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

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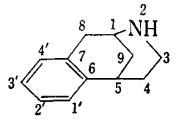
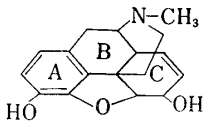
A search for an effective analgesic agent with minimal addiction liability and toxicity in benzomorphan derivatives, in which the third ring of the phenanthrene skeleton of the morphine structure was replaced by an alkyl group or two, was first reported by May and Murphy.[1] Numerous derivatives have since been reported by May and co-workers[2] 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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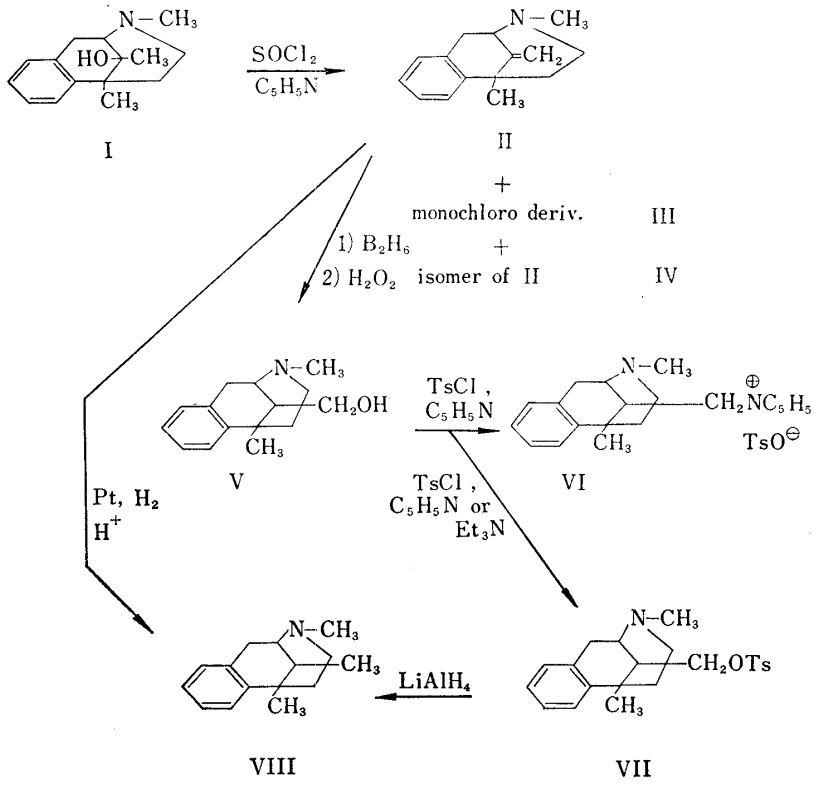
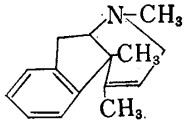
1) E. L. May, J. G. Murphy : J. Org. Chem., **20**, 257 (1955).
2) "Structures Related to Morphine." latest report, *Ibid.*, **27**, 2554 (1962).
3) E. L. May, N. B. Eddy : *Ibid.*, **24**, 294 (1959); E. L. May, N. B. Eddy : *ibid.*, **24**, 1435 (1959).
4) See H. Kugita, S. Saito, E. L. May : J. Med. 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 Commitee 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, $C_{15}H_{20}NCl$, 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 peroxide[12] 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 bond[13] 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 derivatives[9] 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 medium[10] proved to be identical with the 9-methyl derivative (VIII), and that VIII appeared different from the known α-9-methyl derivative[14] 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)——I[9] (11 g.) was mixed with $SOCl_2$ (110 ml.) and pyridine (2 ml.) under cooling and stirred at 40° for 50 hr. $SOCl_2$ was distilled under reduced pressure and the residue was decomposed with ice water, neutralized with NH_4OH, extracted with Et_2O 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 Al_2O_3 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 Et_2O and treated with HCl-MeOH to give, after one crystallization (EtOH-Et_2O), II-HCl, m.p. 236~240° (decomp.) (2.8 g.). Analytical sample cristallized from EtOH-Et_2O, colorless needles, m.p. 242~244° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}NCl$: C, 72.13; H, 8.07; N, 5.61. Found : C, 71.65; H, 7.9; N, 5.77. IR λ_{max}^{Nujol} μ : 6.05, 10.65. Perchlorate. m.p. 217~219°, colorless needles (EtOH) (Lit., m.p. 218~220°[14]). Picrate. Yellow prisms (EtOH-Me_2CO), m.p. 167~168.5°. *Anal.* Calcd. for $C_{21}H_{22}O_7N_4$: 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 NH_4OH, extracted with Et_2O and evaporated. The recovered base was added to the fraction (A) and treated with picric acid in Et_2O. The crude picrate was recrystallized twice from Me_2CO to give IV-picrate (2.5 g.), m.p. 191~195°. Analytical sample crystallized from Me_2CO in yellow rods, m.p. 193~195°. *Anal.* Calcd. for $C_{21}H_{22}O_7N_4$: 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-Et_2O in hygroscopic colorless needles, m.p. 200~202° (decomp.).[16] Methoiodide. Colorless plates (EtOH), m.p. 240~242°. *Anal.* Calcd. for $C_{16}H_{22}NI$: 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 Me_2CO-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 Me_2CO 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 Me_2CO, yellow cubes, m.p. 194~196°. *Anal.* Calcd. for $C_{21}H_{23}O_7N_4Cl$: 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.), $NaBH_4$ (0.46 g.) and tetrahydrofuran (THF) (35 ml.) was added a solution of BF_3-Et_2O (2.3 g.) in THF (8 ml.) at 5~10° under N_2 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 H_2O (2 ml.) to decompose an excess of BH_3. After addition of 3*N* NaOH (6 ml.) and 30% H_2O_2 (6 ml.) (during 1.5 hr.) the mixture was stirred at room temperature for 3 hr., filtered from inorganic material, extracted with Et_2O and dried (K_2CO_3). Evaporation of Et_2O left a paste (1.9 g.) which was dissolved in Et_2O and extracted repeatedly with 5% HCl. The extracts were basified with K_2CO_3, extracted with Et_2O, dried and evaporated to give a crystalline residue (0.4 g.), m.p. 89~93°. Analytical sample crystallized from Et_2O 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 methoiodide-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 methoiodide-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 : λ_{max}^{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 λ_{max}^{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 underr educed 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.

The authors with to express their appreciations to Dr. Everette L. May, Chief, Section on Medicinal Chemistry, National Institutes of Health, U.S.A. for providing encouragement and useful suggestion during the course of this work. They also thank Dr. Norio Sugimoto for his interest in this work, Dr. Keishi Kotera for infrared determinations, and Mrs. Fumiko Hisamichi and Mr. Takeo Kono for microanalyses.

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.