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Synthesis of Some *N*-Substituted 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines (6,7-Benzomorphans)

Mikio Hori,* Eiji Imai, Norihiro Kawamura, Tatsunori Iwamura, Tadashi Kataoka, and Hiroshi Shimizu

Gifu Pharmaceutical University, 6–1, Mitahora-higashi 5-chome, Gifu 502, Japan

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In order to study the effects of *N*-substituents of benzomorphans on antagonist–agonist activity we synthesized several benzomorphan derivatives having *N*-alkenyl, alkynyl, pyranyl or oxetanylmethyl groups.

Reduction of *N*-(hepta-2,5-diyn-4-yl)benzomorphan (**13**) with Lindlar catalyst resulted in dealkylation to afford normetazocine (**1**), whereas reduction with diisobutylaluminum hydride gave *N*-(hept-2-en-5-yn-4-yl)benzomorphan (**17**). *N*-Dihydro- (**14**) and tetrahydropyran derivatives (**15**) were obtained by the reaction of **1** with 4-methoxypyrylium salt followed by reduction with sodium borohydride.

Keywords——*N*-substitutent effect; 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine; benzomorphan; normetazocine; 2,6-dimethyl-4-methoxypyrylium salt; diisobutylaluminum hydride reduction

Structural variations of *N*-substituents in 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (6,7-benzomorphans) affect the antagonist–agonist activity. A study of structure–activity relationships indicated that three carbon chains such as a chloropropylmethyl or *cis*-3-chloroallyl group increase the agonist activity.[1)]

We have reported on the synthesis and analgesic activities of benzomorphans in which N-lone pair electrons are fixed in the equatorial conformation.[2)] In connection with our previous report,[2)] we wish to describe the synthesis of some benzomorphan derivatives in order to discuss the structure–activity relationships from three structural viewpoints, *i.e.*, carbon chain length, number and position of the unsaturated bond, and bulkiness.

Normetazocine (**1**) was alkylated with alkyl halides to give compounds **2**—**12**. The *N*-diyne derivative **13** with two antagonistic functions[1)] was prepared from **1** and hepta-2,5-diyn-4-yl methanesulfonate in 46.0% yield.

It is known that 4-methoxy-2,6-disubstituted pyrylium salts undergo the substitution reaction at C-4 with secondary amines.[3)] This reaction was applied for the preparation of *N*-pyranyl congeners, **14** and **15**. 4-Methoxy-2,6-dimethylpyrylium perchlorate was allowed to react with **1** followed by reduction with sodium borohydride to give *N*-dihydropyranylbenzomorphan **14** and the *N*-tetrahydropyranyl derivative **15** in 23.4 and 13.0% yields, respcetively. The structure of **14** was determined from the mass spectrum (MS) (M^+, m/z 237) and the nuclear magnetic resonance (NMR) spectrum, which exhibited signals due to an olefinic proton at δ 4.6 and two methyl groups of the pyran ring at δ 1.2 and 1.8. The tetrahydro derivative **15** showed a parent peak at m/z 329 in the MS, with no olefinic proton but two methyl signals at δ 1.1—1.4 in the NMR spectrum. Compounds **14** and **15** were mixtures of stereoisomers of the *N*-dihydropyranyl and *N*-tetrahydropyranyl moieties, respectively, on the basis of their NMR spectra. We attempted to lead **14** to **16** (bearing two

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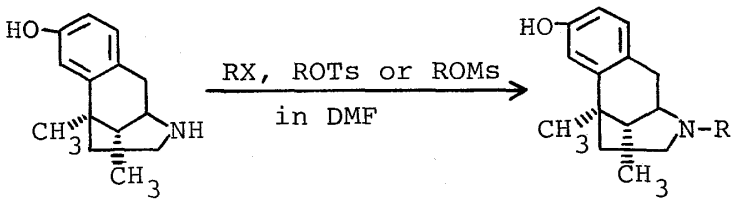
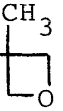
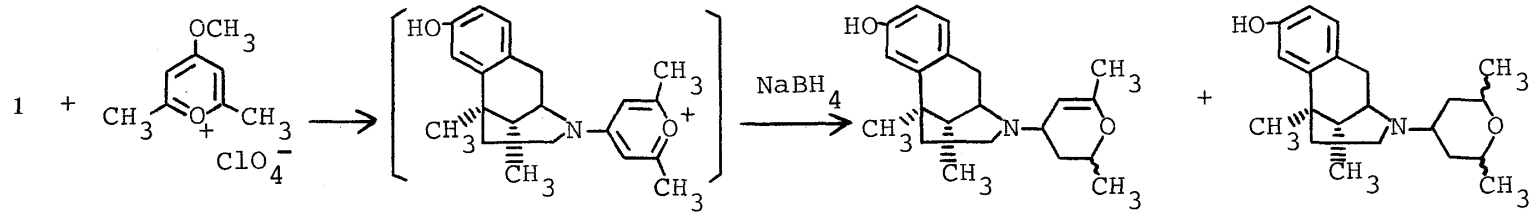
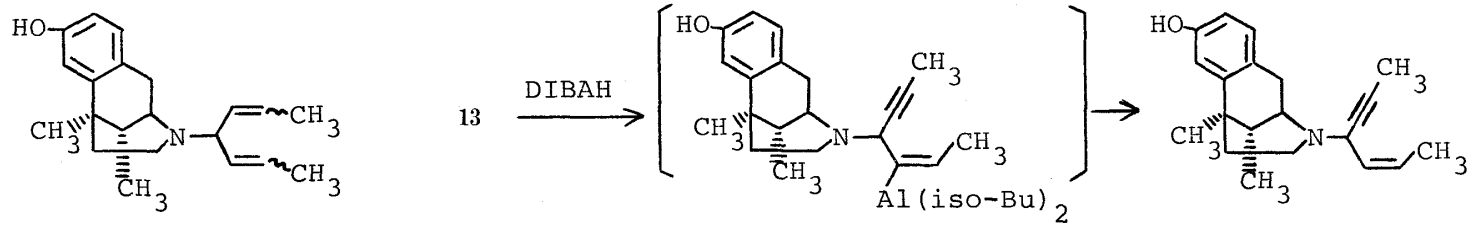


1

2 : R=CH_3
3 : R=$CH_2CH_2C(CH_3)=CH_2$
4 : R=$CH_2CH_2CH=C(CH_3)_2$
5 : R=$CH(CH_3)_2$
6 : R=$CH_2CH=C(CH_3)_2$
7 : R=$CH_2CH=CCl_2$
8 : R=$CH_2CH(CH_3)_2$
9 : R=$CH_2CH_2CH_3$
10 : R=$CH_2CH=CH_2$
11 : R=$CH_2C(CH_3)=CH_2$
12 : R=$CH_2C\equiv CH$
13 : R=$CH(C\equiv CCH_3)_2$
18 : R= 



14 15



16 17

Chart

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allylic functions) *via* ring opening, reduction and dehydration, but the first step, ring opening, was unsuccessful. Reduction of **13** with Lindlar catalyst did not afford **16** but gave the dealkylated product **1**. Therefore, **13** was reduced with diisobutylaluminum hydride (DIBAH) in ether to give a partially reduced compound **17** as the main product. The configuration of the newly formed double bond was determined to be *Z*-form from the coupling constant of the vicinal olefinic protons, $J=6.8$ Hz, in the NMR spectrum. Reduction of propargyl amines with DIBAH afforded *E*-olefins, whereas that of a diacetylenic amine gave an *E,Z*-olefin.[4] In the case of **13**, a vinylaluminum intermediate formed by *cis* addition would be more stable than that formed by *trans*-addition because of the steric repulsion.

N-Tetrahydrofurfurylbenzomorphans possess unique pharmacological action profiles: they do not elicit the Straub tail phenomenon in mice nor do they substitute for morphine in morphine-dependent monkeys, although analgesic activity up to more than 100 times that of morphine is attained.[5] Therefore, it seemed interesting to change the *N*-tetrahydrofurfuryl group into an *N*-oxetanyl methyl substituent. The oxetanylmethyl derivative **18** was synthesized from **1** and the tosylate of 3-methyloxetanyl-3-methanol in 50.5% yield.

A part of the pharmacological studies has been reported.[6] The new compounds (**17**, **18**) showed very weak analgesic activity and did not exert significant antagonist activity. Opioid receptor binding of these compounds was also examined. Large IC_{50} values were obtained. From these results, it appears that bulky *N*-substituents, in particular those branched at $C_{1'}$, may interfere with the binding of the nitrogen atom to the opioid receptor.

Experimental

All melting points are uncorrected. The infrared (IR) absorption spectra were recorded on a JASCO A-1. ^{1}H-NMR spectra were determined with a Hitachi R-20B spectrometer with tetramethylsilane as an internal standard. Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument with a direct inlet system at 70 eV.

Materials——Compounds **6**—**7**, and **9**—**12** were prepared by the method of Archer *et al.*[7] This synthetic method was also applied for the preparations of compounds **2**—**3**, **5**, and **8**.[1]

(2*S,6*R**,11*R**)-6,11-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-(4-methyl-3-pentenyl)-3-benzazocin-8-ol (4)**——A solution of normetazocine[8] (**1**) (0.50 g, 2.3 mmol), 5-bromo-2-methyl-2-pentene (0.56 g, 3.45 mmol) and sodium hydrogen carbonate (0.31 g, 3.68 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) was stirred at 100 °C for 5 h under nitrogen. After removal of the solvent, water (50 ml) was added to the residue and the resulting mixture was extracted with chloroform. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel with ether–hexane–triethylamine (2 : 4 : 1) as an eluent to give **4** (0.62 g, 89.9%). NMR ($CDCl_3$) δ: 0.83 (3H, d, $J=7.0$ Hz, 11-CH_3), 1.30 (3H, s, 6-CH_3), 1.55, 1.65 [each 3H, s, C=C(CH_3)$_2$], 4.87—5.50 (2H, m, OH and CH=), 6.42—7.00 (3H, m, ArH). MS *m/z*: 299 (M^+). This compound was converted to the fumarate, mp 181—183.5 °C (dec.) (colorless prisms from MeOH–acetone). *Anal.* Calcd for $C_{20}H_{29}NO \cdot 1/2C_4H_4O_4 \cdot C_3H_6O$: C, 72.26; H, 8.97; N, 3.37. Found: C, 72.38; H, 9.30; N, 3.38.

(2*S,6*R**,11*R**)-3-(Hepta-2,5-diyn-4-yl)-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-5-benzazocin-8-ol (13)**——A solution of **1** (3.00 g, 13.8 mmol), hepta-2,5-diyn-4-yl methanesulfonate [prepared from hepta-2,5-diyn-4-ol[9] (2.16 g, 20 mmol) and methanesulfonyl chloride (1.70 ml, 28.8 mmol)], and potassium carbonate (3.00 g, 21.7 mmol) in DMF (50 ml) and dichloromethane (100 ml) was stirred at room temperature for a day. The reaction mixture was poured into water (80 ml) and extracted with dichloromethane. The extract was washed with water, then dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with chloroform–methanol (100 : 1) as an eluent to give **13** (1.95 g, 46.0%) as colorless prisms, mp 187—189 °C (dec.) (chloroform–hexane). IR ν_{max}^{KBr} cm^{-1}: 2200 (C≡C). NMR ($CDCl_3$) δ: 0.83 (3H, d, $J=7.0$ Hz, 11-CH_3), 1.32 (3H, s, 6-CH_3), 1.81 (6H, d, $J=2.3$ Hz, C≡C-CH_3), 4.18—4.50 [1H, m, N-CH(C≡C)$_2$], 6.48—7.01 (3H, m, ArH). MS *m/z*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO \cdot 1/5H_2O$: C, 81.09; H, 8.23; N, 4.56. Found: C, 81.32; H, 8.26; N, 4.44. This compound was converted to the fumarate, mp 127—129 °C (dec.) (colorless prisms from acetone). *Anal.* Calcd for $C_{21}H_{25}NO \cdot 1/2C_4H_4O_4 \cdot C_3H_6O$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.62; H, 7.93; N, 3.37.

(2*S,6*R**,11*R**)-6,11-Dimethyl-3-(4*H*-2,6-dimethyl-2,3-dihydropyran-4-yl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol (14) and the Tetrahydropyran Derivative (15)**——A mixture of **1** (0.87 g, 4.0 mmol), 2,6-dimethyl-4-methoxypyrylium perchlorate[10] (1.05 g, 4.4 mmol) in ethanol (40 ml) was refluxed for 1 h. Sodium borohydride (0.60 g, 15.8 mmol) was added to the reaction mixture with cooling in an ice-bath and then the mixture was stirred at

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room temperature for 2 h. After being treated with water (70 ml), the mixture was extracted with dichloromethane. The extract was dried over anhydrous potassium carbonate and evaporated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate–hexane–triethylamine (1 : 5 : 0.5) as an eluent to give **14** (0.31 g, 23.4%) and **15** (0.17 g, 13.0%). **14**: Colorless prisms (ether), mp 164—166 °C. NMR ($CDCl_3$) δ: 0.79 (3H, d, J=7.2 Hz, 11-CH_3), 1.11—1.38 (6H, m, 6- and 5′-CH_3) 1.80 (3H, s, 3′-CH_3), 4.38—4.72 (1H, m, 2′-CH), 6.44—7.16 (4H, m, ArH and OH). MS m/z: 327 (M^+). *Anal.* Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.80; H, 9.14; N, 4.21. This compound was converted to the fumarate, mp 184—186 °C (colorless prisms from methyl ethyl ketone). *Anal.* Calcd for $C_{21}H_{29}NO_2 \cdot 1/2H_2O$: C, 66.35; H, 7.57; N, 3.10. Found: C, 66.50; H, 7.98; N, 3.32. **15**: Oil. NMR ($CDCl_3$) δ: 0.84 (3H, d, J=7.0 Hz, 11-CH_3), 1.14—1.42 (9H, m, 6-, 3′- and 5′-CH_3), 6.45—7.03 (3H, m, ArH). High-resolution MS m/z: Calcd for $C_{21}H_{31}NO_2$ (M^+) 329.2353. Found: 329.2343.

(2*S,6*R**,11*R**)-6,11-Dimethyl-1,2,3,4,5,6-hexahydro-3-(hex-2-en-5-yn-4-yl)-2,6-methano-3-benzazocin-8-ol (17)**——A solution of DIBAH (1 M solution in hexane) (7.5 ml) was added to a suspension of **1** (307 mg, 1 mmol) in dry ether (20 ml). The reaction mixture was refluxed for 3 h and then stirred at room temperature for a day. The reaction was quenched by the addition of water and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The dichloromethane extract was combined with the organic layer, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with chloroform–methanol (100 : 3) as an eluent to give **17** (160 mg, 51.8%). NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.5 Hz, 11-CH_3), 1.28 (3H, s, 6-CH_3), 1.55—1.90 (6H, m, C=C−CH_3 and C≡C-CH_3), 3.75—4.0 [1H, m, N-CH(C=C)C≡C], 5.65 (1H, dd, J=6.8, 5.3 Hz, C$\underline{H}$=C-CH_3), 6.0—6.25 (1H, m, C=C$\underline{H}$-CH_3). MS m/z: 309 (M^+). This compound was converted to the fumarate, mp 228—230 °C (dec.) (colorless prisms from methyl ethyl ketone). *Anal.* Calcd for $C_{21}H_{27}NO \cdot 1/2C_4H_4O_4 \cdot 3/4H_2O$: C, 72.51; H, 8.07; N, 3.68. Found: C, 72.44; H, 7.97; N, 3.39.

(2*S,6*R**,11*R**)-6,11-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-[(3-methyl-3-oxetanyl)methyl]-3-benzazocin-8-ol (18)**——A solution of **1** (1.00 g, 4.60 mmol), 3-methyl-3-oxetanylmethyl *p*-toluenesulfonate (1.41 g, 5.52 mmol) (prepared from 3-methyl-oxetanyl-3-methanol[11] and *p*-toluenesulfonyl chloride), and sodium hydrogen carbonate (0.58, 6.90 mmol) in DMF (80 ml) was stirred at 90 °C for 20 h under nitrogen. The reaction mixture was then evaporated *in vacuo*. Water (80 ml) was added to the residue and the mixture was extracted with chloroform. The extract was washed with water, and dried over anhydrous magnesium sulfate, then the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate–hexane–triethylamine (1 : 5 : 0.5) as an eluent to give **18** (0.70 g, 50.5%) as colorless prisms, mp 149—152.5 °C (dichloromethane–hexane). NMR ($CDCl_3$) δ: 0.79 (3H, d, J=7.0 Hz, 11-CH_3), 1.28 (3H, s, 6-CH_3), 1.37 (3H, s, 3′-CH_3), 2.66 [2H, s, N-C$\underline{H}_2$C(CH_3)], 4.20—4.68 (4H, m, CH_2-O), 6.22—7.10 (4H, m, ArH and OH). MS m/z: 301 (M^+). *Anal.* Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.61; H, 9.07; N, 4.62. This compound was converted to the fumarate, mp 153—156 °C (colorless needles from methanol–acetone). *Anal.* Calcd for $C_{19}H_{27}NO_2 \cdot 1/2C_4H_4O_4 \cdot 1/3H_2O$: C, 69.01; H, 8.18; N, 3.83. Found: C, 68.82; H, 8.42; N, 3.83.

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