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The C-N Fission of Dibenzo[*b,g*]indolizinium Salts with Dimsylsodium

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Reactions of dibenzo[*b,g*]indolizinium iodide (**5**), (**13**), (**19**) with sodium methylsulfinylmethanide were examined and the substantial differences were observed between the phenolic dibenzo[*b,g*]indolizinium iodide (**5**), (**13**) and non-phenolic one (**19**). Dibenzo[*b,f*]azonines (**7**) and (**15**), formed through the fission of the C_{12a}-N bond, were obtained from **5** and **13**, respectively, as main products. The 2-phenylindoline (**21**) was yielded from **19** by the fission of the C_6–N bond.

We have previously investigated the benzyne reaction of 1-halogenobenzyl- and 1-halogenophenethylisoquinolines using sodium methylsulfinylmethanide as a base and found that this reagent showed the interesting behaviour to these reactions.[2-4] The reaction of the isoquinoline (**1**) with sodium methylsulfinylmethanide afforded the 5,6,12,12a-tetrahydro-12a-methyldibenzo[*b,g*]indolizine (**2**).[2] The similar reaction using the isoquinoline (**3**) possessing a hydroxyl group at the 6-position gave the 13-(methylsulfinyl)methyldibenzo[*b,f*]azonine (**4**), and the hydroxyl group at the 6-position was found to play an important role on fission of the C–N bond.[4] From this point, we successively investigated the cleavage of the C–N bond of several kinds of N-methyldibenzo[*b,g*]indolizinium salts, which would be possible intermediate during the formation of the dibenzo[*b,f*]azonine systems and the 12a-methyltetrahydrodibenzo[*b,g*]indolizines. These results are described in this paper.

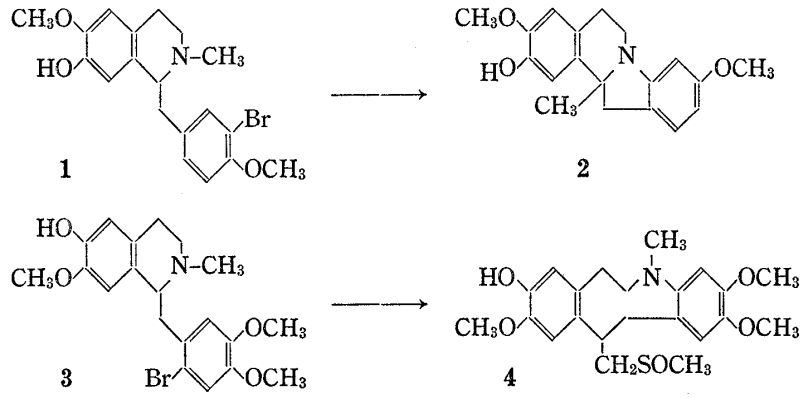

Chart 1

The N-methyl-5,6,12,12a-tetrahydrodibenzo[*b,g*]indolizinium iodide (**5**)[5] was treated with sodium methylsulfinylmethanide in dimethyl sulfoxide and chromatographic separation of the crude product gave two products. The molecular formula, $C_{20}H_{23}O_4N$, of the first product was confirmed by microanalysis and mass spectrum (M^+, *m/e* 341). Its nuclear

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, E. Komiyama, T. Ogawa, Y. Takahagi, T. Yokomatsu, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **23**, 2058 (1975).
5) T. Kametani and K. Ogasawara, *J. Chem. Soc.* (C), **1967**, 2208.

magnetic resonance (NMR) ($CDCl_3$) spectrum showed a singlet due to 12a-CH_3 at 1.70 ppm and three methoxy protons resonated at 3.75, 3.78 and 3.83 ppm as singlets, respectively. Four aromatic proton signals appeared at 6.27, 6.37, 6.62 and 6.80 ppm as singlets, respectively. The *m/e* 326 ion, formed by elimination of the 12a-CH_3 from the molecular ion, was observed as the base peak in its mass spectrum. These facts indicated the first product to be the 5,6,-12,12a-tetrahydro-12a-methyldibenzo[*b*,*g*]indolizine (**6**). The structure of the second one, obtained from the 2% methanol–chloroform fraction, was determined as the 13-(methylsulfinyl)methyldibenzo[*b*,*f*]azonine (**7**) based upon the following transformations. Its NMR ($CDCl_3$) spectrum showed the product (**7**) would be a mixture of diastereoisomers but separation of each isomer was unsuccessful. Reductive deoxygenation of **7** with amalgamated zinc afforded the 13-(methylthio)methyldibenzo[*b*,*f*]azonine (**8**), the NMR ($CDCl_3$) spectrum of which showed two singlets attributable to SCH_3 and NCH_3 at 2.08 and 2.57 ppm, respectively, and four aromatic protons resonated at 6.57, 6.70, 6.75 and 6.88 ppm as singlets, respectively. Desulfurization of **8** with Raney Ni catalyst gave the 13-methyl derivative (**9**), mp 124—125°. The NMR ($CDCl_3$) spectrum of **9** exhibited a doublet due to 13-CH_3 at 1.48 ppm (J=7 Hz), and NCH_3 resonated at 2.60 ppm. Four aromatic proton signals appeared at 6.57, 6.60, 6.75 and 6.77 ppm as singlets, respectively. Microanalysis and mass spectrum (M^+, *m/e* 357) were also agreeable with the structure (**9**). Therefore, the second product obtained by the reaction of the isoquinoline (**5**) with sodium methylsulfinylmethanide was assigned to the dibenzo[*b*,*f*]-azonine (**7**). These products (**6**) and **7** were also obtained by the reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**10**)[6] with sodium methylsulfinylmethanide. In this reaction the formation of the aporphine (**11**)[6] and the morphinandienone (**12**),[6] obtained by the reaction of **10** with sodium amide in liquid ammonia, was not observed.

The reaction of N-methyl-5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizinium iodide (**13**)[5] with sodium methylsulfinylmethanide also gave the similar results. Two products were yielded

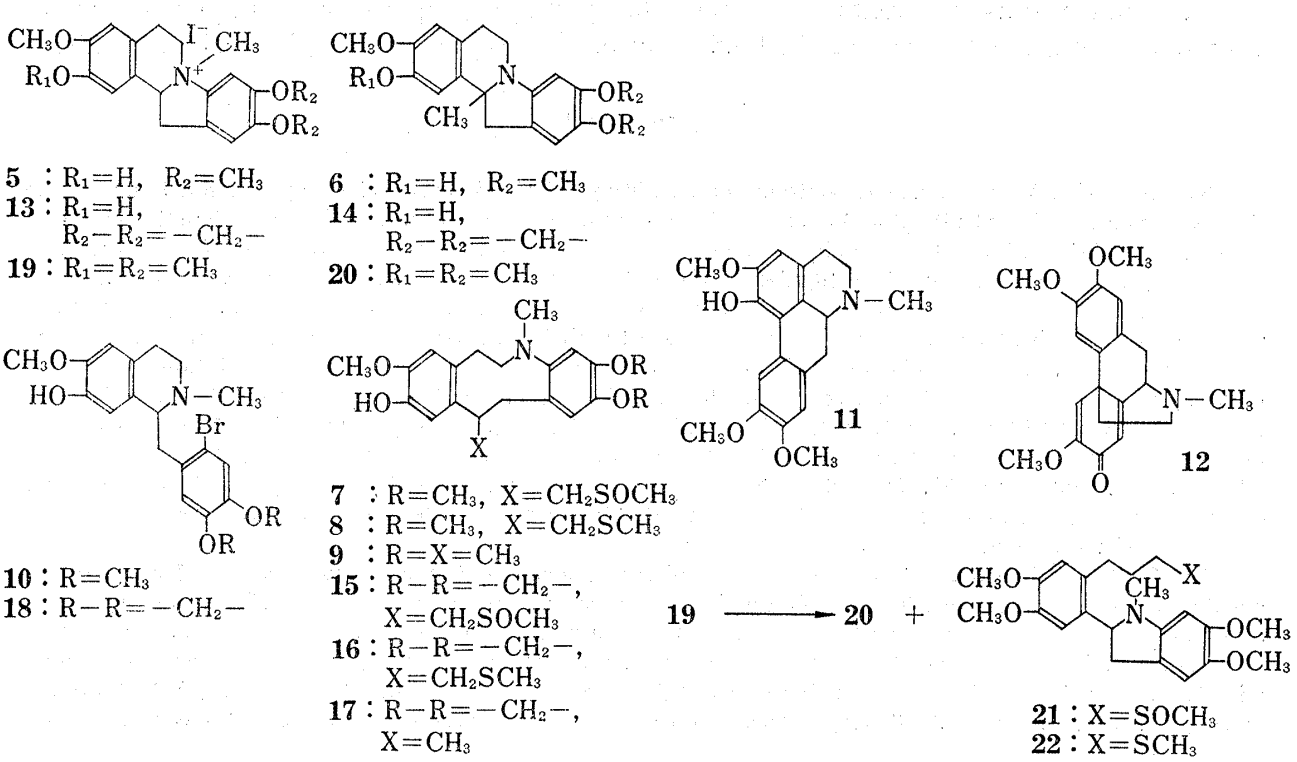

Chart 2

6) T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Suzuki, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 766 (1973).

on chromatographic separation of the crude product and the first one was assigned to the 5,6,12,12a-tetrahydro-12a-methyldibenzo[*b*,*g*]indolizine (**14**). The molecular formula, $C_{19}H_{19}O_4N$, was determined by mass spectral (M^+, *m/e* 325) and microanalysis. The 12a-CH_3 signal was observed at 1.65 ppm as a singlet in its NMR ($CDCl_3$) spectrum. The structure of the second one was determined as a diastereoisomeric mixture of 13-(methylsulfinyl)methyldibenzo[*b*,*f*]azonine (**15**) by the methods as in the case of **7**. Deoxygenation of **15** with amalgamated zinc afforded the 13-(methylthio)methyldibenzo[*b*,*f*]azonine (**16**) the NMR ($CDCl_3$) spectrum of which showed a singlet attributable to SCH_3 at 2.11 ppm. The NCH_3 signal was observed at 2.55 ppm as singlet and four aromatic protons resonated at 6.85, 6.75, 6.72 and 6.60 ppm as singlets, respectively. Desulfurization of **16** with Raney Ni catalyst gave the corresponding 13-methyl derivative (**17**). One-step synthesis of **15** was achieved by the reaction of 1-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**18**)[7] with sodium methylsulfinylmethanide.

On the other hand, in the case of the non-phenolic N-methyl-5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizinium iodide (**19**), different mode of C–N fission was observed. The reaction of **19** with sodium methylsulfinylmethanide gave the 5,6,12,12a-tetrahydro-12a-methyldibenzo[*b*,*g*]indolizine (**20**) and 2-(4,5-dimethoxyphenyl)indoline (**21**). The structure of the former was confirmed by direct comparison of the authentic specimen.[2] The NMR ($CDCl_3$) spectrum of **21** exhibited a pair of doublet at 4.45 ppm (J=8 and 10 Hz) as a characteristic signal of α-proton of α-phenylindoline. The CH_3SO and NCH_3 signals appeared at 2.50 and 2.57 ppm, respectively. Four aromatic protons resonated at 6.22, 6.55, 6.70 and 7.20 ppm as singlets, respectively. Deoxygenation of **21** afforded the methyl sulfide (**22**), the NMR ($CDCl_3$) spectrum of which showed two singlets at 2.07 and 2.57 ppm due to SCH_3 and NCH_3, respectively. α-Proton of **22** appeared at 4.50 ppm as a pair of doublet (J=7 and 9 Hz).

It is interesting that the significant difference were observed between the reaction of the phenolic and non-phenolic dibenzo[*b*,*g*]indolizinium iodide with sodium methylsulfinylmethanide. These results indicated that the phenolic hydroxyl group was found to play an important role during the cleavage of the C–N bond of N-methyldibenzo[*b*,*g*]indolizinium salts.

Experimental[8]

Reaction of N-Methyl-5,6,12,12a-tetrahydro-2-hydroxy-3,9,10-trimethoxydibenzo[*b*,*g*]indolizinium Iodide (5)[5] with Sodium Methylsulfinylmethanide——To a solution of sodium methylsulfinylmethanide (prepared from 2.0 g of NaH and 35 ml of dimethylsulfoxide (DMSO) was added a solution of 2.5 g of the N-methyldibenzo[*b*,*g*]indolizinium iodide (**5**) in 40 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. Evaporation of the solvent afforded 1.6 g of brownish oil, which was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (100 ml) gave 0.2 g of 5,6,12,12a-tetrahydro-12a-methyldibenzo[*b*,*g*]indolizine (**6**), mp 122—124° (MeOH–ether). NMR ($CDCl_3$) δ: 1.70 (3H, s, 12a–CH_3), 3.75, 3.78, 3.83 (9H, each s, 3×OCH_3), 6.27, 6.37, 6.62, 6.80 (4H, each s, Ar–H), Mass Spectrum *m/e*: 341 (M^+), 326 (M^+-15). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.57; H, 6.59; N, 3.90. Elution with 2% MeOH–$CHCl_3$ (150 ml) afforded 1.3 g of **7** as hydgoscopic solid, mp 168—170° (MeOH–ether), which was subjected to the following reaction. Mass Spectrum *m/e*: 419 (M^+).

5,6,12,13-Tetrahydro-2-hydroxy-3,9,10-trimethoxy-7-methyl-13-(methylthio)methyl-7*H*-dibenzo[*b*,*f*]azonine (8)——A mixture of 1.0 g of **7**, obtained as above, Zn–Hg (prepared from 1g of $HgCl_2$ and 10 g of Zn) and 90 ml of 50% AcOH–conc. HCl (1 : 1) was heated on a water bath for 1 hr. After removal of inorganic material, the mixture 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 to give 0.7 g of **8** as a colorless oil. NMR ($CDCl_3$) δ: 2.08 (3H, s, SCH_3), 2.57 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 3.87 (6H, s, 2×OCH_3), 6.47, 6.70, 6.75, 6.88 (4H, each s, Ar–H);

7) T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.* (C), **1971**, 2712.

8) All melting points were uncorrected. NMR spectra were taken with a Varian T-60 spectrometer using tetramethylsilane as an internal standard, and mass spectra were measured with Hitachi RMU-7L spectrometer.

this was characterized as the picrate, mp 167—168° (EtOH). *Anal.* Calcd. for $C_{22}H_{29}O_4NS \cdot C_6H_3O_7N_3$: C, 53.16; H, 5.10; N, 8.86. Found: C, 52.91; H, 5.19; N, 8.61.

5,6,12,13-Tetrahydro-2-hydroxy-3,9,10-trimethoxy-7,13-dimethyl-7*H*-dibenzo[*b*,*f*]azonine (9)——A mixture of 0.5 g of **8**, 2 ml of Raney Ni catalyst and 50 ml of EtOH was refluxed 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 (100 ml) gave **9**, mp 124—125°. NMR ($CDCl_3$) δ: 1.48 (3H, d, $J=7$ Hz, 13-CH_3), 2.60 (3H, s, NCH_3), 3.87 (9H, s, $3\times OCH_3$), 6.57, 6.60, 6.75, 6.77 (4H, each s, Ar-H). Mass Spectrum *m/e*: 357 (M^+). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.38; H, 7.76; N, 4.03.

Reaction of 1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (10) with Sodium Methylsulfinylmethanide——To a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 35 ml of DMSO) was added a solution of 3 g of the isoquinoline (**10**) in 50 ml of DMSO under stirring at room temperature. After the stirring had been continued for 14 hr, the mixture was poured into 500 ml of H_2O containing excess NH_4Cl, and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The remaining residue was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (50 ml) gave 0.3 g of the 12a-methyldibenzo[*b*,*g*]indolizine (**6**) as colorless needles, which was identical with the sample obtained from **5** in all respects. Elution with 2% MeOH–$CHCl_3$ (150 ml) afforded 0.8 g of **7**, the spectroscopic data of which was identical with those of the authentic specimen, obtained from **5**.

Reaction of N-Methyl-5,6,12,12a-tetrahydro-2-hydroxy-3-methoxy-9,10-methylenedioxydibenzo[*b*,*g*]indolizinium Iodide (13) with Sodium Methylsulfinylmethanide——To a solution of sodium methylsulfinylmethanide (prepared from 2.0 g of NaH and 35 ml of DMSO) was added a solution of 2 g of N-methyldibenzo[*b*,*g*]indolizinium iodide (**13**) under stirring at room temperature within 10 min. After the stirring had been continued for 14 hr, the mixture was poured into 400 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. Evaporation of the solvent left 1.4 g of brownish oil, which was chromatographed on 15 g of silica gel. Elution with $CHCl_3$ (50 ml) gave 150 mg of 12a-methyldibenzo[*b*,*g*]indolizine (**14**), mp 141—142° (MeOH–ether). NMR ($CDCl_3$) δ: 1.65 (3H, s, 12a-CH_3), 3.89 (3H, s, OCH_3), 5.91 (2H, s, OCH_2O), 6.27, 6.40, 6.52, 6.80 (4H, each s, Ar-H). Mass Spectrum *m/e*: 325 (M^+), 310 (M^+-15). *Anal.* Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.87; H, 5.96; N, 4.25. Elution with 2% MeOH–$CHCl_3$ (100 ml) gave 0.8 g of **15** as an oil, which was used for the following reaction.

5,6,12,13-Tetrahydro-2-hydroxy-3-methoxy-7-methyl-9,10-methylenedioxy-13-(methylthio)methyl-7*H*-dibenzo[*b*,*f*]azonine (16)——A mixture of 0.5 g of **15**, Zn–Hg (prepared from 0.5 g of $HgCl_2$ and 5 g of Zn) and 45 ml of 50% AcOH–conc. HCl (1:1) was heated on a water bath for 1 hr. After removal of inorganic substance, the mixture was made basic with 28% NH_4OH, extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting residue was recrystallized from MeOH–ether gave 0.3 g of **16**, mp 174—175°. NMR ($CDCl_3$) δ: 2.11 (3H, s, SCH_3), 2.55 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 5.92 (2H, s, OCH_2O), 6.60, 6.72, 6.75, 6.85 (4H, each s, Ar-H). Mass Spectrum *m/e*: 387 (M^+). *Anal.* Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50; N, 3.62. Found: C, 64.84; H, 6.50; N, 3.39.

5,6,12,13-Tetrahydro-2-hydroxy-3-methoxy-7,13-dimethyl-9,10-methylenedioxy-7*H*-dibenzo[*b*,*f*]azonine (17)——A mixture of 0.8 g of **16**, 3 ml of Raney Ni catalyst and 50 ml of EtOH was refluxed 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 (120 ml) yielded 0.5 g of colorless needles, which was recrystallized from MeOH–ether to give **17**, mp 154—155°. NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=7$ Hz, 13-CH_3), 2.53 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 5.87 (2H, s, OCH_2O), 6.57, 6.60, 6.73, 6.77 (4H, each s, Ar-H). Mass Spectrum *m/e*: 341 (M^+). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.46; H, 6.88; N, 4.39.

Reaction of 1-(2-Bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (18) with Sodium Methylsulfinylmethanide——To a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 35 ml of DMSO) was added a solution of 2.5 g of the isoquinoline (**18**) in 40 ml of DMSO under stirring at room temperature. After the stirring had been continued for 14 hr, the mixture was poured into 400 ml of H_2O containing excess NH_4Cl, and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (50 ml) gave 0.3 g of the 12a-methyldibenzo[*b*,*g*]indolizine (**14**) as colorless needles, mp 141—142°, which was identical with the authentic specimen obtained from **13** in all respects. Elution with 2% MeOH-$CHCl_3$ (150 ml) afforded 0.8 g of **15**, the spectroscopic data of which was identical with those of the authentic sample, obtained from **13**.

Reaction of N-Methyl-5,6,12,12a-tetrahydro-2,3,9,10-tetramethoxydibenzo[*b*,*f*]indolizinium Iodide (19) with Sodium Methylsulfinylmethanide——To a solution of sodium methylsulfinylmethanide (prepared from 2 g of NaH and 35 ml of DMSO) was added a solution of 2.5 g of the N-methyldibenzo[*b*,*g*]indolizinium iodide (**19**) in 40 ml of DMSO under stirring at room temperature within 10 min. After the stirring had been continued for 14 hr, the mixture was poured into 300 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 gave 1.6 g of brownish oil, which was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (50 ml) yielded 0.8 g of 12a-methyldibenzo[*b*,*g*]indolizine (**20**), mp 112—114°, which was identical with the authentic specimen[2] in all respects. Successive elution with the same solvent (50 ml) and elution with 2% MeOH–$CHCl_3$ (50 ml) afforded 0.3 g of the 2-(4,5-dimethoxyphenyl)-5,6-dimethoxyphenylindoline (**21**) as a colorless oil. NMR ($CDCl_3$) δ: 2.50 (3H, s, $OSCH_3$), 2.57 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.87 (6H, s, $2\times OCH_3$), 4.45 (1H, d,d, $J=8$ and 11 Hz), 6.62, 6.65, 6.70, 7.20 (4H, each s, Ar–H); this was used for the following reaction because of difficulty of crystallization.

5,6-Dimethoxy-2-(4,5-dimethoxy-2-methylthiopropyl)-1-methylindoline (**22**)——A solution of 0.2 g of **21** in 45 ml of 50% AcOH–conc. HCl (1: 1) was heated on a water bath in the presence of Zn–Hg (prepared from 0.5 g of $HgCl_2$ and 5 g of Zn). After removal of inorganic material the mixture 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 to leave 150 mg of **22** as colorless oil. NMR ($CDCl_3$) δ: 2.07 (3H, s, SCH_3), 2.57 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.87 (6H, s, $2\times OCH_3$). 6.23, 6.67, 6.70, 7.23 (4H, each s, Ar–H). Mass Spectrum *m/e*: 417 (M^+), 402, 370, 340, 192; this was characterized as the hydrochloride, mp 168—169° (EtOH–ether). *Anal.* Calcd. for $C_{23}H_{31}O_4NS\cdot HCl$: C, 60.84; H, 7.10; N, 3.09. Found: C, 60.79; H, 7.23; N, 2.91.

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