

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

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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-halogenophenethylisoquinolines 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-methylisoquinoline (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, C₂₂H₂₇O₅NS, of the product (14) was confirmed by mass spectrum (M⁺, *m/e* 417) and microanalysis. Its nuclear magnetic resonance (NMR) (CDCl₃) spectrum showed that the product (14) would be a mixture of diastereoisomers. 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 (CDCl₃) spectrum of which showed two singlets attributable to SCH₃ and NCH₃ at 1.77 and 2.37 ppm. Desulfurization of 15 with Raney Ni catalyst yielded the corresponding 14-CH₃ derivative (16). The 14-CH₃ signal was observed at 1.05 ppm as a doublet (*J*=7 Hz) in its NMR (CDCl₃) spectrum. The NCH₃ 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).

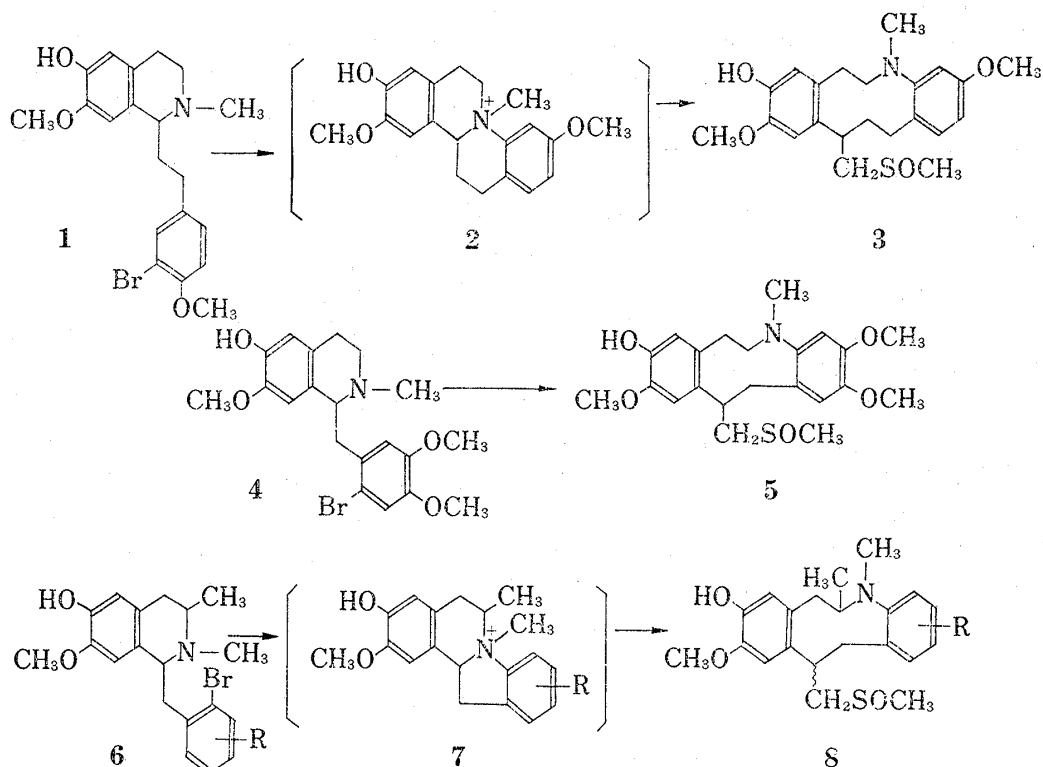


Chart 1

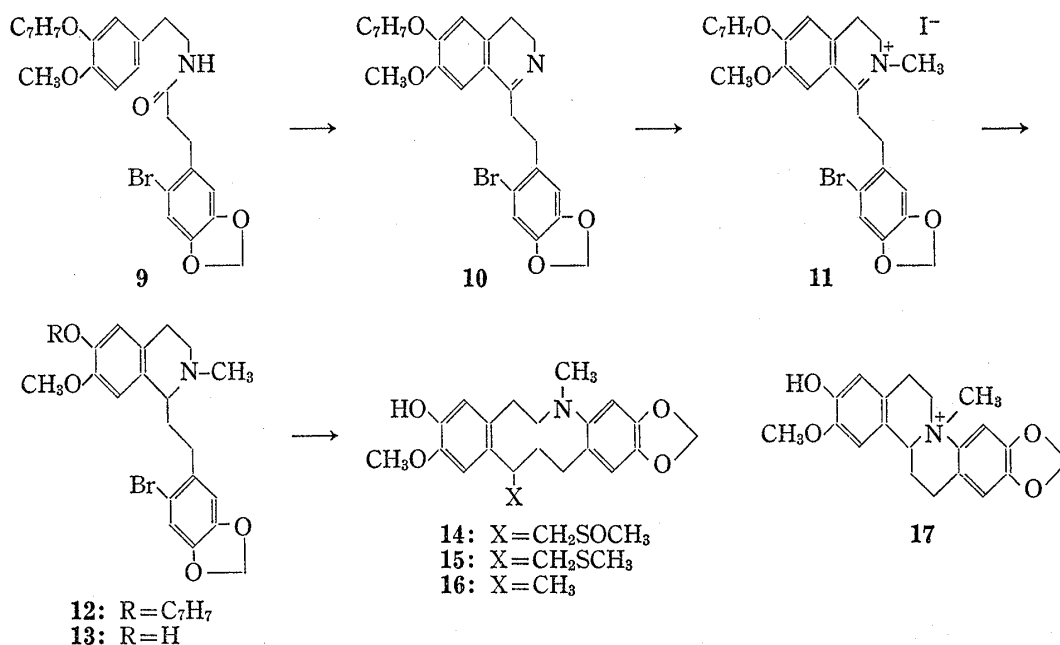


Chart 2

considerably high aromatic NCH₃ signals in the NMR (CDCl₃) 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 cyclization⁴) 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 (CDCl₃) spectrum exhibited two singlets due to NCH₃ and OCH₃ 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 C₆–N bond. The signals due to CH₃CH₂ was not observed in the NMR (CDCl₃) spectrum of the product. Its ¹³CNMR (CDCl₃) spectrum⁵) showed the presence of five CH₂ at 23.84, 26.55, 30.59, 33.37, 59.60 ppm, attributable to C₁₂, C₁₄, C₅, C₁₃ and C₆ 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 ¹³CNMR (CDCl₃) spectrum of **22** exhibited four CH₂ signals at 26.03, 28.61, 28.81 and 45.03 ppm attributable to C₁₂, C₅, C₁₃ and C₆, respectively. The C_{13a} resonated at 55.36 ppm. The CH₂ 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 ¹³CNMR (CDCl₃) spectra of **22** and **24**.

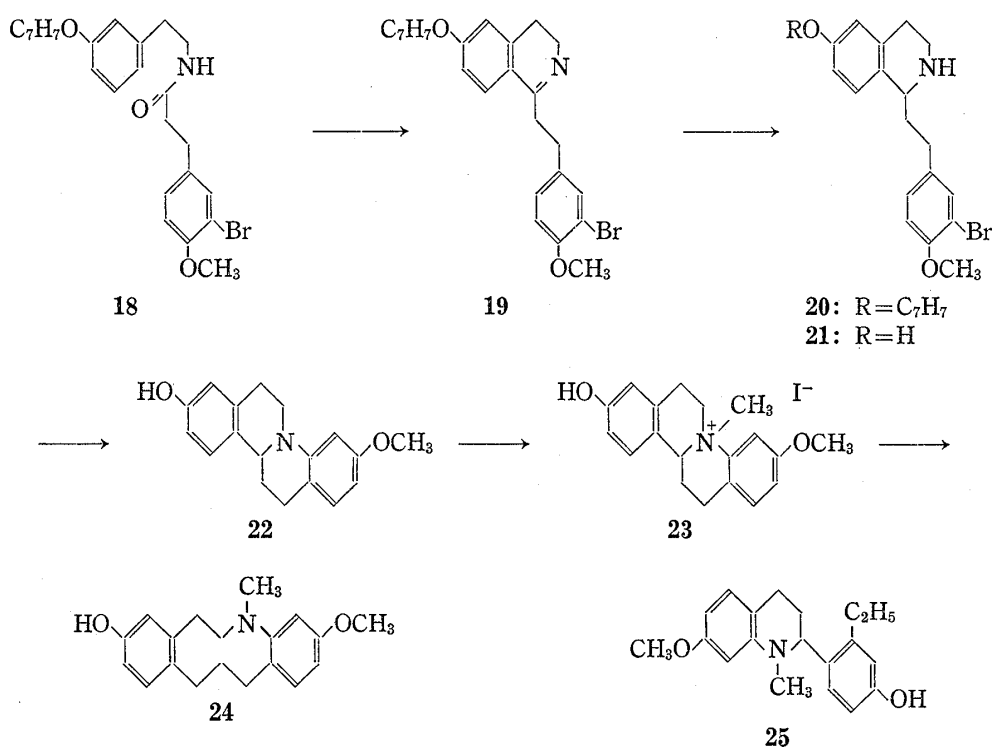


Chart 3

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*]azocine system. The isoquinoline (**32**) was prepared through the method as Gal reported⁶) 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) ¹³C NMR spectra were taken with Varian NV-14 spectrometer in CDCl₃ 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)methyl dibenzo[*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}C NMR ($CDCl_3$) spectrum was also agreeable with the structure (35), and 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.

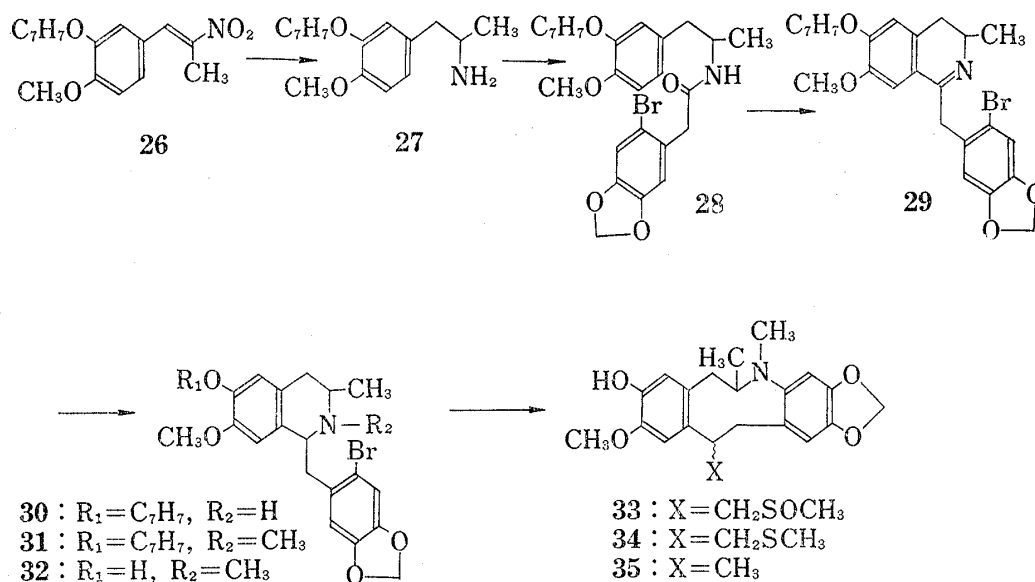


Chart 4

Experimental⁷⁾

N-(3-Benzoyloxy-4-methoxyphenethyl)-2-(2-bromo-4,5-methylenedioxyphenyl)propionamide (9)—A mixture of 7.0 g of 3-benzoyloxy-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-Benzoyloxy-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-Benzoyloxy-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 ($CDCl_3$) δ : 2.47 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 5.07 (2H, s, $PhCH_2O$), 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 $C_{27}H_{25}O_4NBr \cdot HCl$: 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 ($CDCl_3$) δ : 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 ($CDCl_3$) δ : 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 ($CDCl_3$) δ : 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-Benzoyloxyphenethyl)-2-(3-bromo-4-methoxyphenyl)propionamide (18)—A mixture of 7.0 g of 3-benzoyloxyphenethylamine 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 $C_{25}H_{23}O_3NBr$: 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 $C_{25}H_{23}O_3NBr \cdot HCl$: 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 ($CDCl_3$) δ : 3.80 (3H, s, OCH_3), 6.43—7.17 (6H, m, Ar-H). *Anal.* Calcd. for $C_{15}H_{20}O_2NBr$: 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 ($CDCl_3$) δ : 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 atmospheric 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 ($CDCl_3$) δ : 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 $C_{19}H_{22}O_2N$: 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 tetrahydrofuran (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 ($CDCl_3$) δ : 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) δ : 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) δ : 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 $\text{C}_{20}\text{H}_{22}\text{O}_4\text{NBr}$: 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-7H-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 been 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 $\text{C}_{22}\text{H}_{27}\text{O}_5\text{NS}$: 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-7H-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) δ : 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-7H-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) δ : 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 $\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.85; H, 7.22; N, 3.87.

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