

inhibiting materials such as eserine (10^{-3} mol.), prostigmin (10^{-3} mol.), DFP (10^{-3} mol.) must cause the complete inhibition of AChE on the tongue, however no increase in impulse was observed. On the contrary bitter substances were applied after the application of such ChE inhibiting materials yields the somewhat increment in the number of impulse than the single application of bitter substances.⁷⁾ These results are compatible with the report of Landgren, Liljestrand and Zotterman.⁴⁾

Based on these results it is assumed that the bitter substance stimulates the taste buds and liberate the active ACh from receptor. Resulted active ACh produce the impulse in the nerve and transport the taste. On the other hand the bitter substance inhibits AChE in taste bud simultaneously and this caused the reduction of the capacity decomposing ACh.

It would be premature to conclude the definite mechanism of the bitter transmission, so the further electrophysiological experiment is now under investigation.

The author is grateful to Dr. K. Okazaki for his valuable advices and encouragements throughout this work. Thanks are also due to Dr. H. Ozawa and Dr. M. Uchiyama of this institute for his kind advices.

Summary

A marked decrease in impulse count which is produced by bitter substances when tongue (frog) was pretreated with AChE. It was assumed that there is a close relationship between AChE and the sensation of bitter taste. Factors affecting the strength and durability of bitter taste were discussed.

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7) K. Sakai : Unpublished data.

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159. Hiroshi Kugita and Mikio Takeda : Syntheses of Morphine-like Structures. II.*¹ 2'-Methoxy-9-hydroxymethyl-2,5-dimethyl-6,7-benzomorphan.

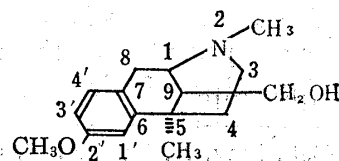
(Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.*²)

In a previous paper*¹ it was described that hydroboration of 9-methylene-2,5-dimethyl-6,7-benzomorphan with diborane followed by hydrogen peroxide oxidation produces stereospecifically the 9 β -hydroxymethyl derivative.*³ With such a reaction the corresponding 2'-methoxy compound (I) was expected to provide a new benzomorphan derivative as analgesics.

*¹ Part I : This Bulletin, 11, 986 (1963).

*² Kashima-cho, Higashiyodogawa-ku, Osaka (釘田博至, 武田幹男).

*³ The hydroxymethyl group is oriented toward nitrogen, *trans* to the 5-methyl group.



Dehydration of 2'-methoxy-9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan¹⁾ with thionyl chloride in the presence of a catalytic amount of pyridine²⁾ gave the 9-methylene derivative (II), a rearrangement product (III) and two other minor products, one of which was shown to be a monochloro derivative. A considerable amount of tar was also

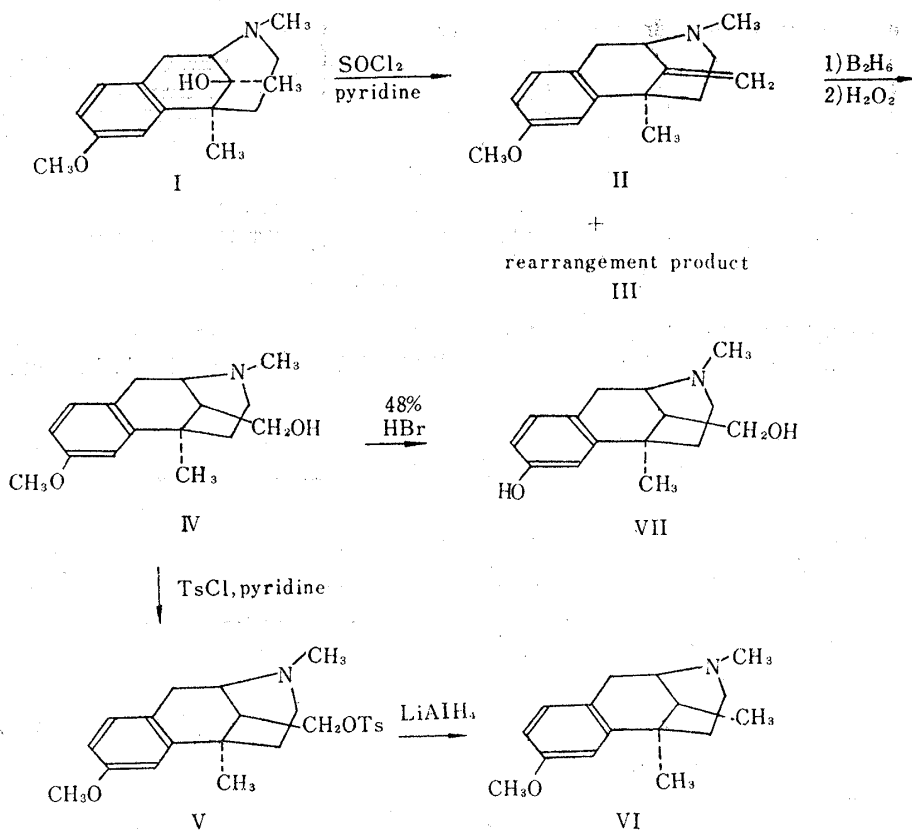


Chart 1.

formed by this reaction. The reaction time and temperature were examined and a moderate yield of II was achieved by adding thionyl chloride and pyridine to I below 5°, and stirring at this temperature for 6 hours then at room temperature (25~30°) for 24 hours, finally at 45° for 30 hours, affording II in 50% yield with 9~12% yield of III and 1~3% yield of the two minor products. The dehydrating reagents were also investigated for further improvement of the yield. Thionyl chloride (1.7 moles) and an excess of pyridine as solvent gave a clear-cut result; the yield of distillable base amounted to 92% and this crude base was shown to be a 55:45 mixture of II and III by gas chromatography. The rearrangement product (III) produced concomitantly under all conditions was shown to have the same molecular formula as that of II. Presence of either the terminal methylene or the benzene-conjugated double bond in III was ruled out by the infrared and ultraviolet spectral data. A speculation was made previously for the structure of rearrangement product of the demethoxy analogue.*¹ However this appeared to be inappropriate for the present case and detailed studies for the elucidation of structure of III will be discussed in a later communication.

Reaction of II with diborane in tetrahydrofuran followed by oxidation with alkaline hydrogen peroxide in the usual manner gave the 9-hydroxymethyl derivative (IV). The β -orientation of the hydroxymethyl group was established by converting IV to the

1) E. L. May, H. Kugita : J. Org. Chem., **26**, 188 (1961).

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

p-toluenesulfonate (V) and then to the known 9 β -methyl derivative (VI).^{3,4)} The 9 β -hydroxymethyl derivative was demethylated to give the 2'-hydroxy derivative (VII).

Experimental^{*4}

Dehydration of 2'-Methoxy-9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I)—a) SOCl_2 (110 ml.) and pyridine (2.7 ml.) were added to a cooled solution (0–3°) of I (13.5 g.) in CHCl_3 (20 ml.) and the mixture was stirred at that temperature for 4 hr., at room temperature for 20 hr., then at 40° for 40 hr. The solution was concentrated under reduced pressure, the residue was decomposed with ice-water, basified with NH_4OH and extracted with Et_2O . Evaporation of Et_2O and distillation of the residue gave a colorless oil (8.7 g.), b.p._{0.5} 128–140°, which was shown to be the mixture of 4 components in a ratio of 75.4:15.7:5.2:3.7 by gas chromatography analysis. The crude base was converted to the hydrochloride and recrystallized from $\text{EtOH-Et}_2\text{O}$ to give $\text{II}\cdot\text{HCl}$ (5.8 g.), m.p. 250–253° (40% yield based on I). IR $\lambda_{\text{Nujol}}^{\text{max}}$ μ : 10.7 ($=\text{CH}_2$). Picrate: Yellow needles ($\text{EtOH-Me}_2\text{CO}$), m.p. 142–144°. Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{O}_8\text{N}_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.04; H, 5.07; N, 11.45.

The mother liquor was concentrated, the residue was dissolved in H_2O , basified with NH_4OH and extracted with Et_2O . The recovered free base was converted to the picrate and recrystallized from $\text{EtOH-Me}_2\text{CO}$ to give $\text{III}\cdot\text{picrate}$ (1.7 g., 7% yield from I), yellow plates, m.p. 143–146°. Admixture with $\text{II}\cdot\text{picrate}$ depressed the melting point. Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{O}_8\text{N}_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.97; H, 4.99; N, 11.61. Two other picrates, m.p. 167–168° (yellow plates from EtOH) and m.p. 203–205° (yellow plates from Me_2CO) were obtained from the mother liquor. The latter was analyzed for a monochloro derivative. Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{O}_8\text{N}_4\text{Cl}$: C, 51.92; H, 4.95; N, 11.01; Cl, 6.97. Found: C, 51.66; H, 4.92; N, 11.01; Cl, 7.06.

b) A solution of I (17 g.) in pyridine (140 ml.) was added during 1.5 hr. to a mixture of SOCl_2 (13.6 g.), pyridine (40 ml.) and CHCl_3 (120 ml.) at 1–3°, the mixture was stirred at that temperature for 3 hr., then at room temperature for 40 hr. The reaction mixture was worked up as mentioned previously. Distillation of the product gave a crude base (14.5 g., 92%) which was a mixture of II and III in a ratio of 55:45 as shown by gas chromatography analysis. The crude base was purified as mentioned before to give $\text{II}\cdot\text{HCl}$ (43% based on I) and $\text{III}\cdot\text{picrate}$ (24%).

***dl*-2'-Methoxy-9 β -hydroxymethyl-2,5-dimethyl-6,7-benzomorphan (IV)**— $\text{BF}_3\cdot\text{Et}_2\text{O}$ (3.05 g.) was added to a boiling mixture of NaBH_4 (0.62 g.) and tetrahydrofuran (THF) (15 ml.) over a period of 1 hr. and B_2H_6 was introduced into a flask containing II (1 g.) and THF (30 ml.) at 12–17° under N_2 stream. After the completion of the B_2H_6 introduction the reaction mixture was kept at room temperature for 1.5 hr., then decomposed with H_2O , added with 3*N* NaOH (2.5 ml.) then with 32% H_2O_2 (1.5 ml.) gradually. The mixture was stirred at room temperature for 1 hr., filtered, diluted with H_2O and extracted with Et_2O . The ethereal solution was extracted with 10% HCl ,^{*5} basified with K_2CO_3 , extracted with Et_2O , dried and evaporated to give an oil (465 mg.), which was purified as the hydrobromide. $\text{IV}\cdot\text{HBr}$ (425 mg., 30.2%) was obtained in colorless needles (EtOH), m.p. 216–218°. Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_2\text{NBr}$: C, 56.14; H, 7.07; N, 4.09. Found: C, 55.90; H, 7.01; N, 4.17. IR $\lambda_{\text{Nujol}}^{\text{max}}$ μ : 3.0. Picrate: Yellow plates (Me_2CO), m.p. 201–203 (decomp.). Free base: Colorless plates (hexane), m.p. 95–97°. Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.70; H, 8.78; N, 5.49. IR $\lambda_{\text{Nujol}}^{\text{max}}$ μ : 3.13.

***dl*-2'-Methoxy-9 β -hydroxymethyl-2,5-dimethyl-6,7-benzomorphan *p*-Toluenesulfonate (V)**— TsCl (80 mg.) was added to IV (78 mg.) in dry pyridine (0.7 ml.) under cooling, the mixture was kept in a refrigerator for 3 days, diluted with ice-water, extracted with Et_2O , dried and evaporated. The residue was dissolved in Et_2O , treated with picric acid and the picrate was filtered. Yellow plates (Me_2CO), m.p. 171.5–173°; yield, 125 mg. Anal. Calcd. for $\text{C}_{20}\text{H}_{31}\text{O}_{11}\text{N}_4\text{S}$: C, 54.11; H, 4.85; N, 8.71; S, 4.98. Found: C, 54.00; H, 5.05; N, 9.01; S, 5.02.

***dl*-2'-Methoxy-2,5,9 β -trimethyl-6,7-benzomorphan (VI)**—V (380 mg.), LiAlH_4 (200 mg.) and Et_2O (40 ml.) were refluxed for 70 hr., H_2O was added to the mixture, filtered from inorganic material and the ethereal solution was dried and evaporated. The residue was converted to the hydrochloride (150 mg.), m.p. 222–226° (decomp.), and recrystallized from $\text{EtOH-Et}_2\text{O}$ in colorless needles, m.p. 228–231° (decomp.). IR spectrum of the hydrochloride was identical with the authentic sample.^{*6}

^{*4} Melting points are uncorrected.

^{*5} The neutral portion obtained from the ethereal solution gave, after standing for a month, a salt-like substance which was soluble in H_2O . Addition of K_2CO_3 to the water solution separated base which was composed of IV and very small amount of α -isomer of IV.

^{*6} We thank Dr. E. L. May for providing us with the sample.

3) S. Saito, E. L. May: *J. Org. Chem.*, **27**, 1087 (1962).

4) S. E. Fullerton, E. L. May, E. D. Becker: *Ibid.*, **27**, 2144 (1962).

dl-2'-Hydroxy-9 β -hydroxymethyl-2,5-dimethyl-6,7-benzomorphan (VII)—IV·HBr (300 mg.) was refluxed with 48% HBr (5 ml.) for 20 min., concentrated under reduced pressure, the residue was dissolved in H₂O, basified with NH₄OH and filtered. The crude base was recrystallized from MeOH to give VII (150 mg.), m.p. 210~216°. Analytical sample crystallized in colorless plates (MeOH), m.p. 218~220° (decomp.). *Anal.* Calcd. for C₁₅H₂₁O₂N: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.67; H, 8.57; N, 5.80. Hydrobromide: Colorless needles (EtOH), m.p. 246~248° (decomp.).

Summary

dl-2'-Methoxy-9 β -hydroxymethyl-2,5-dimethyl-6,7-benzomorphan was synthesized by hydroboration of 2'-methoxy-9-methylene-2,5-dimethyl-6,7-benzomorphan. The β -orientation of the hydroxymethyl group was established by converting IV to the known 9 β -methyl derivative.

Dehydration of 2'-methoxy-9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) to the 9-methylene derivative (II) produced also a rearrangement product isomeric with II.

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160. Hiroshi Kugita and Mikio Takeda: Syntheses of Morphin-like Structures. III.*¹ Stereochemical Control of Addition of Borane to 9-Methylenebenzomorphan.

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In our previous papers,^{*1, 1)} that addition of borane to 9-methylene-6,7-benzomorphan followed by hydrogen peroxide oxidation produced selectively one of the two possible stereoisomers, *i.e.* the 9 β -hydroxymethyl derivative^{*3} was reported. It was considered probable that the electrophilic addition of borane to nitrogen would take place first and another borane add to the double bond from the less hindered α side to give the 9 β derivative.^{*4} This interpretation has led to the idea that under such conditions that prevent the first addition of borane to the nitrogen, the hydroboration with one mole of borane would yield isomeric 9 α derivative. Realization of this stereochemical control would

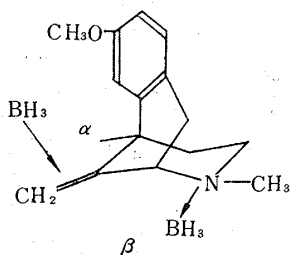


Chart 1.

*¹ Part II: This Bulletin, 12, 1163 (1964).

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*³ The hydroxymethyl group is oriented toward nitrogen.

