Syneses of 13a-Substituted Dibenzo[α,f]quinolizines

SHINZO KANO, TSUTOMU YOKOMATSU and SHIROSHI SHIBUYA

Tokyo College of Pharmacy

(Received October 3, 1974)

The reaction of a series of 1-halogenophenethyl-3,4-dihydroisoquinolines (6), (10), (14) and (20) with sodium methylsulfinylmethanide was investigated to yield 5,6,12,13,13a-pentahydro-13a-(methylsulfinyl)methylidibenz[a,f]quinolizines (7), (12), (18) and (23) which were converted to the corresponding 13a-(methylthio)methyl derivatives (8), (13), (17) and (24), respectively. Desulfurization of 8 and 24 afforded the 13a-methyl derivatives (9) and (25), respectively.

The benzyn reaction of 1-halogenobenzyl-1,2,3,4-tetrahydroisoquinolines and 1-halogenophenethyl-1,2,3,4-tetrahydrosoquinoline (1) has been widely used for the syntheses of the tetrahydrodibenzo[b,g]indolizines\(^2,3\) and the pentahydrodibenzo[a,f]quinolizine (2),\(^4\) respectively, though, few work on the benzyn reaction of 3,4-dihydroisoquinolines have been investigated. Kametani reported the benzyn reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (3) using sodium methylsulfinylmethanide as a base in dimethyl sulfoxide to yield the dihydroidibenzo[b,g]indolizine (4).\(^5\) We examined the similar reaction of a series of 1-halogenophenethyl-3,4-dihydroisoquinolines. These results were described in this paper.

---

**Chart 1**

---

1) Location: 3-20-1, Kitashinjuku, Shinjuku-ku, Tokyo.
First, 1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6,7-dimethoxyisouquinoline (6), prepared by cyclization of the amide (5), was treated with sodium methylsulfinylmethanide in dimethyl sulfoxide. The crude product, obtained by the usual work-up, was chromatographed on silica gel to give the 13a-(methylsulfinyl)methylidibeno[a,f]quinolizine (7). The molecular formula, C_{42}H_{30}O_5NS, was confirmed by microanalysis and mass spectrum (M^+, m/e 431). Its nuclear magnetic resonance (NMR) (CDCl_3) spectrum showed that the product (7) would be a mixture of diastereoisomers and separation of each isomer was unsuccessful. The structural proof of 7 was based upon the following transformation. Reductive deoxygenation of 7 with amalgamated zinc in a mixture of 50% acetic acid and conc. hydrochloric acid afforded the 13a-(methylthio)methylidibeno[a,f]quinolizine (8). The NMR (CDCl_3) spectrum showed a singlet due to CH_3S at 1.97 ppm. Microanalysis and mass spectrum (M^+, m/e 385) were also agreeable with the structure (8). Desulfurization of 8 with Raney Ni catalyst gave the 13a-methylidibeno[a,f]quinolizine (9). The NMR (CDCl_3) spectrum of 9 showed a singlet at 1.63 ppm which was characteristic of 13a-CH_3 signal. Therefore the product obtained from 6 through the reaction with sodium methylenalsulfinylmethanide was assigned to be 7.

![Chart 2](image)

Secondly, 1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-7-hydroxy-6-methoxyisouquinoline (10), obtained by hydrolysis of the 3,4-dihydroisouquinoline (11), was treated with sodium methylsulfinylmethanide as in formation of 7 to yield the 13a-(methylsulfinyl)methylidibeno[a,f]quinolizine (12). Reductive deoxygenation of 12 afforded the 13a-(methylthio)methylidibeno[a,f]quinolizine (13). The benzyne reaction of 1-(2-bromo-4,5-methylenedioxyphenethyl)-7-hydroxy-6-methoxyisouquinoline (14) also examined to give the similar results. The chromatographic separation of the crude product, obtained through the usual work-up, gave two products. The first one was assigned to be a diastereoisomeric mixture of 13a-(methylsulfinyl)methylidibeno[a,f]quinolizine (17), which was converted to the 13a-(methyl-

---

thio)methyl derivative (18) by reductive deoxygenation with amalgamated zinc. The NMR (CDCl₃) spectrum of 18 was similar to those of 8 and 13. The molecular formula of the second product (19), C₃₈H₆₃O₇NS, was established by microanalysis and mass spectrum (M⁺, m/z 587). Its NMR (CDCl₃) spectrum showed a singlet due to CH₂S at 2.45 ppm and three aromatic protons resonated at 6.50, 6.60 and 7.07 ppm as singlets, respectively.

Finally, the benzene reaction of 1-[3-bromo-4-methoxyphenethyl]-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (20) was investigated in order to examine whether any difference was observed between the position isomers according to the location of the bromine atom. The isoquinoline (20) was prepared by debenzylation of the 3,4-dihydroisoquinoline (21) which was obtained from the amide (22). The isoquinoline (20) also yielded the similar product (23) in moderate yields. Reductive deoxygenation of 23 gave the 13α-(methylthio)methyl dibenzo[a,f]quinolizine (24). Desulfurization of 24 gave the 13-methyl dibenzo[a,f]quinolizine (25).

Thus, as mentioned above, the benzene reaction of 1-halogenophenethyl-3,4-dihydroisoquinoline with sodium methylsulfinylmethanide was found to be an excellent method to yield 13α-substituted dibenzo[a,f]quinolizine.

Experimental

N-(3,4-Dimethoxyphenethyl)-2-(bromo-4,5-dimethoxyphenyl)propionamide (5) — A mixture of 5.4 g of 3,4-dimethoxyphenethylamine and 8.7 g of 2-bromo-4,5-dimethoxyphenylpropionic acid was heated at 180°C for 1.5 hr. After cooling, the mixture was recrystallized from benzene to give 9.8 g of 5 as colorless needles, mp 123—125°C. Anal. Calcd. for C₃₁H₃₂O₅NBr: C, 55.74; H, 5.79; N, 3.12. Found: C, 55.83; H, 5.60; N, 3.25.

1-[2-Bromo-4,5-dimethoxyphenethyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (6) — A mixture of 8 g of the amide (5) and 8 g of POCl₃ in 100 ml of dry benzene was refluxed for 2 hr. After the reaction, excess n-hexane was added to the reaction mixture. The supernatant liquid was decanted and the precipitate was made basic with 28% NH₄OH and extracted with CHCl₃. The extract was washed with H₂O and dried (Na₂SO₄). Evaporation of the solvent gave 7 g of the 3,4-dihydroisoquinoline (6), mp 95—96°C (from MeOH). Anal. Calcd. for C₃₁H₃₂O₅NBr: C, 58.08; H, 5.05; N, 3.25. Found: C, 58.25; H, 5.21; N, 3.18.

The Reaction of 1-[2-Bromo-4,5-dimethoxyphenethyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (6) with Sodium Methylsulfinylmethanide — A solution of 4 g of the isoquinoline (6) in 40 ml of dimethyl sulfoxide (DMSO) was added to a solution of sodium methylsulfinylmethanide (prepared from 2.0 g of NaH and 30 ml of DMSO) within 15 min under stirring at room temperature. After the stirring had continued for 14 hr, the mixture was poured into 300 ml of H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried (Na₂SO₄), and evaporated. The remaining residue was chromatographed on 25 g of silica gel. The eluant with CHCl₃ (200 ml) was discarded and the successive elution with 2% MeOH—CHCl₃ (100 ml) afforded the stereoisomeric mixture of the 13α-(methylsulfinyl)methyl dibenzo[a,f]quinolizine (7). Recrystallization from MeOH—ether gave 1.1 g of colorless needles, mp 191—192°C. Mass Spectrum m/z: 431 (M⁺). Anal. Calcd. for C₃₂H₃₃O₅NS: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.31; H, 6.90; N, 3.55.

5,6,12,13,13a-Pentahydro-2,3,9,10-tetramethoxy-13α-(methylthio) methyl dibenzo[a,f]quinolizine (8) — A mixture of 0.4 g of 7 and Zn-Hg (prepared from 5 g of Zn and 0.5 g of HgCl₂) in 60 ml of a mixture of 50% AcOH and conc. HCl (1:1) was heated on a water bath for 1 hr. Inorganic material was filtered and the filtrate was made basic with 28% NH₄OH and extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄ and evaporated. Recrystallization of the remaining residue from MeOH—ether afforded 0.3 g of 8 as colorless needles, mp 168—170°C. NMR (CDCl₃) δ: 1.97 (3H, s, SCH₃), 6.50 (1H, s, Ar-H), 6.60 (2H, s, Ar-H), 6.35 (1H, s, Ar-H). Mass Spectrum m/z: 415 (M⁺). Anal. Calcd. for C₃₃H₃₅O₇NS: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.66; H, 7.23; N, 3.18.

5,6,12,13,13a-Pentahydro-2,3,9,10-tetramethoxy-13α-methyl dibenzo[a,f]quinolizine (9) — A solution of 200 mg of 8 in 70 ml of EtOH was refluxed in the presence of 1 ml of Raney Ni catalyst for 8 hr. After removal of the catalyst, the solvent was evaporated. The resulting solid was recrystallized from ether—n-hexane to give 150 mg of 9 as colorless needles, mp 125—126°C. Mass Spectrum m/z: 369 (M⁺), 354 (M—15). NMR (CDCl₃) δ: 1.63 (3H, s, 13α—CH₃), 6.60 (3H, broad s, Ar-H), 6.70 (1H, s, Ar-H). Anal. Calcd. for C₃₃H₃₅O₇N: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.55; H, 7.58; N, 3.52.

1-[2-Bromo-4,5-dimethoxyphenethyl]-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (10) — A solution of 6.5 g of 7-benzoyloxy-1-[2-bromo-4,5-dimethoxyphenethyl]-3,4-dihydro-6-methoxyisoquinoline (11) in

7) All melting points were uncorrected. NMR spectra were taken with Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard.
100 ml of EtOH–conc. HCl (1: 1) was refluxed for 1.5 hr. After removal of the solvent, the resulting residue was basified with 28% NH4OH and extracted with CHCl3. The extract was washed with H2O, dried (Na2SO4) and evaporated to leave 4.9 g of 10 as pale yellowish needles, mp 179.5–180.5°C (from MeOH–ether). Anal. Calcd. for C26H26O2NBr4: C, 57.15; H, 5.28; N, 3.33. Found: C, 57.14; H, 5.27; N, 3.21.

5,6,12,13,13a-Pentahydro-2-hydroxy-3,9,10-trimethoxy-13a-(methylene)methylidenzo[a,f]quinolizine (13) — A solution of 3.5 g of the 3,4-dihydroisoquinoline (10) in 40 ml of DMSO was added to a solution of sodium methyldisulfonylmethanide (prepared from 2 g of NaH and 30 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 H2O containing excess NH4Cl and extracted with CHCl3. The extract was washed with H2O, dried (Na2SO4) and evaporated. The resulting residue was chromatographed on 20 g of silica gel. After removal of the eluant with CHCl3 (200 ml), the elution with 2% MeOH–CHCl3 afforded 1.3 g of 12 as an oil, which was treated with Zn–Hg (prepared from 7 g of Zn and 0.7 g of HgCl2) in 60 ml of a mixture of 50% of AcOH and conc. HCl (1: 1) in the case of 7. The reaction mixture was worked up as usual to give 1 g of 13 as colorless needles, mp 136–138°C (from MeOH). NMR (CDCl3) δ: 1.98 (3H), s, CH3), 3.82 (3H, s, OCH3), 3.90 (6H, s, 2 × OCH3), 6.5 (1H, s, Ar–H), 6.55 (2H, s, Ar–H), 6.60 (1H, s, Ar–H). Mass Spectrum m/e: 401 (M+), 355. Anal. Calcd. for C26H25O2NBr: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.99; H, 6.94; N, 3.31.

N-(4-Benzoyloxy-3-methoxyphenethyl)-2-(3-bromo-4,5-methylenedioxyphenyl) propionamide (15) — A mixture of 7 g of 4-benzoyloxy-3-methoxyphenylacetonitrile and 7 g of 2-bromo-4,5-methylenedioxyphenylpropionamide was heated at 180°C for 1.5 hr. After cooling, the mixture was recrystallized from benzene containing small portion of n-hexane to yield 10 g of the amide (15), mp 146–148°C. Anal. Calcd. for C34H24O2NBr: C, 66.95; H, 5.11; N, 2.73. Found: C, 66.18; H, 4.82; N, 2.53.

7-Benzoyloxy-1-(2-bromo-4,5-methylenedioxyphenethyl)-3,4-dihydro-6-methoxysquinoalin (16) — A mixture of 8 g of the amide (14), 8 g of POCl3 and 100 ml of dry benzene was refluxed for 2 hr. To the reaction mixture was added 400 ml of n-hexane and allowed to stand for several hr. The supernatant liquid was removed by decantation and the precipitate was made basic with 28% NH4OH and extracted with CHCl3. The extract was washed with H2O, dried (Na2SO4). Evaporation of the solvent afforded 6.2 g of the isoquinoline (16), mp 148.5–149°C (from benzene–n-hexane). Anal. Calcd. for C34H23O2NBr: C, 63.17; H, 4.89; N, 2.53. Found: C, 63.44; H, 4.86; N, 2.92.

1-(2-Bromo-4,5-methylenedioxyphenethyl)-3,4-dihydro-7-hydroxy-6-methoxysquinoline (17) — A mixture of 5 g of the isoquinoline (16), 40 ml of conc. HCl and 55 ml of EtOH was refluxed for 1.5 hr. The solvent was evaporated and the residue was basified with 28% NH4OH and extracted with CHCl3. The extract was washed with H2O, dried over Na2SO4 and evaporated to leave 3.2 g of the solid. Recrystallization from MeOH yielded colorless needles, mp 184–186°C. Anal. Calcd. for C29H23O2NBr: C, 56.45; H, 4.49; N, 3.47. Found: C, 56.20; H, 4.38; N, 3.02.

The Reaction of the Isoquinoline (14) with Sodium Methylsulfonylmethide — A solution of 3 g of the isoquinoline (14) in 40 ml of DMSO was added to a solution of sodium methylsulfonylmethanide (prepared from 2 g of NaH and 35 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 H2O containing excess NH4Cl and extracted with CHCl3. The extract was washed with H2O, dried (Na2SO4). The solvent was evaporated and the remaining residue was chromatographed on 25 g of silica gel. The eluant with CHCl3 (150 ml) was discarded and the elution with 2% MeOH–CHCl3 (100 ml) yielded 0.9 g of 17, which was subjected to the following reaction without purification. The successive elution with the same eluant (100 ml) afforded 0.5 g of the 1-(2-hydroxy-3-methylthio-4,5-methylenedioxyphenethyl)isoquinoline (19), mp 162.5–163°C (from MeOH–ether). Mass Spectrum m/e: 387 (M+), NMR (CDCl3) δ: 2.47 (3H, s, CH3), 3.93 (3H, s, OCH3), 3.90 (2H, s, –OCH2O–), 6.57, 6.65, 7.13 (3H, each s, Ar–H). Anal. Calcd. for C34H23O2NBr: C, 62.00; H, 5.46; N, 3.62. Found: C, 62.25; H, 5.21; N, 3.66.

5,6,12,13,13a-Pentahydro-2-hydroxy-3-methoxy-9,10-methylenedioxy-13a-(methylene)methylidenzo[a,f]quinolizine (18) — A solution of 0.8 g of the preceding crude 13a-(methylene)methylidenzo[a,f]quinolizine (16) in 60 ml of 50% AcOH–conc. HCl (1: 1) was heated on a water bath in the presence of Zn–Hg (prepared from 5 g of Zn and 0.5 g of HgCl2) for 1.5 hr. After removal of the inorganic material, the mixture was basified with 28% NH4OH, and extracted with CHCl3. The extract was washed with H2O, dried (Na2SO4) and evaporated. The resulting solid was recrystallized from ether–n-hexane afforded 0.5 g of 18 as colorless needles, mp 175–176°C. Mass Spectrum m/e: 385 (M+), 324, NMR (CDCl3) δ: 1.98 (3H, s, CH3), 3.85 (3H, s, OCH3), 5.83 (2H, s, –OCH2O–), 6.42, 6.53, 6.57, 6.83 (4H, each s, Ar–H). Anal. Calcd. for C34H23O2NBr: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.08; H, 5.87; N, 3.91.

N-(4-Benzoyloxy-3-methoxyphenethyl)-2-(3-bromo-4-methoxyphenyl)propionamide (22) — A mixture of 7 g of 4-benzoyloxy-3-methoxyphenylacetonitrile and 7 g of 2-bromo-4-methoxyphenylpropionic acid was heated at 180°C for 1.5 hr. After cooling, the reaction mixture was recrystallized from benzene to yield 9.2 g of the amide (22), mp 114–116°C. Anal. Calcd. for C26H25O2NBr: C, 62.66; H, 5.66; N, 2.81. Found: C, 62.84; H, 5.73; N, 2.70.

7-Benzoyloxy-1-(3-bromo-4-methoxyphenethyl)-3,4-dihydro-6-methoxysquinoline (21) — A mixture of 8 g of the amide (22), 8 g of POCl3 and 100 ml of dry benzene was refluxed for 2 hr, and worked up as usual.
to give 7.2 g of the 3,4-dihydroisoquinoline (21), mp 88–88.5° (from benzene–n-hexane). *Anal.* Calcd. for C_{16}H_{15}NBr: C, 65.01; H, 5.46; N, 2.92. Found: C, 65.08; H, 5.48; N, 2.64.

1-(3-Bromo-4-methoxyphenethyl)-3,4-dihydro-7-hydroxy-6-methoxoisouquinoline (20) — A solution of 7 g of the 3,4-dihydroisoquinoline (21) in a mixture of 110 ml of EtOH–conc. HCl (1:1) was refluxed for 1.5 hr. The solvent was evaporated and the residue was basified with 28% NH_4OH and extracted with CHCl_3. The extract was washed with H_2O, dried (Na_sO_4) and evaporated. The resulting residue was recrystallized from ether to give 4.2 g of the isouquinoline (20), mp 134–134.5°. *Anal.* Calcd. for C_{16}H_{15}NBr: C, 58.47; H, 5.17; N, 3.59. Found: C, 58.31; H, 5.15; N, 3.64.

5,6,12,13,13a-Pentahydro-2-hydroxy-3,9-dimethoxy-13a-(methylthio)methylidibenzo[a,f]quinolizine (24) — A solution of 3 g of the isouquinoline (20) in 40 ml of DMSO was added to a solution of sodium methanethiolate (prepared from 2 g of NaH and 30 ml of DMSO) under stirring at room temperature. After the stirring had been continued for 14 hr, the mixture was worked up as in the case of 10, and the crude product was chromatographed on 25 g of silica gel. The eluant with CHCl_3 (150 ml) was discarded and the elution with 2% MeOH–CHCl_3 (200 ml) gave 1.2 g of 23 as pale brownish syrup; this was subjected to the following reaction.

A solution of 23 in 60 ml of 50% AcOH–conc. HCl (1:1) was heated on a water bath in the presence of Zn–Hg (prepared from 7 g of Zn and 0.7 g of HgCl_2) for 1.5 hr. After removal of the 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_sO_4) and evaporated. The remaining solid was recrystallized from MeOH to give 0.8 g of 24 as colorless needles, mp 115–116°. Mass Spectrum m/z: 371 (M^+), 310. NMR (CDCl_3) δ: 1.97 (3H, s, SCH_3), 3.50, 3.87 (6H, each s, 2 × OCH_3), 6.23 (1H, d, J_{19,11}=7 Hz, J_{18,10}=2 Hz, C_{10}–H), 6.50 (1H, d, J_{18,10}=2 Hz, C_{10}–H), 6.57 (1H, s, C_{11}–H), 6.87 (1H, d, J_{16,11}=7 Hz, C_{11}–H), 6.92 (1H, s, C_{12}–H or C_{13}–H). *Anal.* Calcd. for C_{20}H_{22}O_2N: C, 76.29; H, 6.78; N, 3.77. Found: C, 76.25; H, 6.73; N, 3.64.

5,6,12,13,13a-Pentahydro-2-hydroxy-3,9-dimethoxy-13a-methylidibenzo[a,f]quinolizine (25) — A mixture of 0.4 g of 24 and 1.5 ml of Raney Ni catalyst in 70 ml of EtOH was refluxed for 8 hr. The residual solid was recrystallized from ether–n-hexane to give 250 mg of 24 as colorless needles, mp 66–67°. Mass Spectrum m/z: 325 (M^+), 310 (M^+–15), NMR (CDCl_3) δ: 1.47 (3H, s, 13a–CH_3), 3.78, 3.82 (6H, each s, 2 × OCH_3), 6.20 (1H, d, J_{19,11}=7 Hz, J_{18,10}=2 Hz, C_{10}–H), 6.43 (1H, d, J_{18,10}=2 Hz, C_{10}–H), 6.52, 6.80 (2H, each s, Ar–H), 6.87 (1H, d, J_{16,11}=7 Hz, C_{11}–H). *Anal.* Calcd. for C_{20}H_{21}O_2N: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.36; H, 7.17; N, 4.80.

Acknowledgement We are grateful to Mr. S. Suzuki and Miss K. Maeda for microanalyses, Mr. Y. Shida for measurement of Mass Spectra.