UDC 547.94 : 547.913.6

135. Akira Ogiso, Bunji Shimizu, and Issei Iwai: An Approach to Synthesis of Diterpenoid Alkaloids. III.[*1]

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In the previous paper of this series,[*1] it was reported that the attempted synthesis of atisine skeleton from 1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one by the method of the total synthesis of totarol was unsuccessful, because the dehydration of 9-(*p*-methoxyphenethyl)-1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol (I) did not occur to the bridged head in a cyclization reaction according to Bredt's rule. It was cyclized to give a spiro compound which was assumed to be II.

We have attempted to synthesize the atisine skeleton by building up the ring B starting from 1-(*p*-methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (VI)[*3] as shown in Chart 1. (1 → 3).

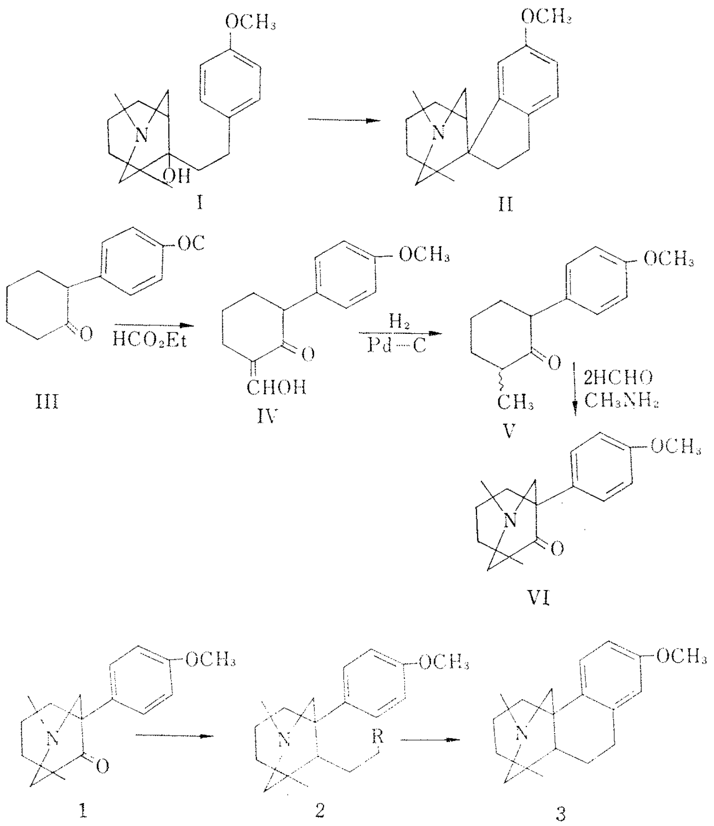

Chart 1.

The synthesis of phenanthrene derivatives from phenylcyclohexanone derivatives were reported,[1)] but their conversion to diterpenoids has not been known. Then, we investigated the cunversion of the basic ketone (VI) to a convenient derivative for the synthesis of the atisine-type alkaloid.

[*1] Part II. B. Shimizu, A. Ogiso, I. Iwai: This Bulletin, **11**, 766 (1963).

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[*3] This substance was obtained as prisms, m.p. 52°, at this time.

1) J. W. Cook, C. L. Hewett, C. A. Lawrence: J. Chem. Soc., **1936**, 71; M. S. Newman, M. D. Farbman: J. Am. Chem. Soc., **66**, 1550 (1944); W. E. Bachmann, G. I. Fujimoto, L. B. Wick: *Ibid.*, **72**, 1995 (1950).

The synthetic method of the basic ketone (VI) from 2-(*p*-methoxyphenyl)cyclohexanone (III) by formylation and hydrogenation followed by Mannich reaction was reported in Part I of this series.[2] The hydrogenation of the formate (IV) to 2-(*p*-methoxyphenyl)-6-methylcyclohexanone (V) gave an epimeric mixture of the 6-methyl derivatives. However, separation of these epimers was not necessary since the hetero ring must be formed with the axial bonds of the cyclohexanone by the Mannich reaction.

The ketone (VI) was reacted with ethynyllithium in liquid ammonia to give the ethynyl carbinol (VII), which showed absorption bands at 3260 cm^{-1} and 3500 cm^{-1} indicating a terminal acetylenic and a hydroxyl group, respectively. This ethynyl carbinol (VII) failed in a Meyer-Schuster rearrangement to form an α,β-unsaturated aldehyde under various acidic conditions. Hydrogenation of the ethynyl carbinol (VII) using Lindlar's catalyst gave the vinyl carbinol (VIII), which resisted an allylic rearrangement.

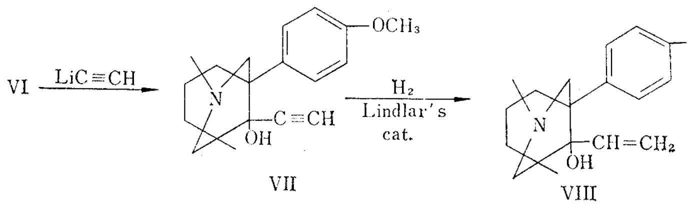

Chart 2.

Because the exocyclic double bond may have a great strain in azabicyclononane compounds, these carbinol derivatives are hard to form a carbonium cation having an exocyclic double bond as the intermediate which is considered to be essential for these rearrangements. Accordingly, the ethynyl carbinol (VII) is not a suitable starting material for the synthesis of atisine skeleton.

The ketone (VI) was reacted with ethoxyethynyllithium to give an oily product, which was separated into two compounds by alumina chromatography. The one obtained in 41% yield was crystalline product, m.p. 80~81°, which corresponded to $C_{21}H_{29}O_3N$. The infrared spectrum showed absorption bands corresponding to an ethynyl group at 2270 cm^{-1} and a hydroxyl group at 3500 cm^{-1}. These data were consistent with the structure illustrated as IX. The other product obtained in about 40% yield by the chromatography was a colorless oil, which showed absorption band at 3500 cm^{-1} corresponding to a hydroxyl group and an intense band at 1568 cm^{-1}, but no bands in the ethynyl and carbonyl region. Although further investigations on this oily product were not carried out, this product would be resulted from the epimer of the ethoxyethynyl derivative (IX). The yield of the crystalline ethoxyethynyl derivative (IX) did not exceed above 50% under any conditions. The cyclohexane and the piperidine ring may be sterically equivalent to the carbonyl group in the azabicyclononanone system, but the epimer of the ethoxyethynyl derivatives could not be isolated.

Hydration of the ethoxyethynyl carbinol (IX) under acidic condition gave colorless plates, m.p. 125~126°. The infrared spectrum showed an absorption band at 1700 cm^{-1} corresponding to an ester carbonyl, and hydrolysis of the product (X) yielded an amphoteric substance (XI) showing an intense band at 1600 cm^{-1} indicative of an ionized carboxyl group. These results provided the structure (X) for the ester.

The ester (X) could not be dehydrated to the compound having an exocyclic double bond with any reagents alike to the fact that the ethynyl carbinol (VII) and vinyl carbinol (VIII) failed in rearrangement. When the alcohol derivatives (XII) containing the tertiary

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[2] B. Shimizu, A. Ogiso, I. Iwai: This Bulletin, **11**, 333 (1963).

hydroxyl group, prepared from the ester (X) by reduction with lithium aluminum hydride, was treated with polyphosphoric acid, the expected compound (XIII) could not be obtained. Consequently, the compounds containing the tertiary hydroxyl group are not suitable for the cyclization of ring B.

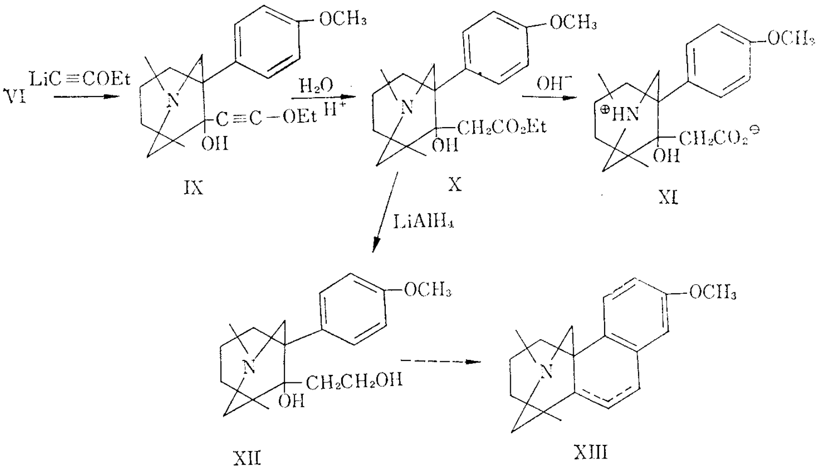

Chart 3.

Catalytic reduction of the ethoxyethynyl carbinol (IX) using Lindlar's catalyst gave the ethoxyvinyl carbinol (XIV) in a quantitative yield, which showed an absorption band at 1600 cm^{-1} due to a double bond. Treatment of the ethoxyvinyl carbinol (XIV) with phosphorus tribromide[3] gave prisms in 90% yield, m.p. 127~128°. The infrared spectrum showed a band at 1667 cm^{-1} corresponding to an α,β-unsaturated carbonyl group but no absorption band in the hydroxyl region. The ultraviolet spectrum showed an absorption maximum at 225 mμ (27,600) and a shoulder at 240 mμ (14,300).

These results confirm the structure of the α,β-unsaturated aldehyde (XV), which is a suitable starting material for the synthesis of atisine skeleton by building up the ring B as shown in Chart 1.

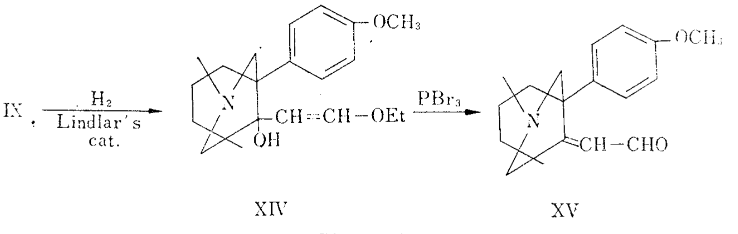

Chart 4.

Experimental

2-(p-Methoxyphenyl)-6-methylcyclohexanone (V)——30 g. of the crude formate (IV), prepared from 2-(p-methoxyphenyl)cyclohexanone (III) by the method reported in Part I., was hydrogenated on 5 g. of 10% Pd-C in 300 ml. of EtOH. Treatment of the reaction mixture by the usual way yielded 30 g. of an oily product, which was recrystallized from hexane to give 17 g. of colorless plates, m.p. 74~75°. The residual oil was gradually crystallized for a few days to give 5.0 g. of plates, which was identical with the above substance of m.p. 74~75°. Further crops of the same crystals were obtained from the residual oil. Consequently, 26 g. of the crystalline (V) was obtained overall. The oily stereoisomer, separated from the crystalline (V), was immediately reacted with 2 moles of HCHO and 1 mole of CH_3NH_2 to give the basic ketone (VI) as the same yield as the case of the crystalline epimer V.

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3) cf. J.F. Arens: "Advances in Organic Chemistry," Vol. 2, 117 (1960), Interscience Publishers.

1-(*p*-Methoxyphenyl)-9-ethynyl-3,5-dimethyl-3-azabicyclo [3.3.1] nonan-9-ol (VII)——130 ml. of dry liquid NH_3 was saturated with dry acetylene and treated with 0.7 g. of finely cut Li. After stirring for 1 hr., 6.0 g. of the basic ketone (VI) in 80 ml. of dry Et_2O was added under bubbling dry acetylene over a period of 0.5 hr. at $-70°$, and the stirring was continued for 4 hr. To the reaction mixture was added 15 g. of NH_4Cl. The flask was removed from the cooling bath and stood overnight to evaporate NH_3. The residue was poured into ice-water 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 hexane yielded 3.5 g. of colorless prisms, m.p. 112～113°. IR ν_{max}^{KBr} cm^{-1} : 3500 (OH), 3260 (C≡CH). *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found : C, 76.29; H, 8.24; N, 4.84.

1-(*p*-Methoxyphenyl)-9-vinyl-3,5-dimethyl-3-azabicyclo[3.5.1]nonan-9-ol (VIII)——Catalytic reduction of 1.5 g. of the ethynyl carbinol (VII), using 1 g. of Lindlar's catalyst and 30 ml. of EtOH was allowed to proceed until 1 mole of H_2 was absorbed. The mixture was filtered and the filtrate was evaporated to dryness. Recrystallization from MeOH gave 1.2 g. of prisms, m.p. 103～104°.. IR ν_{max}^{KBr} cm^{-1} : 3500 (OH), 1638 (C=C). *Anal.* Calcd. for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found : C, 75.67; H, 9.21; N, 4.55.

1-(*p*-Methoxyphenyl)-9-ethoxyethynyl-3,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol (IX)——To a solution of $LiCH_3$, prepared from 0.87 g. of Li and 8.7 g. of CH_3I in 50 ml. of dry Et_2O, was added a solution of 4.4 g. of ethoxyacetylene in 10 ml. of dry Et_2O with stirring under N_2 atmosphere. After 10 min., 5.7 g. of the ketone (VI) in 20 ml. of dry Et_2O was added dropwise to the mixture in 0.5 hr. at $-20°$. Stirring and cooling were continued for another hour, the cooling bath was removed. After standing 3 hr. at room temperature, the reaction mixture was poured into 50 ml. of H_2O, the ethereal layer was separated, and it was worked up as usual. The oily crude product (5.8 g.) was chromatographed on alumina (grade I, 180 g.). Elution with benzene gave a solid which was recrystallized from MeOH to give 3.0 g. of plates, m.p. 80～81°. *Anal.* Calcd. for $C_{21}H_{29}O_3N$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.29; H, 8.33; N, 4.09. IR ν_{max}^{KBr} cm^{-1} : 3500 (OH), 2270 (C≡C).

Ethyl 1-(*p*-Methoxyphenyl)-9-hydroxy-3,5-dimethyl-3-azabicyclo[3.3.1]nonane-9-acetate (X)——A solution of 3.2 g. of the ethoxyethynylcarbinol (IX) and 5 ml. of 15% H_2SO_4 in 30 ml. of tetrahydrofuran was refluxed for 15 min. The reaction mixture was poured into ice-water containing 1.4 g. of $NaHCO_3$, and it was concentrated, and extracted with Et_2O. Evaporation of the solvent yielded 2.7 g. of a crystalline residue, which was recrystallized from MeOH to give plates, m.p. 125～126°. IR : ν_{max}^{Nujol} 1700 cm^{-1} (C=O). *Anal.* Calcd. for $C_{21}H_{31}O_4N$: C, 69.77; H, 8.65; N, 3.88. Found : C, 69.84; H, 8.80; N, 4.04.

1-(*p*-Methoxyphenyl)-9-hydroxy-3,5-dimethyl-3-azabicyclo[3.3.1]nonane-9-acetic Acid (XI)——A solution of 1.0 g. of the ester (X) in 10 ml. of 5% KOH-EtOH was refluxed for 2 hr. The reaction mixture was poured into H_2O and concentrated under vacuum. The aqueous solution was washed with Et_2O and neutralized with dil. AcOH to pH 6.4～6.6. Concentration under vacuum yielded crystatalline precipitate, which was separated and recrystallized from AcOEt-MeOH to give needles, m.p. 165～166°. IR : ν_{max}^{KBr} 1585 cm^{-1}.

9-Hydroxy-3,5-dimethyl-3-azabicyclo[3.3.1]-nonane-9-ethanol (XII)——To a solution of 500 mg. of $LiAlH_4$ in 50 ml. of dry Et_2O was added a solution of 1.0 g. of the ester (X) in 30 ml. of dry Et_2O. The mixture was refluxed for 1 hr. under stirring, cooled, and the excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O. Evaporation of the Et_2O solution to dryness yielded 800 mg. of a cryslline residue, which was recrystallized from MeOH to give needles, m.p. 146～147°. *Anal.* Calcd. for $C_{19}H_{29}O_3N$: C, 71.44; H, 9.15; N, 4.39. Found : C, 71.12; H, 9.17; N, 4.40.

Cyclization of the Alcohol (XII)——A mixture of 500 mg. of the alcohol (XII) and polyphosphoric acid, prepared from 6.0 g. of P_2O_5 and 4.0 ml. of 85% H_3PO_4, was stirred for 30 min, at 80～85°. The 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 350 mg. of an oily product, which was chromatographed on alumina (grade II, 12 g.). Petr. ether eluates yielded 200 mg. of a colorless oil. UV : λ_{max}^{EtOH} 300 mμ (log ε 4.23). IR : ν_{max}^{liquid} 1600 cm^{-1}. To a solution of 100 mg. of the oil in 1 ml. of MeOH was added a solution of 100 mg. of picric acid in 1 ml. of MeOH. The resulted precipitate was separated and crystallized from MeOH to give 80 mg. of yellow greenish prisms, m.p. 179～183° (decomp.). *Anal.* Calcd. for $C_{25}H_{28}O_8N_4$: C, 58.58; H, 5.51; N, 10.93. Found : C, 58.45; H, 5.57; N, 10.90.

1-(*p*-Methoxyphenyl)-9-ethoxyvinyl-3,5-dimethyl-3-azabicyclo [3.3.1] nonan-9-ol (XIV)——Catalytic reduction of 3.0 g. of the ethoxyethynyl carbinol (IX), using 1.5 g. of Lindlar's catalyst and 20 ml. of EtOH was allowed to proceed until 1 mole of H_2 was absorbed. The mixture was filtered and the filtrate was evaporated to dryness. Recrystallization from MeOH gave 3.0 g. of plates, m.p. 96～97°. IR : ν_{max}^{KBr} 1660 cm^{-1} (C=C). *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found : C, 73.18; H, 9.01; N, 4.13.

1-(*p*-Methoxyphenyl)-3,5-dimethyl-3-azabicyclo[3.3.1]nonane-$\Delta^{9,\alpha}$-acetaldehyde (XV)——To a solution of 5.0 g. of ethoxyvinyl carbinol (XIV) in 100 ml. of alcohol-free dry $CHCl_3$ was added a mixture of 7.5 ml. of PBr_3, 25 ml. of pyridine and 100 ml. of $CHCl_3$, with stirring under N_2 atmosphere at 0°. The 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.

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

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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.

[*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).