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207. Zen-ichi Horii, Masazumi Ikeda, Miyoji Hanaoka, Masashige Yamauchi, Yasumitsu Tamura,*1 Seiichi Saito, Tadasu Tanaka, Keishi Kotera, and Norio Sugimoto*2 : Structure of Securitinine.

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A new alkaloid, securitinine, was isolated from the root barks of *Securinega suffruticosa* Rehd. in Formosa, and the structure of this alkaloid was established as I.

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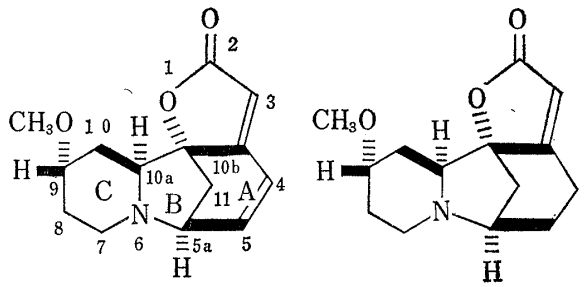
In continuation of the studies on constituents of Securinega species,[1] we isolated a new alkaloid from the roots of *S. suffruticosa* Rehd. growing in Hou-lung (Formosa) and designated it securitinine. In a preliminary communication,[2] spectral and chemical evidences established the structure of this alkaloid as I. A full account of this work is given in this paper.

Securitinine (I), yellow plates, m.p. 129~130°, $[\alpha]_D$ −952.3°, possesses a molecular formula $C_{14}H_{17}O_3N$. It contains an $\alpha,\beta,\gamma',\delta'$-unsaturated γ-lactone ring [IR bands at 1818 (sh.), 1758 and 1628 cm^{-1}; UV maximum at 257mμ (log ε 4.20)] and one methoxyl group [NMR peak at 6.75 τ (singlet, 3H)]. The nuclear magnetic resonance spectrum exhibited an octet (2H) at 4.05~3.47 τ and a singlet (1H) at 4.25 τ, typical of H_4, H_5 and H_3, respectively, of type found in securinine[3] or allosecurinine.[4,5] Reduction of I with sodium borohydride gave a dihydro derivative (II), m.p. 118~119°, which showed an ultraviolet absorption maximum at 215mμ (log ε 4.26).



I II

Chart 1.

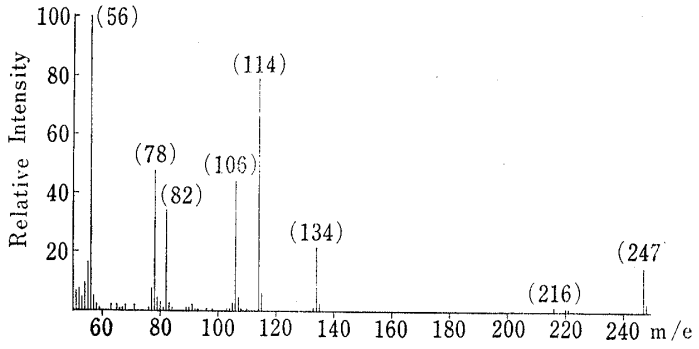


Fig. 1. Mass Spectrum of Securitinine (I)

The mass spectrum (Fig. 1) of securitinine showed characteristic peaks at m/e 247 (M^+, 15), 134 (21), 114 (79), 106 (44), 82 (34), 56 (base peak). Their empirical formulae were determined by the high-resolution mass spectrometry (Table I). The main

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1) Z. Horii, M. Ikeda, Y. Tamura, S. Saito, K. Kotera, T. Iwamoto : This Bulletin, **13**, 1307 (1965), and references therein.

2) Z. Horii, M. Ikeda, M. Hanaoka, M. Yamauchi, Y. Tamura, S. Saito, T. Tanaka, K. Kotera, N. Sugimoto : *Ibid.*, **14**, 917 (1966).

3) S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura : Tetrahedron, **19**, 2085 (1963).

4) I. Satoda, M. Murayama, J. Tsuji, E. Yoshii : Tetrahedron Letters, **1962**, 1199.

5) J. Parello, A. Melera, R. Goutarel : Bull. soc. chim. France, **1963**, 197, 898.

Table I. Exact Masses and Compositions of Ions

m/e observed	m/e calculated	composition
247.1215	247.1222	$C_{14}H_{17}O_3N$
134.0402	134.0408	$C_8H_6O_2$
114.0947	114.0975	$C_6H_{12}ON$
106.0435	106.0451	C_7H_6O
82.0680	82.0703	C_5H_8N
56.0490	56.0480	C_3H_6N

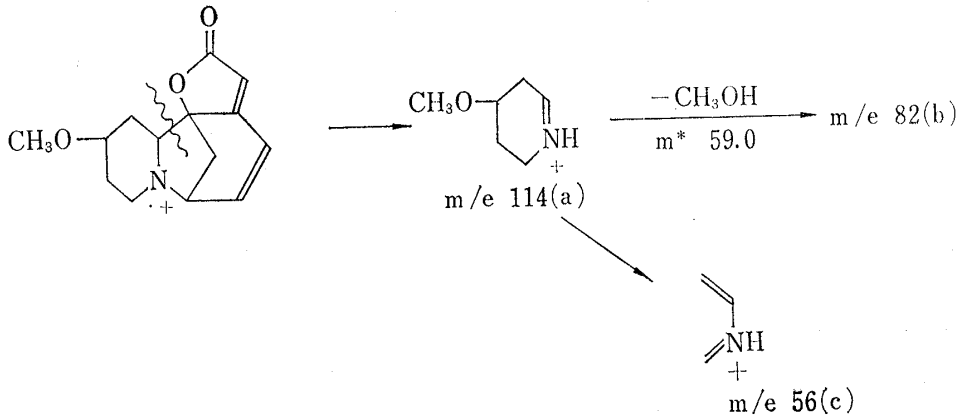

Chart 2.

fragmentation process of this alkaloid (Chart 2) can be rationalized on the basis of that proposed for securinine*3,5) except for the 30 mass unit increment due to the methoxyl group, and hence the two prominent peaks at m/e 114 and m/e 82 can be explained by assuming the cleavage between C_{10a} and C_{10b} with associated hydrogen transfer to give a (m/e 114) and further elimination of methanol to b (m/e 82). This feature, in conjunction with the above-mentioned physical and chemical data, suggests securitinine to be a securinine or allosecurinine derivative with one methoxyl group in the piperidine (or C) ring. A further information on the location of the methoxyl group came from the following inspection of the spectrum. Appearance of the base peak at m/e 56 (c), supposed to result from the m/e 114 ion (a), rules out the possibility that the methoxyl group is situated at C_7. Furthermore, if the methoxyl group is substituted at β-position of nitrogen, *i.e.* C_8 or C_{10}, the fragment ion resulting from the α-cleavage between the new oxygen function and nitrogen should be expected, as observed in the cases of securinol A[1] or tropane alkaloids.[6] However, this is not the case and thus the methoxyl group should be located most probably at C_9. This result was confirmed by the nuclear magnetic double resonance experiments and the synthesis of a degradation product (III).

Judging from the similarity of the nuclear magnetic resonance spectra of securitinine and allosecurinine, a multiplet near 6.16 τ (2H) is readily assigned to H_{5a} and H_{10a}, and a symmetrical multiplet centered at 6.41 τ to $>CH$-OCH_3. As can be seen from Fig. 2, irradiation of H_{10a} near 6.16 τ caused the multiplet at the highest field (8.84 τ) to collapse to a quartet (J=3.5 and 14.4 c.p.s.) and irradiation near 6.41 τ ($>CH$-OCH_3) caused the multiplet at 8.84 τ to a quartet (J=8.5 and 14.3 c.p.s.). These findings indicate that the

*3 It has been found that securinine and allosecurinine showed an identical mass spectrum.[5]

6) E. L. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor, C. Djerassi: Tetrahedron, **20**, 585 (1964).

upfield multiplet, assignable to one of two methylene protons at C_{10}, is coupled to both H_{10a} and the proton attached to the carbon bearing the methoxyl group, and hence the methoxyl group must be situated at C_9. The more detailed discussion about the upfield multiplet will be done later.

Treatment of securitinine with zinc and sulfuric acid followed by lithium aluminum hydride reduction of the resulting lactam gave the oily base (Ⅲ), $[\alpha]_D$ −89.5°, characterized as the methiodide, m.p. 242~243°. The following synthesis of the methiodide of the amine (Ⅺb), the racemic Ⅲ, proved the structure of Ⅲ, leading to the conclusion that the methoxyl group is located at C_9 and in a 1,3-*cis* relationship to the C_{10a}-hydrogen.

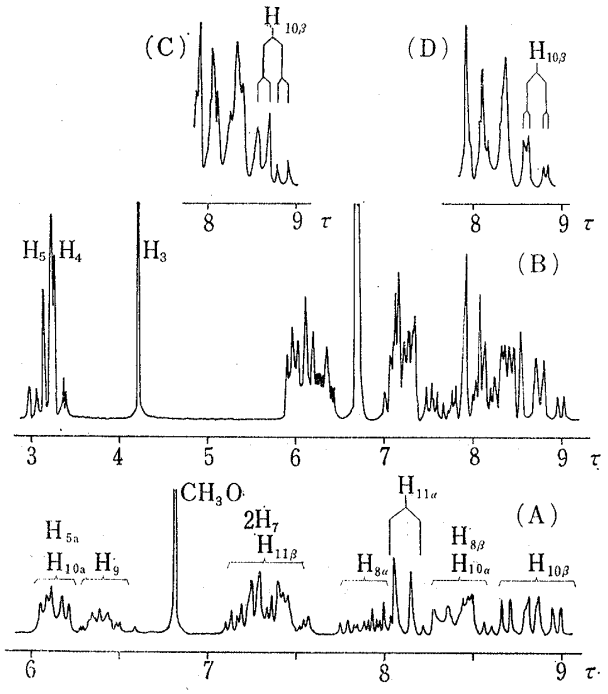

Fig. 2. NMR Spectra of Securitinine (I): (A) at 100 Mc., and (B) at 60 Mc. Double-resonance at 60 Mc.: (C) decoupling $H_{10\beta}$ from H_9, and (D) decoupling $H_{10\beta}$ from H_{10a}.

Condensation of ethyl 1,2,3,4-tetrahydro-1-isoquinolineacetate[7] (Ⅳ) with acrylonitrile followed by ethanolysis, Dieckmann cyclization*4 and then hydrolysis with 10% hydrochloric acid gave 1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizin-2-one (Ⅷ), in 30% overall yield. Reduction of the amino ketone (Ⅷ) with sodium borohydride in methanol gave the amino alcohol (Ⅸa), m.p. 142~143°, after recrystallization from benzene. On the other hand, reduction of Ⅷ with aluminum isopropoxide followed by acetylation and then column chromatography on silica gel gave the acetate (Xa), m.p. 105°, and the oily acetate (Xb). Alkaline hydrolysis of the acetates (Xa) and (Xb) gave the amino alcohols (Ⅸa) and (Ⅸb), m.p. 142~143°, respectively. The both amino alcohols (Ⅸa) and (Ⅸb) differed in the infrared or nuclear magnetic resonance spectra and depressed on admixture.

The configurational assignments of the epimeric alcohols (Ⅸa) and (Ⅸb) were made on the basis of the nuclear magnetic resonance data. As can be seen from Table Ⅱ, the C-2 proton signal of Ⅸa (or Xa) appeared at higher field than the corresponding one on Ⅸb (or Xb). In addition, this proton can be regarded as forming the X portion of the system approximating to A_2B_2X, and it was found that in the former series the signal was split into a heptet (J=10 and 5 c.p.s), while in the latter series the signal into a quintet (J=3 c.p.s). These findings indicate that Ⅸa and Ⅸb possess equatorial and axial hydroxyl groups, respectively.[9] This result also establishes the *trans* ring fusion for the quinolizidines (Ⅸa) and (Ⅸb), since a *cis* ring fusion should permit each epimer to be assumed a predominant equatorial conformation for the respective hydroxyl groups; the *trans* ring fusion was supported by the fact that both compounds showed Bohlmann's bands in their infrared spectra. Unfortunately, since the C-2 proton signal of Ⅲ was overlapped by other signals, we could not use it for these assignments.

*4 The location of the ester group in Ⅶ at C_3 was assigned on the basis of the positive ferric chloride test and lack of bands above 1700 cm^{-1} in the infrared spectrum.[8]

7) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, A. I. Meyer: J. Org. Chem., **30**, 3667 (1965).
8) E. Wenkert, B. G. Jackson: J. Am. Chem. Soc., **81**, 560 (1959).
9) N. S. Bhacca, D. H. Williams: "Applications of NMR spectroscopy in Organic Chemistry," 77 (1964). Holden-Day, Inc., San Francisco.

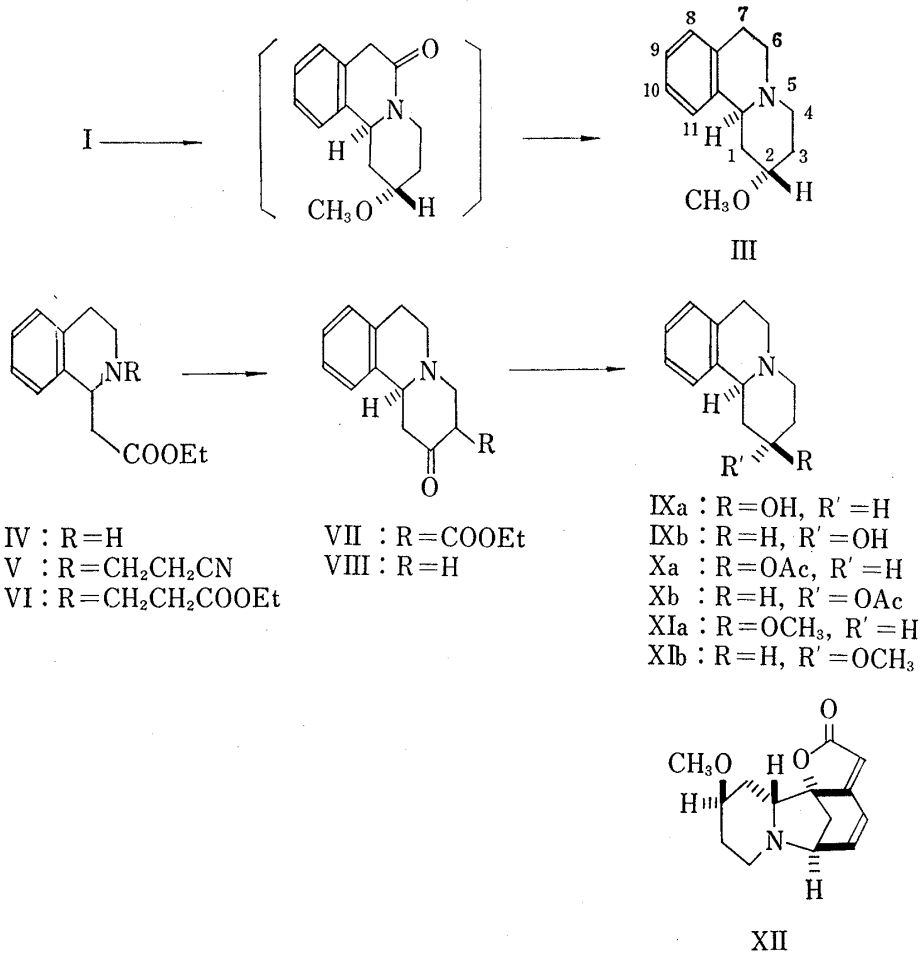

Chart 3.

TABLE II. NMR Spectral Data for C-2 Protons of IXa, b and Xa, b

Compound	Configuration of OH or OAc	Chemical shift (τ)	Splitting	J (c.p.s.)
IXa	equatorial	6.21	heptet	$J_{aa}=10$, $J_{ea}=5$
Xa	equatorial	5.08	heptet	$J_{aa}=10$, $J_{ea}=5$
IXb	axial	5.78	quintet	$J_{ea}=J_{ee}=3$
Xb	axial	4.76	quintet	$J_{ea}=J_{ee}=3$

TABLE III. Composition of Mixtures resulting from Reductions of the Amino Ketone (VIII)

Reducing agent	Products IXa	IXb	(%)[a] Starting material (VIII)
H_2, PtO_2 in AcOH	83	17	—
$NaBH_4$ in MeOH	89	11	—
Na in toluene-EtOH	84	16	—
Al(iso-PrO)$_3$ in benzene	52	41	7

a) The analyses were made by gas-liquid chromatography as the acetates (see Experimental).

The configurational assignments as given above are compatible with behavior of the amino ketone (Ⅷ) towards the reducing agents summarized in Table Ⅲ. It is well known[10] that in the reduction of a non-hindered six-membered ketone thermodynamic control will govern the stereochemistry of metal hydride or metal-alcohol reductions and it was found that the more stable equatorial isomer (Ⅸa) was formed in more than 80% yield by the use of sodium borohydride or sodium-alcohol. However, when the amino ketone (Ⅷ) was reduced with aluminum isopropoxide in benzene at 40° for 15 min., some kinetic control should be exerted and it was found that the amount of the less stable axial isomer (Ⅸb) increased.

Compounds Ⅸa and Ⅸb thus obtained were treated with dimethyl sulfate and potassium hydroxide and then potassium iodide to give the methiodide of the amine (Ⅺa), m.p. 221~223°, and that of the amine (Ⅺb), m.p. 210~212°, respectively. The latter methiodide was found to be identical with the methiodide of Ⅲ in the infrared spectrum (chloroform solution).

The relative configurations at C_{10a} and C_{10b} in securitinine were established on the following grounds : i) Securitinine showed the second ultraviolet absorption maximum at 308 mμ (log ε 3.33) and 302 mμ (log ε 3.47) in ethanol and methanol, respectively, which disappeared by addition of hydrochloric acid and shifted to 341 mμ (log ε 3.21) in dioxane. It has been already pointed out in the studies[11] of securinine and allosecurinine that this absorption band is due to "homoconjugation" between the nitrogen and the conjugated system and that in allosecurinine the absorption maximum is solvent-dependent, while in securinine this remains almost unaffected. An application of this situation to securitinine suggests that the stereochemistry at C_{10a} and C_{10b} is the same as that of allosecurinine. ii) The unusually low chemical shift for H_{10a} (near 6.16 τ) in the nuclear magnetic resonance spectrum of securitinine is interpreted by the magnetic anisotropy of the conjugated system,[12] leading to the same conclusion. Therefore, the structure of securitinine should be represented by I or its antipode.

This structure accounts for the high-field signal in the nuclear magnetic resonance spectrum of securitinine, which showed a multiplet centered at 8.84 τ, being equivalent to one proton. As mentioned earlier, spin-spin decoupling experiments on securitinine revealed that the multiplet in question was a signal of one of two methylene protons at C_{10}. Examination of a Dreiding model of securitinine based on the stereochemistry depicted in I, indicates that two methylene protons at C_{10} are strongly shielded by the conjugated system, and hence this must be responsible for the upfield multiplet. However, if the Dreiding model was made on the basis of a securinine-type stereochemistry, the C_{10} methylene protons lie close to the plane of zero shielding, and thus this structure can not satisfactorily account for the observed chemical shift.

The upfield multiplet is an octet and its pattern could be explained by assuming H_9, H_{10a}, $H_{10\beta}$ and $H_{10\alpha}$ to form an ABXY system : $H_{10\beta}$ (or H_{10a}) gives a quartet, as X portion of an ABX system, which is further split by a geminal coupling to the octet. Decoupling experiments mentioned before bore out the validity of this assumption and further gave the following approximate coupling constants : $J_{10a\cdot10\beta}=8.5$, $J_{10\beta\cdot9}=3.5$, $J_{10\alpha\cdot10\beta}=14.3$ c.p.s. The large vicinal coupling constant (8.5 c.p.s.) found for H_{10a} and $H_{10\beta}$ requires the dihedral angle between these two protons to be near 180°, *i.e.* H_{10a} and $H_{10\beta}$ are diaxial, and the multiplet in question must be assigned to $H_{10\beta}$.

Finally, the optical rotatory dispersion curve of securitinine showed a strong negative Cotton effect ($a=-8.2\times10^5$) in dioxane, indicating that this alkaloid belongs to

10) W.G. Dauben, G.J. Fonken, D.S. Noyce : J. Am. Chem. Soc., **78**, 2579 (1956).
11) Z. Horii, M. Ikeda, Y. Tamura, S. Saito, M. Suzuki, K. Kodera : This Bulletin **12**, 1118 (1964).
12) T. Nakano, T.H. Yang, S. Terao, J. Durham : Chem. & Ind., **1963**, 1763.

securinine (or allosecurinine) group but not to virosecurinine group.[11] The full stereostructure of securitinine is, therefore, represented by I.

Recently, Parello, *et al.*[13] have isolated a new alkaloid phyllantine from *Phyllanthus discoides* and proposed the structure (XII),[14] which showed that phyllantine is a diastereoisomer of securitinine.

Experimental[*5]

Isolation of Securitinine——Dried and finely powdered root barks of *S. suffruticosa* (1 kg.) were extracted with $ClCH_2CH_2Cl$ (3.5 L.) containing 10% NH_4OH (130 ml.) at room temperature for 20 hr. The extract was evaporated *in vacuo* under 60° to give a dark green residue (26 g.), which was chromatographed on alumina (500 g.). Elution with ether gave a neutral oil (11.5 g.), securinine (trace) and allosecurinine (3.0 g.). Continued elution of the column with ether gave yellow plates of securitinine (I, 1.4 g.), m.p. 129~130°, after recrystallization from AcOEt. $[\alpha]_D$ −952.3° (c, 1, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1818 (sh.), 1758, 1628, 860; UV λ_{max}^{EtOH} mμ (log ε): 257 (4.20), 308 (3.33); ORD (c, 0.043, dioxane): $[\phi]_{650}$ −2840°, $[\phi]_{589}$ −3180°, $[\phi]_{400}$ −19600°, $[\phi]_{376}$ −26500°, $[\phi]_{296}$ +54500°, $[\phi]_{275}$ +31400°. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.96; H, 7.13; N, 5.77.

4,5-Dihydrosecuritinine (II)——A solution of securitinine (0.126 g.) in MeOH (4 ml.) was added dropwise at room temperature with stirring to a solution of $NaBH_4$ (0.113 g.) in MeOH (5 ml.). The yellow color of reaction mixture changed gradually into colorless. After stirring for 2 hr., the mixture was treated with AcOH (1 ml.) and evaporated *in vacuo*. The residue was dissolved in H_2O (15 ml.), made alkaline with K_2CO_3, and extracted with ether. The dried extract was evaporated and the residue was recrystallized from iso-Pr_2O to give colorless needles of II (0.089 g., 72%), m.p. 118~119°. IR ν_{max}^{Nujol} cm^{-1}: 1815 (sh.), 1750, 1630; UV λ_{max}^{EtOH} mμ (log ε): 215 (4.15); NMR: 4.4 (singlet, 1H), 6.75 (singlet, 3H, OCH_3). *Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.88; N, 5.81.

1,3,4,6,7,11b-Hexahydro-2-methoxy-2*H*-benzo[a]quinolizin-6-one——To a stirred solution of securitinine (I, 400 mg.) in conc. H_2SO_4 (8 g.) and abs. EtOH (20 ml.), Zn-dust (4 g.) was added over a period of 30 min. and the mixture stirred at room temperature for 5 hr. The inorganic material was filtered off and washed with EtOH. The filtrate and washings, made alkaline with aqueous ammonia, were concentrated, saturated with K_2CO_3 and extracted with $CHCl_3$. The dried extract was evaporated to give a yellow viscous oil (350 mg.), which was chromatographed on silica gel (5 g.) using $CHCl_3$ as eluent to furnish a colorless viscous oil (196 mg.) of the lactam. $[\alpha]_D$ −24° (c, 0.21, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1634 (C=O). NMR: 6.48 τ (singlet, 3H, OCH_3).

Further elution with the same solvent gave the starting material (I, 80 mg.).

1,3,4,6,7,11b-Hexahydro-2-methoxy-2*H*-benzo[a]quinolizine (III)——A solution of the above-obtained lactam (190 mg.) in anhyd. ether (15 ml.) was added dropwise to a stirred suspension of $LiAlH_4$ (200 mg.) in anhyd. ether (25 ml.). After the mixture was refluxed for 4 hr., the excess hydride was decomposed with water. The inorganic material was filtered off and washed with ether. Evaporation of the dried filtrate and distillation of the residue gave a colorless oil (150 mg.), $b.p_5$ 180° (bath temperature). $[\alpha]_D$ −89.5° (c, 0.19, EtOH). NMR: 6.50 τ (singlet, 3H, OCH_3).

The methiodide was recrystallized from iso-PrOH, m.p. 242~243°. *Anal.* Calcd. for $C_{15}H_{22}ONI$: C, 50.15; H, 6.17; N, 3.90. Found: C, 50.05; H, 6.05; N, 3.78.

Ethyl 2-Cyanoethyl-1,2,3,4-tetrahydro-1-isoquinolineacetate (V)——A solution of ethyl 1,2,3,4-tetrahydro-1-isoquinolineacetate[7] (IV, 21.0 g.) and acrylonitrile (10.0 g.) in EtOH (50 ml.) was refluxed for 3 hr. The solvent and excess acrylonitrile were removed and the residual oil was distilled to give a light yellow oil (25 g., 96%), $b.p_{0.4}$ 170~175°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2230 (C≡N), 1735 (C=O).

Ethyl 2-(Carboethoxyethyl)-1,2,3,4-tetrahydro-1-isoquinolineacetate (VI)——A solution of V (25 g.) in EtOH (60 ml.) was saturated with dry HCl gas at 0°. The solution was stood at room temperature overnight, then refluxed for 2 hr. The precipitated NH_4Cl was filtered off and the filtrate was evaporated to dryness. The residue was made alkaline with conc. K_2CO_3 solution and extracted with ether. The

*5 Melting points are uncorrected. Extracts were dried over anhyd. Na_2SO_4. Column chromatographies were carried out with alumina (E. Merck's Brockmann, grade II-III, neutral) and silica gel (Mallinckrodt). The NMR spectra were measured with a Hitachi Perkin-Elmer H-60 type (60 Mc.) and Varian HR-100 (100 Mc.) spectrometers with tetramethylsilane as internal referance. Mass spectra were measured with a Hitachi RMU-6D mass spectrometer, the ionizing energy having set at 80 V and the ionizing current at 80 μA. A high resolution mass spectrum was measured with a JEOL JMSOIS mass spectrometer. Analyses of gas-liquid chromatography (GLC) were conducted with a Perkin-Elmer gas chromatography 800, employing SE-30 column (column temperature 175°).

13) J. Parello, S. Munavalli: Compt. rend., **1965**, 260, 337.

14) Private communication from Dr. J. Parello, Institut de Chemie des Substances Naturelles.

dried extract was evaporated and the residual oil was distilled to give a light yellow oil of VI (28 g., 97%), b.$p_{0.5}$ 167~170°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (C=O).

Ethyl 1,3,4,6,7,11b-Hexahydro-2-oxo-2*H*-benzo[a]quinolizine-3-carboxylate (VII)——A solution of the diester (VI, 28.0 g.) in dry C_6H_6 (25 ml.) was added to a suspension of NaH (4 g., 50% oil dispersion) in dry C_6H_6 (80 ml.) and the reaction mixture was refluxed with stirring for 3 hr. After cooling, the mixture was treated with cold glac. AcOH (13 g.), water (13 g.), and 10% HCl (60 ml.). The aqueous layer was made alkaline with conc. K_2CO_3 solution and extracted with ether. The dried extract was evaporated to give a crude solid (13.5 g., 56%), which was recrystallized from petroleum ether to give colorless plates of VII, m.p. 115~116°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1666 (C=O), 1625 (C=C). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.42; H, 7.10; N, 5.19.

This alcoholic solution gave a reddish-purple color with $FeCl_3$.

1,3,4,6,7,11b-Hexahydro-2*H*-benzo[a]quinolizin-2-one (VIII)——A solution of the ketoester (VII, 11.0 g.) in 10% HCl (80 ml.) was refluxed for 2 hr. The cooled mixture was made alkaline with conc. K_2CO_3 solution and extracted with ehter. The dried extract was evaporated to give a yellow solid (5.0 g., 62%), which gave a single peak by GLC analysis. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1723 (C=O).

The oxime was recrystallized from iso-PrOH to give colorless plates, m.p. 182~183° (lit.[15] m.p. 180°). *Anal.* Calcd. for $C_{13}H_{16}ON$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.43; H, 7.50; N, 12.74.

Reduction of the Amino Ketone (VIII)——a) Catalytic Hydrogenation——The ketone (VIII, 100 mg.) was hydrogenated over PtO_2 (10 mg.) in glac. AcOH (20 ml.) at room temperature and atmospheric pressure. After cessation of H_2 uptake (6 hr.), the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was made alkaline with conc. K_2CO_3 solution and extracted with $CHCl_3$. The dried extract was evaporated to give a mixture (100 mg.) of the alcohols IXa and IXb in ratio of 83:17, by GLC analysis.*6

b) Sodium Borohydride Reduction——To a solution of the ketone (VIII, 100 mg.) in MeOH (10 ml.), $NaBH_4$ (100 mg.) was added in small portions and the reaction mixture was refluxed for 2 hr. The cooled mixture was treated with glac. AcOH, evaporated to dryness, made alkaline with conc. K_2CO_3 solution and extracted with $CHCl_3$. Evaporation of the dried extract gave a mixture (100 mg.) of IXa and IXb in a ratio of 89:11, by GLC analysis.*6

c) Sodium-ethanol Reduction——A solution of the ketone (VIII, 500 mg.) in toluene (5 ml.) and abs. EtOH (5 ml.) was added to a suspension of Na (500 mg.) in dry toluene (50 ml.) over a period of 30 min. Then the reaction mixture was refluxed with stirring for 3 hr., cooled and treated with water. The toluene layer was dried and evaporated to give a reddish brown oil (500 mg.), which was shown to be a mixture of IXa and IXb in a ratio of 84:16, by GLC analysis.*6

d) Aluminum-*iso*propoxide Reduction——A solution of the ketone (VIII, 1.8 g.) in dry C_6H_6 (35 ml.) was added to a solution of Al(iso-PrO)$_3$ (20 g.) in dry C_6H_6 (100 ml.) at 40° over a period of 20 min. After addition was complete, the mixture was treated with 5% HCl and the acid layer was made alkaline with conc. K_2CO_3 solution and extracted with $CHCl_3$. Evaporation of the dried extract gave a mixture (1.8 g.) of IXa, IXb and the starting material (VIII) in a ratio of 52:41:7, by GLC analysis.*6

***cis*- and *trans*-2-Acetoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]-quinolizine (Xa and Xb)**——A mixture of the Al(iso-PrO)$_3$ reduction product (1.8 g.) of VIII, Ac_2O (10 ml.) and pyridine (20 ml.) was warmed at 50° for 2 hr. After standing overnight, the pyridine and excess Ac_2O were removed *in vacuo*. The residue was made alkaline with conc. K_2CO_3 solution and extracted with ether. Evaporation of the dried extract gave a viscous oil (1.9 g.), which was chromatographed on silica gel. Elution with $CHCl_3$ afforded a white solid, which was recrystallized from petroleum ether to give colorless plates of the *cis*-acetate (Xa), m.p. 105°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2817, 2736 (*trans*-quinolizidine bands), 1736 (C=O). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.67; H, 7.65; N, 5.51.

Continued elution with AcOEt afforded a viscous oil, which was converted to the hydrochloride. Recrystallization from iso-PrOH gave white crystals of the *trans*-acetate (Xb), m.p. 202~203°. *Anal.* Calcd. for $C_{15}H_{20}O_2NCl$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.34; H, 7.05; N, 4.98.

The free base (Xb) recovered from the hydrochloride was shown to be homogeneous by TLC. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2811, 2764 (*trans*-quinolizidine bands), 1733 (C=O).

***cis*-2-Hydroxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine (IXa)**——a) Three recrystallizations of the crude $NaBH_4$ reduction product of VIII from C_6H_6 gave pure colorless crystals of the *cis*-alcohol (IXa), m.p. 142~143°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 2818, 2748 (*trans*-quinolizidine bands). *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.80; H, 8.40; N, 7.12.

b) A solution of the *cis*-acetate (Xa, 100 mg.) and KOH (150 mg.) in MeOH (5 ml.) was refluxed for 2 hr. After removal of the MeOH *in vacuo*, the residue was dissolved in a small amount of water and extracted with $CHCl_3$. Evaporation of the dried extract gave a solid (45 mg.), which was recrystallized from

*6 Crude reduction product was acetylated in the same way as for the preparations of Xa and Xb, and a sample of 1% MeOH-solution of the resulting crude product was injected with a Hamilton microsyringe.

15) D. Beke, C. Szantay: Chem. Ber., **95**, 2132 (1962).

C_6H_6 to give colorless crystals of the *cis*-alcohol (IXa), m.p. 142~143°, which was identical in all respects with the product obtained by (a).

***trans*-2-Hydroxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine (IXb)**——The *trans*-acetate (Xb, 100 mg.) was hydrolyzed in the same way as for the *cis*-acetate (Xa). Recrystallization of the resulting solid from C_6H_6 gave colorless crystals of the *trans*-alcohol (IXb), m.p. 142~143° (depressed to 109~115° on admixture with the *cis*-alcohol (IXa)). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3620 (OH), 2818, 2750 (*trans*-quinolizidine bands). *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found : C, 76.62; H, 8.24; N, 6.98

***cis*-2-Methoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine (XIa)**——To a stirred suspension of the *cis*-alcohol (IXa, 100 mg.) in 10% NaOH solution (10 ml.), dimethyl sulfate (2 g.) was added at room temperature during a period of 30 min. After stirring at 40° for 2 hr., the mixture was neutralized with 10% H_2SO_4 and evaporated to dryness *in vacuo*. The residue was extracted with MeOH and the MeOH extract was evaporated. To the residue dissolved in water (5 ml.), a solution of KI (1 g.) in water (10 ml.) was added. The solution was stirred at room temperature for 15 min., and extracted with $CHCl_3$. The dried extract was evaporated to give a white solid (40 mg.) which was recrystallized from iso-PrOH-MeOH to give white needles of the methiodide of the *cis*-methyl ether (XIa), m.p. 221~223°. *Anal.* Calcd. for $C_{15}H_{22}ONI$: C, 50.15; H, 6.17; N, 3.90. Found : C, 50.36; H, 6.46; N, 3.67.

***trans*-2-Methoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine (XIb)**——The *trans*-alcohol (IXb, 100 mg.) was treated in the same way as for the *cis*-alcohol (IXa) to give white needles of the methiodide of the *trans*-methyl ether (XIb), which was recrystallized from iso-PrOH, m.p. 210~212°. *Anal.* Calcd. for $C_{15}H_{22}ONI$: C, 50.15; H, 6.17; N, 3.90. Found : C, 49.94; H, 5.90; N, 3.57.

The IR spectrum of this methiodide in $CHCl_3$ solution was identical with that of the methiodide of III derived from securitinine.

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