UDC 547.94 : 547.836.7

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

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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).

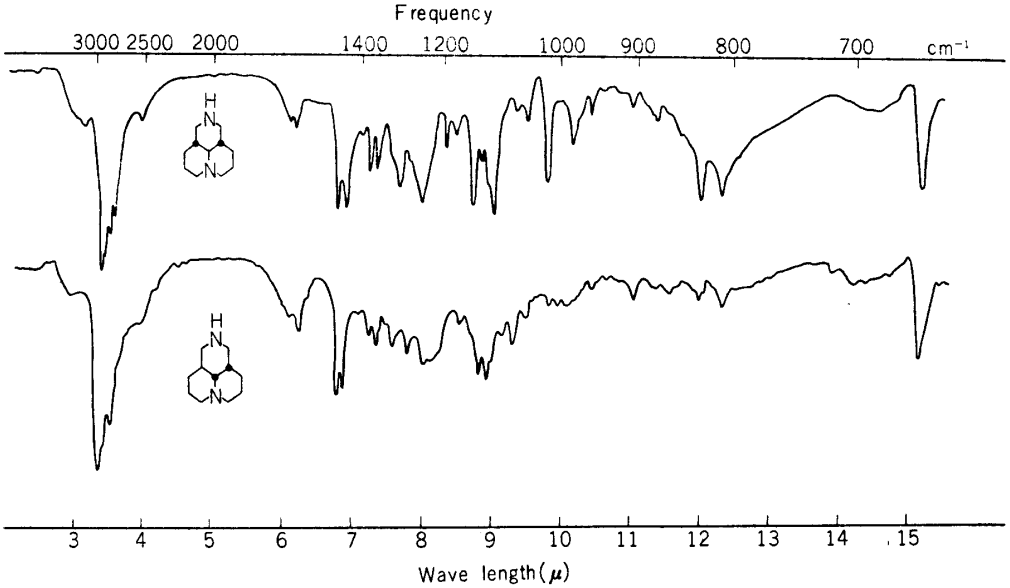

Fig. 1. Infrared Absorption Spectra (in $CHCl_3$)

The compounds (II) and (III) so obtained differed from the all-*trans* type, i.e. the meso form[3] 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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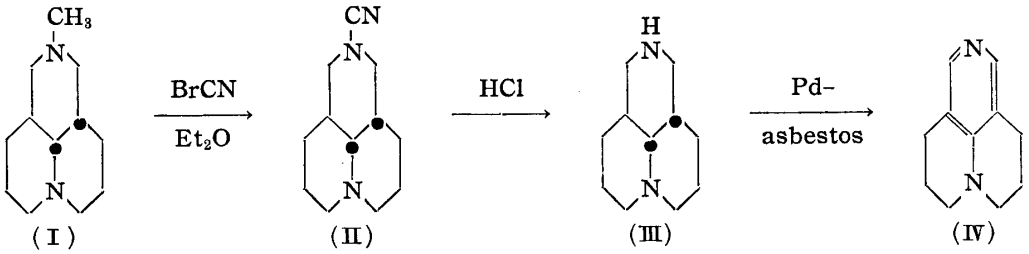
1) Part IV : This Bulletin, **7**, 247(1959).
2) B. Eda, K. Tsuda, M. Kubo : J. Am. Chem. Soc., **80**, 2426(1958).
3) K. Tsuda, *et al.* : J. Org. Chem., **21**, 1481(1956).

Heating of (III) with palladium-asbestos in nitrogen atmosphere at 230~270° 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 mμ, 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. 278~280°. 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*]quinolizine[1] (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.

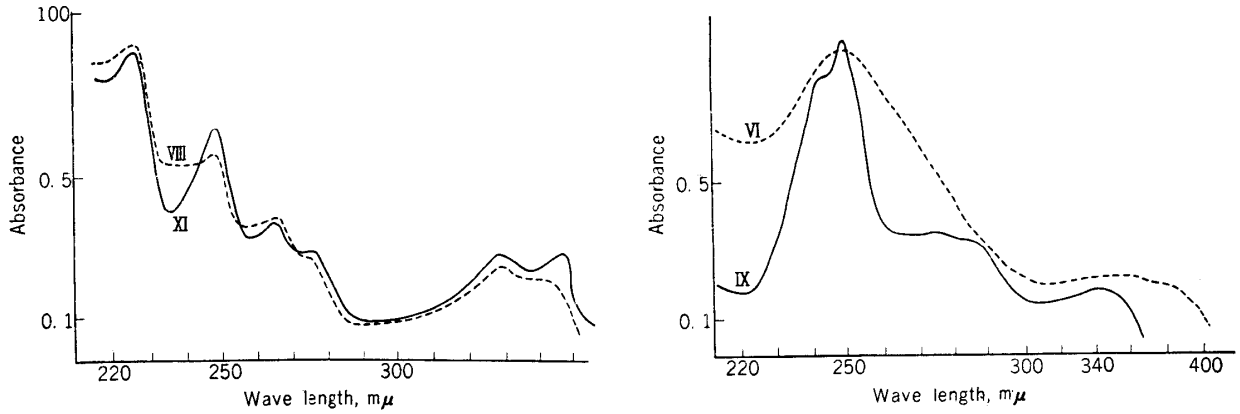
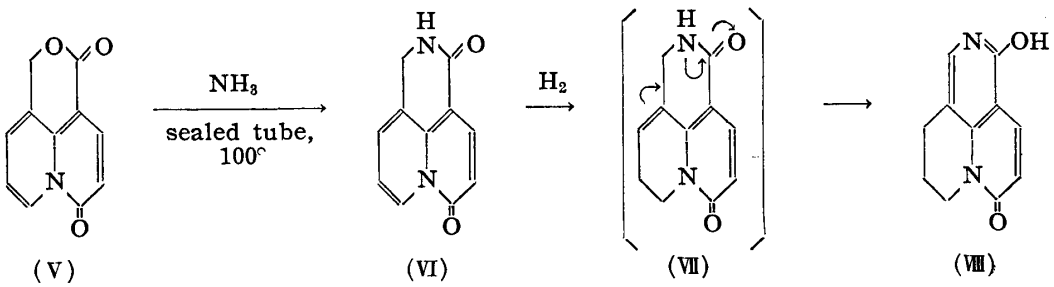
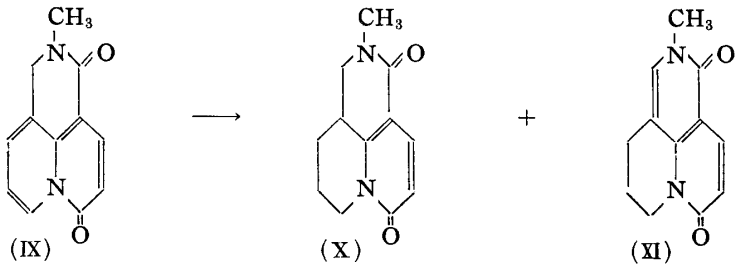


Fig. 2. Ultraviolet Absorption Spectra (in EtOH)



It was reported in the preceding paper[1] 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[3,4,5-*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.



(IX) (X) (XI)

The writer expresses his deep gratitude to Prof. K. Tsuda of the Institute of Applied Microbiology, University of Tokyo, for his kind and helpful guidance, and to Mr. M. Matsui, Director of this Laboratory, for kind encouragement. The writer is also indebted to Misses T. Furukawa and H. Otsuka, and Mr. T. Onoe for microanalytical data, and to Messrs. H. Shindo, O. Amakasu, and N. Higosaki for spectral measurement.

Experimental

2-Cyanoperhydropyrido[3,4,5-*i*,*j*]quinolizine (II)—A solution of 0.5193 g. of (I) dissolved in 20 cc. of dehyd. Et_2O was poured into a solution of 0.3 g. of BrCN dissolved in 30 cc. of Et_2O, 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 : $\delta_{max}^{CHCl_3}$ 2217 cm^{-1} (-C≡N).

Dipicrate : m.p. 180° (from EtOH). *Anal.* Calcd. for $C_{24}H_{25}O_{14}N_9$: 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 Et_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent was evaporated, leaving 0.29 g. of oil.

Dipicrate : m.p. 240° (from EtOH). *Anal.* Calcd. for $C_{23}H_{26}O_{14}N_8$: 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 N_2 stream at 230~270°. Evolution of H_2 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 Et_2O, and the solvent was evaporated from the extract after drying over anhyd. Na_2SO_4, 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 Et_2O to prepare a picrate. UV λ_{max}^{EtOH} 271 mμ, λ_{min}^{EtOH} 246 mμ.

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[3,4,5-*i*,*j*]quinolizine (VI)—A mixture of 320 mg. of (V) and 20 cc. of liquid NH_3 was heated in an autoclave at 100° for 8 hr., NH_3 was allowed to evaporate, and the residue was recrystallized from EtOH. m.p. 278~280°. Yield, 30 mg. *Anal.* Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 13.99. Found : C, 65.94; H, 3.88; N, 13.80. UV λ_{max}^{EtOH} mμ (log ε) : 248.5(4.21), 358(3.84), 394(3.84). IR δ_{max}^{KBr} cm^{-1} : 1646, 1668 (lactam), 1575, 1533, 1477 (ring).

Reduction of 3,6-Dioxo-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i*,*j*]quinolizine (VI)—A solution of 72 mg. of (VI) dissolved in 50 cc. of glacial AcOH was shaken in H_2 stream, with PtO_2 as a catalyst. The reaction stopped after absorption of ca. 1 mole of H_2 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 $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.62. Found : C, 65.68; H, 4.48; N, 14.08. UV λ_{max}^{EtOH} mμ (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*]quinolizine (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, Ryozo Hayashi, and Makoto Shirasaka : Steroid Series. I. Microbial Oxidation of Steroids by *Sclerotinia libertiana*.*1

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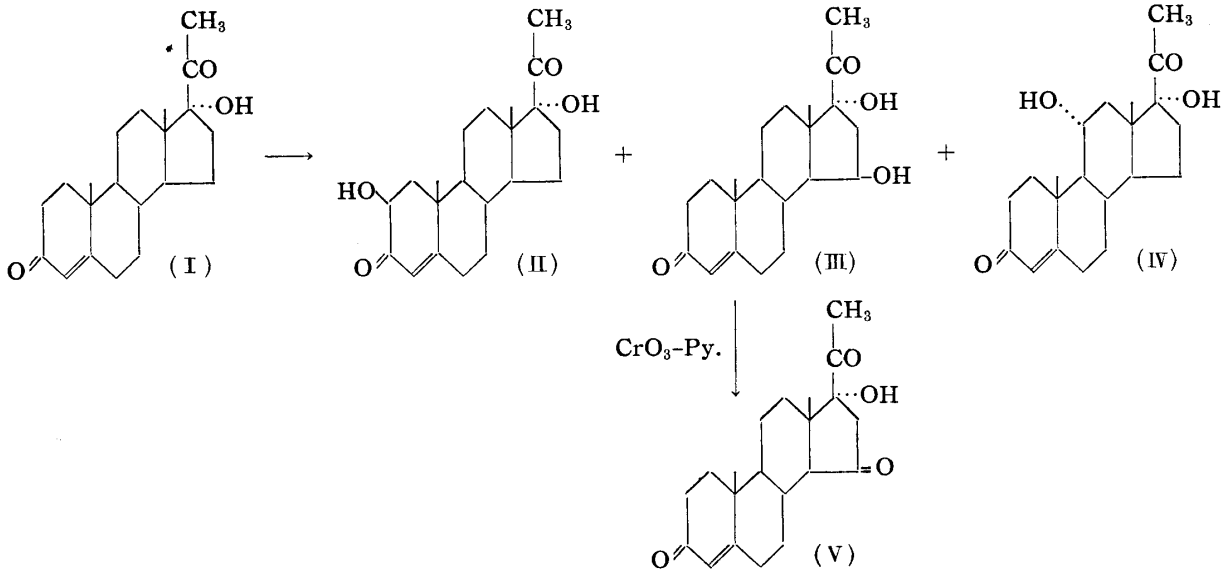
Since Peterson and others[1] succeeded in hydroxylation of 11α-position in progesterone by the use of the Phycomycetes of Rhizopus species and introduced a new process for synthesis of adrenocortical hormones, microbiological transformation of steroids has drawn the interest of many workers. Microbial 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 2β-position. 2β-Hydroxylation of steroids with microörganisms was reported only recently by two research groups, using Penicillium sp.,[2] *Rhizoctonia ferrugena*,[3] and Streptomyces sp.[4]



*1 A brief report of this work was published as a Communication to the Editor in Bull. Agr. Chem. Soc. Japan, **22**, 273(1958); **23**, 245(1959).

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1) D. H. Peterson, *et al.* : J. Am. Chem. Soc., **74**, 5933(1952).
2) R. M. Dodson, A. H. Goldkamp, R. D. Muir : *Ibid.*, **79**, 3921(1957).
3) G. Greenspon, *et al.* : *Ibid.*, **79**, 3922(1957).
4) H. L. Herzog, *et al.* : *Ibid.*, **79**, 3921(1957).