ii) From 1-Cyano-9-methoxymethyl-4-oxo-4*H*-quinolizine (XX) : 0.9129 g. of (XX) was boiled under reflux for 5 hr. with 80 cc. of 20% HCl. The mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. From the $CHCl_3$ layer 0.537 g.(62.5%) of yellow crystals, m.p. 252~254° (from EtOH), was obtained.

1-Ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXIII)—1.3 g. of 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXII) was boiled under reflux for 1 hr. with 75 cc. of 18% HCl. After the mixture was cooled, K_2CO_3 was added and neutralized solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried, the solvent was distilled off, and the residual crystals were recrystallized to give 0.0611 g. of yellow crystals, m.p. 252~254° (from EtOH). This showed no depression on admixture with the crystals of m.p. 252~254° obtained from (XIX) or (XX).

From the alcoholic filtrate left after separation of above crystals of m.p. 252~254°, yellow crystals, m.p. 82~84°, were obtained; yield, 0.09 g. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: N, 5.36. Found : N, 5.24. U.V. λ_{max}^{EtOH} mμ(log ε) : 260(4.14), 381(4.16). I.R. ν_{max}^{KBr} cm^{-1} : 1712(ester C=O), 1680(-CON<).

Summary

2-Cyanomethyl-3-methoxymethylpyridine and ethyl (3-methoxymethyl-2-pyridyl)acetate were prepared from ethyl 2-methylnicotinate. Condensation of these compounds with diethyl ethoxymethylenemalonate afforded 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine and 1-cyano-3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine. The ethoxycarbonyl group in these compounds was saponified and further decarboxylated on being heated with hydrochloric acid. A more drastic condition easily afforded 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine.

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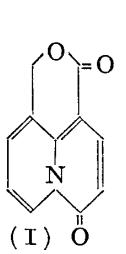
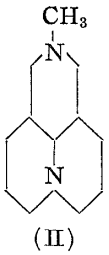
UDC 547.94 : 547.836.7

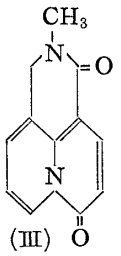
49. Yoshinobu Sato : Syntheses of Allied Compounds of Lupine Alkaloids. IV.[1] Synthesis and Hydrogenation of 4-Oxo-4*H*-quinolizine Derivatives.

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

Experiments were carried out to prepare 2-methylperhydropyrido[3,4,5-*i*,*j*]quinolizine (II) (9-methyl-9-azahexahydrojulolidine), an intermediate obtained during synthesis of matrine by Tsuda and others,[2] from 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (I) whose synthesis was described in the preceding report.[1]


(I)


(II)


(III)

On heating (I) with excess of methylamine in a sealed tube at 80~100°, yellow crystals, m.p. 259°, are obtained. This substance shows fluorescence like (I) and its infrared spectrum exhibits a new additional absorption for a lactam but not that for hydroxyl or C=O in δ-lactone. Therefore, this compound must be 3,6-dioxo-2-methyl-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i*,*j*]quinolizine (III).

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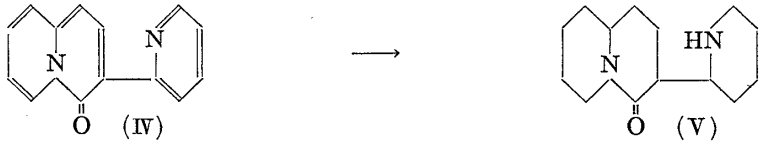
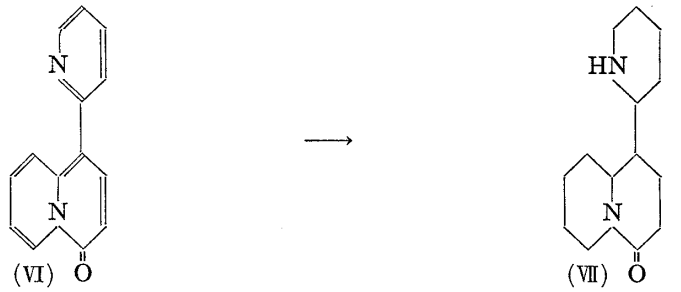
1) Part III : This Bulletin, **7**, 241(1959); *ibid.*, **6**, 222(1958).

2) K. Tsuda, *et al.* : J. Org. Chem., **21**, 1481(1956).

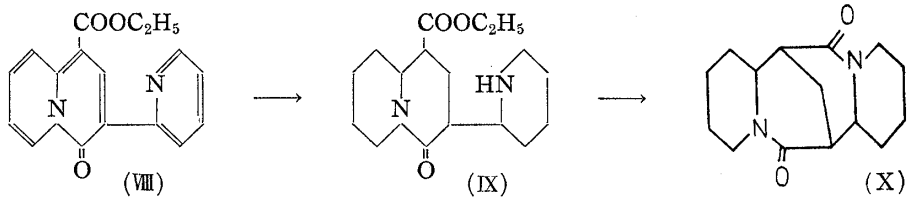
Many workers have carried out the reduction of 4-oxo-4*H*-quinolizine compounds and their results can be roughly divided into two groups. One of these is the reduction over platinum oxide in acid medium to afford the octahydro compound. Reduction of 3-(2-pyridyl)-4-oxo-4*H*-quinolizine (IV)[3] in 5% hydrochloric acid in the presence of platinum oxide affords 3-(2-piperidyl)-4-oxo-4*H*-quinolizidine (V), while the same reduction of 1-(2-pyridyl)-4-oxo-4*H*-quinolizine (VI) gives 1-(2-piperidyl)-4-oxo-4*H*-quinolizidine (VII).[4] Catalytic reduction of 1-ethoxycarbonyl-3-(2-pyridyl)-4-oxo-4*H*-quinolizine (VIII) in acid medium over platinum oxide results in the formation of dioxosparteine[5] (X) or its intermediate compound, 1-ethoxycarbonyl-3-(2-piperidyl)-4-oxo-4*H*-quinolizidine[6] (IX).



(IV) (V)

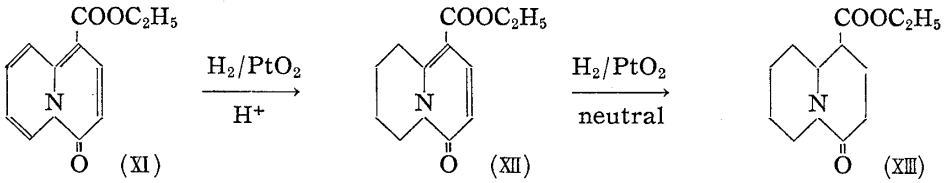


(VI) (VII)



(VIII) (IX) (X)

On the other hand, Boekelheide[7] reported an abnormal phenomenon that the catalytic reduction of 1-ethoxycarbonyl-4-oxo-4*H*-quinolizine (XI) over platinum oxide in acid solution stops at the tetrahydro (XII) stage while the same reduction in neutral medium proceeds until the formation of an octahydro compound (XIII).



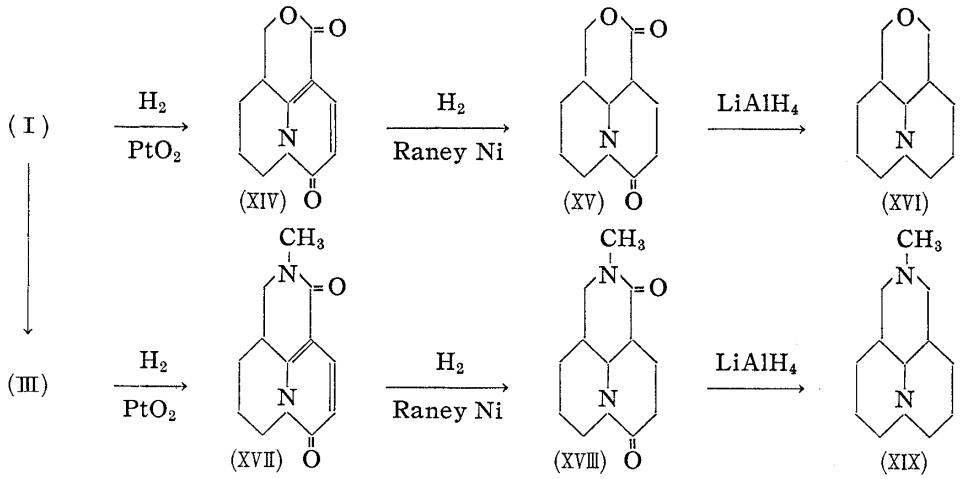
(XI) (XII) (XIII)

Catalytic reduction of (I) and (III) over platinum oxide at ordinary temperature and pressure, either in acid or neutral solution, results in comparatively rapid absorption of two moles of hydrogen to form the tetrahydro compounds, 3,6-dioxo-8,9,10,10a-tetrahydro-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (XIV) and 2-methyl-3,6-dioxo-2,3,8,9,10,10a-hexahydro-1*H*,6*H*-pyrido[3,4,5-*i*,*j*]quinolizine (XVII). The fact that the reaction stops at the tetrahydro stage in acid solution is similar to the report of Boekelheide but the reduction did not proceed further even in neutral medium, differing from the report

3) P. Knoth : Monatsh., **86**, 210(1955).
4) Y. Sato : This Bulletin, **5**, 412(1957).
5) a) K. Tsuda, Y. Sato : This Bulletin, **2**, 190(1954); b) F. Gulinovsky, G. Kainz : Monatsh., **77**, 137(1949); c) F. Sorm, B. Keil : Collection Czech. Chem. Communs., **13**, 544(1948).
6) F. Bohlmann, *et al.* : Chem. Ber., **90**, 653(1957).
7) V. Boekelheide, J.P. Lodge, Jr. : J. Am. Chem. Soc., **73**, 3681(1951).

of Boekelheide. Neither (XIV) nor (XVII) shows any fluorescence and they respectively melt at 169° and 155°.

The ultraviolet spectrum of (XIV) resembles those[8] of cytisine, 4-oxo-6,7,8,9-tetrahydro-4*H*-quinolizine, and 1,3-diethoxycarbonyl-4-oxo-6,7,8,9-tetrahydro-4*H*-quinolizine, while the infrared spectrum of (XIV) shows absorptions of a lactam and =CO in δ-lactone. Therefore, the pyridine portion of 4-oxo-4*H*-quinolizine ring must have been hydrogenated. By analogy, (XVII) must have been hydrogenated in the pyridine portion of the 4-oxo-4*H*-quinolizine ring. In the reduction of (III), only a very small amount of a by-product was obtained as colorless crystals of m.p. 240°. Details of this point will be discussed in the forthcoming report.



Further hydrogenation of (XIV) and (XVII) is effected only when these compounds are shaken in hydrogen stream, as an ethanol solution over Raney nickel catalyst, at 100 atm. and 60° for six hours, respectively affording 3,6-dioxoperhydropyrano[3,4,5-*i,j*]-quinolizine (XV) and 3,6-dioxo-2-methylperhydropyrido[3,4,5-*i,j*]quinolizine (XVIII). Neither (XV) nor (XVIII) shows any absorptions in the ultraviolet region and shows absorption for double bond in the infrared spectrum.

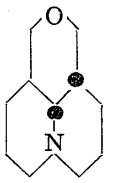
Reaction of (XV) in tetrahydrofuran with lithium aluminum hydride effects reduction of the lactam portion as well as the δ-lactone to form a diol compound, and the reaction further proceeds to effect dehydrative cyclization to form a pyran ring, affording perhydropyrano[3,4,5-*i,j*]quinolizine (XVI), an oily substance which forms a picrate, and oily methiodide and chloroaurate.

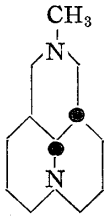
Reduction of (XVIII) with lithium aluminum hydride as in the case of (XV) affords 2-methylperhydropyrido[3,4,5-*i,j*]quinolizine (XIX) (9-methyl-9-azahexahydrojulolidine), an oily substance, whose dipicrate, dimethiodide, and dichloroaurate do not agree with all-*trans* form of 9-methyl-9-azahexahydrojulolidine obtained by Tsuda and others.[9] (XIX) did not undergo isomerisation when heated with aluminum trichloride in a sealed tube, whose air had been replaced with nitrogen, at 200~210° for 7 hours.

Bohlmann[10] reported that compounds possessing a *trans*-quinolizidine ring exhibit characteristic absorption in the region of 2700~2800 cm^{-1}. Tsuda and others[11] proved chemically that the two kinds of hexahydrojulolidine obtained by reduction of julolidine both have *trans*-quinolizidine ring. These compounds also show strong absorptions in the region of 2700~2800 cm^{-1}.

8) F. Bohlmann, N. Ottawa, R. Keller: Ann., **587**, 162(1954).
9) K. Tsuda, S. Saeki: This Bulletin, **6**, 391(1958).
10) F. Bohlmann, *et al.*: Chem. Ber., **90**, 653(1957); F. Bohlmann, W. Weise, D. Rahtz: Angew. Chem., **69**, 642(1957).

The compound (XIX) obtained in this experiment shows only a very weak absorption in the region of 2700~2800 cm^{-1} compared to hexahydrojulolidine or (II).[11] The absorption at 2786 cm^{-1} appearing in the infrared spectrum of (XIX) agrees completely with that in N-methyltetrahydrocytisine and is thought to be the absorption of N-methyl in piperidine. The infrared spectrum of (XVI) does not show the characteristic absorption of *trans*-quinolizidine. It is therefore assumed that the quinolizidine ring in both (XVI) and (XIX) is in *cis*-bonding, and should have the configurations shown as (XX) and (XXI).


(XX)


(XXI)

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

Experimental

3,6-Dioxo-8,9,10,10a-tetrahydro-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (XIV)—A mixture of 537 mg. of 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (I), 200 mg. of PtO_2, and 30 cc. of EtOH was subjected to hydrogenation at room temperature and atmospheric pressure. Hydrogen uptake stopped after 2 molar equivalents of H_2 had been absorbed (ca. 2 hr.). After removal of the catalyst, the solvent was evaporated to give colorless prisms, m.p. 168~169°(from EtOH). Yield, 450 mg. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.44; H, 5.29; N, 6.54. U.V. λ_{max}^{MeOH}: 274 mμ(log ε 4.19). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1721(lactone C=O), 1667(CON<), 1595, 1572, 1481 (ring).

3,6-Dioxoperhydropyrano[3,4,5-*i*,*j*]quinolizine (XV)—A mixture of 1.0 g. of (XIV), 0.5 g. of Raney Ni, and 50 cc. of EtOH was subjected to hydrogenation at 60° and 120 atm. for 8 hr. After removal of the catalyst and the solvent, the residual oil was treated with a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue was chromatographed over Al_2O_3. Colorless crystals, m.p. 120~122°(from Et_2O-EtOH). Yield, 0.55 g. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.42; H, 6.86; N, 6.51. I.R. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1739(lactone C=O), 1629(CON<).

Perhydropyrano[3,4,5-*i*,*j*]quinolizine(XVI)—To a solution of 1 g. of $LiAlH_4$ in 60 cc. of tetrahydrofuran, a solution of 0.65 g. of (XV) in 20 cc. of tetrahydrofuran was added gradually under chilling and stirring. The mixture was refluxed for 6 hr. Moist Et_2O was added to decompose Li-complex salt. The Et_2O layer was separated and dried over anhyd. Na_2SO_4, the solvent was distilled off, and residual oil was distilled under reduced pressure to give pale yellow oil, $b.p_{13}$ 120~130°. Yield, 0.25 g. I.R. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1116, 1104(ether, C-N<).

Picrate: m.p. 189~191° (from EtOH). *Anal.* Calcd. for $C_{17}H_{22}O_8N_4$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.56; H, 5.58; N, 14.00.

Chloroaurate: m.p. 125~127°(decomp.)(from EtOH). The oily methiodide was dissolved in water, converted to methochloride by treatment with AgCl, and aqueous $AuCl_3$ solution was added to its aqueous solution to deposit the chloroaurate. *Anal.* Calcd. for $C_{12}H_{21}ON \cdot AuCl_4$: C, 27.0; H, 3.93; N, 2.62. Found: C, 27.04; H, 4.06, N, 2.83.

3,6-Dioxo-2-methyl-2,3-dihydropyrido[3,4,5-*i*,*j*]quinolizine (III)—A mixture of 8 g. of (I) and 40 cc. of liq. $MeNH_2$ was heated at 80~100° for 8 hr. in an autoclave. The pressure rose to 40 atm. After the reaction was complete, excess $MeNH_2$ was evaporated, the residue was treated with a small amount of water, and then extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residue was recrystallized from EtOH to yellow crystals, m.p. 257~259°. Yield, 2.85 g. *Anal.* Calcd. for $C_{12}H_{10}O_2N_2$: C, 67.28; H, 4.71; N, 13.08; O, 14.93. Found: C, 67.39; H. 4.94; N, 12.93; O, 15.23. U.V. λ_{max}^{EtOH} mμ(log ε): 248.5(4.56), 268(4.18), 288(4.07), 347(3.85). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678, 1650(CON<); 1618, 1543(ring).

11) The fact that (II) has all-*trans* configuration was proved by measurement of its dipole moment. cf. B. Eda, K. Tsuda, M. Kubo: This Bulletin, **6**, 624(1958); *idem.*: J. Am. Chem. Soc., 88, 2426(1958).

3,6-Dioxo-2-methyl-2,3,8,9,10,10a-hexahydro-1*H*,6*H*-pyrido[3,4,5-*i*, *j*]quinolizine (XVII)—A mixture of 1.15 g. of (III), 370 mg. of PtO_2, and 60 cc. of glacial AcOH was subjected to hydrogenation at room temperature and atmospheric pressure. Hydrogen uptake stopped after 2 molar equivalents of H_2 had been absorbed (about 1.5 hr.). After removal of the catalyst and the solvent, the residue was taken up in a small amount of water, neutralized with K_2CO_3, and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue was recrystallized from EtOH to colorless prisms, m.p. 153~155°. Yield, 0.75 g. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.52; N, 12.62. U.V. λ_{max}^{EtOH}: 272 mμ(log ε 4.13). I.R. $\nu_{max}^{CHCl_3}$: 1661 cm^{-1}(CON<).

2-Methyl-3,6-dioxoperhydropyrido[3,4,5-*i*, *j*]quinolizine (XVIII)—A mixture of 500 mg. of (XVII), 300 mg. of Raney Ni, and 50 cc. of EtOH was subjected to hydrogenation at 60° and 120 atm. for 8 hr. After removal of the catalyst and the solvent, the residual oil was treated with a small amount of water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue, m.p. 84~86°, was recrystallized from Et_2O to a monohydrate, m.p. 106~108°. Yield, 350 mg. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2 \cdot H_2O$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.71; H, 7.94; N, 11.81. I.R. $\nu_{max}^{CHCl_3}$: 1613 cm^{-1}(CON<).

2-Methylperhydropyrido[3,4,5-*i*, *j*]quinolizine (XIX)—To a solution of 1 g. of $LiAlH_4$ in 60 cc. of tetrahydrofuran, a solution of 0.48 g. of (XVIII) in 15 cc. of tetrahydrofuran was added gradually under chilling and stirring. After the addition was complete, the mixture was refluxed for 8 hr. with stirring. After cool, moist Et_2O was added to decompose the Li-complex salt, the inorganic salt filtered off, and washed with Et_2O. The filtrate and ether washings were combined and dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residual oil was distilled under reduced pressure to give a pale yellow oil, $b.p_4$ 140~150°. Yield, 0.29 g. *Anal.* Calcd. for $C_{12}H_{22}N_2 \cdot H_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 68.25; H, 11.98; N, 13.07. I.R. ν_{max}^{oil} cm^{-1}: 2915(CH_2), 2786(CH_3N<).

Dipicrate: m.p. 240~242° (from EtOH). *Anal.* Calcd. for $C_{24}H_{28}O_{14}N_8$: C, 44.2; H, 4.3; N, 17.2. Found: C, 44.13; H, 4.13; N, 17.20.

Dichloroaurate: m.p. 255~256° (decomp.) (from EtOH). Prepared from dimethiodide (hygroscopic crystals) by a method similar to that for preparation of the chloroaurate of (XVI). *Anal.* Calcd. for $C_{14}H_{28}N_2 \cdot Au_2Cl_8$: C, 18.65; H, 3.12; N, 3.12. Found: C, 18.93; N, 3.10; N, 3.61.

Attempted Isomerisation of 2-Methylperhydropyrido[3,4,5-*i*, *j*]quinolizine by $AlCl_3$—A mixture of 0.29 g. of 2-methylperhydropyrido[3,4,5-*i*, *j*]quinolizine and 1.5 g. of $AlCl_3$ was heated at 200~210° for 7 hr. in N_2 atmosphere. The mixture was dissolved in dil. HCl and filtered. The filtrate was treated with Et_2O. The acid layer was basified with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residual oil was distilled under reduced pressure to give a pale yellow oil, $b.p_1$ 150°(bath temp.). Yield, 0.17 g.

Picrate: m.p. 240~242°(from EtOH). This showed no depression on admixture with the picrate of 2-methylperhydropyrido[3,4,5-*i*, *j*]quinolizine.

Summary

Three-step reduction of 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (I) and a compound derived from it, 3,6-dioxo-2-methyl-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i*,*j*]quinolizine (III), respectively afforded perhydropyrano[3,4,5-*i*,*j*]quinolizine (XVI) and 2-methylperhydropyrido[3,4,5-*i*,*j*]quinolizine (XIX). It was concluded that both compounds possess the *cis*-quinolizidine ring.

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