 g of **4** and 8 g of $POCl_3$ in 100 ml of dry benzene was refluxed for 2 hr. To the reaction mixture was added excess *n*–hexane and allowed to stand for 10 hr and the supernatant liquid was decanted. The precipitate was made basic with 28% NH_4OH and extracted with $CHCl_3$. The residual solid was recrystallized from MeOH–ether to give 7 g (91.5%) of **7**, mp 124—126°. *Anal.* Calcd. for $C_{27}H_{28}O_4NBr$: C, 63.53; H, 5.53; N, 2.74. Found. C, 63.36; H, 5.60; N, 2.54.

6-Benzyloxy-1-(3-bromo-4-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (8)——A solution of a mixture of 9.5 g of the amide (**5**) and 9 g of $POCl_3$ in 120 ml of dry benzene was refluxed for 2 hr, and the reaction mixture was worked-up as above to give 8.4 g (91.7%) of **8**, mp 122—123° (benzene–*n*–hexane). *Anal.* Calcd. for $C_{26}H_{26}O_3NBr$: C, 65.00; H, 5.46; N, 2.92. Found: C, 65.28; H, 5.22; N, 3.21.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (10)——A mixture of 6.5 g of **7**, 10 ml of methyl iodide and 30 ml of MeOH was refluxed for 5 hr, and the solvent was evaporated. To a solution of the residue in 100 ml of MeOH was added 2 g of $NaBH_4$ under stirring at room temperature within 0.5 hr, and the mixture was refluxed for 1 hr. The remaining residue, obtained after evaporation of the solvent, was suspended in 150 ml of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4. Evaporation of the solvent yielded 5.8 g of **10** as colorless needles, mp 86—88° (benzene–*n*–hexane), NMR ($CDCl_3$) δ: 2.50 (3H, s, NCH_3), 3.85 (9H, s, $3\times OCH_3$), 5.07 (2H, s, $C_6H_5CH_2O$–), 6.52, 6.62, 6.77, 7.02 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{28}H_{32}O_4NBr$: C, 63.88; H, 6.13; N, 2.66. Found: C, 63.55; H, 6.30; N, 2.88.

6-Benzyloxy-1-(3-bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (11)——A mixture of 7.8 g of **8**, 10 ml of methyl iodide and 30 ml of MeOH was gently refluxed for 5 hr and then the solvent was evaporated. To a methanolic solution of the remaining residue was added 2 g of $NaBH_4$ under stirring at room temperature and the reaction mixture was worked-up as above to give 6.5 g of **11** as an oil, NMR ($CDCl_3$) δ: 2.43 (3H, s, NCH_3), 3.82 (6H, s, $2\times OCH_3$), 5.07 (2H, s, $C_6H_5CH_2O$–), 6.55—7.42 (10H, m, Ar–H); this was characterized as the methiodide, mp 140—142° (MeOH). *Anal.* Calcd. for $C_{28}H_{33}O_3NBrI$: C, 52.68; H, 5.21; N, 2.19. Found: C, 52.44; H, 5.26; N, 1.92.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (13)——A mixture of 5 g of **10**, 30 ml of conc. HCl and 50 ml of EtOH was refluxed for 2 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. Removal of the solvent afforded 3.5 g of **13** as an oil, NMR ($CDCl_3$) δ: 2.50 (3H, s, NCH_3), 3.83 (9H, s, $3\times OCH_3$), 6.57, 6.62, 6.70. 6.95 (4H, each s, Ar–H). Since any attempt to crystallize was unsuccessful, this was used for the following reaction without further purification.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9,10-trimethoxy-7-methyl-14-(methylsulfinyl) methyldibenzo-[*b*,*g*]azecine (16)——a) A solution of 2.8 g of **13** in 35 ml of dimethylsulfoxide (DMSO) was added to a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 30 ml of DMSO) under stirring at room temperature. After the stirring had been continued for 8 hr, the mixture was poured into 300 ml of H_2O containing excess NH_4Cl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining residue was chromatographed on 20 g of silica gel. The eluant with 2% MeOH–$CHCl_3$ (100 ml) was evaporated to give 1.1 g of **16** as colorless needles, mp 239—241° (MeOH–ether), Mass Spectrum *m/e*: 433 (M^+). *Anal.* Calcd. for $C_{23}H_{31}O_5NS$: C, 63.71; H, 7.21; N, 3.23. Found: C, 63.72; H, 7.20; N, 3.25. b) A solution of 1 g of the dibenzo[*a*,*f*]quinolizine methiodide (**28**), prepared as described later, in 20 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 0.5 of NaH and 20 ml of DMSO) under stirring at room temperature. After the stirring had been continued for 8 hr, the mixture was poured into 200 ml of H_2O containing excess NH_4Cl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining residue was chromato-

5) All melting points were uncorrected. NMR spectra were taken with a Varian T-60 spectrometer and ^{13}CNMR spectra with a Varian NV-14 spectrometer using Me_4Si as an internal standard. Mass Spectra were measured with a Hitachi RMU-7L spectrometer.

graphed on 5 g of silica gel. The elution with 2% MeOH–$CHCl_3$ (70 ml) gave 0.3 g of **16** as colorless needles which was identical with **16** obtained from **13** in all aspects.

1-(3-Bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (14)——A mixture of 5.8 g of **11**, 30 ml of conc. HCl and 50 ml of EtOH was refluxed for 2 hr and the mixture was worked-up as above to give 4.1 g of **14** as an oil, NMR ($CDCl_3$) δ: 2.44 (3H, s, NCH_3), 3.85 (6H, s, $2\times OCH_3$), 6.50, 6.62 (2H, each s, Ar–H), 6.67—7.40 (3H, m, Ar–H); this was used for the following reaction because of difficulty of crystallization.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9-dimethoxy-7-methyl-14-(methylsulfinyl)methyldibenzo[*b*,*g*]azecine (17)——A solution of 2.5 g of **14** in 35 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 35 ml of DMSO) at room temperature under stirring and the mixture was worked-up as above to give 1.0 g of **17** as colorless needles, mp 213—215° (MeOH–ether), Mass Spectrum *m/e*: 403 (M^+). *Anal.* Calcd. for $C_{22}H_{29}O_4NS$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.33; H, 7.12; N, 3.18.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9,10-trimethoxy-7-methyl-14-(methylthio)methyldibenzo[*b*,*g*]azecine (18)——A mixture of 0.6 g of **16**, 50% AcOH–conc. HCl (1:1) (60 ml) and Zn–Hg (prepared from 5 g of Zn and 0.5 g of $HgCl_2$) was heated on a water bath for 1 hr. Inorganic material was filtered and the filtrate 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. The remaining solid was recrystallized from MeOH–ether to give 0.5 g of **18** as colorless needles, mp 155.5—157°, Mass Spectrum *m/e*: 417 (M^+), NMR ($CDCl_3$) δ: 1.75 (3H, s, SCH_3), 2.38 (3H, s, NCH_3), 3.90 (9H, s, $3\times OCH_3$), 6.65, 6.78, 6.80, 6.87 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{23}H_{31}O_4NS$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.24; H, 7.47; N, 3.22.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9-dimethoxy-7-methyl-14-(methylthio)methyldibenzo[*b*,*g*]azecine (19)——A mixture of 0.8 g of **17**, 60 ml of 50% AcOH–conc. HCl (1:1) and Zn–Hg (prepared from 5 g of Zn and 0.5 g of $HgCl_2$) was heated on a water bath for 1 hr and the mixture was worked-up as above to yield 0.72 g of **19** as colorless needles, mp 112—113° (MeOH–ether), Mass Spectrum *m/e*: 387 (M^+). NMR ($CDCl_3$) δ: 1.72 (3H, s, SCH_3), 2.40 (3H, s, NCH_3), 3.80, 3.87 (6H, each s, $2\times OCH_3$). *Anal.* Calcd. for $C_{22}H_{29}O_4NS$: C, 67.49; H, 7.54; N, 3.61. Found: C, 67.89; H, 7.65; N, 3.45.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9,10-trimethoxy-7,14-dimethyldibenzo[*b*,*g*]azecine (20)——A solution of 0.5 g of **18** in 70 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 14 hr. The Ni catalyst was filtered and the filtrate was evaporated. The remaining residue was chromatographed on 2 g of silica gel using $CHCl_3$ as an eluant. Removal of the solvent gave 440 mg of **20** as colorless needles, mp 174—175° (MeOH–ether), Mass Spectrum *m/e*: 371 (M^+), NMR ($CDCl_3$) δ: 1.05 (3H, d, $J=7$ Hz, 14-CH_3), 2.40 (3H, s, NCH_3), 3.93 (9H, s, $3\times OCH_3$), 6.68 (1H, s, Ar–H), 6.75 (2H, s, Ar–H), 6.87 (1H, s, Ar–H). *Anal.* Calcd. for $C_{22}H_{29}O_4N$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.91; H, 7.89; N, 3.48.

5,6,7,12,13,14-Hexahydro-3-hydroxy-2,9-dimethoxy-7,14-dimethyldibenzo[*b*,*g*]azecine (21)——A solution of 0.5 g of **19** in 70 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 14 hr. The reaction mixture was worked-up as above to yield 360 mg of **21** as colorless needles, mp 169—170° (ether), Mass Spectrum *m/e*: 341 (M^+), NMR ($CDCl_3$) δ: 1.00 (3H, d, $J=7$ Hz, 14-CH_3), 2.40 (3H, s, NCH_3), 3.80, 3.87 (6H, each s, $2\times OCH_3$). *Anal.* Calcd. for $C_{21}H_{27}O_3N$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.77; H, 8.05; N, 3.90.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-methoxyisoquinoline (25)——To a solution of 8 g of **7** in 100 ml of MeOH was added 2 g of $NaBH_4$ under stirring at room temperature within 0.5 hr and then the mixture was refluxed for 1 hr, and worked-up as usual to give 7.7 g of **25** as colorless needles, mp 118—119° (ether), NMR ($CDCl_3$) δ: 3.82 (9H, s, $3\times OCH_3$), 5.07 (2H, s, $C_6H_5CH_2O$–), 6.62 (2H, s, Ar–H), 6.58 (1H, s, Ar–H), 6.97 (1H, s, Ar–H), 7.37 (5H, s, Ar–H). *Anal.* Calcd. for $C_{27}H_{30}O_4NBr$: C, 63.24; H, 5.90; N, 2.73. Found: C, 63.53; H, 6.02; N, 3.04.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxyisoquinoline (26)——A mixture of 7 g of **25**, 30 ml of conc. HCl and 50 ml of EtOH was refluxed for 2 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. Evaporation of the solvent gave 5.2 g of **26** as colorless needles, mp 181—182° (MeOH–ether), NMR ($CDCl_3$) δ: 3.83 (9H, s, $3\times OCH_3$), 6.65 (2H, s, Ar–H), 6.72, 6.98 (2H, each s, Ar-H). *Anal.* Calcd. for $C_{20}H_{24}O_4NBr$: C, 56.88; H, 5.73; N, 3.32. Found: C, 57.08; H, 6.05; N, 3.02.

5,6,12,13,13a-Pentahydro-3-hydroxy-2,9,10-trimethoxydibenzo[*a*,*f*]quinolizine (27)——A solution of 4 g of **26** in 35 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 30 ml of DMSO) under stirring at room temperature. After the stirring had been continued for 8 hr, the mixture was poured into 300 ml of H_2O containing excess NH_4Cl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining residue was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (150 ml) gave 1.8 g of **27** as colorless needles, mp 144—146° (MeOH–ether), NMR ($CDCl_3$) δ: 3.83 (9H, s, $3\times OCH_3$), 6.50, 6.53, 6.63, 6.66 (4H, each s, Ar–H); this was characterized as the methiodide (**28**) prepared as usual, mp 247—248° (MeOH). *Anal.* Calcd. for $C_{21}H_{26}O_4NI$: C, 52.18; H, 5.42; N, 2.90. Found: C, 51.83; H, 5.55; N, 2.64.

N-(3-Benzyloxy-4-methoxyphenethyl)-2-bromo-4,5-dimethoxyphenylacetamide (6)——A mixture of 7 g of 3-benzyloxy-4-methoxyphenethylamine and 7.4 g of 2-bromo-4,5-dimethoxyphenylacetic acid was heated

at 180° for 1 hr. After cooling, the mixture was recrystallized from MeOH–ether to give 10.5 g of **6**, mp 139—140.5°. *Anal.* Calcd. for $C_{26}H_{28}O_5NBr$: C, 60.65; H, 5.32; N, 2.79. Found: C, 60.71; H, 5.49; N, 2.73.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-7-methoxyisoquinoline (9)——A mixture of 9.5 g of **6**, 9 g of $POCl_3$ and 120 ml of dry benzene was refluxed for 2 hr. To the reaction mixture was added excess *n*-hexane and allowed to stand for 5 hr. The supernatant liquid was discarded and the precipitate was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4. Removal of the solvent afforded 7.8 g of **9**, mp 110—111° (MeOH–ether). *Anal.* Calcd. for $C_{26}H_{26}O_4NBr$: C, 62.91; H, 5.28; N, 2.82. Found: C, 62.63; H, 5.26; N, 2.73.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (12)——A mixture of 6.5 g of **9**, 12 ml of methyl iodide and 30 ml of MeOH was gently refluxed for 5 hr, and the solvent was evaporated. To a solution of the remaining residue in 100 ml of MeOH was added 2 g of $NaBH_4$ under stirring at room temperature within 0.5 hr and then the mixture was refluxed for 1 hr. The remaining residue, obtained after evaporation of the solvent, was suspended in 150 ml of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4). Evaporation of the solvent yielded 5.7 g of **12** as colorless needles, mp 94—96° (benzene–*n*–hexane), NMR ($CDCl_3$) δ: 2.53 (3H, s, NCH_3), 3.57, 3.70, 3.87 (9H, each s, $3\times OCH_3$), 5.93, 6.47, 6.58, 7.00 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{27}H_{30}O_4NBr$: C, 63.28; H, 5.90; N, 2.73. Found: C, 63.52; H, 6.08; N, 2.70.

1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (15)——A mixture of 5 g of **12**, 30 ml of conc. HCl and 50 ml EtOH was refluxed for 2 hr. The solvent was evaporated and then 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. Evaporation of the solvent afforded 3.4 g of **15** as colorless needles, mp 124—125° (MeOH–ether), NMR ($CDCl_3$) δ: 2.58 (3H, s, NCH_3), 3.57, 3.70, 3.87 (9H, each s, $3\times OCH_3$), 5.93, 6.48, 6.63, 7.00 (4H, each, Ar–H). *Anal.* Calcd. for $C_{20}H_{24}O_4NBr$: C, 56.88; H, 5.73; N, 3.32. Found: C, 57.10; H, 5.87; N, 3.20.

5,6,12,13-Tetrahydro-3-hydroxy-2,9,10-trimethoxy-7-methyl-13-(methylsulfinyl)methyl-7*H*-dibenzo[*b*,*f*]azonine (29)——A solution of 2 g of **15** in 40 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 35 ml of DMSO) under stirring at room temperature. After the stirring had been continued for 7 hr, the mixture was worked-up as in formation of **16** to give 1.8 g of **29**, mp 184—186° (MeOH), Mass Spectrum *m/e*: 419 (M^+). *Anal.* Calcd. for $C_{22}H_{29}O_5NS$: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.91; H, 7.28; N, 3.06.

5,6,12,13-Tetrahydro-3-hydroxy-2,9,10-trimethoxy-7-methyl-13-(methylthio)methyl-7*H*-dibenzo[*b*,*f*]azonine (30)——A mixture of 0.5 g of **29**, 60 ml of 50% AcOH–conc. HCl (1:1) and Zn–Hg (prepared from 5 g of Zn and 0.5 g of $HgCl_2$) was heated on a water bath for 1 hr. Inorganic material was filtered and the filtrate 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. The resulting solid was recrystallized from MeOH–ether to give 0.4 g of **30**, mp 129—131°, Mass Spectrum *m/e*: 403 (M^+), NMR ($CDCl_3$) δ: 2.08 (3H, s, SCH_3), 2.53 (3H, s, NCH_3), 3.85 (9H, s, $3\times OCH_3$), 6.57, 6.65, 6.73, 6.88 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{20}H_{33}O_4NS$: C, 65.62; H, 7.72; N, 3.61. Found: C, 65.48; H, 7.24; N, 3.47.

5,6,12,13-Tetrahydro-3-hydroxy-2,9,10-trimethoxy-7,13-dimethyl-7*H*-dibenzo[*b*,*f*]azonine (31)——A solution of 0.3 g of **30** in 70 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 15 hr. The Ni catalyst was filtered and the filtrate was evaporated. The residual solid was recrystallized from MeOH–ether to yield 0.2 g of **31**, mp 121—122°, Mass Spectrum *m/e*: 357 (M^+), NMR ($CDCl_3$) δ: 1.53 (3H, d, $J=7$ Hz, 13-CH_3), 2.53 (3H, s, NCH_3), 3.85 (9H, s, $3\times OCH_3$), 6.58, 6.65, 6.67, 6.75 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.22; H, 7.72; N, 3.61. Found: C, 70.56; H, 7.61; N, 3.92.

5,6,12,13-Tetrahydro-3-hydroxy-2,9,10-trimethoxy-7-methyl-13-(methylsulfonyl)methyl-7*H*-dibenzo[*b*,*f*]azonine (32)——A mixture of 0.2 g of **29**, 1 ml of 30% H_2O_2 and 3 ml of EtOH was refluxed for 4 hr and the solvent was evaporated. The remaining residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting solid was recrystallized from MeOH–ether to give 0.1 g of **32** as colorless needles, mp 178—179°, Mass Spectrum *m/e*: 451 (M^+), NMR ($CDCl_3$) δ: 2.03 (3H, s, SO_2CH_3), 2.45 (3H, s, NCH_3), 3.77 (9H, $3\times OCH_3$), 6.42 (1H, s, Ar–H), 6.52 (2H, s, Ar–H), 6.60 (1H, s, Ar–H). *Anal.* Calcd. for $C_{22}H_{29}O_6NS$: C, 60.67; H, 6.72; N, 3.22. Found: C, 60.76; H, 6.89; N, 2.96.

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