# A New Synthesis of the Aporphine Alkaloids (±)-Glaucine and (±)-Nantenine. Application of [3C+3C] Annelation to the D-Ring Formation[1)]

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**A [3C+3C] annelation using 1,1-bis(ethylthio)-2-propanone was applied to a new synthesis of the aporphine alkaloids. Condensation of the ketone with the Mannich base gave two isomeric cyclohexenones, which were converted into the aporphine framework by aromatization. (±)-Glaucine and (±)-nantenine were prepared by employing this new aromatic synthesis.**

**Keywords** aromatic synthesis; glaucine; nantenine; Mannich base; [3C+3C] annelation

In a previous paper, we reported a new synthesis of 1,2-benzenediols using a [3C+3C] annelation involving 1,1-bis(ethylthio)-2-propanone (**1**) and Mannich bases.[2)] The annelation gave cyclohexenones *via* 1,4-addition and aldol condensation. The constructed enones were converted into the phenolic compounds by hydrolytic aromatization. We attempted to apply this method to a synthesis of two aporphine alkaloids, glaucine[3)] (**2**) and nantenine[4)] (**3**), in order to show the utility of the new aromatic synthesis. Both target molecules (**2**, **3**) consist of four rings, A—D. Most of their total syntheses reported in the literature were achieved by the formation of a dihydrophenanthrene structure (A, C, and D rings) by various intramolecular couplings of two benzene rings of bibenzyl structure (A and D rings).[5)] Our attention was focused on their D rings, which are 1,2-benzenediol structures suitable for application of our aromatic synthesis. In this paper we describe in detail a new synthesis of the aporphines, **2** and **3** in racemic form.

Our synthetic strategy for the alkaloids is based on D-ring formation as a key step *via* the intermediary ketone (**5**), which consists of three rings (A, B, and C). The D ring was constructed by [3C+3C] condensation of two kinds of three-carbon (3C) unit. One of them was the Mannich base (**4**), which was derived from the ketone (**5**)[6)] on treatment with dimethylamine hydrochloride and formalin in MeOH. The other was 1,1-bis(ethylthio)-2-propanone (**1**),[7)] which has been used for aromatic annelation in our laboratory.[2,8)] This compound was prepared from 1,1-dichloro-2-propanone and ethanethiol using anhydrous $K_2CO_3$ and Adogen$_{464}$ in 87% yield.

The Mannich base (**4**) was condensed with **1** in the presence of NaH in dimethoxyethane (DME) to give two isomeric cyclohexenones, **6** and **7** (47% and 11% yields from **5**, respectively), which were readily separated by column chromatography. Their proton nuclear magnetic resonance ($^1$H-NMR) spectra showed a significant difference in the chemical shift of the olefinic protons (C=C<u>H</u>–C=O), $\delta$ 7.58 for compound **6** and $\delta$ 6.50 for compound **7**. Inspection of molecular models of the two isomers showed that the enone part of **6** is located on the same plane as the benzene ring of the molecule, while that of **7** is twisted from the plane. The olefinic proton of the former isomer (**6**) suffers appreciable deshielding from the aromatic ring, while that of the latter isomer (**7**) is less deshielded. The structural characteristics of these compounds are also supported by differences of their UV and IR spectral data (see Experimental).

The cyclohexenone (**6**) was dethioacetalized by N-bromosuccinimide (NBS) in MeCN–AcOH–$H_2O$ at room temperature followed by treatment with boiling AcOH to give the diol (**8**) and the thioether (**9**) in 38% and 5% yields, respectively. The isomeric enone (**7**) was also converted to **8** and **9** in the same manner (32% and 5%, respectively). Methylation of **8** with diazomethane in $Et_2O$–MeOH gave (±)-glaucine (**2**) in 71% yield. The melting points of compound **2** (mp 134—136 °C) and its picrate [mp 192—194 °C (dec.)] were the same as those reported in the literature.[3b-i,k)] The IR, $^1$H-NMR, and UV spectral data of **2** were superimposable on those of natural glaucine.

Methylenation of **8** with KOH and $CH_2Cl_2$ in dimethyl sulfoxide (DMSO) gave (±)-nantenine (**3**) in 43% yield. Its melting point (mp 140—141 °C) and spectral data ($^1$H-NMR and MS) were identical with those reported in the literature.[3d,4,9)]

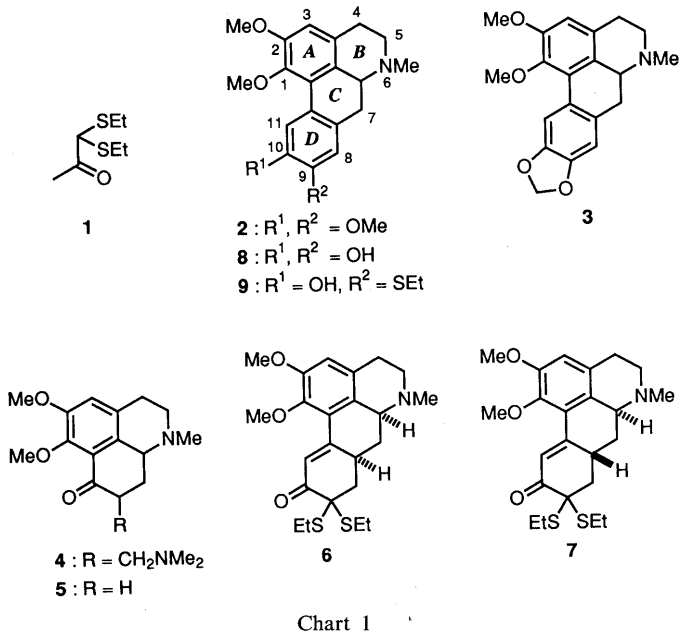


Chart 1

In conclusion, (±)-glaucine (**2**) and (±)-nantenine (**3**) were prepared from the cyclohexenones (**6** and **7**), which were obtained by the condensation of two 3C units, 1,1-bis(ethylthio)-2-propanone (**1**) and the Mannich base (**4**). The utility of the new 1,2-benzenediol synthesis *via* [3C+3C] annelation using 1,1-bis(ethylthio)-2-propanone (**1**) has now been established.

## Experimental

IR spectra were recorded on a Hitachi 270-30 infrared spectrometer. $^1$H-NMR spectra were recorded with a JEOL JNM-PMX 60si spectrometer (60 MHz) using tetramethylsilane as an internal standard. UV spectra were recorded on a Hitachi U-3200 spectrophotometer. Melting points were measured on a Yanaco model MP micro melting point apparatus and are uncorrected. High-resolution mass spectra were obtained on a JEOL JMS-DX300 mass spectrometer. NaH refers to sodium hydride suspended in mineral oil (60%). All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was performed with Kieselgel 60 (70—230 mesh).

**1,1-Bis(ethylthio)-2-propanone (1)**[7] A mixture of 1,1-dichloro-2-propanone (25.4 g), anhydrous $K_2CO_3$ (30.4 g), and Adogen$_{464}$ (0.1 g) in ethanethiol (59 ml) was refluxed with stirring for 6 h. Excess ethanethiol was evaporated off under reduced pressure, then water was added to the residue and the product was extracted with $Et_2O$. The organic extract was washed with brine, dried, and evaporated *in vacuo*. The residual oil was distilled under reduced pressure to give **1** (30.1 g, 87%) as a pale yellow oil with a penetrating leek-like odor, bp 110—120 °C (8 mmHg). IR (film): 1716 cm$^{-1}$. $^1$H-NMR (60 MHz, $CDCl_3$) $\delta$: 1.25 (6H, t, $J$=7 Hz, $SCH_2C\underline{H}_3\times2$), 2.24 (3H, s, $COCH_3$), 2.55 (4H, q, $J$=7 Hz, $SC\underline{H}_2CH_3\times2$), 4.18 (1H, s, CHCO).

**1,2,3,8,9,9a-Hexahydro-5,6-dimethoxy-1-methyl-8-[(dimethylamino)-methyl]-7*H*-benzo[*de*]quinolin-7-one (4)** A mixture of dimethylamine hydrochloride (2 g) and 37% formalin (2 g) was added to a solution of 1,2,3,8,9,9a-hexahydro-5,6-dimethoxy-1-methyl-7*H*-benzo[*de*]quinolin-7-one (**5**)[6] (2 g) in MeOH (2 ml) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated off under reduced pressure and then 5% aqueous $K_2CO_3$ was added to the residue. The product was extracted with $Et_2O$ and the organic extract was washed with brine and dried. Evaporation of the solvent under reduced pressure at 20 °C gave crude **4** as a pale yellow oil (1.9 g, 78%). IR (film): 1690 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.1—2.5 (13H, m, N–$CH_2\times2$ and N–$CH_3\times3$), 2.6—3.5 (m), 3.80 (6H, s, $OCH_3\times2$), 6.81 (1H, s, $C_4$-H). This compound was used for the next reaction without purification.

**9,9-Bis(ethylthio)-5,6,6a,7,7a,8,9,10-octahydro-1,2-dimethoxy-6-methyl-4*H*-dibenzo[*de*,*g*]quinolin-10-one (6) and Its Isomer (7)** A solution of 1,1-bis(ethylthio)-2-propanone (**1**) (2.05 g) in DME (10 ml) was added at 0 °C to a suspension of NaH (138 mg) in DME (5 ml) with stirring. A solution of **4** (1.9 g) in DME (10 ml) was added to the resulting clear solution at room temperature. The reaction mixture was refluxed for 10 min and the solvent was evaporated off under reduced pressure. Water was added to the residue, and the product was extracted with $Et_2O$. The organic extract was washed with water and brine, and then dried. The solvent was evaporated off under reduced pressure and the residue was subjected to column chromatography with AcOEt–MeOH (5:1) to give compound **6** (1.55 g, 47% from **5**) and an isomer of **6** (**7**) (0.37 g, 11% from **5**). **6**: a viscous oil. IR ($CHCl_3$): 1646 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.19 and 1.29 (each 3H, t, $J$=7 Hz, $C\underline{H}_3CH_2S\times2$), 2.45 (3H, s, $CH_3N$), 2.35—3.3 (m), 3.75 and 3.85 (each 3H, s, $CH_3O\times2$), 6.70 (1H, s, aromatic proton), 7.58 (1H, d, $J$=2.5 Hz, olefinic proton). HRMS: Calcd for $C_{23}H_{31}NO_3S_2$: 433.1745. Found $m/z$: 433.1719 ($M^+$). *Anal.* Calcd for $C_{23}H_{31}NO_3S_2$: C, 63.71; H, 7.21; N, 3.23. Found: C, 63.52; H, 7.19; N, 3.24. UV $\lambda_{max}^{ethanol}$ nm ($\varepsilon$): 315.4 (17990). **7**: a viscous oil. IR ($CHCl_3$): 1652 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 and 1.30 (each 3H, t, $J$=7 Hz, $C\underline{H}_3CH_2S\times2$), 2.49 (3H, s, $CH_3N$), 2.35—3.3 (m), 3.74 and 3.86 (each 3H, s, $CH_3O\times2$), 6.50 (1H, d, $J$=2.5 Hz, olefinic proton), 6.69 (1H, s, aromatic proton). HRMS: Calcd for $C_{23}H_{31}NO_3S_2$: 433.1745. Found $m/z$: 433.1733 ($M^+$). *Anal.* Calcd for $C_{23}H_{31}NO_3S_2$: C, 63.71; H, 7.21; N, 3.23. Found: C, 63.82; H, 7.10; N, 3.11. UV $\lambda_{max}^{ethanol}$ nm ($\varepsilon$): 302.4 (13008).

**5,6,6a,7-Tetrahydro-1,2-dimethoxy-6-methyl-4*H*-dibenzo[*de*,*g*]quinoline-9,10-diol (8) and 9-Ethylthio-5,6,6a,7-tetrahydro-1,2-dimethoxy-6-methyl-4*H*-dibenzo[*de*,*g*]quinoline-10-ol (9)** A solution of NBS (440 mg) in AcOH–$H_2O$–MeCN (1:1:3, 10 ml) was added to a solution of the enone **6** (378 mg) in AcOH–$H_2O$–MeCN (1:1:3, 5 ml) at 0 °C with stirring. Stirring was continued for 2 h at 0 °C, then aqueous $Na_2CO_3$ was added to the mixture. The product was extracted with AcOEt. The extract was washed with brine, dried and evaporated under reduced pressure. AcOH (3 ml) was added to the residue and the mixture was refluxed for 5 min. After evaporation of the solvent, the residue was chromatographed with AcOEt–MeOH (5:1) to give **8** (108 mg, 38%) and **9** (16 mg, 5%). **8**: pale yellow needles, mp 173—178 °C (from $CH_2Cl_2$). IR (Nujol): 3408 cm$^{-1}$. $^1$H-NMR (10% $CD_3OD$–$CDCl_3$) $\delta$: 2.50 (3H, s, $NCH_3$), 2.3—3.2 (m), 3.61 (3H, s, $OCH_3$), 3.85 (3H, s, $OCH_3$), 6.55 (1H, s, $C_3$-H or $C_8$-H), 6.62 (1H, s, $C_3$-H or $C_8$-H), 7.87 (1H, s, $C_{11}$-H). MS $m/z$: 327 ($M^+$), 326 ($M^+-1$), 312 ($M^+-15$), 296 ($M^+-31$), 284 ($M^+-43$), 269 ($M^+-58$), 253 ($M^+-74$). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1470. Found $m/z$: 327.1457 ($M^+$). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.73; H, 6.31; N, 3.99. **9**: pale yellow needles, mp 110—115 °C. IR (KBr): 1595 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.26 (3H, t, $J$=8 Hz, $SCH_2C\underline{H}_3$), 2.53 (3H, s, $NCH_3$), 2.4—3.2 (m), 3.66 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$), 6.60 (1H, s, $C_3$-H), 7.26 (1H, s, $C_8$-H), 7.96 (1H, s, $C_{11}$-H). MS $m/z$: 371 ($M^+$), 370 ($M^+-1$), 356 ($M^+-15$), 340 ($M^+-31$), 328 ($M^+-43$), 309 ($M^+-62$), 297 ($M^+-74$). HRMS: Calcd for $C_{21}H_{25}NO_3S$: 371.1556. Found $m/z$: 371.1548 ($M^+$). Compounds **8** and **9** were also obtained from **7** in the same manner in 32% and 5% yields, respectively.

**(±)-Glaucine (2)** A solution of diazomethane in $Et_2O$ was added to a solution of compound **8** (48 mg) in MeOH (2 ml) at room temperature. The reaction mixture was allowed to stand at room temperature for 3 h. After the solvent had been evaporated off under reduced pressure, the residue was crystallized from $Et_2O$ to give **2** (37 mg, 71%) as pale yellow needles, mp 134—136 °C (lit. mp 118—120 °C[3b]; mp 134—136 °C[3c]; mp 127—129 °C[3f]; mp 137—139 °C[3g]). IR ($CHCl_3$): 1611, 1580 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.52 (3H, s, $NCH_3$), 2.5—3.2 (m), 3.63, 3.86, 3.89, 3.92 (each 3H, s, $OCH_3\times4$), 6.53 (1H, s, $C_3$-H or $C_8$-H), 6.73 (1H, s, $C_3$-H or $C_8$-H), 8.04 (1H, s, $C_{11}$-H). MS $m/z$: 355 ($M^+$), 354 ($M^+-1$), 340 ($M^+-15$), 324 ($M^+-31$), 312 ($M^+-43$), 297 ($M^+-58$), 281 ($M^+-74$). UV $\lambda_{max}^{ethanol}$ nm ($\varepsilon$): 280.8 (14372), 302.0 (13689). Picrate (from EtOH): mp 192—194 °C (dec.) (lit. mp 190—193 °C (dec.)[3d]; mp 191—193 °C (dec.)[3e]; mp 199—200 °C (dec.)[3f] mp 191—192 °C (dec.)[3h]; mp 191— 193 °C (dec.)[3i]; mp 193—194 °C[3k]).

**(±)-Nantenine (3)** A solution of compound **8** (153 mg), KOH (56 mg), and $CH_2Cl_2$ (100 mg) in DMSO (2 ml) was heated at 80 °C for 1 h with stirring. The reaction mixture was acidified with 10% HCl and washed with $Et_2O$. Saturated aqueous $Na_2CO_3$ was added to the aqueous layer and the product was extracted with AcOEt. The extract was washed with brine, dried, and then evaporated. The residue was chromatographed with AcOEt–MeOH (4:1) to give compound **3** (68 mg, 43%) as colorless needles, mp 140—141 °C (from *n*-hexane) (mp 138—139 °C[4d]; mp 140—142 °C[4a]; mp 141—142 °C[4b]). IR (KBr): 1590 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.50 (3H, s, $NCH_3$), 2.5—3.2 (m), 3.62, 3.83 (each 3H, s, $OCH_3\times2$), 5.91 (2H, s, $OCH_2O$), 6.50 (1H, s, $C_3$-H or $C_8$-H), 6.66 (1H, s, $C_3$-H or $C_8$-H), 7.82 (1H, s, $C_{11}$-H). MS $m/z$: 339 ($M^+$), 338 ($M^+-1$), 324 ($M^+-15$), 308 ($M^+-31$), 296 ($M^+-43$), 281 ($M^+-58$), 265 ($M^+-74$). HRMS: Calcd for $C_{20}H_{21}NO_4$: 339.1471. Found $m/z$: 339.1472 ($M^+$).

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