May 1991 Communications to the Editor *Chem. Pharm. Bull.* **39**(5) 1349—1351 (1991) 1349

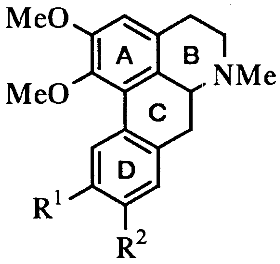
A NEW SYNTHESIS OF THE APORPHINE ALKALOIDS (±)-GLAUCINE AND (±)-NANTENINE

Yutaka OZAKI and Sang-Won KIM*
Faculty of Pharmaceutical Sciences, Josai University, Keyakidai, Sakado, Saitama 350-02, Japan

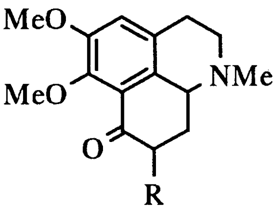
(±)-Glaucine and (±)-nantenine were newly synthesized by aromatization of cyclohexenone derivatives which were prepared by [3C+3C] condensation of two units, 1,1-bis(ethylthio)-2-propanone and the Mannich base.

KEYWORDS aromatic synthesis; [3C+3C] annulation; condensation; aporphine alkaloid; (±)-glaucine; (±)-nantenine

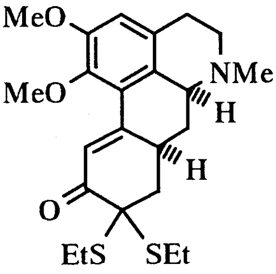
The total synthesis of the aporphine alkaloids has attracted much attention owing to their structural and pharmacological interest.$^{1)}$ Most of the total syntheses of the bases were achieved, as a key step, by constructing the biphenyl frameworks *via* various intramolecular carbon-carbon bond formations between two benzene rings. On the other hand, annulations to construct aromatic rings are useful method in the synthesis of natural products and biologically active compounds.$^{2)}$ We reported a new route to the 1,2-benzenediol congeners using [3C+3C] annulation in our previous papers.$^{3)}$ Here we describe a synthesis of (±)-glaucine (**1**)$^{4)}$ and (±)-nantenine (**2**)$^{5)}$ having a 1,2-benzenediol moiety in the D-ring, which prompted us to apply our aromatic synthesis.



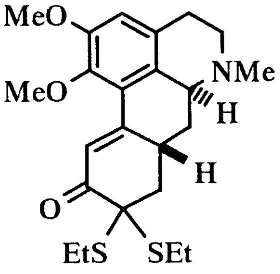
(**1**) $R^1=R^2=$ OMe
(**2**) $R^1, R^2=$ OCH_2O
(**8**) $R^1=R^2=$ OH



(**3**) R= CH_2NMe_2
(**4**) R= H



(**6**)



(**7**)

The Mannich base (**3**) used as a three-carbon unit of [3C+3C] condensation was derived from the ketone (**4**)$^{6)}$ on treatment with dimethylamine hydrochloride and formalin in MeOH. Another three-carbon unit was 1,1-bis(ethylthio)-2-propanone (**5**)$^{7)}$ which has been used for aromatic annulation in our laboratory.$^{3,8)}$ The Mannich base (**3**) was condensed with the ketone (**5**) in the presence of NaH in dimethoxyethane to give two isomeric cyclohexenones (**6**) and (**7**) (47% and 11% yields from compound **4** respectively). These were separated by column chromatography. Inspection of a molecular model shows that the enone part (C=CH-C=O) of **6** is located on the same plane as the benzene ring, while that of **7** is twisted from the aromatic ring. These structural characteristics can be well explained by their IR, ^{1}H-NMR, and UV spectral data.9) The ketone (**6**) was dethioacetalized by NBS in MeCN / AcOH / H_2O and isomerized by refluxing AcOH to give the diol (**8**) in 38% yield. The isomeric ketone (**7**) was also converted to **8** in the same manner (32%). Methylation of **8** with diazomethane in Et_2O / MeOH gave (±)-glaucine (**1**) in 71% yield. The melting points of compound **1** (mp 134-136°C)10) and its picrate [mp 192-194°C (dec.)]11) were the same as those of (±)-glaucine reported in the literature. The IR, ^{1}H-NMR, and UV spectral data of **1** were superimposable over those of (+)-glaucine.

Methylenation of compound **8** with KOH and CH_2Cl_2 in DMSO gave (±)-nantenine (**2**) in 43% yield. Its melting point (mp 140-141°C)12) and spectral data (^{1}H-NMR5) and Mass13)) were also identical with those reported in the literature.

In conclusion, (±)-glaucine (**1**) and (±)-nantenine (**2**) were prepared from both cyclohexenones (**6**) and (**7**), which were obtained from condensation of two 3C units, 1,1-bis(ethylthio)-2-propanone (**5**) and the Mannich base (**3**). The utility of the [3C+3C] annulation was shown by the aromatic synthesis of the aporphine alkaloids which have a 1,2-benzenediol moiety.

ACKNOWLEDGMENT The authors thank Professor Osamu Hoshino of the Science University of Tokyo for providing the authentic sample of natural glaucine.

REFERENCEDS AND NOTES

1) T. Kametani and T. Honda, "The Alkaloids," ed by A. Brossi, Academic Press, London (1985), Vol. 24, pp. 153-251; H. Guinaudeau, *Lloydia,* **51**, 389 (1988).
2) P. Bamfield and P. F. Gordon, *Chem. Soc. Rev.*, **13**, 441 (1984); J.Borgulya, M. Gerold, F. Schneider, and K. Bernauer, *Helv. Chim. Acta,* **60**, 598 (1977).
3) Y. Ozaki, I. Oshio, and S. Kim, *Chem. Pharm. Bull.*, **37**, 1434 (1989); Y. Ozaki, I. Oshio, Y. Ohsuga, S. Kaburagi, Z. Sung, and S. Kim, *ibid.*, in press.
4) a) J. C. Estevez, M. C. Villaverde, R. J. Estevez, and L. Castedo, *Tetrahedron Lett.*, **32**, 529 (1991); b) S. Gupta and D. S. Bhakuni, *Synth. Commun.*, **19**, 393 (1989); c) Y. Landais, D. Rambault, and J. P. Robin, *Tetrahedron Lett.*, **28**, 543 (1987); d) O. Hoshino, M. Ohtani, and B. Umezawa, *Chem. Pharm. Bull.,* **27**, 3101 (1979); e) O. Hoshino, T. Toshioka, and B. Umezawa, *ibid.*, **22**, 1302 (1974); f) M. P. Cava, I. Noguchi, and K. T. Buck, *J. Org. Chem.*, **38**, 2394 (1973); g) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973); h) S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, **38**, 405 (1973); i) S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.*, **18**, 1224 (1970); j) T. Kametani and I. Noguchi, *J. Chem. Soc. (C),* **1967**, 1440; k) A. H. Jackson and J. A. Martin, *J. Chem. Soc. (C),* **1966**, 2061.
5) a) O. Hoshino, H. Hara, N. Serizawa, and B. Umezawa, *Chem. Pharm. Bull.*, **23**, 2048 (1975); b) J. R. Merchant and H. K. Desai, *Indian J. Chem.*, **11**, 342 (1973).
6) F. Schneider, M. Gerold and K. Bernauer, *Helv. Chim. Acta,* **73**, 759 (1973).

7) H. Boehme and H. Huang, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **282**, 9 (1944); Stirring mixture of 1,1-dichloro-2-propanone, anhydrous K_2CO_3, and a catalytic amount of Adogen $_{464}$ (Aldrich Chemical Comany Inc.) in EtSH gave the compound 5 in 87% yield after exothermic reaction.

8) Y. Ozaki, K. Mochida, and S. Kim, *J. Chem. Soc., Perkin Trans. 1,* **1989**, 1219; Y. Ozaki and S. Kim, *Chem. Pharm. Bull.*, **37**, 304 (1989).

9) Compound **6**: IR ($CHCl_3$) 1646 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.58 (1H, d, J=2.5 Hz, olefinic proton). UV (EtOH) λ_{max} nm(ε): 315.4(17990); Compound **7**: IR ($CHCl_3$) 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 6.50 (1H, d, J=2.5 Hz, olefinic proton). UV (EtOH) λ_{max} nm(ε): 302.4(13008).

10) lit.$^{4b)}$ mp 118-120°C; lit.$^{4c)}$ mp 134-136°C; lit.$^{4f)}$ mp 127-129°C; lit.$^{4g)}$ mp 137-139°C.

11) lit.$^{4d)}$ mp 190-193°C(dec.); lit.$^{4e)}$ mp 191-193°C(dec.); lit.$^{4f)}$ mp 199-200°C (dec.); lit.$^{4h)}$ mp191-192°C(dec.); lit.$^{4i)}$ mp 191-193°C (dec.); lit.$^{4k)}$ mp 193-194°C.

12) lit.$^{4d)}$ mp 138-139°C; lit.$^{5a)}$ mp 140-142°C; lit.$^{5b)}$ mp 141-142°C.

13) M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2807 (1963).

(Received March 25, 1991)