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STUDIES ON THE ALKALOIDS OF *SECURINEGA VIROSA* PAX. ET HOFFM.—I

STRUCTURE OF VIROSECURININE[1]

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Abstract—Investigation of Formosan *Securinega virosa* Pax. et Hoffm. of the Euphorbiaceae family has led to the isolation of a new alkaloid named virosecurinine. The structure elucidation of this alkaloid (I) is described. Direct comparison of this alkaloid with securinine isolated from *S. suffruticosa* Rehd. reveals that securinine has the antipodal configuration of virosecurinine.

IN 1956, Murav'eva *et al.*[2] reported the isolation of an alkaloid securinine, $C_{13}H_{15}NO_2$, from the leaves of Russian *Securinega suffruticosa* (Pall.) Rehd. (Euphorbiaceae), and characterized some of its functional groups by preparation of several derivatives. Since then, the only publications on this subject concern the physiological activity of this alkaloids.[3] Meanwhile, we have investigated the alkaloid constituents of *S. virosa* Pax. et Hoffm. (Euphorbiaceae), which grows in Formosa. Extraction of the dried leaves of the plant and crystallization of the basic fraction yields an alkaloid in approximately 0·5 per cent, with the same empirical formula as securinine. As some of the derivatives of this alkaloid differ in physical properties from those of securinine (Table 1), we have named this new alkaloid virosecurinine, and the present paper summarizes the experimental results on the structure of this alkaloid.

TABLE 1

	M.p.	$[\alpha]_D$		M.p.	$[\alpha]_D$
Virosecurinine	141–142°	+1035°	Securinine	139–140°	+1042·3°*
Virosecurinine hydrochloride	252–253°	+344°	Securinine hydrochloride	230°	−259·2°
Virosecurinine nitrate	211–213°	−334°	Securinine nitrate	205°	−312·1°

* The literatures recorded + sign for the rotation of securinine, but when we took the rotation of it, it showed $[\alpha]_D$ −1070°.

The mass spectrum of virosecurinine has a parent peak at M/e 217, which is consistent with the molecular weight calculated from the empirical formula $C_{13}H_{15}NO_2$. This alkaloid contains neither methoxyl nor N-methyl groups. Since it shows no absorption of a NH group in the I.R. spectrum and readily gives a methiodide, the nitrogen atom in its molecule must be tertiary. The two oxygen atoms may be present

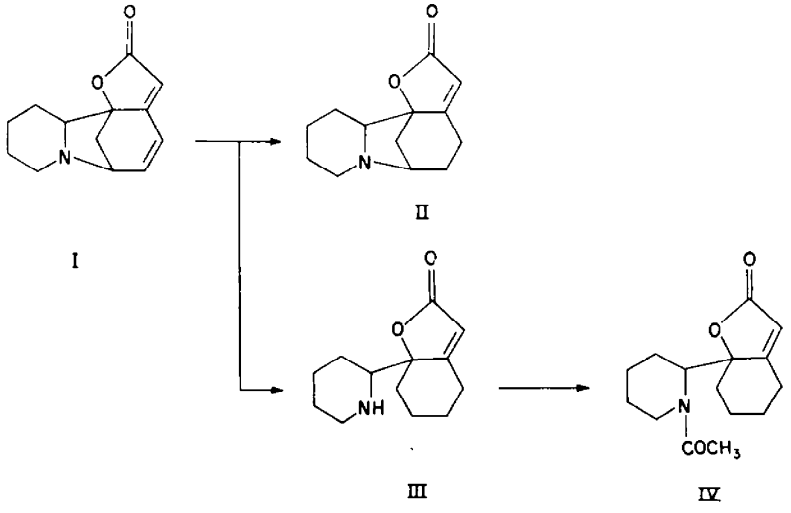
[1] A preliminary communication of this work; T. Nakano, T. H. Yang and S. Terao, *Chem. & Ind.* 1651 (1962).

[2] V. I. Murav'eva and A. I. Ban'kovskii, *Dokl. Akad. Nauk S.S.S.R.* **110**, 998 (1956).

[3] I. Ya. Bobokhodzhaev, *Farmakol. I Toksikol.* 20/1 suppl. (3–5) (1957); A. D. Turov and Ya. A. Aleshkina, *Med. Prom. S.S.S.R.* 11, No. 1, 54 (1957).

as an unsaturated lactone since the I.R. spectrum exhibits absorptions at 5·56, 5·65, 6·09 and 11·70 μ in carbon tetrachloride and at 5·55, 5·73, 6·11 and 11·68 μ in chloroform. These bands are characteristic of the α,β-unsaturated γ-lactone system[4] and the splitting[5] of the carbonyl band suggests the presence of an α-hydrogen. The presence of one ethylenic linkage extending the conjugation of this α,β-unsaturated γ-lactone system in virosecurinine is indicated by its U.V. absorption maximum at 256 mμ (log ε 4·26).[6] For the sake of simplicity, further discussion of the degradative evidence is given in terms of structure I.

Virosecurinine (I), on hydrogenation over palladium charcoal in benzene, rapidly absorbs slightly more than one molar equivalent of hydrogen and then the speed of the hydrogen uptake diminishes. Separation of the reaction mixture by chromatography on alumina furnished two main products. One, dihydrovirosecurinine $C_{13}H_{17}NO_2$ (II), obtained from the benzene–ether (3:1) fractions has an absorption maximum at 215 mμ (log ε 4·25) in the U.V. spectrum, and, therefore, the α,β-unsaturated γ-lactone system is still intact and one ethylenic double bond has been hydrogenated. This assumption is supported by the I.R. spectrum in which the lactone carbonyl exhibits two split bands at 5·54 and 5·66 μ in carbon tetrachloride solution. The second chromatographic product, an oily amino lactone, was eluted with ether-methanol (9:1) and isolated as a crystalline picrate. This amino lactone is assigned structure III since the U.V. absorption of the picrate possesses the intact chromophore involving the α,β-unsaturated γ-lactone moiety, but its I.R. spectrum in Nujol mull exhibits a new band at 3·11 μ attributable to a NH group. Acetylation of III yields a crystalline N-acetyl derivative $C_{15}H_{21}NO_3$ (IV). The amino lactone (III) is formed by the hydrogenolytic cleavage of the allylic C-N bond in virosecurinine (I).



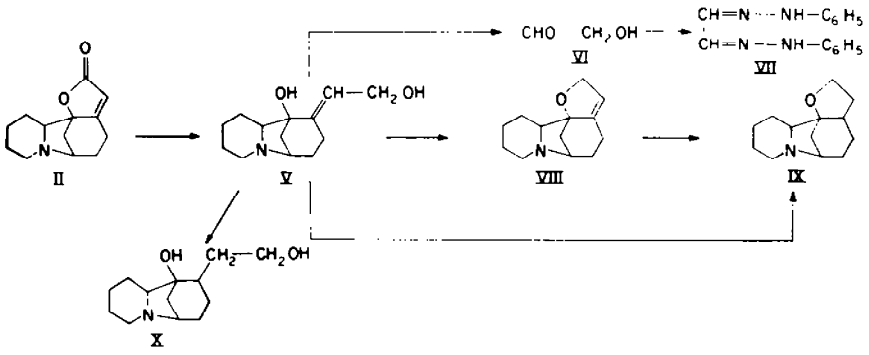
Further experiments revealed the nature of the postulated α,β-unsaturated γ-lactone function. Lithium aluminum hydride reduction of dihydrovirosecurinine (II)

[4] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).

[5] R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.* **81**, 5242 (1959); R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Canad. J. Chem.* **37**, 2007 (1959).

[6] J. D. Connolly and K. H. Overton, *Proc. Chem. Soc.* 188 (1959).

yields a liquid diol $C_{13}H_{21}NO_2$ (V), analysed as its crystalline hydrochloride. Ozonolysis of V in acetic acid and subsequent reductive cleavage of the ozonide with zinc dust furnishes a glycol aldehyde (VI), isolated as the phenyl osazone (VII). The identity of VII was established by direct I.R. spectral comparison and admixture with a sample prepared from allyl alcohol by an analogous series of reactions.[7]



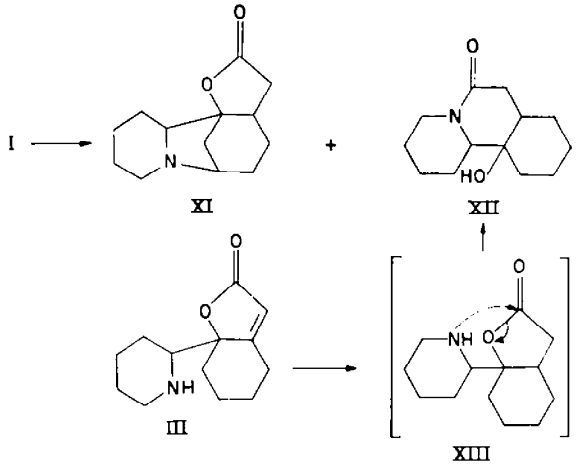
During the preparation of the crystalline hydrochloride of diol V, an oily substance was obtained the free base of which did not show any hydroxyl band in the I.R. spectrum. This substance forms a crystalline picrate with an elementary analysis suggesting the loss of one mole of water from the molecule of V. The N.M.R. spectrum confirms the presence of two protons adjacent to oxygen which appears as a doublet at 4·59 p.p.m.[8] due to spin coupling with a neighboring olefinic proton. In addition, one proton attached to an olefinic double bond may be clearly detected by a triplet peak at 5·23 p.p.m. This substance is apparently produced by the intramolecular ether formation of the diol (V) in the presence of a proton donating catalyst, and hence may be formulated as VIII. Catalytic hydrogenation of VIII with palladized charcoal results in the uptake of one molar equivalent of hydrogen to give a liquid saturated ether compound $C_{13}H_{21}NO_2$ (IX), characterized as its picrate. The hydrochloride of the diol (V), on hydrogenation in the presence of palladium charcoal catalyst in alcohol, also yields IX, while the diol (V) itself, on hydrogenation, yields a liquid saturated diol $C_{13}H_{23}NO$ (X), analysed as the picrate.

Virosecurinine (I), on catalytic hydrogenation with palladized charcoal in alcohol solution for 24 hours, absorbs 2·25 molar equivalents of hydrogen, and separation of the reaction mixture by chromatography yields tetrahydro-virosecurinine $C_{13}H_{19}NO_2$ and the lactam carbinol $C_{13}H_{21}NO_2$. Since tetrahydro-virosecurinine exhibits absorption at 5·58 μ in the I.R. spectrum in carbon tetrachloride and has no selective U.V. absorption maximum, it is a saturated γ-lactone (XI). On the other hand, the lactam carbinol is assigned structure XII since it exhibits no selective absorption in the U.V. region and the presence of a hydroxyl as well as a lactam grouping is indicated by the appearance of the I.R. absorption bands at 3·05 and 6·21 μ. This lactam carbinol (XII) is also obtained, probably through the intermediate XIII, by hydrogenation of III with palladium charcoal followed by chromatography of the resultant product through an alumina column.

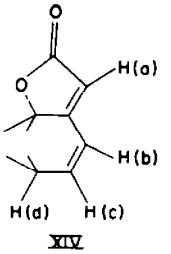
The N.M.R. spectra supports the experimental evidence. In virosecurinine (I),

[7] Hermann O. L. Fisher and Carl Taube, *Ber. Dtsch. Chem. Ges.* **60**, 1707 (1927).

[8] The spectra were measured with a Varian-Spectrometer in $CDCl_3$ with $Si(CH_3)_4$ as an internal standard. Chemical shifts in p.p.m. relative to $Si(CH_3)_4 = 0$.



one proton at C—(a) appears as a singlet at 5·53 p.p.m. A pattern of lines observed as eight peaks over the range 6·27 to 6·78 p.p.m. is the AB part of an ABX (protons at C—(b), C—(c) and C—(d)) coupling pattern[9] and is assigned to the two protons at C—(b) and C—(c). The multiplet centered at 3·81 p.p.m. corresponding to one proton is due to the proton at C—(d). In the dihydroderivative (II), the lines due to the two protons at C—(b) and C—(c) disappear, whereas a peak at 5·55 p.p.m. remains which is absent in the tetrahydro derivative (XI). These data are completely compatible with the partial structure XIV contained in the molecule of virosecurinine.



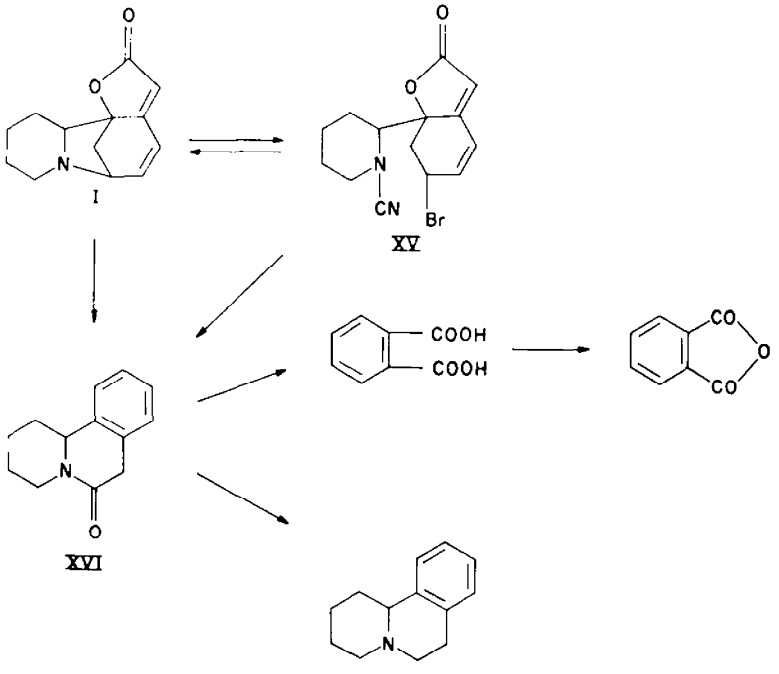
Action of cyanogen bromide upon virosecurinine (I) yields the bromocyanide $C_{14}H_{15}N_2O_2Br$ (XV) in a quantitative yield. The U.V. absorption spectrum (λ_{max} 260·5 mμ, log ε 4·26) indicates the presence of the intact α,β-unsaturated γ-lactone chromophore of the original compound, while the I.R. spectrum contains a new band at 4·51 μ due to the C≡N group. In the N.M.R. spectrum of XV, a proton at C—(d) which appears as a multiplet at 3·82 p.p.m. in virosecurinine (I) undergoes a downfield shift to 4·92 p.p.m. This indicates that the rupture of the C—N bond proceeds with substitution of a bromine atom at the allylic carbon atom of the molecule.

During an attempt to hydrolyse virosecurinine bromocyanide (XV) with aqueous sulphuric acid, cyclization occurred and virosecurinine (I) was recovered. Consequently, hydrolysis was carried out with aqueous sulphuric acid in the presence of zinc dust so that both the removal of the bromine atom and the hydrolysis of the N-CN bond might be effected simultaneously. Chromatographic separation of the resulting oily product on alumina, yielded a crystalline substance, m.p. 75–76°, $[\alpha]_D$ − 35·7°,

[9] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, p. 98, McGraw-Hill, New York (1959).

exhibiting the lactam absorption at 6·15 μ in the I.R. spectrum. The analytical values of this compound correspond to the formula $C_{13}H_{15}NO$, and since the U.V. absorption spectrum exhibits maxima at 265 mμ (log ε 2·67) and 272 mμ (log ε 2·54), typical of a 1,2-disubstituted benzenoid derivative, this lactam must possess structure XVI. Oxidation of XVI with potassium permanganate yields phthalic acid, the identity of which was proved by conversion to phthalic anhydride. It is pertinent to mention[10] that the lactam (XVI) is also obtained when virosecurinine (I) itself is treated with zinc dust and sulphuric acid.

Lithium aluminum hydride reduction of XVI furnishes a basic oil (XVII) the I.R. spectrum of which shows no lactam function. This compound forms a crystalline hydrochloride $C_{13}H_{17}N{\cdot}HCl$, m.p. 260–261° (in a sealed tube), $[\alpha]_D$ −84·4°, λ_{max}^{Nujol} 12·61, 12·88 and 13·24 μ[11], λ_{max} 265 mμ, log ε 2·65 and 272 mμ, log ε 2·58, identical with a synthetic sample of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[a] quinolizine hydrochloride[12] kindly supplied by Dr. S. Akaboshi of the University of Tokyo. Both samples have identical I.R. spectra in chloroform solution. The identification of XVII thus accounts for all the features of the skeleton of virosecurinine.



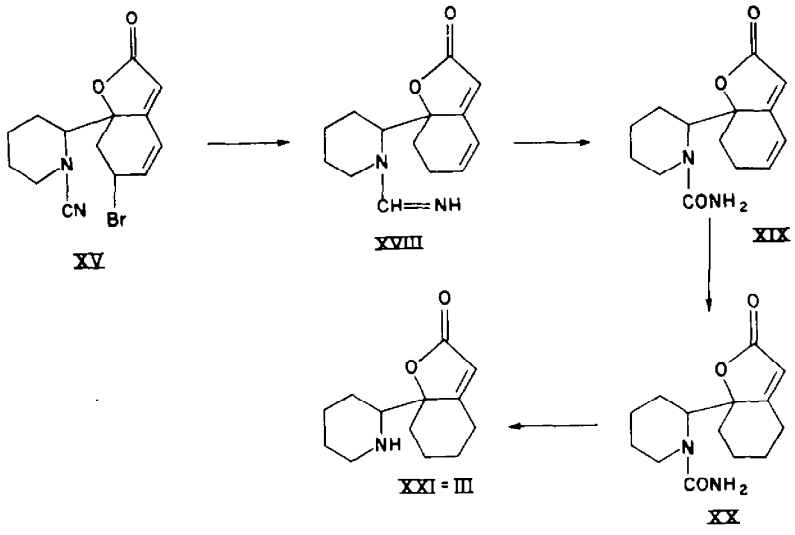
The bromocyanide (XV), on catalytic hydrogenation with palladized charcoal in alcohol, rapidly absorbs approximately two molar equivalents of hydrogen. The hydrogenation product at this stage must be XVIII since it reveals no C≡N absorption but instead a new band at 5·93 μ in the I.R. spectrum. Subsequent hydrolysis of

[10] This aromatization was reported in a preliminary communication. See reference 1.

[11] These bands are typical of the out-of-plane CH deformation vibrations of a 1,2-disubstituted benzene ring. L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (2nd edition) p. 77, Methuen, London (1958).

[12] S. Akaboshi, T. Kutsuma and K. Achiwa, *Chem. Pharm. Bull. Japan* **8**, 14 (1960).

this product with sulphuric acid yields the amide $C_{14}H_{18}N_2O_3$. The U.V. absorption spectrum (λ_{max} 258 mμ, log ε 3·91) as well as the I.R. spectrum (λ_{max} 2·85, 2·92 (NH), 5·72 (α,β-unsaturated γ-lactone) and 6·06 μ (—CO—N<)) supports the assignment of structure XIX for this compound. On catalytic hydrogenation with palladium charcoal, XIX rapidly absorbs one molar equivalent of hydrogen to afford a dihydro derivative $C_{14}H_{20}N_2O_3$ (XX). During treatment of XX with sulphuric acid, an oily amino lactone (XXI) the picrate of which is identical with that of III was obtained.



These experimental results complete the assignment of the structure of virosecurinine in terms of the expression I. A comparison of virosecurinine with securinine[13] reveals that they are mirror-images. This automatically establishes that securinine has an antipodal configuration of virosecurinine. The stereochemistry of virosecurinine is now being investigated.

EXPERIMENTAL

U.V. absorption spectra were recorded on the Shimazu Self-Recording U.V.-Spectrophotometer "SV-50" in 95% ethanol. I.R. spectra were taken on the Hitachi Infra-red Spectrophotometer "EPI-S" in chloroform unless otherwise specified. Rotations were determined with Kreispolarimeter "0·01°" (Carl Zeiss Co., Ltd.) in ethanol, unless otherwise stated. M.ps. were measured by use of the Micro-Melting Point Apparatus (Yanagimoto Co., Ltd., Kyoto) and uncorrected. Alumina for chromatography was "Woelm" Neutral, Activity Grade I. The elementary analyses were carried out by Miss S. Tomita and Miss Y. Saito of the Microanalytical Laboratory of this Faculty.

Isolation of virosecurinine (I)

The dried leaves (17 kg) of *Securinega virosa* Pax. et Hoffm. collected in Formosa early in Spring, were refluxed with 160 l. methanol for 4 hr, cooled overnight, and filtered. After 3 such operations, the methanolic extracts were combined, concentrated to 5 l., and diluted with 3% aqueous acetic acid solution to 15 l. After removal of neutral and acidic substances by extraction with ether, the aqueous solution was diluted with water and the precipitates filtered and washed thoroughly with aqueous acetic acid solution. The filtrate and washings were made alkaline with aqueous ammonia, and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated, giving 87 g of yellow *crystals* after recrystallization from ethanol, m.p. 141–142°, $[\alpha]_D^{20}$ +1035° (*c*, 0·43),

[13] We are indebted to Dr. I. Satoda of the Research Laboratory, Nippon Shinyaku Co., Kyoto for a gift of a sample of securinine for direct comparison and his stimulating discussion.

λ_{max} μ 5·55, 5·73 (CO), 6·11 (—C=C—), 11·68 (—C=CH—CO—), $\lambda_{max}^{CCl_4}$ μ 5·56, 5·65 (CO), 6·09 (—C=C—), 11·70 (—C=CH—CO—), λ_{max} 256 mμ (log ε 4·26). (Found: C, 71·86; H, 6·96; N, 6·45. $C_{13}H_{15}NO_2$ requires: C, 71·98; H, 7·10; N, 6·28%). Zeisel determination showed the absence of O-methyl and N-methyl groups.

Hydrochloride m.p. 252–253° (in a sealed tube), from acetone, $[\alpha]_D^{21}$ +344° (*c*, 0·52). (Found: C, 61·33; H, 6·35; N, 5·51. $C_{13}H_{15}NO_2 \cdot HCl$ requires: C, 61·43; H, 6·47; N, 5·74%).

Nitrate m.p. 211–213° (dec), from acetone, $[\alpha]_D^{21}$ +330° (*c*, 0·56). (Found: C, 55·71; H, 5·75; N, 10·00. $C_{13}H_{15}NO_2 \cdot HNO_3$ requires: C, 55·74; H, 5·92; N, 10·20%).

Picrate m.p. 218°, from acetone. (Found: C, 51·12; H, 4·06; N, 12·55. $C_{13}H_{15}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 51·31; H, 4·26; N, 12·74%)

Methiodide m.p. 239–240°, from acetone, $[\alpha]_D^{21}$ −135·3° (*c*, 0·59) λ_{max}^{Nujol} μ 5·70 (CO), 6·10 (—C=C—), 11·41 (—C=CH—CO—), λ_{max} 219·5 mμ (log ε 4·11), 256 mμ (log ε 4·10). (Found: C, 46·48; H, 4·95; N, 3·90. $C_{13}H_{15}NO_2 \cdot CH_3I$ requires: C, 46·69; H, 5·24; N, 4·06%).

Formation of dihydrovirosecurinine (II) *and the amino lactone* (III)

(A) *Hydrogenation of virosecurinine* (I) *with palladium charcoal*

Virosecurinine (I; 990 mg) was hydrogenated in 50 cc 95% ethanol with 100 mg prehydrogenated 5% palladium charcoal catalyst at atm. press. and 15°; 132 cc of hydrogen were rapidly absorbed. After removal of the catalyst and evaporation of the filtrate *in vacuo*, the residue was dissolved in benzene:ether (3:1) and chromatographed on alumina. The benzene:ether (3:1) fractions afforded 380 mg II which crystallized from petroleum ether as prisms, m.p. 52°, $[\alpha]_D^{19}$ −3·7° (*c*, 0·61, $CHCl_3$), λ_{max} μ 5·55, 5·73 (CO), 6·11 (—C=C—), 11·68 (—C=CH—CO—), $\lambda_{max}^{CCl_4}$ μ 5·54, 5·66 (CO), 6·09 (—C=C—), 11·70 (—C=CH—CO—), λ_{max} 215 mμ (log ε 4·25). (Found: C, 70·95; H, 7·93; N, 6·49. $C_{13}H_{17}NO_2$ requires: C, 71·23; H, 7·83; N, 6·39%).

Hydrochloride m.p. 235–237° (in a sealed tube), from acetone, $[\alpha]_D^{26}$ +40·3° (*c*, 0·83), λ_{max} 214 mμ (log ε 4·12). (Found; C, 60·31; H, 7·54; N, 5·67. $C_{13}H_{17}NO_2 \cdot HCl$ requires: C, 60·52; H, 7·42; N, 5·43%).

Picrate m.p. 252–254° (dec), from ethanol. (Found: C, 51·18; H, 4·67; N, 12·46. $C_{13}H_{17}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 51·26; H, 4·48; N, 12·65%).

Further elution with ether–methanol (9:1) furnished 330 mg III as an oil which formed a *picrate*, m.p. 215° (dec), from acetone. $[\alpha]_D^{24}$ −43·8° (*c*, 0·57), λ_{max}^{Nujol} μ 3·11 (NH), 5·75 (CO), λ_{max} 212 mμ (log ε 4·43). (Found: C, 50·71; H, 4·85; N, 12·61. $C_{13}H_{19}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 50·66; H, 4·92; N, 12·44%).

(B) *Hydrogenation of virosecurinine* (*I*) *with palladium strontium carbonate*

A solution of 1·0 g of I in benzene was treated with 200 mg of prehydrogenated palladium strontium carbonate catalyst (prepared by addition of a solution of 3 cc 1% palladium chloride to 1 g of strontium carbonate) at 20° and atm. press. After 120 cc of hydrogen had been absorbed, the resulting solution was chromatographed on alumina, and benzene–ether eluted 810 mg of II. Elution with ether-methanol gave 40 mg of III.

Acetylation of the amino lactone (III)

The amino lactone (III; 137 mg) was treated with acetic anhydride and pyridine, and the mixture kept at room temp for 3 days. After removal of excess reagents *in vacuo*, the residue was dissolved in ether and washed successively with 5% hydrochloric acid, 2% aqueous sodium bicarbonate and water. Evaporation of the solvent gave IV as prisms, m.p. 166–166·5°, from acetone–hexane. Yield, 121 mg $[\alpha]_D^{26}$ −138° (*c*, 0·74, $CHCl_3$), λ_{max} 210 mμ (log ε 4·13), λ_{max} μ 5·72 (CO), 6·09 (—C=C—), 6·14 (N—$COCH_3$), 11·69 (—C=CH—CO—). (Found: C, 68·48; H, 8·24; N, 5·44. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04; N, 5·32%).

Lithium aluminum hydride reduction of dihydrovirosecurinine (II)

A solution of 1·759 g III in absolute ether was added to a suspension of 800 mg lithium aluminum hydride in absolute ether, and the mixture stirred at room temp overnight. The excess reagent was destroyed with ethyl acetate, saturated aqueous sodium sulphate was added to precipitate inorganic salts, and the solution dried (Na_2SO_4) and filtered from the residue which was triturated with ether. The combined ether solutions were evaporated to give 1·759 g of V as an oil, λ_{max} μ 2·77, 2·93 (OH).

Picrate m.p. 154°, from ethyl acetate. (Found: C, 50·35; H, 5·54; N, 12·23. $C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 50·43; H, 5·35; N, 12·35%).

Hydrochloride. Dry hydrogen chloride gas was passed through a solution of 830 mg of V in absolute ether under cooling with water. The deposited *hydrochloride* was recrystallized from dry acetone, m.p. 181·5°, $[\alpha]_D^{23}$ +20·5° (*c*, 0·71), λ_{max}^{Nujol} μ 3·05, 3·11 (OH). (Found: C, 60·35; H, 8·75; N, 5·41. $C_{13}H_{21}NO_2 \cdot HCl$ requires: C, 60·05; H, 8·53; N, 5·39%). Yield, 672 mg.

An oily substance obtained during the crystallization process of the hydrochloride of V was poured into water, made alkaline with aqueous ammonia and extracted with ether. The ether extract was dried, evaporated, and the oily residue chromatographed on alumina. The hexane eluted fractions afforded VIII as a liquid, which formed a *picrate*, m.p. 194–195°, from acetone. $[\alpha]_D^{20}$ −52·7° (*c*, 0·83). (Found: C, 52·42; H, 5·28; N, 12·76. $C_{13}H_{19}NO \cdot C_6H_3N_3O_7$ requires: C, 52·53; H, 5·10; N, 12·90%).

Ozonolysis of the diol (V) *hydrochloride*

The hydrochloride (611 mg) of V was ozonized in 2 cc of glacial acetic acid at room temp for 1·10 hr. Zinc dust (1 g) was then added and stirring continued overnight. After filtration, the solution was poured into water and extracted with ether. The ether extract was concentrated to a small volume and then treated with 826 mg phenyl hydrazine. The solution was kept overnight and the crystals recrystallized from benzene, m.p. 174–175°. (Found: C, 70·21; H, 5·68; N, 23·57. Calc. for $C_{14}H_{14}N_4$: C, 70·35; H, 5·90; N, 23·44%). Admixture with the phenyl osazone (VII), m.p. 174–175°, of glycol aldehyde (VI) obtained from allyl alcohol by ozonization showed no depression. The I.R. spectra of both samples were also identical.

Attempted transformation of the diol (V) *into the unsaturated ether compound* (VIII)

The diol (V; 300 mg) regenerated from its crystalline hydrochloride was dissolved in acetone, treated with several drops conc hydrochloric acid, and the solution heated on a water bath for 10 min. After removal of the acetone and addition of water, the solution was made alkaline with aqueous ammonia and extracted with ether. The ether extract was dried, evaporated, and the residue chromatographed in hexane on alumina. The hexane eluted 262 mg of a liquid, $[\alpha]_D^{21}$ +58·5° (*c*, 1·32), which showed no absorption of a hydroxyl group but instead a strong band at 9·85 μ in the I.R. spectrum. It formed a picrate, m.p. 194–195°, from acetone, $[\alpha]_D^{21}$ +52·7° (*c*, 0·87), which was shown to be identical by direct I.R. spectral comparison with the picrate of VIII obtained before during the crystallization procedure of the hydrochloride of V.

A similar treatment of the hydrochloride of V with dil. aqueous hydrochloric acid also furnished VIII in a good yield.

Catalytic hydrogenation of the unsaturated ether compound (VIII)

Compound VIII (251 mg) was hydrogenated in ethanol in the presence of 30 mg of prehydrogenated 5% palladium charcoal at atm. press. and room temp overnight, the hydrogen absorbed corresponding to one double bond. After filtration the solution was evaporated *in vacuo*, and the product chromatographed on alumina. Hexane eluted 246 mg of an oily *substance*, $[\alpha]_D^{26}$ +16·1° (*c*, 3·1), λ_{max} μ 8·84 (—C—O—C—). The N.M.R. spectrum showed the absence of an olefinic proton. *Picrate*: m.p. 192–193°, from acetone, $[\alpha]_D^{24}$ +8·9° (*c*, 0·41). (Found: C, 52·35; H, 5·93; N, 12·92. $C_{13}H_{21}NO \cdot C_6H_3N_3O_7$ requires: C, 52·29; H, 5·54; N, 12·84%).

Catalytic hydrogenation of the diol (V) *hydrochloride*

The crystalline hydrochloride (366 mg) of V was hydrogenated in 99·9% ethanol with 40 mg of prehydrogenated 5% palladized charcoal catalyst at room temp and atm. press., 68 cc of the hydrogen being absorbed overnight. The catalyst was removed by filtration, and the filtrate made alkaline with aqueous ammonia and extracted with ether. The ether solution was evaporated yielding an oil, which showed no hydroxyl group but a strong absorption at 8·84 μ in the I.R. spectrum. The picrate of this compound is identical with that of IX (I.R. spectrum, rotation and mixed m.p.).

Acetylation of the diol (V)

A solution of 100 mg V in acetic anhydride and pyridine was kept at room temp for 2 days. The reaction mixture was evaporated *in vacuo*, and the oily *product* isolated as its *picrate*, m.p. 185°, from acetone–ether. (Found: C, 51·27; H, 5·54; N, 11·56. $C_{15}H_{23}NO_3 \cdot C_6H_3N_3O_7$ requires: C, 51·01; H, 5·30; N, 11·33%).

Catalytic hydrogenation of the diol (V)

A solution 221 mg V in ethanol was treated with 30 mg of prehydrogenated 5% palladium charcoal at room temp and atm. press. Hydrogenation was continued overnight and one molar equivalent of hydrogen absorbed. The *product* (X) was isolated as the *picrate*, which crystallized from acetone-hexane, m.p. 152–153°, $[\alpha]_D^{20}$ +8·4° (*c*, 1·03). (Found: C, 50·42; H, 5·63; N, 12·11. $C_{13}H_{23}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 50·21; H, 5·77; N, 12·33%).

Acetylation of the saturated diol (X)

Acetylation was carried out by treating 100 mg X with acetic anhydride and pyridine at room temp for 2 days. The *picrate* crystallized from ethyl acetate, m.p. 205–206°, λ_{max}^{Nujol} μ 2·91 (OH), 5·76 ($COCH_3$). (Found: C, 50·72; H, 5·74; N, 11·48. $C_{15}H_{25}NO_3 \cdot C_6H_3N_3O_7$ requires: C, 50·80; H, 5·68; N, 11·29%).

Tetrahydrovirosecurinine (XI) *and the lactam carbinol* (XII)

(A) *Hydrogenation of virosecurinine* (I) *with palladium charcoal*

Virosecurinine (I; 525 mg) was exhaustively hydrogenated in ethanol in the presence of 100 mg of prehydrogenated 5% palladium charcoal at room temp and atm. press. for 24 hr, and absorption of 2·25 molar equivalents of hydrogen indicated reduction beyond simple saturation of the double bond. The catalyst was filtered off, the filtrate evaporated *in vacuo*, and the residue chromatographed on 3% water deactivated neutral alumina ("Woelm", Activity Grade I). Elution with benzene–ether (3:1) and crystallization from petroleum ether afforded 293 mg XI as colourless crystals, m.p. 65–66°, $[\alpha]_D^{10}$ −22·8° (*c*, 0·82), λ_{max} μ 5·40 (CO), $\lambda_{max}^{CCl_4}$ μ 5·58 (CO). The U.V. spectrum showed no selective absorption. (Found: C, 70·23; H, 8·81; N, 6·61. $C_{13}H_{19}NO_2$ requires: C, 70·55; H, 8·62; N, 6·33%). The ether–methanol (9:1) fractions yielded 237 mg of XII as colourless crystals, m.p. 220–221°, after recrystallization from acetone. $[\alpha]_D^{10}$ −32·9° (*c*, 0·95), λ_{max}^{Nujol} μ 3·05 (OH), 6·21 (=N—CO—). The U.V. spectrum exhibited no selective absorption. (Found: C, 70·15; H, 9·72; N, 6·12. $C_{13}H_{21}NO_2$ requires: C, 69·91; H, 9·48; N, 6·27%).

(B) *Hydrogenation of virosecurinine* (I) *with platinum oxide*

A solution of 308 mg of I in ethanol was hydrogenated in the presence of 30 mg of prehydrogenated platinum oxide at room temp and atm. press. After 24 hr, hydrogen uptake ceased, and the resulting products were separated by chromatography, yielding 150 mg of XI and 127 mg of XII.

Hydrogenation of the amino lactone (III)

A solution of 224 mg III in ethanol was hydrogenated in the presence of 100 mg prehydrogenated 5% palladium charcoal at room temp and atm. press. After one molar equivalent of hydrogen had been absorbed, the solution was filtered from the catalyst and evaporated *in vacuo* to give an *oil*. The I.R. spectrum showed an absorption band at 5·64 μ due to a saturated γ-lactone grouping. This oil (XIII) was dissolved in ether–methanol (9:1) and poured onto an alumina column. After 1 hr, the column was eluted with the same solvent mixture, whereupon 180 mg of XII was obtained.

Cleavage of virosecurinine (I) *with cyanogen bromide*

A solution of 1·5 g of cyanogen bromide in absolute ether was added gradually to a stirred solution of 2·162 g I in absolute ether at room temp. Stirring was continued for 5 hr, and the separated *crystals* collected by filtration. The filtrate was washed with 2% aqueous sodium bicarbonate, water, dried (Na_2SO_4), and concentrated. The product was recrystallized from ethanol, m.p. 153–154°, $[\alpha]_D^{27}$ −263·1° (*c*, 1·47, $CHCl_3$), λ_{max} μ 4·51 (—C≡N), 5·67 (—CO—), λ_{max} 260·5 mμ (log ε 4·26). (Found: C, 52·10; H, 4·87; N, 8·70. $C_{14}H_{15}N_2O_2Br$ requires: C, 52·03; H, 4·68; N, 8·66%). Yield, 3·12 g.

Attempted hydrolysis of virosecurinine bromocyanide (XV)

A solution of 139 mg XV in 10 cc hot ethanol was heated with 10 cc 30% aqueous sulphuric acid on a water bath for 1 hr. After cooling to room temp, the solution was made basic with aqueous sodium bicarbonate and extracted with ether. Evaporation of the ether solution gave a crystalline mass, which after recrystallization from acetone-ether showed m.p. 141–142°; yield, 58 mg. Identity with I was confirmed by mixed m.p., I.R. spectrum, and rotation.

Reaction of virosecurinine bromocyanide (XV) *with zinc dust and dilute sulphuric acid*

To a stirred solution of 2 g XV in 30 cc hot ethanol was added in small portions 5 g of zinc powder followed by 7 cc of conc sulphuric acid. After 10 min, 25 cc water were added, and the mixture refluxed on a water bath for 3 hr. After cooling the solution was filtered from the zinc dust and concentrated *in vacuo* to remove the alcohol. It was then diluted with water, basified with aqueous ammonia and extracted with ether. After evaporation of the ether the oily product was purified by chromatography on alumina. The ether eluate fractions gave 614 mg of XVI; m.p. 75–76°, $[\alpha]_D^{21}$ −35·7° (*c*, 1·02), λ_{max} μ 6·15 (=N—CO—), λ_{max} 265 mμ (log ε 2·65), 272 mμ (log ε 2·54). (Found: C, 77·58; H, 7·72; N, 7·03. $C_{13}H_{15}NO$ requires: C, 77·58; H, 7·51; N, 6·96%).

Oxidation of the lactam (XVI) *with potassium permanganate*

To a suspension of 0·48 g XVI in 50 cc 1% aqueous potassium hydroxide was added 55 cc 4% aqueous potassium permanganate solution under stirring and heating on a water bath over a period of 4 hr. After cooling the solution was filtered from the precipitates of manganese dioxide, concentrated *in vacuo* to a small volume, and extracted with ether to remove the neutral fraction. Acidification of the aqueous phase with sulphuric acid followed by extraction with ethyl acetate yielded 96 mg of a crystalline acid. Heating of this acid with acetic anhydride and subsequent sublimation afforded phthalic anhydride, m.p. 127° (sublime). (Found: C, 64·56; H, 2·88. Cal. for $C_8H_4O_3$: C, 64·87; H, 2·72%).

Lithium aluminum hydride reduction of the lactam (XVI)

A solution of 307 mg XVI in absolute ether was added to a suspension of 300 mg lithium aluminum hydride in absolute ether, and the mixture stirred at room temp overnight. The excess reagent was destroyed with ethyl acetate and a conc. aqueous sodium sulphate solution added to precipitate inorganic salts followed by the addition of anhydrous sodium sulphate. Filtration and evaporation of the ether solution left an oily basic *substance*, I.R. spectrum of which showed the absence of the lactam absorption at 6·21 μ. This substance (XVII) formed a *hydrochloride*, m.p. 260–261° (in a sealed tube), $[\alpha]_D^{29}$ −84·4° (*c*, 1·96), which was shown by direct I.R. spectral comparison in chloroform solution to be identical with synthetic 1,2,3,4,6,7-hexahydro-11b*H*-benzo[a] quinolizine hydrochloride, supplied by Dr. S. Akaboshi of the university of Tokyo. λ_{max}^{Nujol} μ 12·61, 12·88, 13·24 (CH out-of-plane), λ_{max} 265 mμ (log ε 2·65), 272 mμ (log ε 2·58). (Found: C, 69·82; H, 8·32; N, 6·46. $C_{13}H_{17}N{\cdot}HCl$ requires: C, 70·01; H, 8·14; N, 6·28%).

Aromatization of virosecurinine (I) *with zinc dust and sulphuric acid*

To a stirred cooled solution of 2 g I in 30 cc 99.9% alcohol 6 cc of conc. sulphuric acid and then 4 g zinc dust were added in small portions and the solution kept stirred at room temp for 20 hr. After filtration, the solution was concentrated *in vacuo* to remove the alcohol, diluted with water, and basified with aqueous ammonia. Extraction with ether gave 1·793 g of an oily product, which was purified by chromatography on alumina. Elution with ether furnished 1·153 g of a lactam. Identity with XVI obtained by reaction of XV with zinc dust and sulphuric acid was confirmed by I.R. spectrum, mixed m.p. and rotation.

Hydrogenation of virosecurinine bromocyanide (XV) *with palladium charcoal*

The bromocyanide (XV; 1·183 g) was hydrogenated in ethanol in the presence of 120 mg prehydrogenated 5% palladium charcoal at room temp and atm. press. After two molar equivalents of hydrogen had been absorbed, the catalyst was filtered off and the filtrate, on concentration *in vacuo*, turned green. The I.R. spectrum of this colored oily *product* showed no —C≡N absorption but instead a band at 5·93 μ due to a —CH=NH group. This oil (XVIII) was heated with 10 cc conc. hydrochloric acid on a boiling water bath for 3 hr. After cooling, the solution was extracted with chloroform, and the extract, after drying and evaporating, afforded 550 mg XIX which crystallized from acetone, m.p. 186–187°, $[\alpha]_D^{27}$ −73·9° (*c*, 0·48), λ_{max} μ 2·85, 2·92 (NH), 5·73 (—CO—), 6·06, 6·31 (—$CONH_2$), λ_{max} 258 mμ (log ε 3·91). (Found: C, 63·94; H, 7·21; N, 10·53. $C_{14}H_{18}N_2O_3$ requires: C, 64·10; H, 6·92; N, 10·68%).

Catalytic hydrogenation of the amide (XIX)

A solution of XIX in ethanol was treated with 20 mg prehydrogenated 5% palladium charcoal at 26° and atm. press. One molar equivalent of hydrogen was rapidly absorbed and the *product* (XX)

was crystallized from acetone, m.p. 201–202°, yield, 128 mg. $[\alpha]_D^{27}$ −118° (*c*, 0·74), λ_{max} μ 2·86, 2·94 (NH), 5·73 (CO), 6·06, 6·31 (—$CONH_2$), λ_{max} 211 mμ (log ε 4·02). (Found: C, 63·67; H, 7·88; N, 10·52. $C_{14}H_{20}N_2O_3$ requires: C, 63·61; H, 7·63; N, 10·63%).

Hydrolysis of the amide (XX)

A solution of 100 mg XX in 2 cc ethanol was heated with 10 cc conc. hydrochloric acid under reflux for 12 hr. After cooling, the solution was made alkaline with aqueous ammonia and extracted with ether. Evaporation of the ether extract yielded 50 mg XXI as an oil, the picrate and acetate of which were shown by I.R., mixed m.p. and $[\alpha]_D$ to be identical with those of III, obtained by catalytic hydrogenation of I.

Direct comparison of virosecurinine with securinine

Securinine isolated from *S. suffruticosa* Rehd. shows $[\alpha]_D^{31}$ −1070° (*c*, 0·45). The I.R. spectrum of this sample was identical with that of virosecurinine both in chloroform solution and in Nujol mull. Securinine formed a picrate, m.p. 218°, and its I.R. spectrum was also identical with that of virosecurinine picrate, m.p. 218°.

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