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145. Yoshinobu Sato : Syntheses of Allied Compounds of Lupine Alkaloids. V.¹⁾ Synthesis of 9-Azahexahydrojulolidine.

(Takamine Laboratory, Sankyo Co., Ltd.*¹⁾)

A new isomer of 9-methyl-9-azahexahydrojulolidine (2-methylperhydropyrido[3,4,5-*i,j*]quinolizine) was prepared, as described in the preceding paper of this series,¹⁾ and its configuration was assumed to be a racemic form (I). The present series of experiments were carried out in order to ascertain the structure of (I).

Reaction of (I) with equivalent of cyanogen bromide in ether results in the formation of 2-cyanoperhydropyrido[3,4,5-*i,j*]quinolizine (II), accompanied by by-product formation of substances assumed to be the methobromide of (II) and (III). (II) is an oily substance, forms a picrate of m.p. 186°, and its infrared spectrum exhibits absorption of a nitrile at 2217 cm⁻¹, which provided evidence for this structure.

On boiling this cyano compound (II) with 10% hydrochloric acid for four hours, saponification of the nitrile and decarboxylation occurred to produce a secondary amine, i. e. 9-azahexahydrojulolidine (perhydropyrido[3,4,5-*i,j*]quinolizine)(III). This substance also remained oily but formed a picrate of m.p. 245° and its infrared spectrum lacked the absorption of a nitrile (cf. Fig. 1).

Fig. 1. Infrared Absorption Spectra (in CHCl₃)

The compounds (II) and (III) so obtained differed from the all-*trans* type, i.e. the meso form³⁾ of 2-cyanoperhydropyrido[3,4,5-*i,j*]quinolizine, m.p. 53°, and 9-azahexahydrojulolidine(hydrate, m.p. 50°), synthesized by Tsuda and others,³⁾ and must be their stereoisomers. Since there should not occur any change in steric configuration during the reactions from (I) to (II) and then to (III), it is assumed that (II) and (III) have racemic-type steric structure possessing a *cis*-quinolizidine ring.

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Heating of (III) with palladium-asbestos in nitrogen atmosphere at $230\sim 270^\circ$ results in dehydrogenation to form the known substance, 4,5,6,8,9,10-hexahydropyrido[3,4,5-*i,j*]-quinolizine (9-azajulolidine or nordehydro- α -matrinidine)³⁾ (IV). This substance forms a picrate of m.p. 219° and its ultraviolet spectrum shows absorption at $271\text{ m}\mu$, which confirmed the structure of (IV). The conversion of (I) to (IV) as described above proves the structure of (I).

Attempt was then made to prepare 9-azahexahydrojulolidine (III) by reaction routes different from those described above. A mixture of 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i,j*]quinolizine (V) and liquid ammonia was heated in a sealed tube and 3,6-dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i,j*]quinolizine (VI) was obtained as fluorescent crystals of m.p. $278\sim 280^\circ$. Catalytic reduction of (VI) in acid or neutral medium with platinum oxide catalyst was different from that of (V) or 2-methyl-3,6-dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i,j*]quinolizine¹⁾ (IX), and absorption of hydrogen was extremely slow, stopping after absorption of ca. one mole. The product came as non-fluorescent crystals of m.p. 265° and this was further submitted to catalytic reduction over Raney nickel at 60° and 100 atm., but the starting material was recovered completely.

The foregoing result is probably due to the fact that when (VI) absorbs one mole of hydrogen to form (VII), it undergoes rearrangement to (VIII) with stable conjugated system. The ultraviolet absorption spectra of (VI) and (VIII) are indicated in Fig. 2.

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

It was reported in the preceding paper¹⁾ that the formation of the tetrahydro compound (XI) by catalytic reduction of 2-methyl-3,6-dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4-*i,j*]quinolizine (IX) over platinum oxide was accompanied by formation of a small amount of crystals of m.p. 240° as a by-product. Since the ultraviolet absorption spectrum of this substance is very similar to that of (VIII), it is assumed that it has the structure formulated as (XI) and resists reduction.

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Experimental

2-Cyanoperhydropyrido[3,4-*i,j*]quinolizine (II)—A solution of 0.5193 g. of (I) dissolved in 20 cc. of dehyd. Et₂O was poured into a solution of 0.3 g. of BrCN dissolved in 30 cc. of Et₂O, with stirring under ice cooling, and crystals began to separate out after 1 hr. of stirring. After allowing this mixture to stand over night, the crystals were filtered off, ether was evaporated from the filtrate, and the residue was distilled under a reduced pressure to collect a colorless oil of b.p._{0.05} 130~150°. Yield, 0.180 g. IR: $\delta_{\text{max}}^{\text{CHCl}_3}$ 2217 cm⁻¹ (—C≡N).

Dipicrate: m.p. 180° (from EtOH). Anal. Calcd. for C₂₄H₂₅O₁₄N₉: N, 20.0. Found: N, 19.87.

9-Azahexahydrojulolidine (III)—A solution of 0.815 g. of (II) dissolved in 25 cc. of 10% HCl was boiled and refluxed for 4 hr. The reaction mixture was concentrated under a reduced pressure, the residue was basified with NaOH, and extracted with Et₂O. The extract was dried over anhyd. Na₂SO₄ and the solvent was evaporated, leaving 0.29 g. of oil.

Dipicrate: m.p. 240° (from EtOH). Anal. Calcd. for C₂₃H₂₆O₁₄N₈: C, 44.8; H, 4.22; N, 14.6. Found: C, 45.25; H, 3.86; N, 14.22.

9-Azajulolidine (IV)—A mixture of 120 mg. of (III) and 50 mg. of 40% Pd-asbestos was heated in N₂ stream at 230~270°. Evolution of H₂ became 42 cc. after 20 min. and the reaction became extremely slack. The reaction mixture was cooled, treated with EtOH, and the catalyst was filtered off. The filtrate was concentrated under a reduced pressure, the residue was extracted with Et₂O, and the solvent was evaporated from the extract after drying over anhyd. Na₂SO₄, leaving ca. 20 mg. of an oil.

One part of this oil was submitted to ultraviolet spectral measurement as EtOH solution and the other part was dissolved in Et₂O to prepare a picrate. UV $\lambda_{\text{max}}^{\text{EtOH}}$ 271 m μ , $\lambda_{\text{min}}^{\text{EtOH}}$ 246 m μ .

Picrate: m.p. 218~219°, which showed no depression on admixture with the compound obtained by Tsuda and others.

3,6-Dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4-*i,j*]quinolizine (VI)—A mixture of 320 mg. of (V) and 20 cc. of liquid NH₃ was heated in an autoclave at 100° for 8 hr., NH₃ was allowed to evaporate, and the residue was recrystallized from EtOH. m.p. 278~280°. Yield, 30 mg. Anal. Calcd. for C₁₁H₈O₂N₂: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.94; H, 3.88; N, 13.80. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 248.5(4.21), 358(3.84), 394(3.84). IR $\delta_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1646, 1668 (lactam), 1575, 1533, 1477 (ring).

Reduction of 3,6-Dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4-*i,j*]quinolizine (VI)—A solution of 72 mg. of (VI) dissolved in 50 cc. of glacial AcOH was shaken in H₂ stream, with PtO₂ as a catalyst. The reaction stopped after absorption of ca. 1 mole of H₂ in 5 hr. The catalyst was filtered off, the solvent was evaporated from the filtrate, and the residue was recrystallized from EtOH to colorless crystals without fluorescence, m.p. 263~265°. Anal. Calcd. for C₁₁H₁₀O₂N₂: C, 65.33; H, 4.98; N, 13.62. Found: C, 65.68; H, 4.48; N, 14.08. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 224(4.30), 245.5(4.16), 264.5(4.04), 273.5(3.98), 330(3.90), 343(3.86).

The use of EtOH as a solvent in place of AcOH in the above reduction afforded the same colorless crystals, m.p. 263~265°.

Summary

9-Azahexahydrojulolidine (III) was prepared by saponification and decarboxylation of 2-cyanoperhydropyrido[3,4,5-*i,j*]quinolizidine (II) with hydrochloric acid, obtained by reaction of 9-methyl-9-azahexahydrojulolidine (I) and cyanogen bromide. Series of these compounds was assumed to have the *cis*-quinolizidine ring and, in order to ascertain this assumption, (III) was converted to 9-azajulolidine (IV).

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146. Katsumi Tanabe, Rinji Takasaki, Ryoza Hayashi, and Makoto Shirasaka :
Steroid Series. I. Microbial Oxidation of Steroids
by *Sclerotinia libertiana*.^{*1}

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Since Peterson and others¹⁾ succeeded in hydroxylation of 11 α -position in progesterone by the use of the Phycomycetes of *Rhizopus* species and introduced a new process for synthesis of adrenocortical hormones, microbiological transformation of steroids has drawn the interest of many workers. Microbial oxidation of steroids of pregnane series with *Sclerotinia libertiana* was carried out by the present authors and it was found that this organism is capable of hydroxylating the 2 β -position. 2 β -Hydroxylation of steroids with microorganisms was reported only recently by two research groups, using *Penicillium* sp.,²⁾ *Rhizoctonia ferruginea*,³⁾ and *Streptomyces* sp.⁴⁾

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