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

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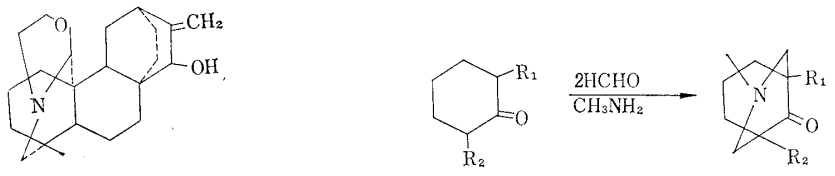
The structure of atisine, one of alkaloids obtained from *Aconitum*, was clarified by Wiesner and Pelletier[1] and its configuration was shown to be as I. Recently, Djerassi, *et al.*[2] investigated between garryfoline and steviol, while Edwards,[3] *et al.* investigated between atisine and podocarpic acid. They have concluded that the absolute configuration of the diterpenoid alkaloids including atisine bears a mirror image relationship to common diterpenes. Consequently, it has become clear that all attempts to synthesize diterpenoid alkaloids from natural diterpenes such as abietic acid are practically useless.

In the previous paper,*1 we have reported the preparation of azabicyclononanones (II) in a good yield by Mannich reaction from many cyclohexanones with two moles of formaldehyde and one mole of monomethylamine.



I II

Chart 1.

We attempted to synthesize the atisine skeleton from II applying the method of total synthesis of totalol.[4] Then, the cyclization reaction of a phenethyl derivative of II to form the ring B of atisine skeleton was investigated.

First of all, 3-methyl-3-azabicyclo[3.3.1]nonan-9-one (III : R=H) was reacted with *p*-methoxyphenylethylmagnesium bromide to give an oily product. From the oil two isomers of 3-methyl-9-(*p*-methoxyphenylethynyl)-3-azabicyclo[3.3.1]nonan-9-ol (IVa : R=H and IVb : R=H) were isolated as their picrates. In the infrared spectra the both isomers showed characteristic bands at 2210 cm^{-1} due to a triple bond and at 3780 cm^{-1} due to a hydroxyl group.

On catalytic hydrogenation over 10% palladium-charcoal or platinum oxide (IVa: R=H and IVb : R=H) gave corresponding phenethyl derivatives (Va : R=H and Vb: R=H) in quantitative yields respectively.

In the similar way, methyl derivatives of Va ($R=CH_3$) and Vb ($R=CH_3$) were obtained starting from 1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (III : $R=CH_3$).

Heating the phenethylcarbinol (Va : R=H) with polyphosphoric acid or phosphoric oxide gave an oily product which showed no absorption band in the hydroxyl region.

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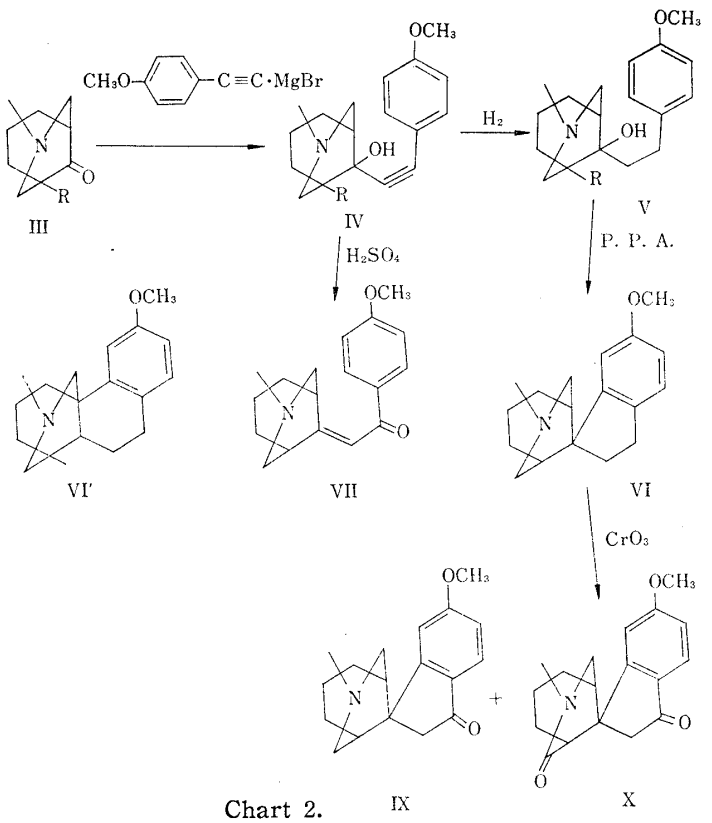

Chart 2.

The values of elemental analysis of its picrate were in good agreement with the composition of $C_{24}H_{28}N_4O_8$. These facts suggest that cyclization occured to afford a compound supposed to be a hydrophenanthrene derivative (VI′) or/and a spiro compound (VI).

Oxidation of the cyclization product with chromium trioxide in acetic acid gave two compounds, one of which showed the characteristic infrared absorption due to an 1-indanone[5] at 1706 cm^{-1}. A hydrophenanthrene structure (VI′) would be oxidized to an 1-tetralone which must show carbonyl absorption at the lower frequency.[6] Therefore, the oxidation product is considered to be IX. The other oxidation product was neutral and showed the infrared absorption bands at 1705 cm^{-1} and 1600 cm^{-1} corresponding to an 1-indanone and an acid amide respectively. Consequently, this oxidation product must be a lactam (X).

For confirmation of the structure (IX), the α,β-unsaturated ketone (VII), which was prepared by Meyer-Schuster rearrangement of VIa with concentrated sulfuric acid, was treated with polyphosphoric acid. However, the expected compound (IX) was not obtained.

Experimental

3-Methyl-9-(*p*-methoxyphenylethynyl)-3-azabicyclo[3.3.1]nonan-9-ol (IVa : R=H and IVb : R=H) ——To a boiling solution of the Grignard reagent, prepared from 0.8 g. of Mg and 3.7 g. of EtBr in 15 ml. of dry Et_2O and 20 ml. of anhyd. tetrahydrofuran under N_2, a solution of 4.2 g. of methoxyphenylacetylene in 8 ml. of tetrahydrofuran was added during 30 min. with stirring. Boiling was continued for 1 hr. and 3.5 g. of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one (III : R=H), in 10 ml. of tetrahydrofuran was added dropwise during 1 hr. The solution was refluxed for 4 hr., and treated cautiously with

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saturated aq. NH_4Cl (40 ml.) under cooling. After extraction with Et_2O, the ethereal solution was extracted with dil. HCl. The acidic solution was made alkaline with 10% NH_4OH and extracted with Et_2O. The ethereal extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to afford 4.9 g. of a viscous oil. This oil was converted into a crystalline picrate which was recrystallized from MeOH to give 5.3 g. of pale brown-yellow prisms, m.p. 218~220° (decomp.). *Anal.* Calcd. for $C_{24}H_{26}O_9N_4$: C, 56.03; H, 5.09. Found : C, 56.00; H, 5.09.

The residue was crystallized from MeOH-Me_2CO. Recrystallization from the same solvent yielded 0.38 g. of the picrate of isomeric ethynyl carbinol (IVb : R=H), m.p. 184~187°, in the form of needles. *Anal.* Calcd. for $C_{24}H_{26}O_9N_4$: C, 56.03; H, 5.09. Found : C, 55.87; H, 5.14.

A suspension of 0.2g. of the picrate (m.p. 218~220° (decomp.)) in 15 ml. of Et_2O was made alkaline with 10% NaOH. The ethereal extracts were washed with H_2O, dried over Na_2SO_4. The residue, after evaporation of the solvent *in vacuo*, was recrystallized from petr. ether to give 0.72 g. of colorless needles (IVa:R=H), m.p. 46~47°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2210 (C≡C), 3780 (OH). *Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12. Found : C, 75.33; H, 8.15.

The isomeric base (IVb : R=H) was obtained from the corresponding picrate (m.p. 184~187°) in the same manner as IVa (R=H). Recrystallization from petr. ether gave pale yellow needles, m.p. 88~89°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2212 (C≡C), 3750 (OH). *Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12. Found: C, 75.20; H, 8.26.

9-(*p*-Methoxyphenylethynyl)-1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol (IVa : R=CH_3 and IVb : R=CH_3)——3.2 g. of III (R=CH_3) was reacted with *p*-methoxyethynylmagnesium bromide in the same manner as IVa (R=H) to give a colorless oil. It gave a crystalline picrate which was recrystallized from MeOH to yield 1.2 g. of pale yellow needles, m.p. 220~223°. *Anal.* Calcd. for $C_{25}H_{28}O_9N_4 \cdot \frac{1}{2}H_2O$: C, 55.85; H, 5.37. Found : C, 55.90; H, 4.72.

From the mother liquor, 3.5 g. of the isomeric amorphous picrate of IVb (R=CH_3) was obtained.

The oily free base (IVa : R=CH_3) was obtained from the picrate (m.p. 220~223°) in the same manner as IVa (R=H). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2241 (C≡C), 3820 (OH). The oily free base IVb (R=CH_3), obtained from the amorphous picrate, showed the almost identical infrared absorption.

3-Methyl-9-(*p*-methoxyphenethyl)-3-azabicyclo[3.3.1]nonan-9-ol (Va : R=H and Vb : R=H)——A mixture of 1.7 g. of the phenylethynyl carbinol (IVa : R=H) and 0.2 g. of PtO_2 in 25 ml. of EtOH was hydrogenated under atmospheric pressure. After removal of the catalyst and the solvent, the residual oil was converted into a crystalline picrate. Recrystallization from MeOH yielded 2.2 g. of pale yellow needles, m.p. 225~227° (decomp.). *Anal.* Calcd. for $C_{24}H_{30}O_9N_4$: C, 55.59; H, 5.83. Found : C, 55.40; H, 5.93.

The free base (Va : R=H) obtained from the above picrate in the same manner as IVa (R=H). It was recrystallized from petr. ether to form needles, m.p. 68~70°. *Anal.* Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found : C, 74.44; H, 9.28.

0.25 g. of IVb (R=H) was hydrogenated to give 0.22 g. of the phenethyl derivative (Vb : R=H), which was recrystallized from petr. ether to form colorless prisms, m.p. 49~51°. *Anal.* Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found : C, 74.26; H, 9.19.

9-(*p*-Methoxyphenethyl)-1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol (Va : R=CH_3)——Catalytic reduction of 0.65 g. of the phenylethynyl carbinol IVa (R=CH_3) by the same method as Va (R=H) gave 0.64 g. of the oily phenethyl derivative (Va : R=CH_3), which was characterized as a picrate. Recrystallization from MeOH yielded 0.83 g. of yellow prisms, m.p. 196~198° (decomp.). *Anal.* Calcd. for $C_{25}H_{32}O_9N_4$: C, 56.38; H, 6.06. Found : C, 56.62; H, 5.86.

3-Methyl-6′-methoxyspiro[3-azabicyclo[3.3.1]nonane-9,1′-indane] (VI : R=H)——A mixture of 0.8 g. of the phenethyl derivative (Va : R=H) and 5.1 g. of polyphosphoric acid was heated under water-pump vacuum (18 mm. Hg), the temperature was raised from 30° to 95° during 30 min., with subsequent heating at 93~98° for 1 hr. The reaction mixture was dissolved in ice-water, made alkaline with 10% NaOH and extracted with Et_2O. The ethereal solution was extracted with dil. HCl and the acidic layer was made alkaline with NH_4OH and extracted with Et_2O. The ethereal extracts were washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent yielded an oily residue, which was converted into a crystalline picrate. Recrystallization from MeOH to give 0.4 g. of yellow prisms, m.p. 221~225° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_8N_4$: C, 57.59; H, 5.64. Found : C, 57.05; H, 5.96.

The oily free base was obtained from the above picrate in the same manner as IVa (R=H).

Oxidation of VI (R=H)——A solution of 100 mg. of CrO_3 in 3 ml. of 90% AcOH was added dropwise to a solution of 200 mg. of the cyclization product (VI : R=H) in 4 ml. of AcOH. The mixture was heated at 70~75° for 15 min., and allowed to stand for 6 hr. at room temperature. After concentration of the solvent, the reaction mixture was poured into ice-water, and made alkaline with dil. NH_4OH. The resulting precipitate was extracted with Et_2O. The combined ethereal extract was washed with H_2O and extracted with dil. HCl. The acidic layer was made alkaline with NH_4OH and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over Na_2SO_4 and evaporated. The oily

residue was dissolved in Et_2O and treated with charcoal to give 75 mg. of a pale yellow oil (IX). IR: $\nu_{max}^{CHCl_3}$ 1706 cm^{-1} (C=O).

The ethereal layer separated from acidic solution was washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residual oil was worked up in the same manner as IX to give 46 mg. of a colorless oil (X). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 1600 (CON<).

3-Methyl-9-(*p*-methoxyphenacylidene)-3-azabicyclo[3.3.1]nonane (VII)——A mixture of 0.6 g. of the phenethyl derivative (IVa: R=H), 18 ml. of dioxane 3 ml. of H_2O and 0.7 ml. of conc. H_2SO_4 was refluxed for 7 hr. After cooling, the reaction mixture was poured into H_2O, and made slightly alkaline with 10% K_2CO_3. The organic product was extracted with Et_2O and the extracts were washed with H_2O saturated with NaCl, and dried over Na_2SO_4. After removal of the solvent, the oily residue was converted into a crystalline picrate which was recrystallized from MeOH to give 0.58 g. of pale yellow prisms m.p. 212~215°. *Anal.* Calcd. for $C_{24}H_{26}O_9N_4$: C, 56.03; H, 5.09. Found: C, 56.17; H, 5.21.

The oily free base (VII) was obtained from the above picrate in the same manner as IVa (R=H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (C=O), 1600 (C=C). UV λ_{max}^{EtOH} mμ (log ε): 220 (4.06), 289 (4.23).

Cyclization reaction of 3-Methyl-9-(*p*-methoxyphenacylidene)-3-azabicyclo[3.3.1]nonane (VII)——0.4 g. of VII was treated with polyphosphoric acid and the reaction mixture was worked up by the similar procedure as the case of VIa (R=H) to give an oil, which gave a crystalline picrate. Recrystallization from MeOH to give 0.52 g. of pale yellow crystals, m.p. 210~212°. The mixed melting point with the picrate of the starting material (VII) was not depressed, and the infrared spectra of the both samples were identical.

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Summary

Cyclyzation of 3-methyl-9-(*p*-methoxyphenethyl)-3-azabicyclo[3.3.1]nonan-9-ol (Va: R=H) with polyphospholic acid gave a spiro compound of azabicyclononane (VI), but not a hydrophenanthrene derivative (VI'). The evidence for the structure of the cyclization product was provided by the fact that on oxidation with chromic acid, VI gave the 1-indanone (IX) showing the infrared absorption at 1706 cm^{-1} and the lactam ketone (X) showing the absorptions at 1705 cm^{-1} and 1600 cm^{-1}.

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