reaction was continued for 4 hr. under cooling and stirring. The reaction mixture was poured into ice-water, made alkaline with NH_4OH and extracted with Et_2O. The extracts were washed with H_2O saturated with NaCl, and dried over Na_2SO_4. Evaporation of the solvent and recrystallization of the residue from MeOH yielded 4.0 g. of colorless prisms, m.p. 127~128°. UV λ_{max}^{EtOH} mμ (log ε) : 225 (4.44), 240 (4.16). IR : ν_{max}^{KBr} 1667 cm^{-1} (α,β-unsaturated C=O). *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found : C, 76.21; H, 8.36; N, 4.46.

We thank Mr. M. Matsui, the Director of this Laboratory, and Prof. Emeritus E. Ochiai for their encouragements.

Summary

1-(*p*-Methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonane-$\Delta^{9,\alpha}$-acetaldehyde was synthesized from 1-(*p*-methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (VI) by reaction with ethoxyethynyllithium and partial hydrogenation of the ethoxyethynyl carbinol (IX) followed by treatment with phosphorus tribromide. This α,β-unsaturated aldehyde would be a suitable starting material for the synthesis of diterpenoid alkaloids, because cyclization of a derivative having a tertiary hydroxyl group at C-9 position of the phenylazabicyclononane did not form an expected compound.

(Received October 18, 1962)

UDC 547.94 : 547.913.6

136. Akira Ogiso, Bunji Shimizu, and Issei Iwai : An Approach to Synthesis of Diterpenoid Alkaloids. IV.*1

(*Takamine Laboratory, Sankyo Co., Ltd.**2)

In the previous paper of this series,[1] it was shown that Mannich condensation was satisfactory to synthesize azabicyclononane derivatives which were expected to give a valuable starting material for the synthesis of diterpenoid alkaloids. And we reported that α,β-unsaturated aldehyde (II) would be a suitable starting material for this purpose, since it was necessary to obtain a derivative having no tertiary hydroxyl group in the formula (I), in order to convert it into the atisine skeleton by building up the ring B.*1 In this paper we wish to report the conversion of the α,β-unsaturated aldehyde (II) into the common skeleton of the atisine-type alkaloids.

Catalytic reduction of the α,β-unsaturated aldehyde (II) on palladium-charcoal gave two epimeric saturated aldehydes. The crystalline aldehyde (IIIa), which melted at 73~74°, gave a picrate, m.p. 209~210° (decomp.). The other one (IIIb) was a colorless oil and gave a picrate, m.p. 181~183° (decomp.). The infrared spectra of the both aldehydes (IIIa) and (IIIb) showed an absorption band at 1730 cm^{-1} corresponding to a carbonyl group of the saturated aldehyde, and they were identical except for a slight difference in the region 1050~1150 cm^{-1}. Of course, the absorptions of ultraviolet spectrum corresponding to an α,β-unsaturated aldehyde disappeared and the spectra of the aldehydes (IIIa) and (IIIb) changed into the absorption curve of an anisol derivative.

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*1 Part III. A. Ogiso, B. Shimizu, I. Iwai : This Bulletin, **11**, 770 (1963).

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1) Part I. B. Shimizu, A. Ogiso, Iwai : This Bulletin, **11**, 333 (1963).

Because the cyclohexane and the piperidine ring of the α,β-unsaturated aldehyde (II) would be sterically equivalent to the exocyclic double bond, the catalyst of hydrogenation must attack the both α- and β-side of the double bond in the same proportion. Actually, the ratio of the yieled of the epimeric aldehydes was about 1:1.

Treatment of the aldehyde (IIIa) with polyphosphoric acid gave a compound showing the ultraviolet absorption maxima at 268, 302, and 312 mμ, which supported the structure (IV). The low yield of this compound (IV) depends upon a by-product with yellow fluorescence.

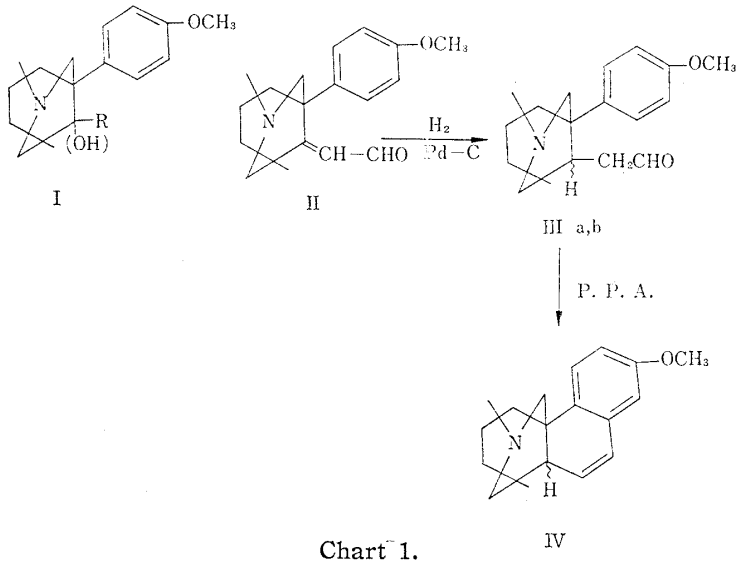


Chart 1.

The aldehydes (IIIa) and (IIIb) were reduced with lithium aluminum hydride to the respective alcohols in quantitative yields. Infrared spectra of these alcohols showed an absorption band at 3500 cm^{-1} and were very similar to each other. The alcohol (Va) gave a picrate of the melting point, 187~188° (decomp.) and the other alcohol (Vb) gave a picrate of the melting point, 166~168° (decomp.).

Heating these alcohols (Va) and (Vb) with polyphosphoric acid gave the corresponding hydrophenanthrene derivatives (VIa) and (VIb) in 70% yield in each case. VIa was a colorless oil giving a picrate of the melting point, 206~207° (decomp.), whereas VIb was a colorless plates, m.p. 85~86°, which gave a picrate of the melting point, 210~211° (decomp.). The infrared spectra of both substances (VIa) and (VIb) were very similar and showed an absorption band at 870 cm^{-1} corresponding to the out-of-plane vibration one free hydrogen atom and no band in the hydroxyl region. Results of the elemental analyses of VIa and VIb, and all their ivatives were in good agreement with the calculated values.

Furthermore, evidence for the ring formation to the hydrophenanthrene derivatives was provided by the fact that VIa and VIb were oxidized with chromic acid in glacial acetic acid to the basic ketones (VIIa) and (VIIb). The infrared spectra of VIIa and VIIb showed an characteristic absorption at 1682 cm^{-1} attributable to a 9-oxooctahydrophenanthrene ring,[2] and the ultraviolet spectra showed absorptions at 220.5, 253, and 318 mμ which coincided with those of 3-methoxyacetophenone.

These results proved the expected structures (VIa) and (VIb) containing a six-membered ring B.

2) E. Wenkert, B.G. Jackson : J. Am. Chem. Soc., **80**, 211 (1958). R. Hodges, R.A. Raphael : J. Chem. Soc., **1960**, 50.

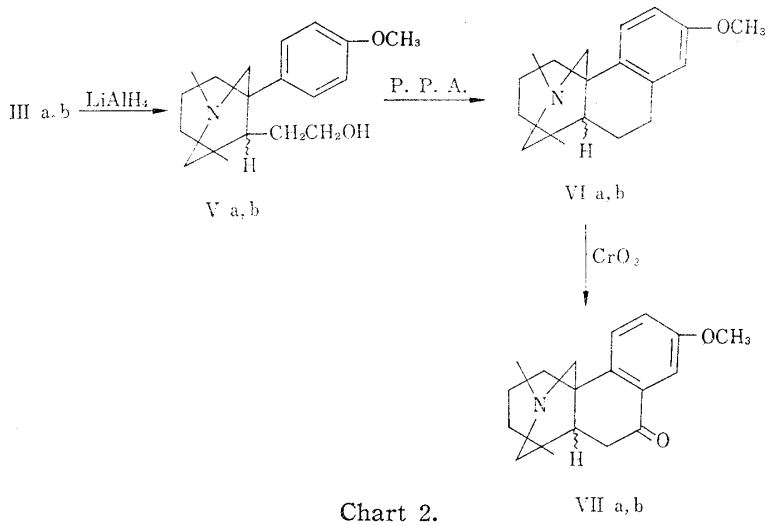


Chart 2.

In order to synthesize a derivative of naturally occurring diterpenoid alkaloid, we intended to eliminate the methyl group from the N-methyl of the compounds (VIa) and (VIb).

Cyanation of the compounds (VIa) and (VIb) with cyanogen bromide gave the N-cyano compounds (VIIIa) and (VIIIb) in 77% yield respectively. Both VIIIa, m.p. 142°, and VIIIb, m.p. 154~155°, showed a characteristic absorption at 2220 cm^{-1} due to a cyanide group in the infrared spectra. These N-cyano derivatives (VIIIa) and (VIIIb) were reduced successfully with lithium aluminum hydride[3] to the respective secondary amines (IXa) and (IXb), which showed an absorption band at 3500 cm^{-1}. IXa gave a hydrochloride of the melting point, 258~260° (decomp.) and IXb gave a hydrochloride, m.p. 278~280° (decomp.).

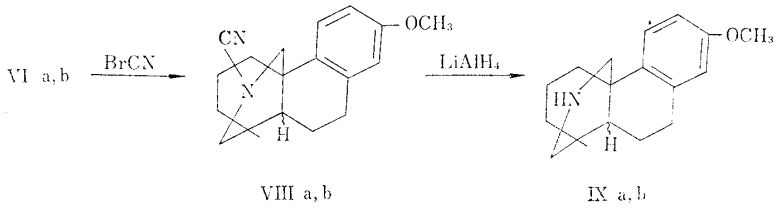


Chart 3.

The secondary amino compounds (IXa) and (IXb) must be *cis* and *trans* stereoisomers of A/B ring junction. It was shown that the atisine-type alkaloid possessed A/B *trans* conformation.[4] Therefore, only the *trans* stereoisomer is available for the synthesis of the alkaloid.

Wenkert, *et al.*[2,5] reported that a monobenzenoid tricyclic diterpene with A/B *cis* fusion was oxidized with chromic acid to a 9-oxo and 9,10-dioxo compound, while a A/B *trans*-fused diterpene was oxidized to only a 9-oxo compound. And they assumed, in the *trans*-fused diterpene, the enol chromate of the 9-oxo compound was hard to accept the axial attack of the reagent depending upon the strong hindrance toward reagent approach at C-10 due to the presence of two axial methyl groups at C-1 and C-12. However, in our synthetic hydrophenanthrene derivatives fused with a hetero ring, the cyclohexane and piperidine ring are equivalent toward the reagent approach at C-10. Accordingly, two stereoisomers must exhibit the same chemical behavior by the

3) V. Prelog, B.C. McKusick, J.R. Merchant, S. Julia, M. Wilhelm : Helv. Chim. Acta, **39**, 498 (1956). A.C. Currie, G.T. Newbold, F.S. Spring : J. Chem. Soc., **1961**, 4693.
4) A.J. Solo, S.W. Pelletier : Chem & Ind. (London), **1960**, 1108.
5) E. Wenkert, J.W. Chamberlin : J. Am. Chem. Soc., **81**, 688 (1959).

oxidation. Under the Wenkert's standerdized condition, the stereoisomers (VIa) and (VIb) were oxidized, practically, to only 9-oxo compounds (VIIa) and (VIIb) respectively in the same yield, which showed identical absorption in the ultraviolet spectra (Fig. 1.).

A/B *trans* A/B *cis*

Chart 4.

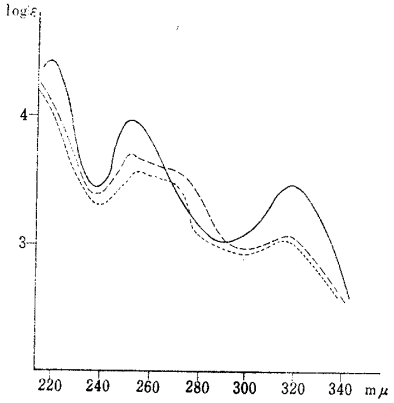
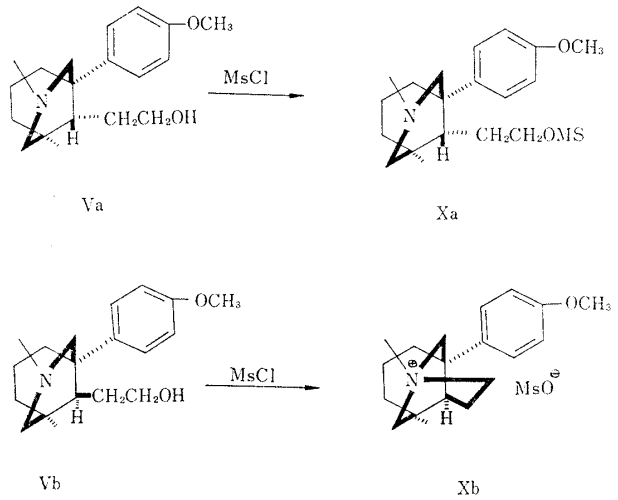


Fig. 1. Ultraviolet Spectra of the Oxidation Products of VIa and VIb

—— VIIa and VIIb
- - - Oxidation product of VIa (without purification)
..... Oxidation Product of VIb (without purification)

We accomplished this problem by determining the configuration of two stereoisomeric alcohols (Va) and (Vb) from which these hydrophenanthrene compounds were derived. These alcohols (Va) and (Vb) were reacted with methanesulfonyl chloride to give the respective mesylates. The one obtained from Va was soluble in ether and showed absorption bands at 1360 cm^{-1} and 1174 cm^{-1}. These results suggested the mesylate was a methanesulfonyl ester (Xa). The other obtained from the stereoisomer (Vb) was insoluble in non-polar solvents such as ether, and showed absorption bands at 1174 cm^{-1} and 1040 cm^{-1} which was attributed to a quaternary ammonium base illustrated as Xb.[6]



Va Xa

Vb Xb

Chart 5.

6) E.A. Robinson : Canad. J. Chem., **39**, 247 (1961).

Because the nitrogen-containing ring is bridged into the both axial bonds of the cyclohexane in the azabicyclononane systems, the hydroxyethyl group in Va is axial to the cyclohexane ring, while in Vb equatorial configuration. Consequently, IXa cyclized from Va possesses a *cis*-fused A/B junction, while IXb from Vb possesses a *trans*-fused A/B junction. Therefore, IXb is the only suitable starting material for the total synthesis of the atisine-type alkaloid.

Experimental

1-(*p*-Methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3. 3. 1]nonane-9-acetaldehyde (IIIa) and (IIIb)——A mixture of 2.7 g. of the unsaturated aldehyde (II) and 1.0 g. of 10% Pd-C in 100 ml. of EtOH was hydrogenated at atmospheric pressure. After the uptake of H_2 ceased, the catalyst was filtered, the filtrate was evaporated to dryness, and chromatographed on alumina (grade IV, 100 g.). Hexane eluates yielded 1.3 g. of the saturated aldehyde (IIIa), forming prisms from pentane, m.p. 73~74°. UV λ_{max}^{EtOH} mμ (log ε): 223.5 (4.17), 275.5 (3.32), 282 (3.24). IR: ν_{max}^{KBr} 1730 cm^{-1} (C=O). *Anal.* Calcd. for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.65; H, 8.82; N, 4.49.

The picrate of IIIa was prepared by reaction with picric acid in MeOH forming yellow prisms, m.p. 209~210° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_9N_4$: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.24; H, 5.80; N, 10.46.

The benzene eluates yielded 1.2 g. of an oily product (IIIb). The infrared and ultraviolet spectra of this product were almost same as those of above substance (IIIa). The oil was characterized as a picrate which was prepared in MeOH and recrystallized from the same solvent to give yellow needles, m.p. 181~183° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_9N_4$MeOH: C, 55.51; H, 6.09; N, 9.96. Found: C, 55.67; H, 5.79; N, 9.76.

Cyclization of the Aldehyde (IIIa)——A mixture of 900 mg. of the aldehyde (IIIa) and polyphosphoric acid, prepared from 6.0 g. of P_2O_5 and 4.0 ml. of 85% H_3PO_4, was stirred for 1 hr. at room temperature. The reaction mixture was dissolved in ice water, made alkaline with 10% NaOH, and extracted with Et_2O. Evaporation of the Et_2O extract to dryness yielded 600 mg. of an yellow fluorescent product, which was chromatographed on alumina (grade II, 2.0 g.). Hexane eluates yielded 60 mg. of a colorless oil (IV). Further purification was not carried out. UV λ_{max}^{EtOH} mμ: 268, 302, 312.

1-(*p*-Methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonane-9-ethanol (Va) and (Vb)——Va: To a solution of 300 mg. of $LiAlH_4$ in 50 ml. of dry Et_2O was added a solution of 1.2 g. of the aldehyde (IIIa) in 20 ml. of dry Et_2O. The mixture was refluxed for 1 hr. under stirring. After cooling, the excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O. Evaporation of the ether solution to dryness yielded 1.2 g. of colorless oil which was distilled at 165~170°, 10^{-3} mm·Hg (bath temp.). IR: ν_{max}^{liquid} 3500cm^{-1} (OH). The oil was characterised as a picrate which was prepared in MeOH and recrystallized from the same solvent to give yellow prisms, m.p. 187~188° (decomp.). *Anal.* Calcd. for $C_{25}H_{32}O_9N_4$: C, 56.38; H, 6.06; N, 10.52. Found: C, 56.04; H, 6.25; N, 10.29.

Vb: 3.0 g. of the oily aldehyde (IIIb) was reduced with $LiAlH_4$ in the same manner as the aldehyde (IIIa) to give 2.5 g. of an oily product. The IR and UV spectra of this product were almost same as those of above substance (Va). The picrate of this product was recrystallized from Me_2CO-Et_2O to give yellow plates, m.p. 166~168° (decomp.). *Anal.* Calcd. for $C_{25}H_{32}O_9N_4$: C, 56.38; H, 6.06; N, 10.52. Found: C, 56.33; H, 6.06; N, 10.74.

Cyclization of the Alcohol——To form VIa: A mixture of 800 mg. of the alcohol (Va) and polyphosphoric acid, prepared from 6.0 g. of P_2O_5 and 4.0 ml. of 85% H_3PO_4, was stirred for 3 hr. at 95°. The reaction mixture was dissolved in ice water, made alkaline with 10% NaOH, and extracted with Et_2O. Evaporation of the ether extract to dryness yielded 750 mg. of an oily product, which was chromatographed on alumina (grade II, 25 g.). Petr. ether eluates yielded 550 mg. of the cyclic compound (VIa) which was distilled at 130°, 10^{-3} mm. Hg (bath temp.). UV λ_{max}^{EtOH} mμ (log ε): 277 (3.39), 285 (3.38). IR: δ_{max}^{liquid} 870 cm^{-1}.

The oil was characterized as a picrate prepared in MeOH and recrystallized from the same solvent to give yellow plates, m.p. 206~207° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_8N_4$: C, 58.36; H, 5.88; N, 10.89. Found: C, 58.16; H, 5.88; N, 10.78.

The hydrochloride of this oily product was prepared by the usual manner, and recrystallized from MeOH-Me_2CO to give colorless needles, m.p. 220~221° (decomp.). *Anal.* Calcd. for $C_{19}H_{27}ON$·HCl: C, 70.90; H, 8.77; N, 4.35. Found: C, 70.55; H, 8.67. ; N, 4.670.

To form VIb: 2.0 g. of the alcohol (Vb) was treated in polyphospholic acid in the same manner as the alcohol (Va) to give 1.7 g. of the cyclic compound (Vb), which was recrystallized from MeOH to give

*3 Just before we submit this manuscript to this Bulletin, we received with thanks the private communication concerning the synthesis of the degradation product of atisine from Dr. Z. Valenta.

colorless plates, m.p. 85~86°. *Anal.* Calcd. for $C_{19}H_{27}ON$: C, 79.95; H, 9.54; N, 4.31. Found : C, 79.76; H, 9.53; N, 4.77.

The picrate of this substance was recrystallized from MeOH to give yellow prisms, m.p. 214~215° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_8N_4$: C, 58.36; H, 5.88; N, 10.89. Found : C, 58.32; H, 5.87; N, 10.88.

Oxidation of the Cyclic Compound——To form VIIa : To a solution of 500 mg. of the cyclic compound (VIa) in 4 ml. of AcOH was added a solution of 625 mg. of chromic acid in 4 ml. of AcOH and 1 ml. of H_2O. Afterstanding overnight at room temperature, the reaction mixture was poured into ice water, made alkaline with NH_4OH and extracted with Et_2O. The ethereal layer was dried over Na_2SO_4 and evaporated to dryness to give 300 mg. of yellow oil. The oily residue was chromatographed on alumina (grade II, 12 g.). Petr. ether eluates yielded 120 mg. of the starting material, and benzene eluates gave 131 mg. of the crystalline 9-oxo compound (VIIa), which was recrystallized from MeOH to give colorless plates, m.p. 111~112°. UV λ_{max}^{EtOH} mμ (log ε): 220.5 (4.44), 253 (3.96), 318 (3.47). IR : ν_{max}^{KBr} 1682 cm^{-1} (C=O). *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found : C, 76.35; H, 8.36; N, 4.58.

To form VIIb : 500 mg. of the cyclic compound (VIb) was oxidized with chromic acid in the same manner as the stereoisomer (VIa) to give 270 mg. of an oily residue. The oily product was chromatographed on alumina (grade II, 12 g.). Petr. ether eluates yielded 100 mg. of the starting material, and benzene eluates gave 135 mg. of a colorless oil. The UV and IR spectra of this compound were almost identical with those of VIIa.

N-Cyanation of the Cyclic Compound——To form VIIIa : To a solution of 2.0 g. of cyclic compound (VIa) in 50 ml. of $CHCl_3$ was added a solution of 850 mg. of cyanogen bromide in 10 ml. of $CHCl_3$. After the mixture was refluxed for 5 hr., $CHCl_3$ solution was washed with 5% HCl, and dried over Na_2SO_4. Evaporation of the solvent to dryness yielded 1.6 g. of the crystalline N-cyano compound (VIIIa) which was recrystallized from AcOEt to give prisms, m.p. 142°. IR : ν_{max}^{KBr} 2220 cm^{-1} (C≡N). *Anal.* Calcd. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16; N, 9.45. Found : C, 77.14; H, 8.08; N, 9.13.

To form VIIIb : 1.0 g. of cyclic compound (VIb) was reacted with cyanogen bromide in the same manner as the stereoisomer (VIa) to give 900 mg. of crystalline N-cyano compound (VIIIb). Recrystallization from MeOH yielded prisms, m.p. 154~155°. *Anal.* Calcd. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16; N, 9.45. Found : C, 76.88; H, 8.00; N, 9.10.

Reduction of the N-Cyano Derivative——To form IXa : To a solution of 500 mg. of $LiAlH_4$ in 50 ml. of dry Et_2O was gradually added a solution of 1.0 g. of N-cyano derivative (VIIIa) in 5 ml. of dry Et_2O and 5 ml. of tetrahydrofuran at room temperature. The reaction mixture was refluxed for 5 hr. under stirring, and after cooling the excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O. After filtration, the solvent was extracted with 5% HCl. Evaporation of the aqueous layer to dryness yielded 800 mg. of a crystalline residue (IXa), which was recrystallized from MeOH-AcOEt to give the secondary amine HCl, m.p. 258~260° (decomp.). IR : ν_{max}^{KBr} 3500 cm^{-1} (N-H). *Anal.* Calcd. for $C_{18}H_{25}ON \cdot HCl$: C, 70.23; H, 8.51; N, 4.55. Found : C, 70.04; H, 8.54; N, 4.60.

To form IXb : 820 mg. of N-cyano derivative (VIIIb) was reduced with $LiAlH_4$ in the same manner as the stereoisomer (IXa) to give 650 mg. of the secondary amine HCl (IXb), which was recrystallized from MeOH to give colorless prisms, m.p. 278~280° (decomp.). *Anal.* Calcd. for $C_{18}H_{25}ON \cdot HCl$: C, 70.23; H, 8.51; N, 4.55. Found : C, 70.05; H, 8.41; N, 4.49.

Reaction of Va with Methanesulfonyl Chloride——350 mg. of methanesulfonyl chloride was added to a solution of 500 mg. of Va in 10 ml. of dry pyridine under ice cooling. After standing for 24 hr. in a refrigerator, the reaction mixture was concentrated under vacuum, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. Removal of the solvent yielded 450 mg. of a crystalline residue, which was recrystallized from MeOH to give prisms, m.p. 67~68°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1360 (asym. SO_2), 1174 (sym. SO_2). *Anal.* Calcd. for $C_{29}H_{31}O_4NS$: C, 62.96; H, 8.19; N, 3.67. Found : C, 63.07; H, 8.43; N, 3.52.

Reaction of Vb with Methanesulfonyl Chloride——600 mg. of Vb was reacted with methanesulfonyl chloride in the same manner as Va to give 175 mg. of a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1174 (asym. SO_2), 1040 (sym. SO_2).

We thank Mr. M. Matsui, the Director of this Laboratory, and Professor Dr. E. Ochiai for their encouragements.

Summary

Catalytic reduction of 1-(*p*-methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonane $\Delta^{9,\alpha}$-acetaldehyde (II) gave two epimeric saturated aldehydes (IIIa) and (IIIb). Both epimers were converted into the stereoisomeric hydrophenanthrene derivatives, VIa and VIb, respectively, by reduction with lithium aluminum hydride followed by cyclization with polyphospholic acid. The conformation of the stereoisomers was confirmed by determining the configuration of two epimeric alcohols (Va) and (Vb) from which these hydrophenanthrene compounds were derived. The A/B *trans*-fused isomer bears the common skeleton of the atisine-type alkaloids. (Received October 18, 1962)