Communications to the Editor

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THE SYNTHESES OF 3,4-DIMETHOXY-6-MORPHINANONE AND ISOMORPHINANONE. SPECTRAL INSPECTION OF THE STEREOCHEMISTRY IN CIS AND TRANS B/C RING FUSION

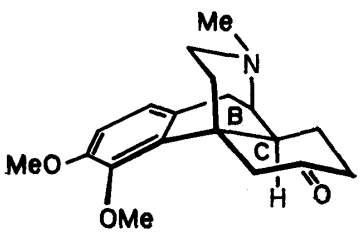
Ikuo Fujii, Masayuki Abe, Kenji Hayakawa, and Ken Kanematsu*
Institute of Synthetic Organic Chemistry, Fuculty of Pharmaceutical Sciences, Kyushu University 62, Fukuoka 812, Japan

3,4-Dimethoxy trans-6-morphinanone (1) and its cis isomer (2) were prepared stereoselectively from thebaine (3) and dihydrocodeinone (9), respectively. A general way of spectrally differentiating between these two stereoisomers is discussed.

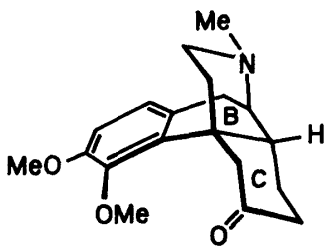
KEYWORDS ——— 3,4-dimethoxy trans-6-morphinanone; 3,4-dimethoxy-cis-6-morphinanone; tricarbonyliron complex; tristriphenylphosphine rhodium chloride; α-stereoselective hydrogenation

Recently, the 6-keto-N-methylmorphinanes (B/C cis) have been synthesized to evaluate the effect of analgesic potency and especially binding to opioid receptors.[1] Generally, the stereochemistry of the B/C-ring fusion in the morphine skeleton is closely related to its biological activity. Therefore, it is important to develop a new general method of synthesizing unnatural (B/C trans) morphine derivatives. During our studies of the synthesis of 3,4-crowned morphinanones, we have found that the β-dihydrothebaine derivative can be stereospecifically hydrogenated from the α-face to give the B/C-trans fused isomorphinane derivative.[2] In this communication, we describe the stereoselective synthesis of 3,4-dimethoxy trans-6-morphinanone (1), utilizing this new method, as well as the cis-isomer (2), and develop a general way of spectrally differentiating these two stereoisomers.

The synthesis of 1 was performed starting from thebaine (3) by initially



1: α-H14 (B/C trans)



2: β-H14 (B/C cis)

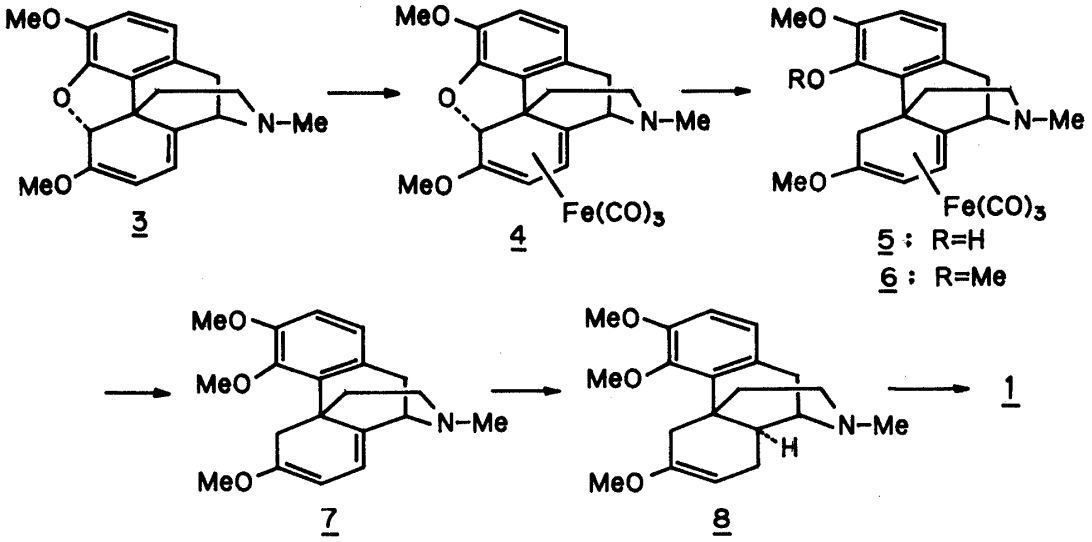


Chart 1

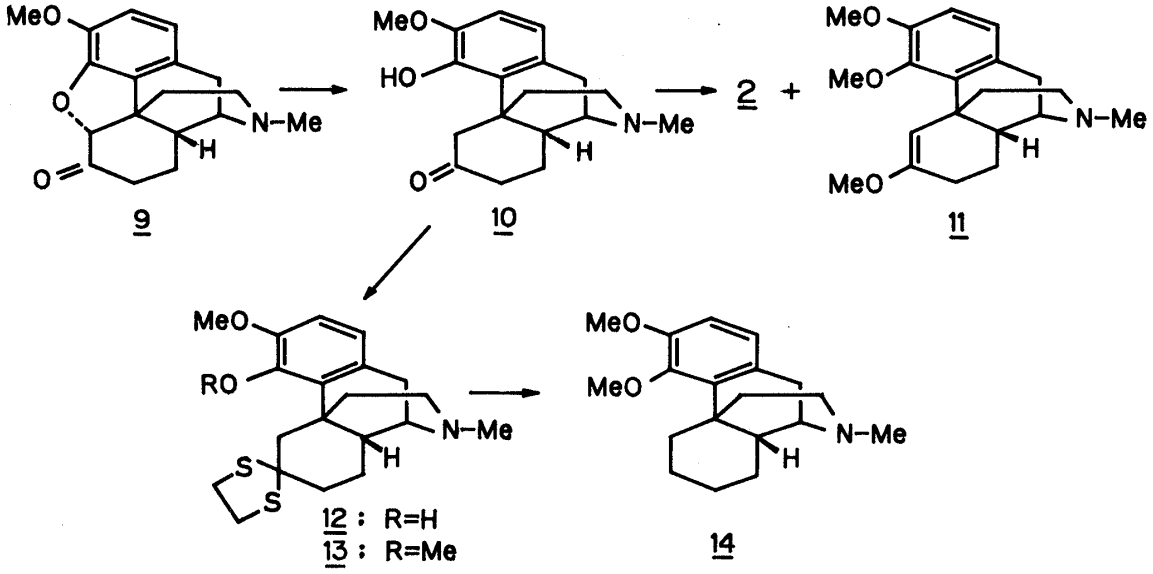


Chart 2

converting to the tricarbonyliron complex (4)[3] (Chart 1). Reductive cleavage of the 4,5-oxide bridge of 4 with Zn-AcOH gave the phenol 5, which was methylated with methyl p-toluensulfonate to afford 6.[4] Decomplexation of 6 with trimethylamine oxide in dry C_6H_6 gave β-dihydrothebaine-4-methyl ether (7) in 47% yield from 3. The protection of the labile diene moiety of 3 by the tricarbonyliron complex is essential for these smooth transformations. The construction of the B/C trans junction was accomplished by α-face selective catalytic hydrogenation. Thus, hydrogenation of 7 over tristriphenylphosphine rhodium chloride[5] in C_6H_6 afforded the 8,14-dihydro compound 8 in 57% yield as the sole product. Compound 8 was treated in turn with 10% HCl in THF to give 1[6] as a viscous oil in 85% yield.

On the other hand, the cis isomer 2 was synthesized from dihydrocodeinone (9) whose stereochemistry at C-14 is firmly established (Chart 2). The treatment of

9 with Zn-NH_4Cl-n-propanol-H_2O gave the phenol 10 in a quantitative yield. O-methylation of 10 with methyl p-toluensulfonate afforded 2[7] in 20% yield along with a small amount of enolether 11.

The isomeric nature of 1 to 2 was examined by ^{1}H-NMR and mass spectra. The mass spectra of 1 and 2 show the same molecular ion peak at m/e 315, but the characteristically different fragmentation patterns which serve to elucidate the stereochemistry of the B/C trans and cis fused rings (Fig. 1). While 1 (trans) shows an intense molecular ion peak, 2 (cis) reveals a relatively weak molecular ion peak and the characteristic fragment peak at m/e 59. This fragmentation (m/e 59; $C_3H_9N^{\cdot+}$) is considerd to arise from the cis-elimination through the four-membered ring transition state as shown in Chart 3 and is indicative of the cis-fused B/C ring system of 2. Accordingly, the trans-isomer 1 shows no intense peak at m/e 59. The similar difference of intensity of molecular ions in 1 and 2 is generally observed in the other morphine derivatives epimeric at C-14.[2]

In the ^{1}H-NMR spectra, the best diagnostic features for differentiating 1 and 2 are the chemical shifts of the C-3 and C-4 methoxy groups. While two singlets of the C-3 and C-4 methoxy groups of the trans-isomer (1) appeared at almost the

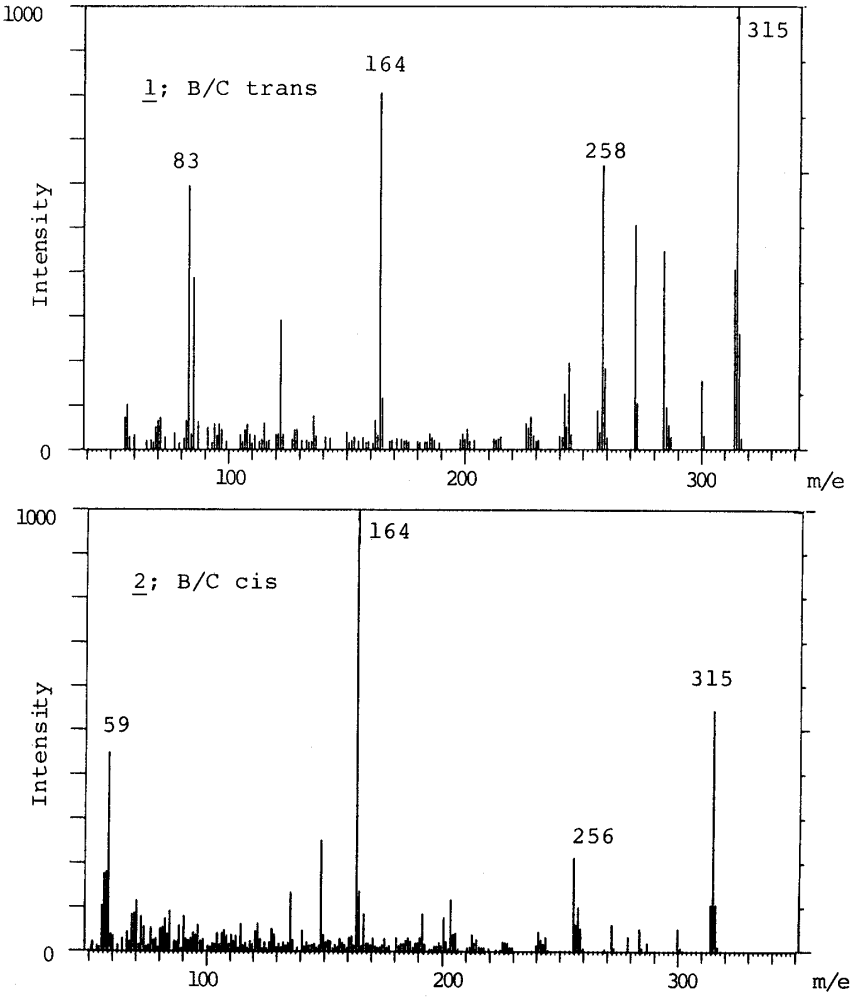


Fig.1. Mass spectra of 1 and 2

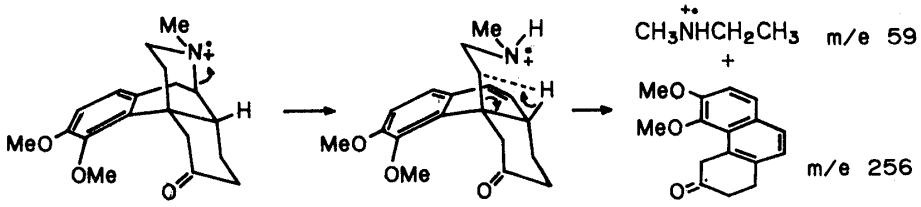


Chart 3

same position (δ 3.80 and δ 3.83), in the cis-isomer (2) the singlet of the C-4 methoxy group was markedly shifted to a lower field (δ 3.93) compared with that of C-3 methoxy group (δ 3.79). This low-field shift of the C-4 methoxy signal in 2 can be attributed to the deshielding effect of the nearby C-6 carbonyl group. In order to confirm this argument, 3,4-dimethoxy cis-morphinane (14) which lacks the C-6 carbonyl group was synthesized (Chart 2). The compound 10 was first converted to thioketal 12 (ethandithiol-BF_3·Et_2O-AcOH, 82%) and then methylated with methyl p-toluensulfonate to afford 13 (78%). Desulfurization of 13 with Raney Ni gave 14 in 43% yield. The ^{1}H-NMR spectrum of 14, as expected, shows the signals of the C-3 and C-4 methoxy groups with the similar chemical shifts (δ 3.82 and δ 3.85) as seen in 1.

In contrast to the well-known β-face selectivity of thebaine, the α-face selective reaction of the β-dihydrothebaine derivatives (like 7) is noteworthy for developing new syntheses of a novel series of isomorphinanones. Furthermore, the close examination of the spectral data provides a powerful method for the stereochemically differentiating trans and cis morphinanones.

REFERENCES AND NOTES

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2) I. Fujii, K. Hayakawa and K. Kanematsu, Tetrahedron Lett., 25, 3335 (1984), and references cited therein.
3) A.J. Birch, and H. Fitton, Aust. J. Chem., 22, 971 (1969).
4) Satisfactory IR, ^{1}H-NMR and mass spectra were obtained for all new compounds. Most of the compounds were purified by silica gel chromatography, as evidenced by TLC analysis.
5) A.J. Birch, and K.A.M. Walker, J. Chem. Soc. (C), 1966, 1894.
6) Compound 1: MS m/e(%): 315 [M^+] (100), 258 (64), 164 (80), 83 (60); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.8-2.3 (m, 6H), 2.33 (s, 3H, NMe), 2.3-2.8 (m, 6H), 2.8-3.3 (m,2H), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.80 and 6.82 (ABq, 2H, J=9Hz, H-1 and2); $[\alpha]_D^{21}$ -53.9° (c=1.2, $CHCl_3$).
7) Compound 2: MS m/e(%): 315 [M^+] (55), 256 (22), 164 (100), 59 (45); IR ($CHCl_3$) 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40-2.66 (m, 10H), 2.41 (s, 3H, NMe), 2.66-3.16 (m, 4H), 3.79 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.78 and 6.80 (ABq, 2H, J=9Hz, H-1 and 2); $[\alpha]_D^{24}$ -40.9° (c=0.64, $CHCl_3$).

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