SYNTHESIS OF 1,2,3,4,4a,5,10,10a-OCTAHYDRO-7-HYDROXY-2,4a,5-TRIMETHYL-1,5-ETHANOBENZO[g]QUINOLINE: BRIDGED BENZOMORPHAN WITH ANTAGONIST ACTIVITY

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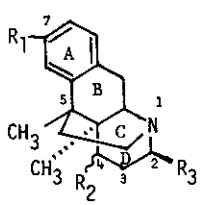
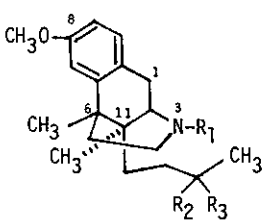
Abstract—— A synthetic approach has been made for the synthesis of 1,5-ethanobenzo[g]quinolines from 11-substituted 2,6-methano-3-benzazocine. The product showed strong antagonist activity.

Although many reports appeared for the explanation of structure-activity relationships of opiates,[1] those of antagonist activity were only a few. Recently Snyder et al.[2] and Kolb[3] reported the importance of orientation of N-substituents (or lone-pair electrons) for both of agonist and antagonist activities. But the directions of N-substituents in their hypotheses were completely opposite each other. In line with our previous report of synthesis and activities of 1,3-bridged 2,6-methano-3-benzazocines,[4] we report here the synthesis of the title compound, namely 3,11-bridged 2,6-methano-3-benzazocine.

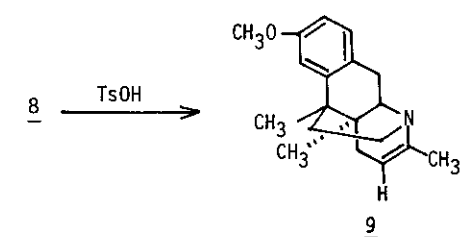
The synthesis of 1,5-ethanobenzo[g]quinoline skeleton (1) from 1-(substituted allyl)-1,2,5,6-tetrahydro-2-benzylpyridines was reported by Kimura et al. in 1975.[5] But the synthetic route including double cyclizations had some limitations for the substituents such that C-4 methyl group in compound 1 was indispensable. So we had to explore more general ones. We selected



	R_1	R_2	R_3
1	CH_3	CH_3	H
2	CH_3O	H	CH_3
3	HO	H	CH_3



	R_1	R_2	R_3
4	CH_3	=O	
5	CH_3	$-OCH_2CH_2O-$	
6	CN	$-OCH_2CH_2O-$	
7	H	$-OCH_2CH_2O-$	
8	H	=O	



8 —TsOH→ 9 —H_2, Pd-C→ 2

title compound 3 as target molecule and the synthetic routes were considered. Recently, Michne et al.[6] reported the synthesis of 11-substituted 2,6-methano-3-benzazocine (4). Therefore we chose the compound 4 as starting material and the ring D formation was investigated. As von Brown reaction of 4 resulted in extensive decomposition, protection of carbonyl group was required. The ketal (5) was obtained from 4 in 93 % yield. Von Brown reaction of 5 with BrCN in $CHCl_3$ gave N-CN derivative (6) followed by the reduction with $LiAlH_4$ to afford 7 (80.2 % yield from 5). Deketalization of 7 was achieved with dil. HCl to give N-demethylated product 8 in 95.5 % yield. Cyclizaion of 8 was performed with excess p-TsOH in refluxing toluene. In the NMR spectrum of the reaction mixture, broad signal at 5.75 ppm was assigned to the C-3 proton of enamine part. Subsequent hydrogenation over palladium in DMF afforded single product (2) in 30.4 % yield. The structure of 2 was proved to be 3,11-bridged 2,6-methano-3-benzazocine from elemental analysis, the mass and NMR spectra. The conformation of piperidine ring (ring C) of 2 was established to be chair form judging from the similar chemical shifts of C-4a and C-5 methyl groups with corresponding 2,6-methano-3-benzazocines. On the other hand, the stereochemistry of C-2 methyl group was speculated by the reports that C-11 methylene[7] and C-1 carbonyl[8] groups of 2,6-methano-3-benzazocines were reduced stereoselectively with H_2 over palladium in acidic media to give derivatives having beta methyl and beta hydroxyl groups, respectively. It is reasonable that the hydrogenation of enamine double bond of 9 occurred from less hindered side to give equatorial C-2 methyl substituent.[9] Demethylation of 2 with BBr_3 in $CHCl_3$ gave phenol derivative 3 in 74.5 % yield.

The analgesic activities of 3 was weak but antagonist activity was strong.[10]

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IR A-1 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-20B spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were determined using JEOL D-300 mass spectrometer at 70 eV by a direct inlet.

Preparation of 1,2,3,4,5,6-Hexahydro-8-methoxy-3,6,11-trimethyl-11-(3,3-ethylenedioxybutano)-2,6-methano-3-benzazocine (5) — A mixture of 4[6] HCl (162 mg) and ethylene glycol (0.5 g) was refluxed in 10 ml of benzene for 2 h and cooled. 10 % K_2CO_3 soln was added and extracted with ether, dried (K_2CO_3) and the solvent was evaporated off to give 173 mg (yield 93 %) of 5 as an oil. NMR ($CDCl_3$) δ 0.78 (3H, s, 11-CH_3), 1.28 (3H, s, 6-CH_3), 1.38 (3H, s, $CH_3C(O)_2$), 2.23 (3H, s, N-CH_3), 3.73 (3H, s, OCH_3), 3.93 (4H, s, OCH_2CH_2O), 6.52-7.08 (3H, m, arom H); MS, m/e 359 (M^+), 272. Picrate was obtained as yellow prisms (EtOH); mp 206-210°C. Anal. Calcd for $C_{22}H_{33}NO_3 \cdot C_6H_3N_3O_7$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.01; H, 5.93; N, 10.14.

Preparation of 6.—A mixture of 5 (1.848 g) and BrCN (3.6 g) in 50 ml of $CHCl_3$ was refluxed for 1 h. After the solvent was evaporated off, the residue was purified by short silica-gel column chromatography using ether as an eluent to give pure 6 as a colorless powder; yield 1.736 g (80.2 %); NMR ($CDCl_3$) δ 0.78 (3H, s, 11-CH_3), 1.25 (3H, s, 6-CH_3), 1.38 (3H, s, $CH_3(O)_2$), 3.75 (3H, s, OCH_3), 3.96 (4H, s, OCH_2CH_2O), 6.55-7.20 (3H, m, arom H); MS m/e 327, 370 (M^+) ;IR (KBr) ν cm^{-1} 2200 (CN).

Peparation of 7.—A mixture of 6 (1.736 g) and $LiAlH_4$ (841 mg) in 87 ml of THF was refluxed for 3 h and cooled. The reaction mixture was poured into a mixture of AcOEt and 10 % of aqueous K_2CO_3 and then extracted with ether. The organic layer was dried over K_2CO_3 and evaporated in vacuo to give 7 as an oil. NMR ($CDCl_3$) δ 0.78 (3H, s, 11-CH_3), 1.28 (3H, s, 6-CH_3), 1.39 (3H, s, $CH_3C(O)_2$), 3.78 (3H, s, OCH_3), 3.94 (4H, s, OCH_2CH_2O), 6.52-7.08 (3H, m, arom H); MS m/e 300, 345 (M^+). IR ν cm^{-1} 2210 (CN).

Preparation of 8.—Compound 7 was stirred in 10% HCl (40 ml) at 50-60°C for 1 h. The solution was neutralized with K_2CO_3 and extracted with $CHCl_3$. The organic layer was dried (K_2CO_3) and evaporated in vacuo to give 8 as an oil; yield 1.347 g (95.5 %); NMR ($CDCl_3$) δ 0.78 (3H, s, 2-CH_3), 1.32 (3H, s, 6-CH_3), 2.18 (3H, s, $COCH_3$), 3.77 (3H, s, OCH_3), 6.55-7.10 (3H, m, arom H) ; MS m/e 301 (M^+).

Preparation of 1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-2,4a,5-trimethyl-1,5-ethanobenzo[g]quinoline (2).—A mixture of 8 (389 mg) and p-toluenesulfonic acid monohydrate (272.3 mg) in toluene (30 ml) was refluxed for 1 h. After the solvent was evaporated off, NMR spectrum of the residue was measured. NMR of 9 ($CDCl_3$) δ 0.87 (3H, s, 4a-CH_3), 1.35 (3H, s, 5-CH_3), 2.05 (3H, bs, 2-CH_3), 3.78 (3H, s, CH_3O), 5.75 (1H, br, 3-H), 6.6-7.1 (3H, m, arom H).

To the residue, 10% Pd-C (350 mg) and *DMF (17.5 ml) were added. The mixture was hydrogenated* for 12 h at rt. After the solvent was evaporated off, the residue was extracted with CH_2Cl_2 and dried over K_2CO_3 and evaporated in vacuo to give a crude oil (190 mg), which was chromatographed on silica-gel (using ether-hexane-Et_3N =2:8:1 as eluent) to give 112 mg of 2 as a colorless powder; yield 30.4 % mp 90-93°C; NMR ($CDCl_3$) δ 0.68 (3H, s, 4a-CH_3), 1.18 (3H, d, 2-CH_3, J=7.0 Hz), 1.32 (3H, s, 5-CH_3), 3.76 (3H, s, OCH_3), 6.55-7.11 (3H, m, arom H). MS m/e 285 (M^+) . Hydrobromide of 2 was obtained as colorless prisms (EtOH);mp 270 °C. Anal. Calcd for $C_{19}H_{27}NO\cdot HBr$: C, 62.29; H, 7.70; N, 3.82. Found: C, 62.04; H, 7.79; N, 3.77.

Preparation of 3.—To a solution of BBr_3 (0.3 g) in $CHCl_3$ (3 ml) was added 2 (24 mg) in $CHCl_3$ (3 ml) at 0°C. After stirring for 0.5 h, the reaction mixture was poured into ice-NH_4OH mixture and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated in vacuo to give 17 mg of crystals (yield 74.5 %). NMR ($CDCl_3$) δ 0.72 (3H, s, 4a-CH_3), 1.19 (3H, d, 2-CH_3, J=7.0 Hz), 1.30 (3H, s, 5-CH_3), 6.40-7.05 (3H, m, arom H); MS m/e 271 (M^+). 3·hydrochloride;

colorless needles (MeOH-AcOEt), mp > 300°C. Anal. Calcd for $C_{18}H_{25}NO \cdot HCl \cdot 1/2H_2O$; C, 68.21; H, 8.59; N, 4.42. Found; C, 68.44; H, 8.54; N, 4.36.

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9. The stereochemistry of 2 was determined by the X-ray analysis and the data will be described in a separated paper.
10. Antagonist activity of 3·HCl to morphine analgesia was evaluated. ED_{50} value of morphine alone (6.9 mg/kg, mice tail pinch method, s.c.) was shifted to 15.0 mg/kg by the simultaneous application of 1.0 mg/kg of 3·HCl.

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