169. Hiroshi Kugita and Mikio Takeda : Syntheses of Morphine-like Structures. I. 9-Hydroxymethyl-2,5-dimethyl-6,7-benzomorphan.

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A search for an effective analgesic agent with minimal addiction liability and toxicity in benzomorphan derivatives, in which the third ring of the phenanthrene skeleton of the morphine structure was replaced by an alkyl group or two, was first reported by May and Murphy.¹⁾ Numerous derivatives have since been reported by May and co-workers²⁾ and it appeared that the C-ring of the morphine structure may be eliminated with retention of the morphine-like activity. One member of this group, 2-phenethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan has been shown to have clinical utility.³⁾

Benzomorphans, as a whole, have shown low ability to suppress morphine abstinence in monkeys.⁴⁾ Although some quantitative differences of this property were

6,7-benzomorphan

morphine

encountered transferring from monkey to man,⁵⁾ separation of the side-effects of morphine from analgesic effect in some degree has been observed generally in the benzomorphan series.

One of the present authors recently was given an opportunity to undertake a study on benzomorphans at the National Institutes of Health in U. S. A.⁶⁾ In the continuing search in this series of compounds, the synthesis of some 9-substituted derivatives was attempted.⁷⁾ Modifications of the morphine structure in its C-ring, which possesses an unsaturated bond and a hydroxyl group, have been reported in connection with the analgesic effectiveness.⁸⁾ By replacing the 9-alkyl group of the 5,9-dialkyl benzomorphans by a substituent containing a functional group, *e.g.* CO, OH, OR, and halogen, one could expect a variation in analgesic activity. This paper describes a preliminary study for the introduction of a hydroxymethyl group into the 9-position of 6,7-benzomorphans.

α -9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I)⁹⁾ was dehydrated with thionyl chloride in the presence of pyridine following the procedure employed in the 2'-methoxy analog.¹⁰⁾ Chromatography of the reaction products afforded the 9-methylene deriv-

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1) E. L. May, J. G. Murphy : J. Org. Chem., **20**, 257 (1955).

2) "Structures Related to Morphine." latest report, *Ibid.*, **27**, 2554 (1962).

3) E. L. May, N. B. Eddy : *Ibid.*, **24**, 294 (1959); E. L. May, N. B. Eddy : *ibid.*, **24**, 1435 (1959).

4) See H. Kugita, S. Saito, E. L. May : J. Med. Pharm. Chem., **5**, 357 (1962), cited reference 3).

5) Phenazocine and some other derivatives. Addenda to the Minutes of the 20th, 21st, 22nd and 23rd Meetings (1959, 1960, 1961, 1962) of the Committee on Drug addiction and Narcotics of the National Research Council, U. S. A., and private communication from Dr. E. L. May.

6) Section on Medicinal Chemistry, Chief, Dr. Everett L. May.

7) We are grateful to Dr. E. L. May for his kind permission on continuing studies on benzomorphan derivatives.

8) O. J. Branden, N. B. Eddy, H. Halbach : Bull. Wld. Hlth. Org., **13**, 937-998 (1955).

9) E. L. May, H. Kugita, J. H. Ager : J. Org. Chem., **26**, 1621 (1961).

10) S. Saito, E. L. May : *Ibid.*, **27**, 1087 (1962).

ative (II) in 33% yield, a halogenated derivative (III) (Beilstein test) and a halogen-free base (IV), both in low yield, being separable by-products. The halogenated base (III) analyzed for the molecular formula, $\text{C}_{15}\text{H}_{20}\text{NCl}$, and has been assigned the structure of 9-chloro-2,5,9-trimethyl-6,7-benzomorphan. Considering the possibility of skeletal rearrangement, however, the actual structure of III remains unknown. Another base (IV) proved to be isomeric, but not identical, with II. Neither the terminal methylene nor the benzene ring-conjugated double bond were detected in infrared and ultraviolet spectra. A skeletal rearrangement apparently has occurred during the reaction, phenyl migration being most probable.¹¹⁾

Hydroboration of II followed by oxidation with hydrogen peroxide¹²⁾ afforded the 9-hydroxymethyl derivative (V). Reaction of V with *p*-toluenesulfonyl chloride in pyridine gave in one instance (three days in a refrigerator and one following day at room temperature) the pyridinium *p*-toluenesulfonate (VI), which was identified as the picrate. Reaction in a refrigerator for three days followed promptly by cautious separation of the reaction product gave the *p*-toluenesulfonate (VII). Reduction of VII with lithium aluminum hydride afforded the 5,9-dimethyl derivative (VIII). Because of the widely accepted *cis* anti-Markovnikoff addition of diborane to a double bond¹³⁾ the structure (V) for the hydroboration product seems most probable. Nonidentity of the product with either of the α - and β -9-hydroxy-9-methyl derivatives⁹⁾ undoubtedly supports this

11) Catalytic hydrogenation of IV gave two isomers, and this result also may support the phenyl-migrated structure. We thank Dr. S. Saito of this laboratory for useful discussion in this point.

12) H.C. Brown, B.C. Subba Rao : J. Org. Chem., 22, 1136 (1957); *idem* : J. Am. Chem. Soc., 81, 6428 (1959); H.C. Brown : 12, 117 (1961).

13) *Idem* : J. Am. Chem. Soc., 81, 6423 (1959); H.C. Brown, G. Zweifel : *Ibid.*, 83, 2544 (1961); W.J. Wechter : Chem. & Ind. (London), 1959, 294.

assignment. The fact that the 9-methyl derivative obtained from II by hydrogenation in acid medium¹⁰⁾ proved to be identical with the 9-methyl derivative (VIII), and that VIII appeared different from the known α -9-methyl derivative¹⁴⁾ indicates that the configuration of the 9-methyl group of VIII as well as that of the hydroxymethyl group of V has the β -configuration.¹⁵⁾ This also seems to provide another method for constructing a β -oriented substituent (at the 9-position) generally considered to be more favorable for analgesic activity than α -substitution.

Experimental*2

Dehydration of α -9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I)—I⁹⁾ (11 g.) was mixed with SOCl₂ (110 ml.) and pyridine (2 ml.) under cooling and stirred at 40° for 50 hr. SOCl₂ was distilled under reduced pressure and the residue was decomposed with ice water, neutralized with NH₄OH, extracted with Et₂O and dried. Evaporation of the solvent and distillation of the residue gave a fraction (8.8 g.) of b.p._{0.5} 105~120°, which was dissolved in benzene and chromatographed over Al₂O₃ and eluted with petr. ether. Evaporation of the solvent gave an oil (4.6 g.)—(A). Further elution with benzene-petr. ether (3:7) and evaporation of the solvents gave another fraction of oil (3.6 g.)—(B). The fraction (B) was dissolved in Et₂O and treated with HCl-MeOH to give, after one crystallization (EtOH-Et₂O), II-HCl, m.p. 236~240° (decomp.) (2.8 g.). Analytical sample crystallized from EtOH-Et₂O, colorless needles, m.p. 242~244° (decomp.). *Anal.* Calcd. for C₁₆H₂₀NCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 71.65; H, 7.9; N, 5.77. IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 6.05, 10.65. Perchlorate, m.p. 217~219°, colorless needles (EtOH) (Lit., m.p. 218~220°¹⁴⁾). Picrate. Yellow prisms (EtOH-Me₂CO), m.p. 167~168.5°. *Anal.* Calcd. for C₂₁H₂₂O₇N₄: C, 57.01; H, 5.01; N, 12.67. Found: C, 57.10; H, 4.70; N, 12.93.

The mother liquors from the II-HCl were evaporated, basified with NH₄OH, extracted with Et₂O and evaporated. The recovered base was added to the fraction (A) and treated with picric acid in Et₂O. The crude picrate was recrystallized twice from Me₂CO to give IV-picrate (2.5 g.), m.p. 191~195°. Analytical sample crystallized from Me₂CO in yellow rods, m.p. 193~195°. *Anal.* Calcd. for C₂₁H₂₂O₇N₄: C, 57.01; H, 5.01; N, 12.67. Found: C, 57.12; H, 4.75; N, 12.42. Recovered base from the picrate, b.p._{0.6} 102~104°, was unstable in the air turning to red viscous material. The hydrochloride crystallized from EtOH-Et₂O in hygroscopic colorless needles, m.p. 200~202° (decomp.).¹⁶⁾ Methiodide. Colorless plates (EtOH), m.p. 240~242°. *Anal.* Calcd. for C₁₆H₂₂NI: C, 54.09; H, 6.24; N, 3.94. Found: C, 53.55; H, 6.02; N, 3.87.

Evaporation of the mother liquors from the IV-picrate, and recrystallization of the residue from Me₂CO-EtOH gave the II-picrate (2 g.), m.p. 164~168° which made total yield of II 33%. The mother liquor from the II-picrate was evaporated and recrystallized from Me₂CO to give the third picrate, m.p. 191~195° (0.4 g.). Admixture with the IV-picrate depressed the melting point. The Beilstein test indicated III as a halogenated product. Analytical sample crystallized from Me₂CO, yellow cubes, m.p. 194~196°. *Anal.* Calcd. for C₂₁H₂₃O₇N₄Cl: C, 52.67; H, 4.84; N, 11.70; Cl, 7.40. Found: C, 52.90; H, 4.63; N, 11.67; Cl, 7.32. Further working up of the mother liquors from the picrate yielded unseparable mixture.

β -9-Hydroxymethyl-2,5-dimethyl-6,7-benzomorphan (V)—To a mixture of II (1.7 g.), NaBH₄ (0.46 g.) and tetrahydrofuran (THF) (35 ml.) was added a solution of BF₃-Et₂O (2.3 g.) in THF (8 ml.) at 5~10° under N₂ stream during 1 hr., the mixture was stirred for 2 hr. at the same temperature and at room temperature for an additional 3 hr. then treated with H₂O (2 ml.) to decompose an excess of BH₃. After addition of 3N NaOH (6 ml.) and 30% H₂O₂ (6 ml.) (during 1.5 hr.) the mixture was stirred at room temperature for 3 hr., filtered from inorganic material, extracted with Et₂O and dried (K₂CO₃). Evaporation of Et₂O left a paste (1.9 g.) which was dissolved in Et₂O and extracted repeatedly with 5% HCl. The extracts were basified with K₂CO₃, extracted with Et₂O, dried and evaporated to give a crystalline residue (0.4 g.), m.p. 89~93°. Analytical sample crystallized from Et₂O in colorless plates, m.p. 95~97°.

*2 All melting point are uncorrected.

- 14) E. L. May, E. M. Fry: J. Org. Chem., **22**, 1366 (1957). The methyl groups at C-5 and C-9 are assigned as *cis* for the hydroaromatic ring, *i.e.* the 9-methyl group oriented away from nitrogen. The stereochemistry of 5,9-dialkylbenzomorphans has been established by the methiodide-rate-formation. S. E. Fullerton, E. L. May, E. D. Becker: *Ibid.*, **27**, 2144 (1962). More recently, β -2,5,9-trimethyl-6,7-benzomorphan (VIII) was synthesized and the configuration of 9-methyl group has been confirmed by the same methiodide-rate-study method. Private communication from Dr. E. L. May.
- 15) The methyl group oriented toward nitrogen, *trans* with 5-methyl group, *i.e.* isomorphinan type.
- 16) No absorption bands characteristic of a terminal methylene group was detected in IR spectrum of $>CH_2$, the free base at 11.18 μ , and the hydrochloride at 10.67 μ .

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.58; H, 8.99; N, 5.74. IR: $\lambda_{\text{max}}^{\text{Nujol}}$ 3.10 μ . Hydrochloride. Colorless prisms (EtOH), m.p. 259~260°. *Anal.* Calcd. for $C_{15}H_{22}ONCl$: C, 67.27; H, 8.28; N, 5.23. Found: C, 66.78; H, 8.12; N, 5.09. IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 3.0, 9.85. Picrate. Yellow rods (EtOH), m.p. 154~156°. *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$: C, 54.78; H, 5.25; N, 12.12. Found: C, 54.89; H, 5.28; N, 12.22.

Tosylation of V—a) To V (140 mg.) in dry pyridine (0.8 ml.) was added TsCl (180 mg.) under cooling. The mixture was kept in a refrigerator for 3 days, ice-water was added, extracted with Et_2O and dried (K_2CO_3). The solvent was removed under reduced pressure, the residue was dissolved in Et_2O and treated with picric acid to yield the picrate of the *p*-toluenesulfonate (VII) (250 mg.), m.p. 173~176°. Analytical sample crystallized in yellow plates (Me_2CO), m.p. 175~177°. *Anal.* Calcd. for $C_{28}H_{29}O_{10}N_4S$: C, 54.80; H, 4.76; N, 9.13; S, 5.23. Found: C, 54.57; H, 4.45; N, 9.19; S, 4.98.

A reaction of V (100 mg.) and TsCl (165 mg.) in Et_3N (2.5 ml.) (2 days at room temperature) and working up as the above gave VII-picrate in 62% yield.

b) To V (140 mg.) in dry pyridine (1.5 ml.) cooled in an ice-bath was added TsCl (230 mg.) and the mixture was kept in a refrigerator for 3 days then at room temperature for 1 day, diluted with ice-water, extracted with $CHCl_3$ and dried. The solvent was evaporated at below 40°, the residue was dissolved in H_2O , extracted with Et_2O , and the aqueous solution was treated with aqueous picric acid to yield the pyridinium picrate (VI) (120 mg.), m.p. 195~200° (decomp.). Analytical sample crystallized in yellow needles (Me_2CO-Et_2O), m.p. 205~207° (decomp.). *Anal.* Calcd. for $C_{32}H_{30}O_{14}N_8$: C, 51.20; H, 4.03; N, 14.93. Found: C, 51.11; H, 4.07; N, 14.53. The Et_2O extract was treated with picric acid to give the VII-picrate, m.p. 170~175° (20 mg.).

β -2,5,9-Trimethyl-6,7-benzomorphan (VIII). From VII—A mixture of VII (180 mg.), $LiAlH_4$ (200 mg.) and anhyd. Et_2O (50 ml.) was refluxed for 65 hr., a little H_2O was added and filtered. The dried Et_2O solution was evaporated, the residue was dissolved in Et_2O and treated with $HCl-MeOH$ to yield VIII-HCl (85 mg.), m.p. 247~250° (decomp.). Analytical sample crystallized from EtOH, colorless prisms, m.p. 253~255° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}NCl$: C, 71.55; H, 8.81; N, 5.56. Found: C, 71.90; H, 8.38; N, 5.47. Picrate. Yellow prisms (EtOH), m.p. 201~202° (decomp.).¹⁷⁾

From II—II-HCl (200 mg.) was hydrogenated in 15% HCl (10 ml.) and EtOH (5 ml.) with PtO_2 (50 mg.). One mole of H_2 was absorbed in 40 min., Pt was filtered, the solution was evaporated under reduced pressure. Addition of Me_2CO to the residue gave VIII-HCl (125 mg.), m.p. 245~247° (decomp.). Recrystallization from EtOH gave colorless prisms, m.p. 253~255° (decomp.). This proved identical with the VIII-HCl obtained from VII by mixed melting point and IR determinations.

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Summary

9-Hydroxymethyl-2,5-dimethyl-6,7-benzomorphan has been synthesized by hydroboration reaction of 9-methylene-2,5-dimethyl-6,7-benzomorphan. Configuration of the newly introduced 9-hydroxymethyl group was confirmed as *trans* with 5-methyl group for the hydroaromatic ring.

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17) We thank Dr. May for providing a sample of β -2,5,9-trimethyl-6,7-benzomorphan hydrobromide. The picrate prepared from the hydrobromide and ours were identical as evidenced by melting point and infrared spectral comparison.