

161. Hiroshi Kugita and Mikio Takeda : Syntheses of Morphine-like Structures. IV.*¹ Further Studies on Addition of Borane to 9-Methylenebenzomorphan.

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

The preceding paper*¹ described that when the 9-methylenebenzomorphan-borane was heated at 140~150°, dissociation of the amine-borane occurred and the released borane reacted with the double bond of the molecule affording the 9 α substituted derivative. This reaction, however, produced also the 9 β derivative in a considerable amount. To interpret this concomitant formation of the 9 β derivative one could more safely assume the competitive addition of borane to the free amine (reaction path 2) and to the amine-borane (reaction path 1) than to assume the addition of borane to the free base from α side.

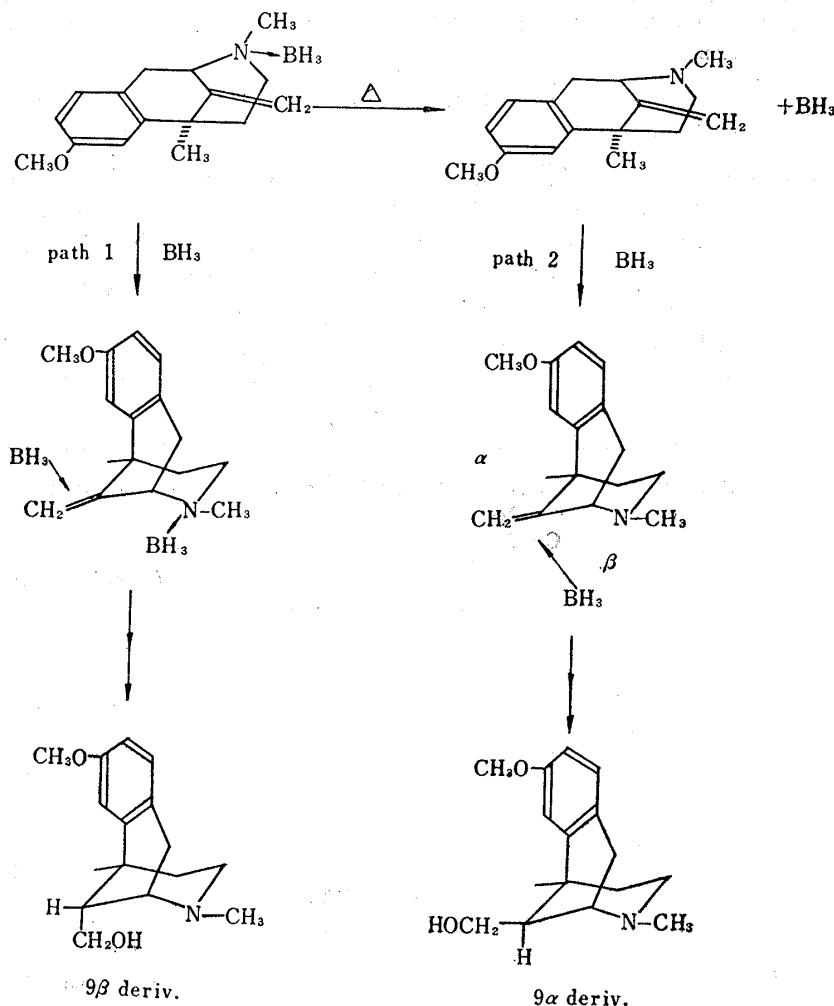


Chart 1.

*¹ Part III: This Bulletin, 12, 1166 (1964).

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A neutral by-product, which was isolated from the reaction mixture and shown to have the structure A,^{*1} was conceivably derived by the reaction path 1 *via* the feasible intermediate (B) which is considered to lose boron hydrides attached to the nitrogen by the continued heating.

It was considered relevant this time to examine the intermediates under the usual hydroboration condition. The free amine (I) was hydroborated and oxidized as described previously.¹⁾ Isolation of a neutral fraction^{*3} and purification of it gave a crystalline substance which showed the same melting point (with decomposition) as that of A. The identity of these substances was further established by infrared spectral comparison. This substance was recovered unchanged when submitted again to oxidation, but after heating with acetic acid-dioxane it was easily oxidized to the 9 β -hydroxymethyl derivative.^{*4} A suspicion may arise here concerning the proposed mechanism that the addition

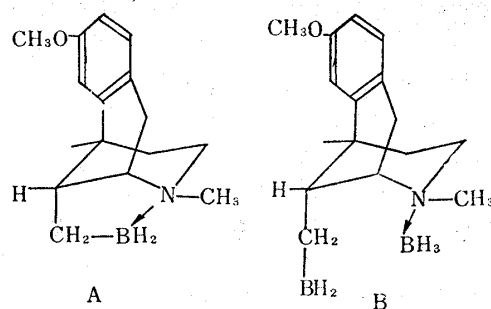


Chart 2.

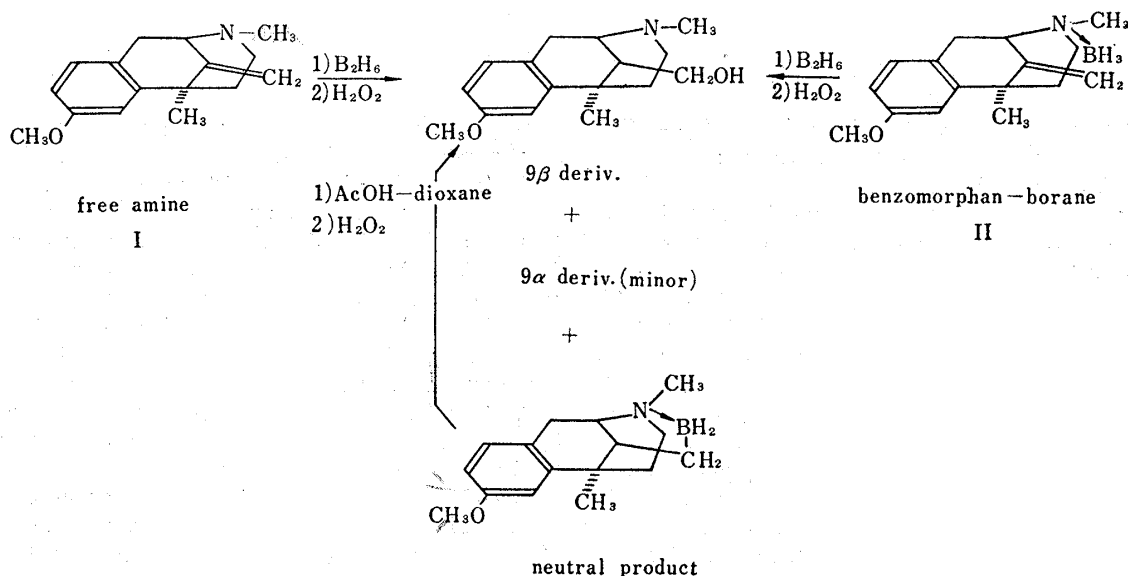


Chart 3.

of borane to the nitrogen would be the first step for the formation of 9 β derivative, as the neutral product (A) seemed to be not coming from B since there was no heating in the hydroboration stage. In order to make the matter clear the free base (I) was treated with one mole of borane by the usual method. The benzomorphan-borane (II) was obtained from the reaction mixture along with some recovery of I. This was in parallel with result obtained by the reaction of I with one mole of pyridine-borane in benzene at 70°^{*1} and clearly indicates that the first one mole of borane adds to the nitrogen without any addition to the double bond. Similar hydroboration of II followed by the oxidation also gave the neutral product (A) along with the basic products in a comparable

^{*3} In the previous experiment there was also obtained a neutral substance, which changed after a month's storage in the air to a basic compound which consisted mostly of the 9 β -hydroxymethyl derivative.¹⁾

^{*4} A boronic acid structure was proposed as an intermediate of this conversion. See reference *1.

1) H. Kugita, M. Takeda: This Bulletin, 12, 1163 (1964).

manner. It may be likely therefore that the alkylborane group of once formed B expelled boron hydrides on the nitrogen probably because of steric crowding.

It has been known²⁾ that hydroboration of hindered olefines gives a mixture of alkylboranes, mono, di, and the like. There must have existed more than one alkylborane in the present case too, and it may be safe to assume that there was one (s) susceptible to oxidation leading to the 9 β -hydroxymethyl derivative while, on the other hand A was recovered unchanged by the oxidation.*⁵ In the hope to isolate the alkylboranes, the hydroboration mixture was chromatographed on silica gel but A was the only isolable product in crystalline form.

To sum up our studies on the addition of borane to 9-methylenebenzomorphane it is concluded that hydroboration with excess diborane gives almost exclusively the 9 β derivative, addition of boron hydrides to the nitrogen being the first step. Otherhand, under such a condition that nullifies the borane-nitrogen coordination, borane adds to the double bond from the less hindered β side to give isomeric 9 α derivative. May and others reported the stereochemical control of addition of organo-metallo compounds³⁾ and hydrogen⁴⁾ to 9-oxobenzomorphane, and of hydrogen to 9-methylenebenzomorphane.⁵⁾ The present study provides an example of stereochemical control of the introduction of 9-substituents into benzomorphans.

Experimental*⁶

Hydroboration of the Free Amine (I)—The hydroboration followed the procedure described in the previous paper;¹⁾ an excess of diborane generated by the reaction of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (5.01 g.) and NaBH_4 (1.02 g.) in THF was introduced into a solution of I (1.3 g.) in THF (40 ml.) at 15–17° under N_2 atmosphere. After completion of the diborane introduction the reaction mixture was allowed to stand at room temperature for 4 hr., then treated with 3N NaOH (1.95 ml.) and 30% H_2O_2 (2.4 ml.) and stirred at room temperature for 20 hr. At the end of the time 3N NaOH (3 ml.) and 30% H_2O_2 (2.4 ml.) were added and the mixture was stirred for another 20 hr. The reaction mixture was extracted with Et_2O and the ethereal solution was extracted with 10% HCl, basified with K_2CO_3 and extracted with Et_2O . The basic portion (420 mg.) was chromatographed over Al_2O_3 . Elution with $\text{Et}_2\text{O}\text{--MeOH}$ (98:2) gave the 9 β -hydroxymethyl derivative (380 mg., 27.2%), m.p. 89–91°. Further elution with $\text{Et}_2\text{O}\text{--MeOH}$ (95:5) gave the 9 α -hydroxymethyl derivative (15 mg., 1%), m.p. 148–151°. The original ethereal solution was evaporated, the residue (900 mg.) was chromatographed over Al_2O_3 and eluted with benzene to yield a neutral product, m.p. 134–137° (600 mg.) which was identified with A*¹ by IR spectral comparison.

The neutral product (500 mg.) was refluxed in AcOH (7 ml.) and dioxane (15 ml.) for 40 min., the solvent was distilled and Et_2O was added to the residue. The ethereal solution was extracted with 10% HCl, basified with K_2CO_3 and extracted with Et_2O . The base in THF (10 ml.) was treated with 3N NaOH (1 ml.) and 30% H_2O_2 (1 ml.) and stirred for 20 hr. Work-up of the mixture in the usual way gave the 9 β -hydroxymethyl derivative (360 mg.), m.p. 90–92°.

Reaction of I with One Mole of Boron Hydrides—Diborane generated from the reaction of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (912 mg.) and NaBH_4 (132 mg.) in THF (3 ml.) was introduced into a reaction flask containing I (1.13 g.) and THF (20 ml.). After completion of the introduction the reaction mixture was allowed to stand for 5 hr., THF was distilled, petr. ether (20 ml.) was added to the residue and filtered to give the benzomorphane-borane (II) (300 mg., 25%), m.p. 123–128° (decomp.). Recrystallization from (iso-Pr)₂O gave colorless plates, m.p. 135–136°, which was identified with the sample obtained by the reaction of I with pyridine-borane*¹ by IR spectral comparison. The petr. ether solution was extracted with 10% HCl. The neutral layer was evaporated to give an additional amount of II (60 mg., 5%), m.p. 133–135° (decomp.). The acid solution was basified with K_2CO_3 , extracted with Et_2O , dried, evaporated and the residue was converted to the hydrochloride. I·HCl, m.p. 252–254° (860 mg., 66%) was recovered.

*⁵ Intramolecular coordination between the boron and the nitrogen might be responsible for this property.

*⁶ Melting points are uncorrected.

2) H. C. Brown: "Hydroboration," W. A. Benjamin, Inc., New York, 1962.

3) E. L. May, H. Kugita: J. Org. Chem., **26**, 188 (1961); E. L. May, H. Kugita, J. H. Ager: *Ibid.*, **26**, 1621 (1961); S. Saito, E. L. May: *Ibid.*, **26**, 4536 (1961).

4) H. Kugita, E. L. May: *Ibid.*, **26**, 1954 (1961).

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

Hydroboration of the Benzomorphan-borane (II)—An excess of diborane was introduced into a solution of II (1.37 g.) in THF (30 ml.) in the same manner as described previously. The reaction mixture was oxidized and worked up in the like manner to give the 9 β -hydroxymethyl derivative (350 mg., 21.6%) along with the 9 α -hydroxymethyl derivative (20 mg., 1.4%). The neutral product weighed 350 mg., m.p. 126~132° and was identified with A by IR spectral comparison.

Attempted Isolation of Alkylborane Intermediates—I (1.2 g.) in THF (25 ml.) was hydroborated with an excess of diborane in the same manner as described previously. The reaction mixture was treated cautiously with H₂O to decompose excess diborane and extracted with Et₂O. Evaporation of dried Et₂O solution gave gum (1.25 g.) which was dissolved in benzene and chromatographed over a silica gel column. Elution with benzene-Et₂O (1:1) gave A (520 mg.), m.p. 130~133°. Other fractions failed to give crystalline product.

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Summary

The stereochemical course of the borane addition to 9-methylenebenzomorphan leading to the 9 β -hydroxymethyl derivative was further examined.

Formation of the intramolecular coordinated amineborane (A) was observed by the reaction of diborane with both the free amine (I) and the benzomorphan-borane (II). That the first one mole of boron hydrides adds to I at the nitrogen to give the amineborane (II) without addition to the double bond was also established. Isolation of intermediates in alkylborane stage was attempted.

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162. Yasuo Inubushi, Hisashi Ishii, Bompei Yasui, Takeshi Konita, and Takashi Harayama : Isolation and Characterization of Alkaloids of the Chinese Drug "Chin-Shih-Hu."*¹

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The Chinese drug "Chin-Shih-Hu" (Japanese name "Kin-Sekkoku") has been used as a tonic and antipyretic. There has been some uncertainty about the plant from which the drug was originally prepared but Kimura¹⁾ and Suzuki, *et al.*²⁾ reported that it was probably *Dendrobium nobile* LINDL.

With regard to its basic components Suzuki, *et al.*²⁾ reported that they isolated a new alkaloid from this drug, which they called dendrobine, m.p. 134°, $[\alpha]_D^{25}$ -51.5° (c=1.0, EtOH), in 1932. They also showed that dendrobine has the molecular formula C₁₆H₂₅O₂N,

*¹ A preliminary communication on the structure of dendrobine appeared in Yakugaku Zasshi, 83, 1184 (1963); for a full report, see Tetrahedron, 20, 2007 (1964). Cf. T. Okamoto, *et al.* : This Bulletin, 12, 506 (1964). Y. Hirata, *et al.* : Tetrahedron Letters, No. 2, 79 (1964).

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1) K. Kimura : Bulletin of the Shanghai Science Institute, 6, 1 (1936); *Ibid.*, 7, 11 (1937).

2) H. Suzuki, I. Keimatsu, K. Ito : Yakugaku Zasshi, 52, 1049 (1932); *Ibid.*, 54, 801 (1934).