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# Syntheses of Dibenzo[*b*,*f*]azonines and Dibenzo[*b*,*g*]azecines through Ring Expansion of 1-Substituted Isoquinolines

Shinzo Kano, Eiji Komiyama, Youko Takahagi, and Shiroshi Shibuya

*Tokyo College of Pharmacy*[1]

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The reaction of 1-(2-bromo-4,5-methylenedioxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (**13**) with sodium methylsulfinylmethanide gave the dibenzo[*b*,*g*]azecine (**14**). The 1-benzyl analog possessing a methyl group at the 3-position was transformed to the 6,13-disubstituted dibenzo[*b*,*f*]azonine (**33**) under the similar conditions. **33** was converted to the corresponding 6,13-dimethyl derivative (**35**). Hydrogenolysis of the N-methyl-dibenzo[*a*,*f*]quinolizinium iodide (**23**) over Adams catalyst was also examined to give the dibenzo[*b*,*g*]azecine (**24**).

We have previously investigated one-step synthesis of dibenzo[*b*,*g*]azecine (3) by the reaction of 1-halogenophenethyl-1,2,3,4-tetrahydro-2-methylisoquinoline (**1**) with sodium methylsulfinylmethanide.[2] Apparently, this ring system would be formed through the fission of the $C_{13a}$–N bond of the possible intermediate, 5,6,12,13,13a-pentahydrodibenzo[*a*,*f*]-quinolizinium salt (**2**), by the nucleophilic attack of this reagent to the $C_{13a}$ of **2**. Application of similar reaction to the 1-halogenobenzylisoquinoline (**4**) also led to the formation of dibenzo-[*b*,*f*]azonine (**5**).[2,3] We had successively occasion to examine the ring expansion of 1-halogeno-phenethylisoquinolines through the reaction involving the cleavage of the C–N bond of the quaternary dibenzo[*a*,*f*]quinolizinium salts. Furthermore, it is interesting to investigate syntheses of 6,13-disubstituted dibenzo[*b*,*f*]azonines (**8**) from 1-halogenobenzyl-3-methyl-isoquinoline (**6**) in order to know whether the ring expansion occurs stereoselectively during the fission of the C–N bond of the quaternary 6-methyldibenzo[*b*,*g*]indolizinium salt (**7**) that is the intermediate, or not. And we have investigated a synthesis of a poly-substituted dibenzo[*b*,*f*]azonine from the 1-halogenobenzyl-3-methylisoquinoline. We wish to report these results in this paper.

First, the reaction of 1-(2-bromo-4,5-methylenedioxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (**13**) with sodium methylsulfinylmethanide was examined. The isoquinoline (**13**) was prepared from the amide (**9**) by the usual way (9→10→11 →12→13), as described in the experimental section. The molecular formula, $C_{22}H_{27}O_5NS$, of the product (**14**) was confirmed by mass spectrum ($M^+$, *m/e* 417) and microanalysis. Its nuclear magnetic resonance (NMR) ($CDCl_3$) spectrum showed that the product (**14**) would be a mixture of diastereosiomers. Although separation of each isomer was not successful, the structure of **14** was determined through the following transformations. Reductive deoxygenation of **14** with amalgamated zinc gave the 14-(methylthio)methyl derivative (**15**), the NMR ($CDCl_3$) spectrum of which showed two singlets attributable to $SCH_3$ and $NCH_3$ at 1.77 and 2.37 ppm. Desulfurization of **15** with Raney Ni catalyst yielded the corresponding 14-$CH_3$ derivative (**16**). The 14-$CH_3$ signal was observed at 1.05 ppm as a doublet ($J$=7 Hz) in its NMR ($CDCl_3$) spectrum. The $NCH_3$ protons resonated at 2.35 ppm as a singlet. These

1) Location: *3–20–1, Kitashinjuku, Shinjuku-ku, Tokyo.*
2) S. Kano, E. Komiyama, T. Ogawa, Y. Takahagi, T. Yokomatsu, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **23**, 2058 (1975).
3) S. Kano, E. Komiyama, K. Nawa, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **24**, 310 (1976).

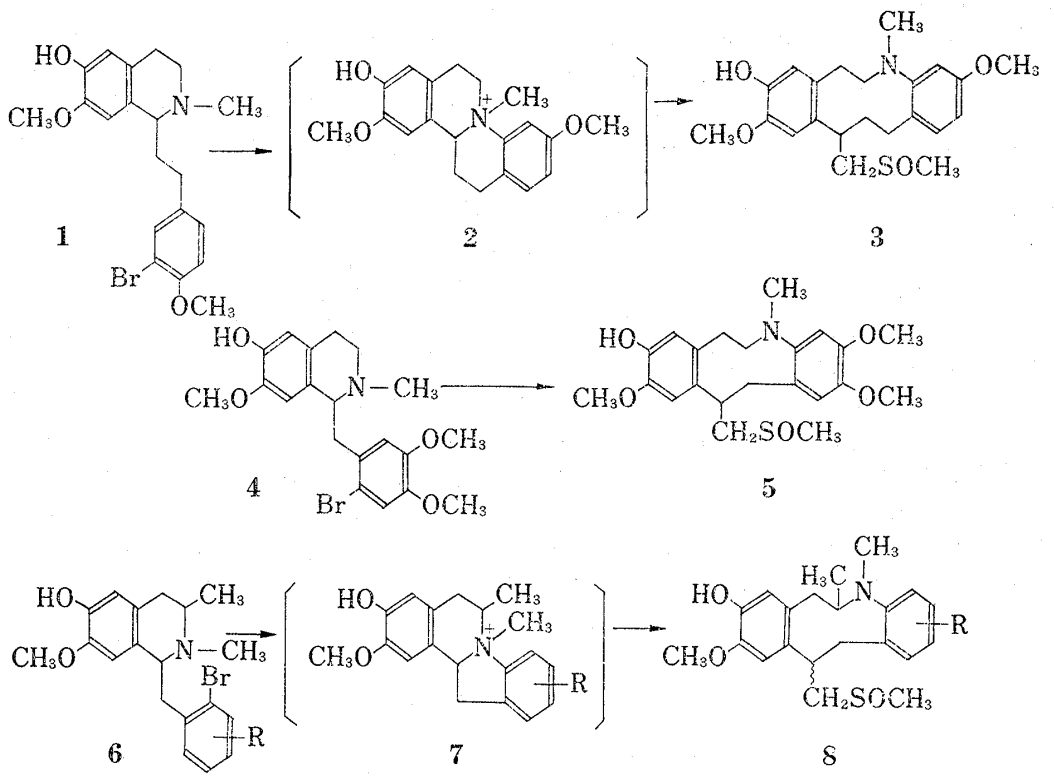

Chart 1

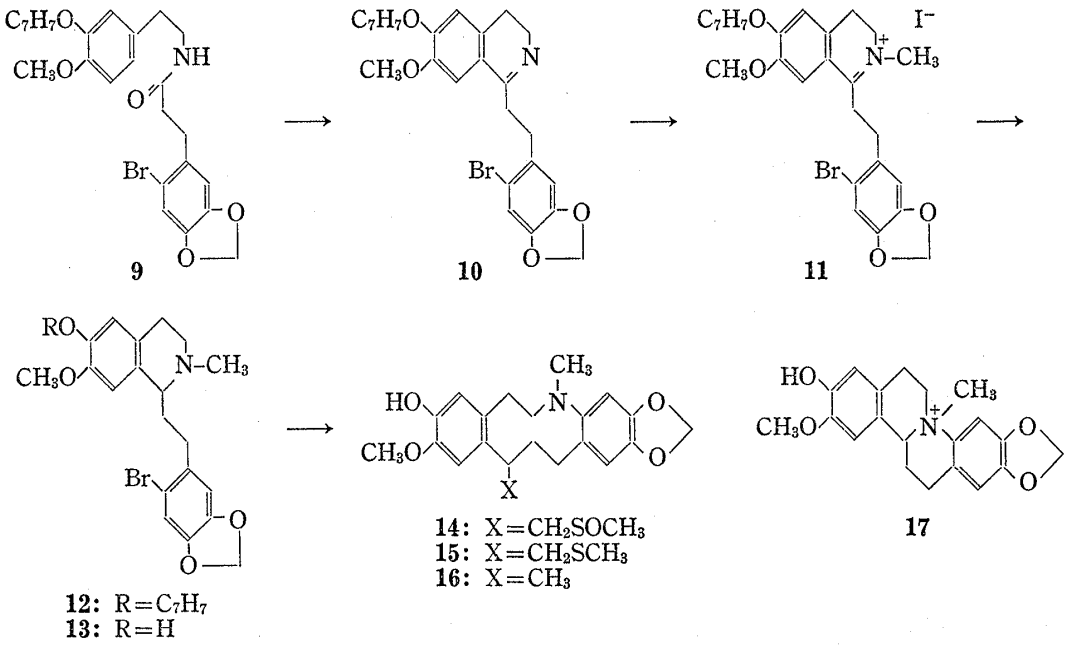

Chart 2

considerably high aromatic $NCH_3$ signals in the NMR ($CDCl_3$) spectra of **15** and **16** would be characteristic of hexahydrodibenzo[*b*,*g*]azecines.

Apparently, the dibenzo[*b*,*g*]azecine (**14**) was formed through the dibenzo[*a*,*f*]quinolizinium salt (**17**) with subsequent cleavage of $C_{13a}$–N bond by the nucleophilic attack of methylsulfinyl carbanion. Since these results indicated that the $C_{13a}$–N bond of dibenzo[*a*,*f*]quinolizinium salt seemed to cleave easily to form the medium ring system, we examined the reductive cleavage of the $C_{13a}$–N bond of N-methyldibenzo[*a*,*f*]quinolizinium iodide (**23**) in the expectation of the formation of the dibenzo[*b*,*g*]azecine (**24**). The N-methyl-5,6,12,13,13a-pentahydro-

dibenzo[*a*,*f*]quinolizinium iodide (**23**) was prepared by methylation of the dibenzo[*a*,*f*]quinolizine (**22**), obtained by cyclization[4] of the 1,2,3,4-tetrahydroisoquinoline (**21**). The isoquinoline (**21**) was obtained from the amide (**18**) through the usual method (Chart 3 and the experimental section). Catalytic hydrogenation of **23** over Adams catalyst in the presence of sodium acetate yielded colorless needles, mp 105—107°. Its NMR ($CDCl_3$) spectrum exhibited two singlets due to $NCH_3$ and $OCH_3$ at 2.43 and 3.83 ppm, respectively. The fission of the $C_{13a}$–N bond would form the hexahydrodibenzo[*b*,*g*]azecine (**24**) and the formation of 2-(2-ethyl-4-hydroxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-1-methylquinoline (**25**) would be expected by the cleavage of the $C_6$–N bond. The signals due to $CH_3CH_2$ was not observed in the NMR ($CDCl_3$) spectrum of the product. Its $^{13}$CNMR ($CDCl_3$) spectrum[5] showed the presence of five $CH_2$ at 23.84, 26.55, 30.59, 33.37, 59.60 ppm, attributable to $C_{12}$, $C_{14}$, $C_5$, $C_{13}$ and $C_6$ of **24**, respectively. Therefore, the structure of the product from **23** was assigned to **24**, not to **25**. This C–N fission reaction would be applicable to syntheses of poly-substituted dibenzo[*b*,*g*]azecines. The $^{13}$CNMR ($CDCl_3$) spectrum of **22** exhibited four $CH_2$ signals at 26.03, 28.61, 28.81 and 45.03 ppm attributable to $C_{12}$, $C_5$, $C_{13}$ and $C_6$, respectively. The $C_{13a}$ resonated at 55.36 ppm. The $CH_2$ signal adjacent to tertiary nitrogen shifted to down field by more than 10 ppm when the $C_{13a}$–N bond was opened as shown in the $^{13}$CNMR ($CDCl_3$) spectra of **22** and **24**.

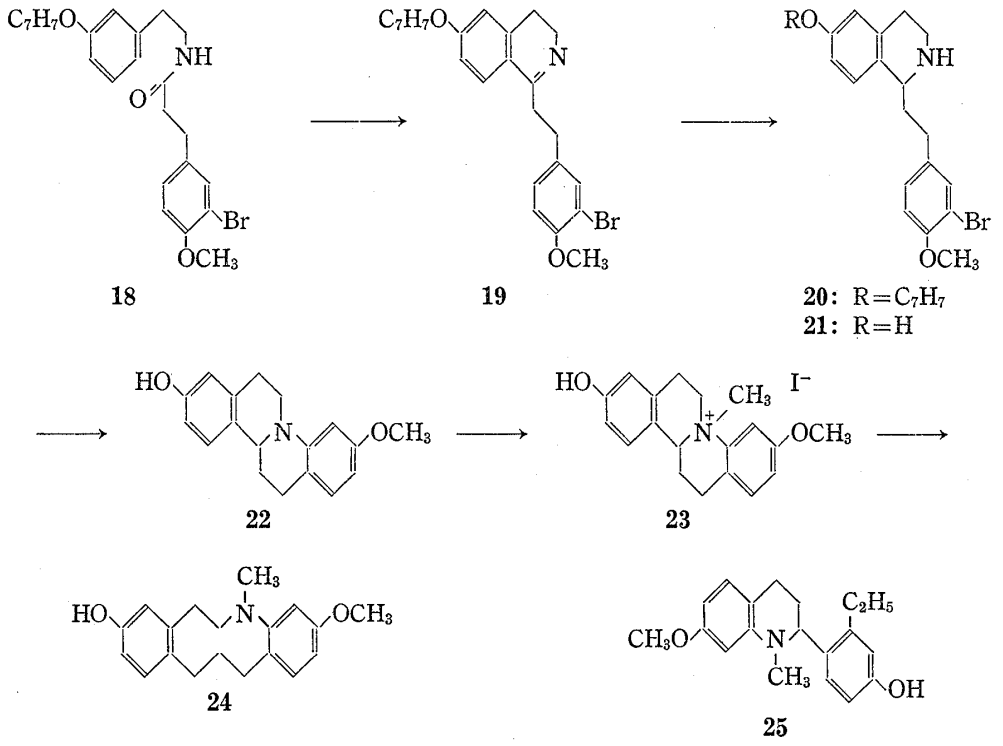


Chart 3

Finally, we investigated the ring expansion of 1-halogenobenzyl-3-substituted isoquinoline by the use of sodium methylsulfinylmethanide to study whether the (methylsulfinyl) methyl group was introduced to the 13-position stereoselectively owing to the methyl group at the 6-position, or not, during the formation of the dibenzo[*b*,*f*]azonine system. The isoquinoline (**32**) was prepared through the method as Gal reported[6] as follows. Condensation of the

4) T. Kametani, T. Terui, and K. Fukumoto, *Yakugaku Zasshi*, **88**, 1388 (1968); S. Kano, T. Yokomatsu, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **23**, 1089 (1975).
5) $^{13}$C NMR spectra were taken with Varian NV-14 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard operating at 15.1 MHz.
6) J. Gal, R.J. Wienkam, and N. Castagnoli, Jr., *J. Org. Chem.*, **39**, 418 (1974).

amine (**27**), prepared from the ω-nitrostyrene (**26**), with 2-bromo-4,5-methylenedioxyphenylacetic acid gave the amide (**28**). Cyclization of the amide (**28**), followed by reduction of the 3,4-dihydroisoquinoline (**29**) with sodium borohydride afforded the corresponding 1,2,3,4-tetrahydroisoquinoline (**30**). The relative configuration of the methyl group at the 3-position and the benzyl group at the 1-position in the tetrahydroisoquinoline, obtained by this method, was assigned to the *cis*-configuration by Gal.[6] Acidic hydrolysis of the 2-methylisoquinoline (**31**), obtained by the Eschweiler-Clarke reaction of **30**, afforded the phenolic isoquinoline (**32**). The reaction of **32**, thus obtained, with sodium methylsulfinylmethanide gave colorless needles, mp 199—201°, whose structure was assigned to 13-(methylsulfinyl)methyldibenzo[*b*,*f*]azonine (**33**) based upon the following spectroscopic and chemical methods. The molecular formula, $C_{22}H_{27}O_5NS$, was confirmed by mass spectrum ($M^+$, *m/e* 417) and microanalysis. Its NMR ($CDCl_3$) spectrum showed that the product would be a mixture of diastereoisomers, but separation of each isomer was not successful as in the case of **14**. Reductive deoxygenation of **33**, with amalgamated zinc gave the 6-methyl-13-(methylthio)methyl derivative (**34**). Its NMR ($CDCl_3$) spectrum exhibited a doublet due to the 6-$CH_3$ at 1.70 ppm. The $SCH_3$ and $NCH_3$ signals appeared at 2.03 and 2.52 ppm as singlets, respectively. Although the dibenzo[*b*,*f*]azonine (**34**) contains two asymmetric carbons, the chromatographic and spectroscopic behavior of the deoxygenated product (**34**) showed that it was obtained as a single product. These facts indicated that the methylsulfinylmethyl group was introduced stereoselectively owing to the 6-methyl group of the intermediate, dibenzo[*b*,*g*]indolizinium salt (**36**). The relative configuration of the 6-methyl and 13-(methylthio)methyl group was not conclusive by the spectroscopic methods. Desulfurization of **34** with Raney Ni catalyst afforded the corresponding 6,13-dimethyl derivative (**35**), the NMR ($CDCl_3$) of which showed two doublets at 1.23 ($J$=7 Hz) and 1.47 ppm ($J$=7 Hz) attributable to the 6-$CH_3$ and 13-$CH_3$, respectively. The $NCH_3$ signal appeared at 2.60 ppm as a singlet. Its $^{13}$CNMR ($CDCl_3$) spectrum was also agreeable with the structure (**35**), and two CH signals appeared at 36.23 and 64.57 ppm, assigned to $C_{13}$ and $C_6$, respectively. Two $CH_2$ signals appeared at 39.14 and 43.18 ppm, attributable to the $C_5$, and $C_{12}$, respectively. The signals due to the 6-$CH_3$ and 13-$CH_3$ were observed at 16.69 and 22.65 ppm, respectively. Thus, the reaction of 1-halogenobenzyl-3-methylisoquinoline with sodium methylsulfinylmethanide also gave the similar results to those of 1-halogenobenzylisoquinolines without a substituent at the 3-position to form the dibenzo[*b*,*f*]azonines.

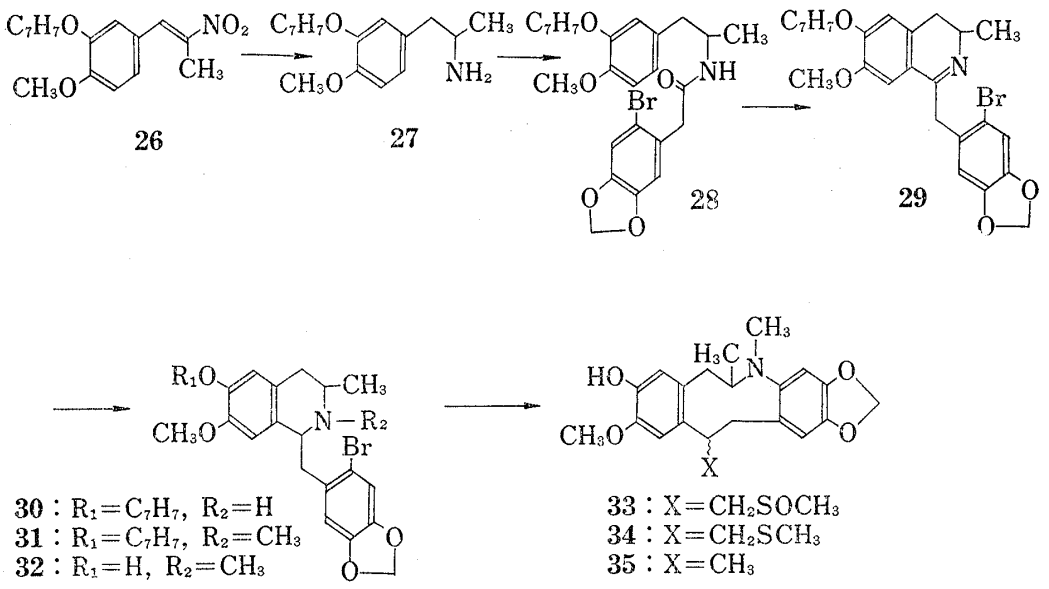


Chart 4

## Experimental[7]

**N-(3-Benzyloxy-4-methoxyphenethyl)-2-(2-bromo-4,5-methylenedioxyphenyl)propionamide** (9)——A mixture of 7.0 g of 3-benzyloxy-4-methoxyphenethylamine and 7.4 g of 2-bromo-4,5-methylenedioxyphenylpropionic acid was heated at 180° for 1.5 hr. After cooling, the mixture was recrystallized from MeOH–ether to give 10 g of **9** as colorless needles, mp 132—134°. *Anal.* Calcd. for $C_{26}H_{26}O_5NBr$: C, 60.94; H, 5.12; N, 2.73. Found: C, 61.05; H, 5.17; N, 2.64.

**6-Benzyloxy-1-(2-bromo-4,5-methylenedioxyphenethyl)-3,4-dihydro-7-methoxyisoquinoline** (10)——A solution of a mixture of 9.2 g of **9** and 9 g of $POCl_3$ in 120 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 extract was washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to give 8.3 g of **10** as an oil, which was characterized as the methiodide, mp 202—204° (MeOH). *Anal.* Calcd. for $C_{27}H_{27}O_4NBrI$: C, 50.96; H, 4.28; N, 2.20. Found: C, 50.75; H, 4.10; N, 2.14.

**6-Benzyloxy-1-(2-bromo-4,5-methylenedioxyphenethyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline** (12)——A mixture of 7.5 g of **10**, 10 ml of methyl iodide and 30 ml of MeOH was gently refluxed for 5 hr, and the solvent was evaporated. To a methanolic solution of the resulting residue, obtained after evaporation of the solvent, was added 2.5 g of $NaBH_4$ under stirring within 0.5 hr at room temperature. The mixture was refluxed for 1 hr and the solvent was removed. A suspension of the remaining residue in 150 ml of $H_2O$ was extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$. Removal of the solvent gave 6.1 g of **12** as an oil. NMR ($CDCl_3$) $\delta$: 2.47 (3H, s, $NCH_3$), 3.83 (3H, s, $OCH_3$), 5.07 (2H, s, Ph $CH_2O$), 5.85 (2H, s, $OCH_2O$), 6.60 (1H, s, Ar–H), 6.63 (2H, s, Ar–H), 6.92 (1H, s, Ar–H), 7.25 (5H, s, Ar–H); this was characterized as the hydrochloride, mp 132—134° (MeOH). *Anal.* Calcd. for $C_{27}H_{28}O_4NBr \cdot HCl$: C, 59.32; H, 5.35; N, 2.56. Found: C, 59.09; H, 5.35; N, 2.45.

**1-(2-Bromo-4,5-methylenedioxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline** (13)——A mixture of 5.5 g of **12**, 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 afforded 3.5 g of **13** as an oil. NMR ($CDCl_3$) $\delta$: 2.48 (3H, s, $NCH_3$), 3.87 (3H, s, $OCH_3$), 5.88 (2H, s, $OCH_2O$), 6.58 (2H, s, Ar–H), 6.65 (1H, s, Ar–H), 6.92 (1H, s, Ar–H); this was characterized as the methiodide, mp 217—219° (MeOH). *Anal.* Calcd. for $C_{21}H_{25}O_4NBrI$: C, 44.85; H, 4.48; N, 2.49. Found: C, 44.67; H, 4.47; N, 2.54.

**5,6,7,12,13,14-Hexahydro-3-hydroxy-2-methoxy-7-methyl-14-(methylsulfinyl)methyl-9,10-methylenedioxydibenzo[*b*,*g*]azecine** (14)——A solution of 2.5 g of **13** in 40 ml of dimethylsulfoxide (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 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 resulting residue was chromatographed on 20 g of silica gel. Elution with 2% MeOH–$CHCl_3$ afforded 1.1 g of **14** as colorless needles, mp 239—241° (MeOH–ether). Mass Spectrum *m/e*: 417 ($M^+$). *Anal.* Calcd. for $C_{22}H_{27}O_5NS$: C, 63.28; H, 6.52; N, 3.36. Found: C, 63.24; H, 6.59; N, 3.14.

**5,6,7,12,13,14-Hexahydro-3-hydroxy-2-methoxy-7-methyl-14-(methylthio)methyl-9,10-methylenedioxydibenzo[*b*,*g*]azecine** (15)——A mixture of 0.8 g of **14**, 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 remaining solid was recrystallized from MeOH–ether to give 0.53 g of **15** as colorless needles, mp 193—194°. Mass Spectrum *m/e*: 401 ($M^+$). NMR ($CDCl_3$) $\delta$: 1.05 (3H, s, $SCH_3$), 2.37 (3H, s, $NCH_3$), 3.88 (3H, s, $OCH_3$), 5.92 (2H, s, $OCH_2O$), 6.62 (1H, s, Ar–H), 6.73 (2H, s, Ar–H), 6.83 (1H, s, Ar–H). *Anal.* Calcd. for $C_{22}H_{27}O_4NS$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.80; H, 6.89; N, 3.21.

**5,6,7,12,13,14-Hexahydro-3-hydroxy-2-methoxy-7,14-dimethyl-9,10-methylenedioxydibenzo[*b*,*g*]azecine** (16)——A solution of 0.5 g of **15** in 70 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 14 hr. The 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 0.4 g of **16** as colorless needles, mp 193—194° (MeOH–ether). Mass Spectrum *m/e*: 355 ($M^+$). NMR ($CDCl_3$) $\delta$: 1.05 (3H, d, $J=7$ Hz, 14-$CH_3$), 2.35 (3H, s, $NCH_3$), 3.87 (3H, s, $OCH_3$), 5.90 (2H, s, $OCH_2O$), 6.67 (1H, s, Ar–H), 6.72 (2H, s, Ar–H), 6.85 (1H, s, Ar–H). *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.98; H, 7.13; N, 4.23.

**N-(3-Benzyloxyphenethyl)-2-(3-bromo-4-methoxyphenyl)propionamide** (18)——A mixture of 7.0 g of 3-benzyloxyphenethylamine and 7.8 g of 3-bromo-4-methoxyphenylpropionic acid was heated at 180° for 1.5 hr. After cooling, the mixture was recrystallized from MeOH–ether to give 13.5 g of **18** as colorless need-

7) All melting points were uncorrected. NMR spectra were taken with Varian T-60 spectrometer using TMS as an internal. Mass spectra were measured with RMU-7L spectrometer.

les, mp 118—119°. *Anal.* Calcd. for $C_{25}H_{25}O_3NBr$: C, 64.10; H, 5.60; N, 2.99. Found: C, 64.20; H, 5.58; N, 2.71.

**6-Benzyloxy-1-(3-bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline (20)**——A mixture of 10 g of **18**, 10 g of $POCl_3$ and 200 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 to leave the 3,4-dihydroisoquinoline (**19**) hydrochloride; this was used for the following reaction. A solution of **19** in 300 ml of MeOH was added 7 g of $NaBH_4$ at room temperature in small portions under stirring. After the mixture was refluxed for 0.5 hr, the solvent was evaporated. A suspension of the resulting residue in $H_2O$ was extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$. Evaporation of the solvent yielded 7.8 g of **20** as an oil; this was characterized as the hydrochloride, mp 215—216° (decomp.) (MeOH–ether). *Anal.* Calcd. for $C_{25}H_{26}O_2NBr \cdot HCl$: C, 61.42; H, 5.57; N, 2.87. Found: C, 61.55; H, 5.60; N, 2.83.

**1-(3-Bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6-hydroxyisoquinoline (21)**——A solution of 5 g of the isoquinoline (**20**) in 50 ml of EtOH was refluxed for 1.5 hr in the presence of 50 ml of conc. HCl. The solvent was evaporated and the resulting 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 3.1 g of **21** as colorless needles, mp 151—152° (MeOH–ether). NMR ($CDCl_3$) $\delta$: 3.80 (3H, s, $OCH_3$), 6.43—7.17 (6H, m, Ar–H). *Anal.* Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.67; H, 5.57; N, 3.87. Found: C, 59.71; H, 5.41; N, 3.76.

**5,6,12,13,13a-Pentahydro-3-hydroxy-9-methoxydibenzo[*a*,*f*]quinolizine (22)**——To a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 40 ml of DMSO) was added a solution of 3.5 g of **21** in 45 ml of DMSO under stirring at room temperature within 15 min. After the stirring had been continued for 14 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 $Na_2SO_4$. The solvent was evaporated and the remaining residue was chromatographed on 20 g of silica gel using $CHCl_3$ as an eluant. Removal of the solvent (150 ml) yielded 2.1 g of **22** as slightly pale brownish oil. NMR ($CDCl_3$) $\delta$: 3.73 (3H, s, $OCH_3$), 4.27 (1H, d, d, $J$=4 and 8 Hz), 6.07—7.10 (6H, m, Ar–H); this was characterized as the methiodide (**23**), mp 201—202° (MeOH). *Anal.* Calcd. for $C_{19}H_{22}O_2NI$: C, 53.91; H, 5.24; N, 3.31. Found: C, 53.56; H, 5.29; N, 3.12.

**Hydrogenolysis of 23**——A suspension of 1.0 g of **23**, 0.5 g of AcONa, 0.5 g of Adams catalyst in 100 ml of EtOH was shaken in atomospheric pressure of $H_2$ until uptake of $H_2$ ceased. After the insoluble material was filtered and the filtrate was evaporated to leave 0.4 g of **24** as colorless needles, mp 105—107° (MeOH–ether). NMR ($CDCl_3$) $\delta$: 2.43 (3H, s, $NCH_3$), 3.83 (3H, s, $OCH_3$), 6.57—7.13 (6H, m, Ar–H). Mass Spectrum *m/e*: 297 ($M^+$). *Anal.* Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.91; H, 8.03; N, 4.50.

**1-(3-Benzyloxy-4-methoxyphenyl)-2-nitroprop-1-ene (26)**——A mixture of 24 g of benzylisovaniline, 15 g of nitroethane, 7 g of $AcONH_4$, and 50 ml of AcOH was heated at 150° for 2 hr. The mixture was poured into 300 ml of $H_2O$ and the yellowish precipitate was filtered. Recrystallization from MeOH gave 19 g of **26** as yellowish needles, mp 104—105°. *Anal.* Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.14; H, 5.78; N, 4.70.

**2-(3-Benzyloxy-4-methoxyphenyl)-1-methyl-ethylamine (27)**——To a suspension of 10 g of $LiAlH_4$ in 200 ml of dry tetrahydrofurane (THF) was added a solution of 30 g of **26** in 300 ml of dry THF, dropwise, under stirring at room temperature. After the stirring had been continued for 5 hr, the mixture was decomposed with 20% NaOH, and 25 g of **27** was obtained as colorless oil after usual work-up. This was characterized as the hydrochloride, mp 166—167° (MeOH–ether). *Anal.* Calcd. for $C_{17}H_{21}O_2N \cdot HCl$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.52; H, 7.03; N, 4.70.

**The Amide (28)**——A mixture of 10 g of **27** and 10 g of 2-bromo-4,5-methylenedioxyphenylacetic acid was heated at 180° for 1.5 hr. The mixture was recrystallized from MeOH to give 16 g of **28** as colorless needles, mp 127—128°. *Anal.* Calcd. for $C_{26}H_{26}NBr$: C, 60.94; H, 4.72; N, 2.73. Found: C, 60.67; H, 5.13; N, 2.70.

**6-Benzyloxy-1-(2-bromo-4,5-methylenedioxybenzyl)-3,4-dihydro-7-methoxy-3-methylisoquinoline (29)**——A mixture of 13 g of **28**, 10 g of $POCl_3$ and 200 ml of dry benzene was refluxed for 2 hr. To the reaction mixture was added excess *n*-hexane and the mixture was allowed to stand for 14 hr. The supernatant liquid was decanted and the precipitate was made basic with 28% $NH_4OH$, and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried ($Na_2SO_4$) and evaporated. The resulting solid was recrystallized from MeOH–ether to give 8.1 g of **29** as colorless needles, mp 108—109°. *Anal.* Calcd. for $C_{26}H_{24}O_4NBr$: C, 63.16; H, 4.89; N, 2.83. Found: C, 63.20; H, 4.88; N, 2.90.

**6-Benzyloxy-1-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-3-methylisoquinoline (30)**——To a solution of 7.5 g of the hydrochloride of **28** in 200 ml of MeOH was added 5 g of $NaBH_4$, in small portions, and the mixture was refluxed for 1 hr. The solvent was evaporated and a suspension of the resulting residue in $H_2O$ was extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to leave 7 g of **30** as colorless needles, mp 92—94° (ether). NMR ($CDCl_3$) $\delta$: 1.13 (3H, d, $J$=7 Hz, 3-$CH_3$), 3.83 (3H, s, $OCH_3$), 5.07 (2H, s, $PhCH_2O$), 5.88 (2H, s, $OCH_2O$), 6.00, 6.85, 6.88, 7.00 (4H, each s, Ar–H), 7.25 (5H, s, Ar–H). *Anal.* Calcd. for $C_{26}H_{26}O_4NBr$: C, 62.91; H, 5.28; N, 2.98. Found: C, 62.90; H, 5.22; N, 2.51.

**6-Benzyloxy-1-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2,3-dimethylisoquinoline (31)**——A mixture of 6.5 g of **30**, 50 ml of 37% HCHO and 50 ml of 90% HCOOH was heated on a

water bath for 4 hr. The mixture 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 5.3 g of **31** as an oil. NMR ($CDCl_3$) $\delta$: 1.17 (3H, d, $J=7$ Hz, 3-$CH_3$), 2.37 (3H, s, $NCH_3$), 3.65 (3H, s, $OCH_3$), 5.05 (2H, s, $PhCH_2O$), 5.83 (2H, s, $OCH_2O$), 6.27. 6.57, 6.60, 6.97 (4H, each s, Ar–H), 7.25 (5H, s, Ar–H); this was used for the following reaction because of difficulty of crystallization.

**1-(2-Bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2,3-dimethylisoquinoline (32)**——A mixture of 5 g of **31**, 40 ml of conc. HCl and 50 ml of EtOH was refluxed for 2 hr. After removal of the solvent, the resulting 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. The remaining residue was recrystallized from MeOH–ether gave 3.2 g of **32** as colorless needles, mp 111—113°. NMR ($CDCl_3$) $\delta$: 1.22 (3H, d, $J=7$ Hz, 3–$CH_3$), 2.38 (3H, s, $NCH_3$), 3.67 (3H, s, $OCH_3$), 5.85 (2H, s, $OCH_2O$), 6.18. 6.57, 6.60, 6.97 (4H, each s, Ar–H). *Anal.* Calcd. for $C_{20}H_{22}O_4NBr$: C, 57.15; H, 5.28; N, 3.33. Found: C, 57.30; H, 5.30; N, 3.18.

**5,6,12,13-Tetrahydro-3-hydroxy-2-methoxy-6,7-dimethyl-9,10-methylenedioxy-13-(methylsulfinyl)methyl-7*H*-dibenzo[*b*,*f*]azonine(33)**——A solution of 2 g of **32** in 40 ml of DMSO under stirring at room temperature. After the stirring had veen continued for 14 hr, the mixture was poured into 300 ml of $H_2O$ containing $NH_4Cl$ and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and evaporated. The resulting residue was chromatographed on 20 g of silica gel. Elution with 2% MeOH–$CHCl_3$ (100 ml) gave 0.9 g of **33**, mp 199—201° (MeOH–ether). Mass Spectrum *m/e*: 417 ($M^+$). *Anal.* Calcd. for $C_{22}H_{27}O_5NS$: C, 63.29; H, 6.52; N, 3.36. Found: C, 62.95; H, 6.67; N, 3.11.

**5,6,12,13-Tetrahydro-3-hydroxy-2-methoxy-6,7-dimethyl-9,10-methylenedioxy-13-(methylthio)methyl-7*H*-dibenzo[*b*,*f*]azonine(34)**——A mixture of 0.5 g of **33**, 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% $NH_4OH$, dried over $Na_2SO_4$ and evaporated to leave 0.42 g of **34** as colorless oil. NMR ($CDCl_3$) $\delta$: 1.35 (3H, d, $J=7$ Hz, 6-$CH_3$), 2.03 (3H, s, $SCH_3$), 2.52 (3H, s, $NCH_3$), 3.70 (3H, s, $OCH_3$), 5.68 (2H, s, $OCH_2O$), 6.42, 6.47, 6.52, 6.67 (4H, each s, Ar–H); this was used for the following reaction because of difficulty of crystallization.

**5,6,12,13-Tetrahydro-3-hydroxy-2-methoxy-6,7,13-trimethyl-9,10-methylenedioxy-7*H*-dibenzo[*b*,*f*]azonine (35)**——A solution of 0.3 g of **34** in 70 ml of EtOH was refluxed in the presence of 2 ml of Raney Ni catalyst for 14 hr. After removal of the catalyst the solvent was evaporated. The resulting residue was chromatographed on 2 g of silica gel using $CHCl_3$ as an eluant. Removal of the solvent (60 ml) afforded **35** as colorless needles, mp 201—202° (MeOH–ether). Mass Spectrum *m/e*: 355 ($M^+$). NMR ($CDCl_3$) $\delta$: 1.23 (3H, d, $J=7$ Hz, 6-$CH_3$), 1.47 (3H, d, $J=7$ Hz, 13-$CH_3$), 2.60 (3H, s, $NCH_3$), 3.90 (3H, s, Ar–H), 5.92 (2H, s, $OCH_2O$), 6.68, 6.73 (2H, each s, Ar–H), 6.75 (2H, s, Ar–H). *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.85; H, 7.22; N, 3.87.

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