***dl*-2′-Hydroxy-9β-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 H_2O, basified with NH_4OH 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 $C_{15}H_{21}O_2N$: 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-9β-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 9β-methyl derivative.

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

(Received June 12, 1964)

Chem. Pharm. Bull. 12(10)1166~1171 (1964)

UDC 615.783.19-012

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

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

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 9β-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 9β 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 9α derivative. Realization of this stereochemical control would

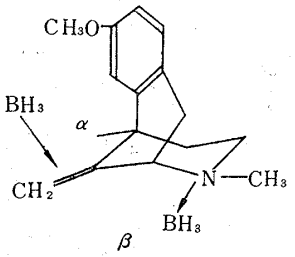
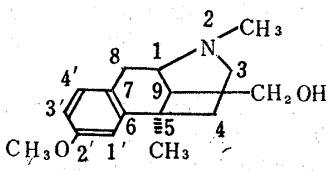


Chart 1.

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

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

*3 The hydroxymethyl group is oriented toward nitrogen.

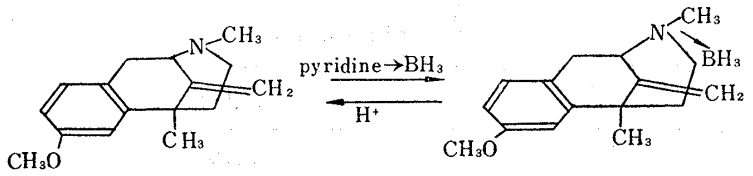


*4 It has been proposed that hydroboration proceeds from the less hindered side of the double bond. H. C. Brown, G. J. Zweifel: J. Am. Chem. Soc., **81**, 247 (1959). See also W. J. Wechter: Chem. & Ind. (London), **1959**, 294.

1) H. Kugita, M. Takeda: This Bulletin, **11**, 986 (1963).

ascertain the deduced reaction mechanism for the addition of borane to the 9-methylene-benzomorphan and, at the same time, provide the 9α-hydroxymethyl derivative now desired in connection with pharmacological interest.

Hydroboration with amino-boranes has been reported in several papers.[2] Ashby synthesized trialkylboranes by heating olefines with an amine-borane at 150~200° where dissociation of the amine-borane took place and the released borane added to the olefine.[3] Brown[4] carried out this reaction in benzene at its boiling temperature. In our



I II

Chart 2.

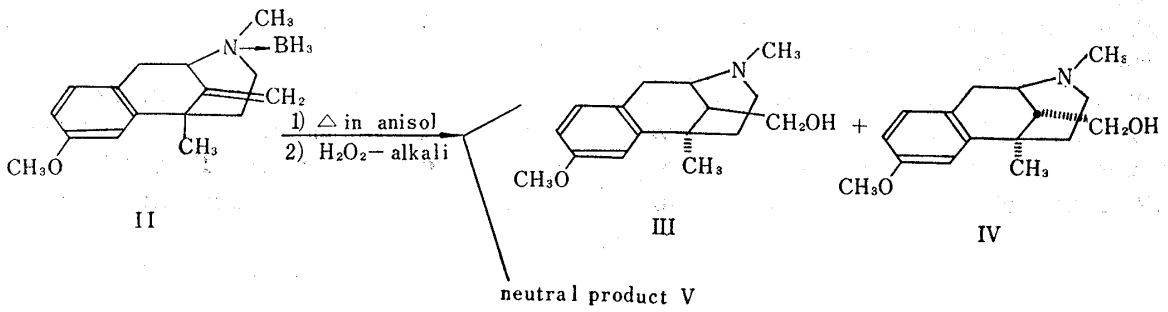
present study the hydroboration with amine-borane was first attempted. Reaction of I with one mole of pyridine-borane[5] in benzene[3] at 70° for 40 hours gave a crystalline product of m.p. 136~137° (decomp.) in 90% yield. Microanalysis showed that this substance has the empirical formula $C_{16}H_{24}ONB$ which corresponds to the addition product of BH_3 to I in a molar ratio 1:1. Infrared spectrum revealed the presence of terminal methylene at 930 cm^{-1} and showed absorptions at 2370 cm^{-1} and 2270 cm^{-1} attributable to B-H. Position of the latter two bands suggested that the boron atom coordinated with the nitrogen.[6] The structure (II) was therefore assigned to the compound. II yielded I in quantitative yield when heated in acetic acid-dioxane. Although the formation of II was not first expected the use of this amine-borane as borane-generating source was now considered, and thermal dissociation of II in appropriate solvent was examined to effect possible internal hydroboration.[7]

An anisole solution*5 of II was heated in a sealed tube at 140~150° for one hour when dissociation of the amine-borane apparently occured. The mixture was oxidized with hydrogen peroxide in the usual manner and the basic product was chromatographed over alumina. Results are presented in Table I. Amount of the solvent used was one and half to two times of the amount of II in the experiment 1) and 3) and one hundred times dilution was employed in the experiment 2). Increase in the yield of 9α-hydroxymethyl derivative (IV) comparing to 1) was seen in 2) and this was interpreted due partly to the increased possibility of intramoleculer addition of the released borane to the double bond. The experiment 3) was carried out in the presence of two moles of the free base (I) in the normal dilution. A great increase in the yield of IV was seen in this experiment showing that the 9α derivative must have been formed by the addition of borane to the double bond of free base.

*5 The use of anisole as solvent of hydroboration was without precedent. Less accessibility to diglyme forced us to use a substitute. Anisole was found satisfactory in our experiment with its high boilling point and relative inertness to diborane.

2) H.C. Brown: "Hydroboration", 100 (1962), W.A. Benjamin, Inc., New York.
3) E.C. Ashby: J. Am. Chem. Soc., **81**, 4791 (1959).
4) H.C. Brown, K.J. Murray, L.J. Murray, J.A. Snover, G. Zweifel: *Ibid.*, **82**, 4233 (1960).
5) M.D. Taylor, L.R. Grant, C.A. Sands: *Ibid.*, **77**, 1506 (1955).
6) B. Rice, R.J. Galiano, W.J. Lehmann: J. Phys. Chem., **61**, 1222 (1957); H.C. Brown: "Hydroboration", 179 (1962), W.A. Benjamin, Inc., New York.
7) Adams and Poholsky observed an uncontrolled reaction while heating dimethylallylamine-borane (this was not characterized) to 120°. R.M. Adams, F.D. Poholsky: Inorg. Chem., **2**, 640 (1963).

Table I.

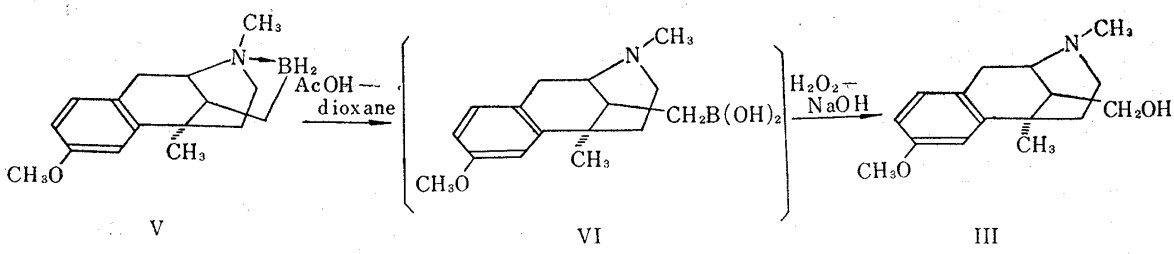


II III IV

		Ⅲ(%)	Ⅳ(%)
1) Ⅱ	⟶	26.5	9.2
2) Ⅱ (100-fold dilution)	⟶	34.6	17.4
3) Ⅱ + 2 moles I	⟶	28[a)]	35.5[a)]

a) Based on Ⅱ

In these experiments there was always obtained a substance which was insoluble in diluted hydrochloric acid and readily separated from the basic product in 30~40% yield.*6 This crystallized upon standing and was analyzed for the molecular formula $C_{16}H_{24}ONB$ after recrystallization from isopropylether. Infrared spectrum indicated the presence of nitrogen-coordinated B-H by the absorption at 2300 cm^{-1} and 2400 cm^{-1} but not the presence of either hydroxyl or terminal methylene. This substance was assigned the structure (Ⅴ)*7 and it was considered probable that survival of this compound by oxidation is attributed to the presence in its molecule of the intramolecular coordination between alkylborane and nitrogen atom.*8 Heating of Ⅴ in acetic acid-dioxane gave a basic compound whose infrared spectrum showed a strong band at 1360 cm^{-1} indicating



Ⅴ Ⅵ Ⅲ

Chart 3.

the presence of B-O[8)] and OH band at 3400 cm^{-1}, both suggesting the boronic acid structure[9)] (Ⅵ). Ⅵ was oxidized easily by the usual method to give the 9β-hydroxymethyl derivative (Ⅲ) in good yield.

Direct hydroboration of I with pyridine-borane was again studied, this time by heating at 145~150° for one hour an anisole solution of I and an equimolar amount of pyridine-borane. The 9α-hydroxymethyl derivative (Ⅳ) was obtained in a comparable yield

*6 Formation of a neutral product was also noticed by hydroboration of the free base with excess diborane. See reference *1.

*7 Synthesis of a five-membered heterocycle of this type appeared recently in the literature. See reference 7).

*8 Molecular models show that this intramolecular coordination is impossible with the isomeric 9α-alkylborane derivative.

8) L. J. Bellamy, W. Gerrard, M. F. Lappert, R. L. Williams: J. Chem. Soc., 1958, 2412.

9) M. F. Lappert: Chem. Rev., 56, 959 (1956).

(22.9%) after oxidation. In this case, too, high dilution as well as the free base (I) in excess would have increased the yield of Ⅳ.

Isomerisations of alkylboranes have been reported in the literature. Braun and Fisher[10] observed an interesting isomerisation at high temperature; oxidation of the hydroboration product of β-pinene gave *cis*-myrtanol, whereas oxidation after heating of the alkylborane yielded the isomerised product, *trans*-myrtanol. To see if such an isomerisation of alkylborane exsisted in the present case, the hydroboration product of

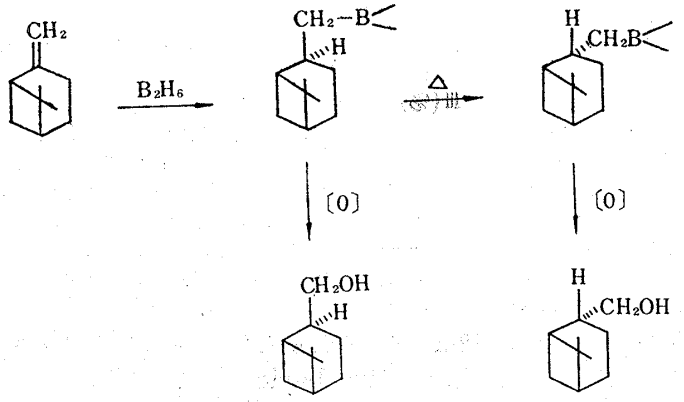


Chart 4.

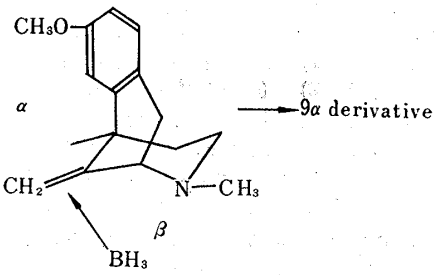


Chart 5.

I with diborane*[1] was heated in anisole at 140~150° for one hour and oxidized in the usual manner. The 9β-hydroxymethyl derivative (Ⅲ) was produced almost exclusively as in the normal case and this indicates that the 9α isomer (Ⅳ) obtained in the present study was not formed by isomerisation of the 9β-alkylborane, but formed by the addition of borane to the double bond from the less hindered β side as was predicted.

The 9α-hydroxymethyl derivative (Ⅳ) was converted to the 9-methyl derivative (Ⅷ) *via* the *p*-toluenesulfonate (Ⅶ). Ⅷ was identified with *dl*-2′-methoxy-2,5,9α-trimethyl-6,7-benzomorphan[11] thus proving the α-orientation of the hydroxymethyl group in Ⅳ. 2′-Hydroxy derivative was prepared from Ⅳ for screening analgesic effect.

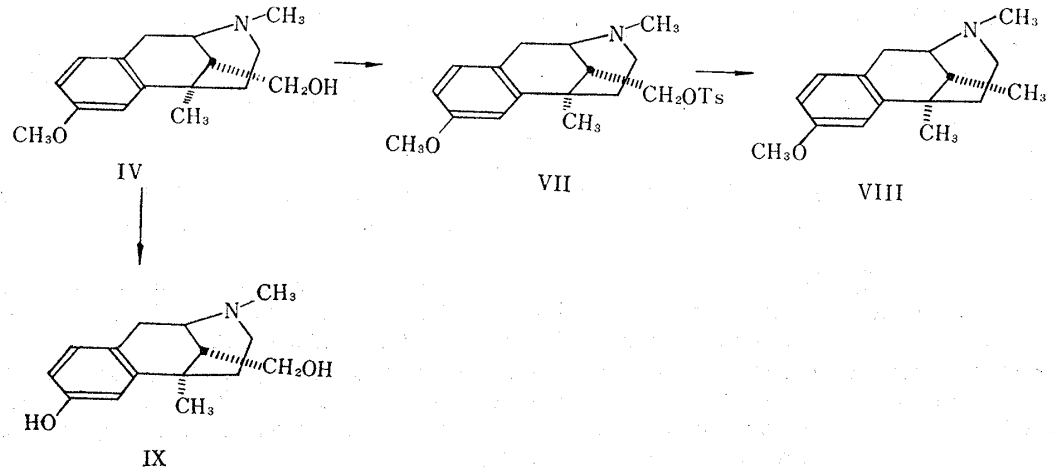


Chart 6.

10) J.C. Braun, G.S. Fisher : Tetrahedron Letters, **21**, 9 (1960).
11) E.L. May, J.H. Ager : J. Org. Chem., **24**, 1432 (1959). We thank Dr. May for providing us with a sample of the derivative.

Experimental*9

2′-Methoxy-9-methylene-2,5-dimethyl-6,7-benzomorphan-borane (II)——A mixture of I (2.86 g.), pyridine-borane (1.26 g.) and anhyd. benzene (14 ml.) was heated under N_2 atmosphere in a sealed tube at 70～80° for 40 hr. The mixture was dissolved in Et_2O (50 ml.), washed twice with H_2O, dried over K_2CO_3 and evaporated. The residue was recrystallized from benzene-petr. ether to give colorless rods (2.72 g., 90%), m.p. 133～135° (decomp.). *Anal.* Calcd. for $C_{16}H_{24}ONB$: C, 74.72; H, 9.41; N, 5.45. Found: C, 75.02; H, 9.09; N, 5.27. IR cm^{-1}: ν_{B-H} 2270, 2370; $\nu_{>=CH_2}$ 930.

A mixture of II (250 mg.), AcOH (3 ml.) and dioxane (6 ml.) was refluxed for 40 min. The mixture was concentrated under reduced pressure, diluted with H_2O, basified with K_2CO_3, extracted with Et_2O, dried and evaporated. The residue was converted into the hydrochloride, m.p. 250～252°, IR spectrum of which was superimposable with that of I·HCl; yield was quantitative.

Internal Hydroboration of II——a) A mixture of II (1.5 g.) and anisole (3 ml.) was heated in a sealed tube under N_2 atmosphere at 140～150° for 1 hr. THF (15 ml.), 3*N* NaOH (1.95 ml.) and 30% H_2O_2 (2.4 ml.) were added and the mixture was stirred at room temperature for 20 hr. At the end of the time THF (20 ml.), 3*N* NaOH (3 ml.) and 30% H_2O_2 (3 ml.) were added and stirred for additional 20 hr. at room temperature. The mixture was diluted with H_2O, extracted with Et_2O, washed with H_2O, the ethereal solution was extracted with 10% HCl, basified with K_2CO_3 and extracted with Et_2O. Evaporation of Et_2O gave residue (770 mg.) which was dissolved in benzene and chromatographed over Al_2O_3. Elution with Et_2O-MeOH (98:2) and recrystallization from hexane gave the 9β-hydroxymethyl derivative (III) (390 mg., 25.6%), m.p. 90～93°.*1 Further elution with Et_2O-MeOH (95:5) gave after recrystallization from benzene-petr. ether the 9α-hydroxymethyl derivative (IV) (140 mg., 9.2%), colorless rods, m.p. 158～159°. *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.31; H, 8.72; N, 5.35. IR: ν_{OH} 3300 cm^{-1}. Hydrobromide: Colorless plates (Me_2CO-EtOH-Et_2O), m.p. 194～197°. *Anal.* Calcd. for $C_{16}H_{24}O_2NBr$: C, 56.14; H, 7.07; N, 4.09. Found: C, 56.35; H, 6.86; N, 4.50. Picrate: Yellow plates (Me_2CO), m.p. 227～229° (decomp.).

Evaporation of the original Et_2O solution (neutral portion) gave a gum (770 mg.) which crystallized on standing. Recrystallization from (iso-Pr)$_2O$ gave colorless plates, m.p. 134～136° (decomp.). IR cm^{-1}: ν_{B-H} 2300, 2400. *Anal.* Calcd. for $C_{16}H_{24}ONB$ (V): C, 74.54; H, 8.83; N, 5.31; mol. wt., 257.1. Found: C, 74.72; H, 9.41; N, 5.45; mol. wt., 246.5 (in benzene).

b) A mixture of II (1.5 g.) and anisole (300 ml.) was heated as described above. The solution was concentrated under reduced pressure and oxidized in a similar way to that mentioned previously. Al_2O_3 chromatography of the basic portion gave III (527 mg., 34.6%) and IV (265 mg., 17.4%). The neutral portion weighed 500 mg. which likewise crystallized upon rubbing, m.p. 133～136°.

c) A mixture of II (1.64 g.), the free base (I) (3.11 g.) and anisole (6 ml.) was heated and oxidized as mentioned previously. Work-up in the usual way yielded III (460 mg., 28%) and IV (590 mg., 35.5%). I was recovered as the hydrochloride, m.p. 250～252° (2.3 g.) from the basic portion. The neutral portion weighed 750 mg.

Conversion of the Neutral Product (V) to III——V (200 mg.) in AcOH (3 ml.) and dioxane (6 ml.) was refluxed for 40 min., concentrated *in vacuo*, the residue was dissolved in Et_2O, extracted with diluted HCl, basified with K_2CO_3 and extracted with Et_2O. The basic portion (140 mg.) was converted to the hydrochloride and recrystallized from iso-PrOH-Et_2O to give colorlesss plates, m.p. 194～196° (decomp.). IR cm^{-1}: ν_{OH} 3300 (v.s.); ν_{B-O} 1350 (v.s.). *Anal.* Calcd. for $C_{16}H_{25}O_3NBCl$ (VI): N, 4.30; Cl, 10.89. Found: N, 4.13; Cl, 10.76.*10

Free base recovered from the hydrochloride melted at 120～125°. Recrystallization of the crude base was unsuccessful. IR cm^{-1}: ν_{OH} 3300～3400 (broad); ν_{B-O} 1360. This base reduced an ammoniacal $AgNO_3$ solution.[12]

To the free base (VI) (190 mg.) in THF (5 ml.) were added 3*N* NaOH (0.4 ml.) and 30% H_2O_2 (0.4 ml.) and the mixture was stirred for 20 hr., extracted with Et_2O, washed with H_2O, dried and evaporated. The residue was recrystallized from hexane to give III (120 mg.), m.p. 94～96°.

Direct Hydroboration with Pyridine-borane——A mixture of I (1.3 g.), pyridine-borane (570 mg.) and anisole (10 ml.) was heated in a sealed tube under N_2 atmosphere at 140～150° for 1 hr. The mixture was oxidized in the usual manner and worked up as previously mentioned in an analogous case. III and IV were obtained in 38.7*11 and 22.9% yield respectively.

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*9 Melting points are uncorrected.

*10 Analysis for C, H in the ordinary way gave an unsatisfactory result. Refer to: H. R. Snyder, J. A. Kuck, J. R. Johnson: J. Am. Chem. Soc., **60**, 105 (1938).

*11 This includes III obtained from the neutral portion by the method mentioned in the preceding paragraph.

12) The Reference cited in *10.

Attempted Isomerisation of alkylborane——I (1.3 g.) was hydroborated with diborane in THF in the same way as described in the previous paper.*1 THF was distilled *in vacuo* (N_2), anisole was added to the residue and the solution was heated under N_2 atmosphere in a sealed tube at 140~150° for 1 hr. The mixture was oxidized and worked up in the usual manner yielding III (300 mg., 21%), IV (15 mg., 1%*12) and the neutral product, m.p. 134~136° (1 g.).

***dl*-2′-Methoxy-9α-hydroxymethyl-2,5-dimethyl-6,7-benzomorphan Toluene *p*-Sulfonate (VII)**——A mixture of IV (78 mg.), TsCl (80 mg.) and pyridine (0.6 ml.) was kept in a refrigerator for 3 days, H_2O was added, extracted with Et_2O, dried over K_2CO_3 and evaporated. Picric acid-Et_2O was added to the residue and the picrate of VII was filtered, m.p. 158~162°; yield, 140 mg. An analytical sample crystallized from EtOH-Me_2CO in yellow plates, m.p. 164~166°. *Anal.* Calcd. for $C_{29}H_{31}O_{11}N_4S$: C, 54.11; H, 4.85; N, 8.71; S, 4.98. Found : C, 54.20; H, 4.97; N, 8.68; S, 4.87.

***dl*-2′-Methoxy-2,5,9α-trimethyl-6,7-benzomorphan (VIII)**——VII (400 mg.) recovered from the picrate was refluxed in Et_2O (60 ml.) with $LiAlH_4$ (250 mg.) for 40 hr. and worked up in the usual way. The basic portion was chromatographed over Al_2O_3 and purified as the hydrobromide, m.p. 234~235° (Me_2CO). This was identified with the authentic sample[11] by the melting point determination and IR spectral comparison.

***dl*-2′-Hydroxy-9α-hydroxymethyl-2,5-dimethyl-6,7-benzomorphan (IX)**——A solution of IV (680 mg.) in 48% HBr (8 ml.) was refluxed in an oil bath for 20 min., concentrated under reduced pressure, H_2O was added, basified with ammonia and the precipitates were filtered and dried. M.p. 208~212° (decomp.), 580 mg. An analytical sample crystallized in colorless plates (Me_2CO-MeOH), m.p. 211~212° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found : C, 72.93; H, 8.29; N, 5.70. IR : ν_{OH} 3160 cm^{-1}. Hydrochloride : Colorless needles (Me_2CO-MeOH-Et_2O), m.p. 168~171° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}O_2NCl$: C, 63.48; H, 7.81; N, 4.94. Found : C, 63.75; H, 7.78; N, 4.64.

Summary

The addition of borane to 9-methylenebenzomorphan at high temperature has been examined in the hope of clarifying stereochemical course of the hydroboration which gave selectively the 9β-hydroxymethyl derivative in the previous study.

Reaction of pyridine-borane with I in benzene at 70° gave the benzomorphan-borane (II) in high yield. Heating II in anisole followed by the oxidation gave the 9α-hydroxymethyl derivative (IV) along with the 9β isomer and a neutral product (V). The formation of 9α isomer was rationalized in terms of the dissociation of the amine-borane prior to the addition of borane to the double bond.

α-Orientation of the 9-hydroxymethyl group of IV was established by converting IV to the known *dl*-2,5,9α-trimethylbenzomorphan (VIII) *via* the toluene-*p*-sulfonate (VII).

(Received June 12, 1964)

*12 A close examination of the ordinary hydroboration of I with diborane also yielded very small amount of IV. See the following paper.