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Novel Syntheses of 5,6,12,12a-Tetrahydro-12a-methyldibenzo-[*b*,*g*]indolizine Systems

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Benzyne reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**6**) using sodium methylsulfinylmethanide afforded 5,6,12,-12a-tetrahydro-2,3,9,10-tetramethoxy-12a-methyldibenzo[*b*,*g*]indolizine (**7**). 1-(3-Bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**9**) also gave 5,6,12,12a-tetrahydro-2-hydroxy-3,9-dimethoxy-12a-methyldibenzo[*b*,*g*]indolizine (**11**) under the similar conditions.

Benzyne of the type (**1**), generated from 1-halogenobenzylisoquinolines has been known as a useful intermediate to yield the dibenzo[*b*,*g*]indolizinium salts (**2**), through arrow a in (**1**), together with the aporphines (**3**), through arrow b, and the morphinandienones (**4**), through arrow c.[2,3] The indolizinium salts (**2**) would be converted to the 12a-methyldibenzo[*b*,*g*]-indolizine derivatives (**5**) in the presence of organic carbanion such as phenyl lithium or sodium methylsulfinylmethanide through the migration of the methyl group at the 7-position to the 12a-position by the Stevens rearrangement. Since sodium methylsulfinylmethanide[4] was found to be useful as a benzyne reagent[5] we examined the benzyne reaction of 1-halogeno-benzyl-1,2,3,4-tetrahydro-2-methylisoquinolines with sodium methylsulfinylmethanide in

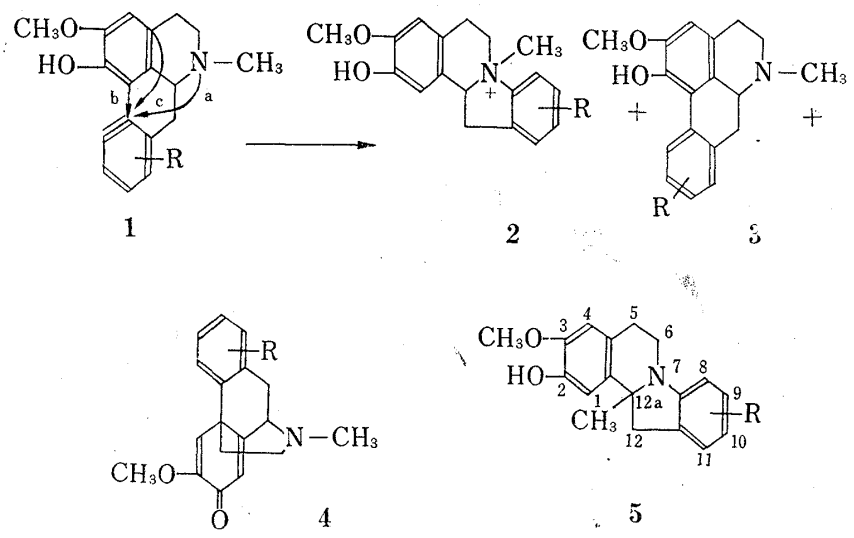

Chart 1

1) Location: *3-20-1, Kitashinjuku, Shinjuku-ku, Tokyo.*
2) T. Kametani, K. Fukumoto, and T. Nakano, *Tetrahedron*, **28**, 4667 (1972).
3) T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Suzuki, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 766 (1973) and references were cited therein.
4) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1315 (1965).
5) T. Kametani, S. Shibuya, and S. Kano, *J. Chem. Soc.*, **1973**, 1212.

the expectation that the 12a-methyldibenzo[*b*,*g*]indolizines would be formed through the Stevnes rearrangement of the dibenzo[*b*,*g*]indolizinium salts (**2**). Herein these results were described.

First, the reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**6**)[6] with sodium methylsulfinylmethanide was investigated. The crude product, obtained by the usual work-up was chromatographed on silica gel. The elution with chloroform afforded the colorless needles, mp 112—114°. The product showed the molecular formula, $C_{21}H_{25}O_4N$, by microanalysis and mass spectrum (*m/e* 355, M^+). The nuclear magnetic resonance (NMR) (δ) ($CDCl_3$) spectrum revealed the expected a methyl resonance at 1.67 ppm attributable to the 12a-CH_3, and four aromatic protons were observed at 6.23, 6.34, 6.60, and 6.70 ppm as singlet, respectively. These data indicated the product to be 5,6,12,12a-tetrahydro-2,3,9,10-tetramethoxy-12a-methyldibenzo[*b*,*g*]indolizine (**7**). The inter-

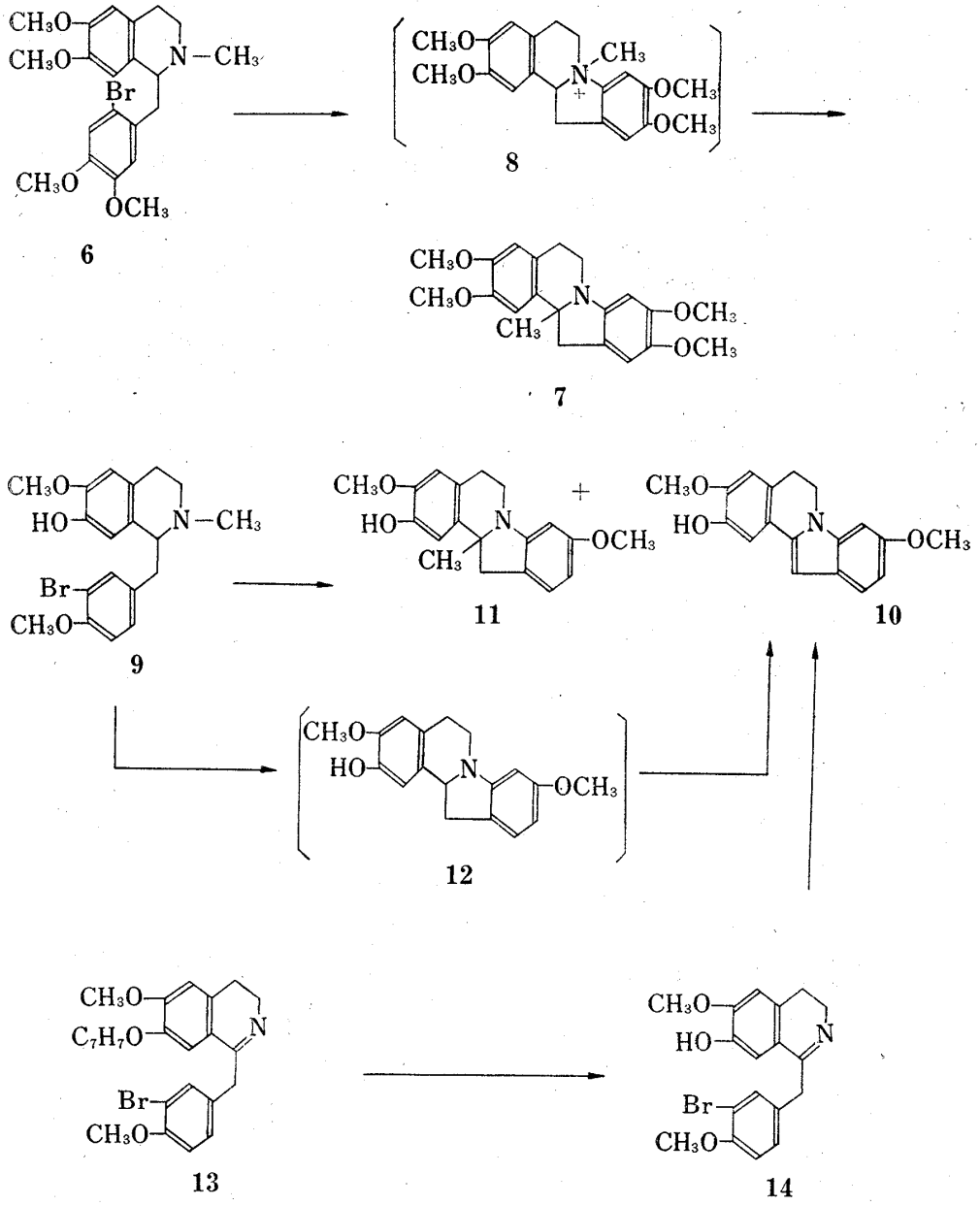

Chart 2

6) C. Schopf and K. Thierfelder, *Ann.*, **537**, 1432 (1939).

mediate in this reaction would be the indolizinium salt (**8**), and the methyl group at the 7-position migrated to the 12a-position.

Secondly, 1-(3-bromo-4-methoxybenzyl)-1, 2, 3, 4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**9**)[7] was treated with sodium methylsulfinylmethanide in order to prove that this type of reaction proceeded through the benzyne intermediate. The crude product, obtained by the work-up as usual was chromatographed on silica gel to give two compounds. The first one, mp 248—249° (decomp.), showed the molecular formula, $C_{18}H_{17}O_3N$, by microanalysis and mass spectrum (*m/e* 295, M^+). The NMR (δ) ($CDCl_3$) showed methylene signals at 3.07 (C_5–H_2) and 4.17 (C_6–H_2) ppm as multiplets. These facts revealed the first compound to be 5,6-dihydro-2-hydroxy-3,9-dimethoxydibenzo[*b*,*g*]indolizine (**10**), which was proved by direct comparison with the authentic specimen prepared by the benzyne reaction of 1-(3-bromo-4-methoxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (**14**). The 5,6-dihydrodibenzoindolizine (**10**) would be converted from (**12**), formed by decomposition of the corresponding dibenzoindolizinium salt.[8] The molecular formula, $C_{19}H_{21}O_3N$, of the second compound (**11**) was verified by microanalysis and mass spectrum (*m/e* 311, M^+). The NMR (δ) ($CDCl_3$) of (**11**) revealed a methyl resonance at 1.63 ppm due to 12a-CH_3 and two OCH_3 signals at 3.70 and 3.73 ppm. The signals due to C_8–H and C_{10}–H appeared at 6.15 (d, $J_{8,9}$= 1 cps) and 6.10 ppm (q, $J_{10,11}$=7 cps). Therefore the second product was assigned to be 5,6,-12,12a-tetrahydro-3,9-dimethoxy-12a-methyldibenzo[*b*,*g*]indolizine (**11**). Although Gibson and his coworkers also examined the benzyne reaction of (**9**) using sodium amide in liquid ammonia, they obtained only unchanged starting material.[7]

Thus the dibenzo[*b*,*g*]indolizinium salts, formed as intermediates during the reaction of 1-halogenobenzyl-1,2,3,4-tetrahydro-2-methylisoquinolines with sodium methylsulfinylmethanide, were found to be transformed to 12a-methyldibenzo[*b*,*g*]indolizine derivatives through the migration of the methyl group at the 7-position.

Experimental[9]

5,6,12,12a-Tetrahydro-2,3,9,10-tetramethoxy-12a-methyldibenzo[*b*,*g*]indolizine (7)——A solution of 2.0 g of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**6**)[6] in 30 ml of dimethyl sulfoxide (DMSO) was added to a solution of sodium methylsulfinylmethanide[4] (prepared from 2.0 g of NaH and 25 ml of DMSO) within 15 min at room temperature under stirring. After the stirring had been continued for 14 hr, the mixture was poured into 200 ml of ice-water and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to leave 1.2 g of brownish oil, which was chromatographed on 20 g of silica gel using $CHCl_3$ as an eluant. The first fraction (100 ml) afforded 0.4 g of pale brownish oil, which was triturated with ether to give colorless needles, mp 112—114°. NMR ($CDCl_3$) δ: 1.67 (3H, s, 12a-CH_3), 3.73, 3.75, 3.83, 3.89 (12H, each s, 4×OCH_3), 6.25, 6.34, 6.60, 6.70 (4H, each s, aromatic protons). Mass Spectrum *m/e*: 355 (M^+), 340 (M-15). *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.97; H, 7.06; N, 3.82.

The Reaction of 1-(3-Bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (9)[7] with Sodium Methylsulfinylmethanide——A solution of 2.0 g of the isoquinoline (**9**) in 40 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 2.0 g of NaH and 25 ml of DMSO) within 15 min under stirring at room temperature. After the stirring had been continued for 14 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 (Na_2SO_4), and evaporated. The remaining residue was chromatographed on 20 g of silica gel. Elution with $CHCl_3$ (50 ml) afforded 0.4 g of 5,6-dihydro-2-hydroxy-3,9-dimethoxydibenzo[*b*,*g*]indolizine (**10**), which was identical with the authentic specimen prepared as described latter, by comparison of those spectroscopic data and mixed melting points. Successive elution with $CHCl_3$ (50 ml) gave 5,6,12,12a-tetrahydro-2-hydroxy-3,9-dimethoxy-12a-methyldibenzo[*b*,*g*]indolizine (**11**), mp 142—143° (from MeOH–ether). NMR ($CDCl_3$) δ: 1.63 (3H, s, 12a-CH_3), 3.70 and 3.73 (6H, each s, 2×OCH_3),

7) M.S. Gibson, G.W. Prenton, and J.M. Walthew, *J. Chem. Soc.* (*C*), **1970**, 2234.
8) T. Kametani and K. Ogasawara, *J. Chem. Soc.* (*C*), **1967**, 2287.
9) All melting points were uncorrected. NMR spectra were taken with a Varian T-60 spectrometer using TMS as an internal standard.

6.15 (1H, d, $J_{8,10}$=1 cps, C_8-H), 6.10 (1H, q, $J_{8,10}$=1, cps, $J_{10,11}$=7 cps). Mass Spectrum *m/e*: 311 (M^+), 296 (M-15). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.91; H, 7.01; N, 4.31.

1-(3-Bromo-4-methoxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (14)——A mixture of 4 g of 7-benzyloxy-1-(3-bromo-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (**13**),[7] 40 ml of EtOH and 40 ml of conc. HCl was refluxed for 1.5 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 (Na_2SO_4) and evaporated to leave pale yellowish needles, mp 155—157° (from MeOH). NMR ($CDCl_3$) δ: 2.43—2.73 (2H, m, C_4–H_2), 3.53—3.83 (2H, m, C_3–H_2), 3.80 and 3.89 (6H, eachs, $2\times OCH_3$). *Anal.* Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.88 ;H, 4.86; N, 3.82.

5,6-Dihydro-2-hydroxy-3,9-dimethoxydibenzo[*b,g*]indolizine (10)——A solution of 2.0 g of the isoquinoline (**14**) in 40 ml of DMSO was added to a solution of sodium methylsulfinylmethanide (prepared from 2.0 g of NaH and 25 ml of DMSO) within 10 min under stirring at room temperature. After the stirring had been continued for 12 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 (Na_2SO_4), and evaporated. The residual solid was chromatographed on 15 g of silica gel using $CHCl_3$ as an eluant. The first fraction (80 ml) yielded the dibenzo[*b,g*]indolizine (**10**). Recrystallization from MeOH afforded 0.9 g of colorless needles, mp 248—249° (decomp.). NMR ($CDCl_3$) δ: 3.07 (2H, m, C_5–H_2), 4.17 (2H, m, C_6–H_2). Mass Spectrum *m/e*: 295 (M^+). *Anal.* Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.05; H, 5.75; N, 4.64.

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