Tetrahedron, 1963, Vol. 19, pp. 2101 to 2110. Pergamon Press Ltd. Printed in Northern Ireland

ABSOLUTE STEREOCHEMISTRY OF SECURININE[1]

Z. HORII, M. IKEDA, Y. YAMAWAKI, Y. TAMURA
School of Pharmacy, Osaka University, Toneyama, Toyonaka, Osaka, Japan

S. SAITO and K. KODERA
Osaka Research Laboratory, Tanabe Seiyaku Co. Ltd. Kashima-cho
Higashiyodogawa-ku, Osaka, Japan

(*Received* 22 *July* 1963)

Abstract—The absolute configuration of securinine was shown to be I from the rotatory dispersion curves and molecular rotations of degradation products of securinine. The conclusion was unequivocally confirmed by the formation of (+)-N-benzoylpipecolic acid on degradation of this alkaloid. The conformation of the bridgehead nitrogen was also discussed.

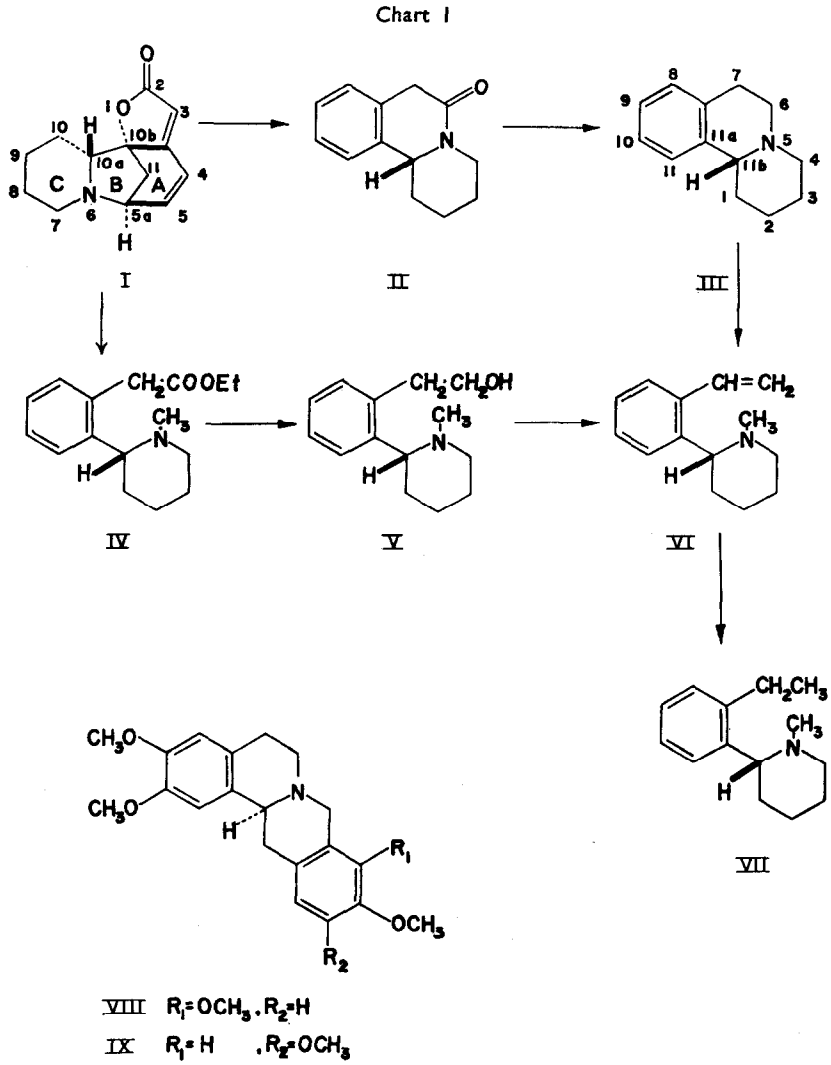
IN a previous communication,[2] we showed that securinine, an alkaloid of a strychnine-like activity isolated from *Securinega suffruticosa Rehd*, is represented by the absolute configuration I on the bases of the rotatory dispersion curves and molecular rotations of the degradation products, and that it would exist most probably in such a conformation that C_{10a}—C_{10b} and N—C_{5a} are *cis* to each other in respect of the piperidine ring. Our subsequent investigation on the degradation of securinine yielding (+)-N-benzoylpipecolic acid (XIV) confirmed unequivocally this absolute stereochemistry. A full account of these experiments is given in this paper.

Satoda *et al.*[3] reported that reduction with zinc-dust and sulfuric acid converted securinine and its methiodide to the lactam (II) and the aminoester (IV), respectively. Reduction of II with lithium aluminum hydride yielded the benzoquinolizidine (III).[4] Hofmann degradation of the methiodide of III gave the styrene (VI), which was hydrogenated to compound VII. That an asymmetric center in these degradation products was not affected during the degradation was confirmed by the fact that lithium aluminum hydride reduction of IV and subsequent dehydration of the resulted aminoalcohol (V) with potassium hydroxide afforded VI with the same optical rotation as that of VI prepared from III. These reactions are summarized in Chart 1. Since the relative configuration of securinine has already been established[1] and the asymmetric center of III corresponds to C_{10a} of securinine, determination of the absolute configuration of securinine is reduced to that of III.

The rotatory dispersion curves of III and its salts were positive (Fig. 1), and were compared with those of S-(−)-tetrahydropalmatine[5] (VIII), its hydrochloride[5] and S-(−)-norcoralydine[6] (IX). As the latter group of compounds have been reported

[1] Structure of securinine, S. Saito, K. Kodera, A. Ide, K. Shigematsu, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki and Y. Tamura, *Tetrahedron* in the press.
[2] Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito and K. Kodera, *Chem. Pharm. Bull., Tokyo* **11**, 817 (1963).
[3] I. Satoda, M. Murayama, J. Tsuji and E. Yoshii, *Tetrahedron Letters*, 1199 (1962).
[4] Cf. T. Nakano, T. H. Yang and S. Terao, *Chem. & Ind.* 1651 (1962).
[5] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960).
[6] A. Brossi, M. Baumann, F. Burkhardt, R. Richle and J. R. Frey, *Helv. Chim. Acta* **45**, 2219 (1962).

Chart I



to show negative rotatory dispersion curves, the asymmetric center of III would be assigned as R-configuration. The same conclusion was also obtained from the molecular rotation study. The molecular rotations,[7] $[M]_D$, of III and its perchlorate (IIIb) were +415° (in pyridine) and +235° (in ethanol), respectively. On the bases of the results reported by Battersby *et al.*[8] and Ban *et al.*[9] on the emetine derivatives, (−)-canadine, (−)-tetrahydroprotoberberine etc., the large positive contribution of C_{11b} in structure III and IIIb would predict that these compounds have the R-configuration. Consequently, it would be concluded that securinine have the R-configuration at C_{10a} and, therefore, the absolute configuration shown by I.

[7] Compounds, (−)(III) and (−)(IIIb), obtained from virosecurinine showed $[M]_D$ − 392° and −217°, respectively (see Experimental).

[8] A. R. Battersby and S. Garratt, *Proc. Chem. Soc.* 86 (1959).

[9] Y. Ban, M. Terashima and O. Yonemitsu, *Chem. & Ind.* 569 (1959).

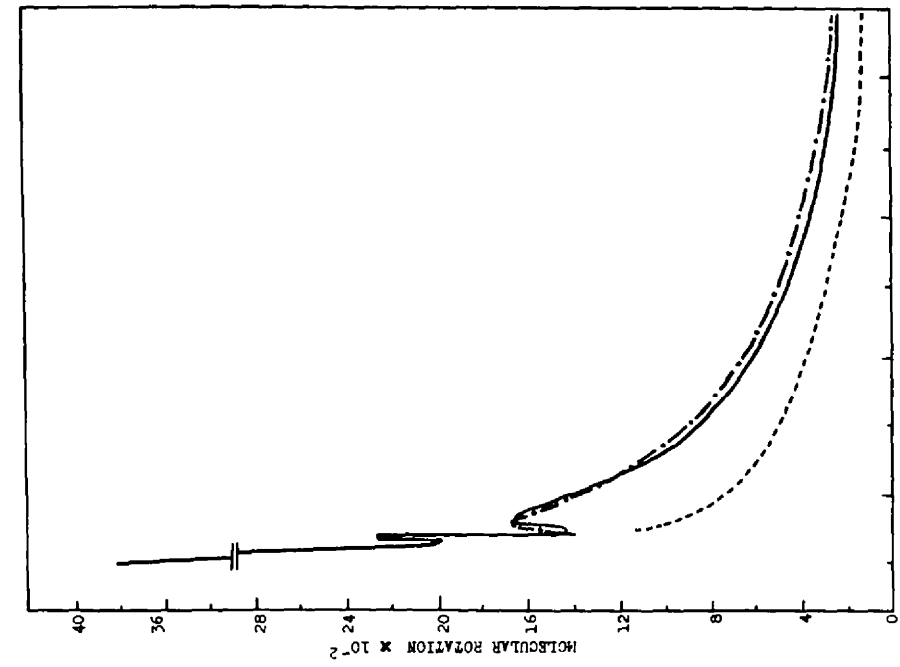


FIG. 2. Optical rotatory dispersion curves of α-ketol and its salts in MeOH.
——— α-ketol (X)
—·—·— the hydrochloride (Xa) ----- the perchlorate (Xb)

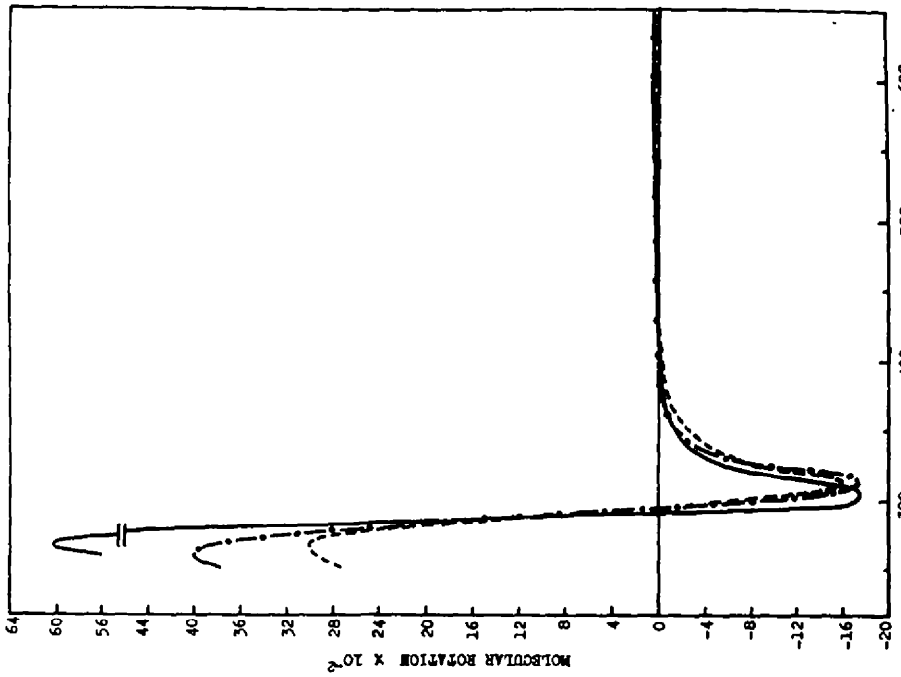
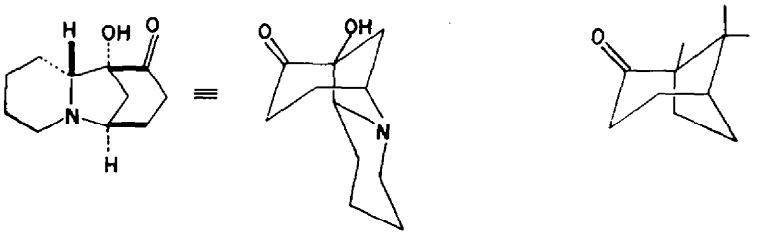


FIG. 1. Optical rotatory dispersion curves of benzoquinolizidine and its salts in MeOH.
——— benzoquinolizidine (III)
—·—·— the hydrochloride (IIIa) ----- the methiodide (IIIc)

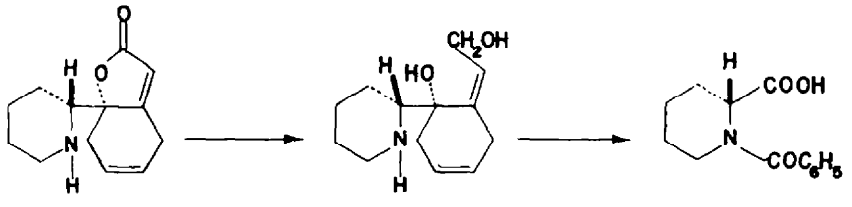
The second evidence for the absolute configuration (I) was provided by an independent assignment of the C_{10b} configuration of securinine. Satoda *et al.*[3] reported that lithium aluminum hydride reduction of dihydrosecurinine[1] followed by ozonolysis gave the α-ketol (X). The optical rotatory dispersion curves of the free base (X) ($a^{10} = -78°$), the perchlorate (Xa; $a = -46°$) and the hydrochloride (Xb; $a = -57°$) showed negative Cotton effects (Fig, 2). Since an equatorial hydroxyl group adjacent to carbonyl group usually does not affect a sign of Cotton effect,[11,12] comparison with the case of (−)-homocamphor[12] (XI; a = ca. −60°) having two methyl substituents in a positive octant, or direct application of the octant rule[12] predict that X should have the R-configuration at the asymmetric center adjacent to the carbonyl group, which corresponds to C_{10b} of securinine. Thus, securinine should have the S-configuration at C_{10b}, suggesting the absolute configuration I.



X XI

Finally, the conclusion thus obtained was confirmed unequivocally by the formation of (+)-N-benzoylpipecolic acid (XIV) on the degradation of securinine (Chart 2). Reduction of a degradation product (XII)[1] of securinine with lithium aluminum hydride gave the diol (XIII). Benzoylation of XIII and subsequent oxidation[13] with potassium permanganate in acetone gave partially racemized (+)-N-benzoylpipecolic acid (XIV), which showed the same IR spectrum through-out the range as that of the authentic sample prepared by the method of Clark-Lewis and Mortimer.[14]

Chart 2



XII XIII XIV

[10] The molecular amplitude (a) = (the molecular rotation at the extremum of longer wavelength minus the molecular rotation at the extremum of shorter wavelength) × 10^{-2}. C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1963).

[11] C. Djerassi, *Optical Rotatory Dispersion* p. 111. McGraw-Hill, New York (1960).

[12] W. Klyne, *Tetrahedron* **13**, 29 (1961).

[13] Cf. T. Nakano, T. H. Yang and S. Terao reported a similar oxidation for (−)-N-benzoylpipecolic acid from virosecurinine at Kinki Local Meeting of the Pharmaceutical Society of Japan, Kyoto, March 17 (1963).

[14] J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.* 189 (1961).

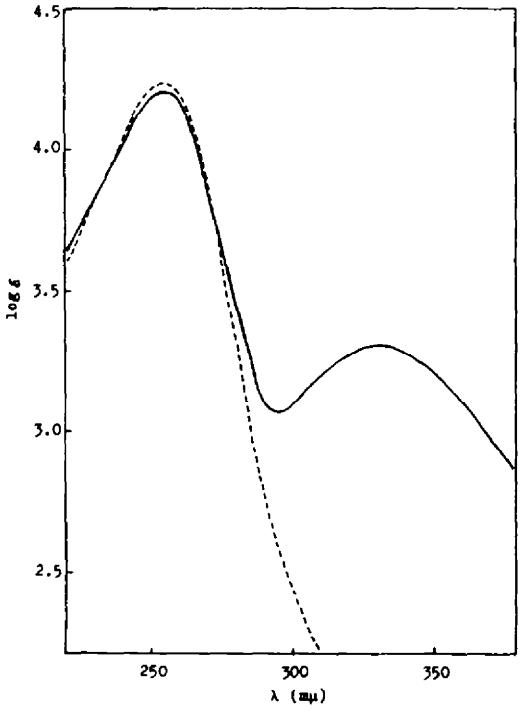


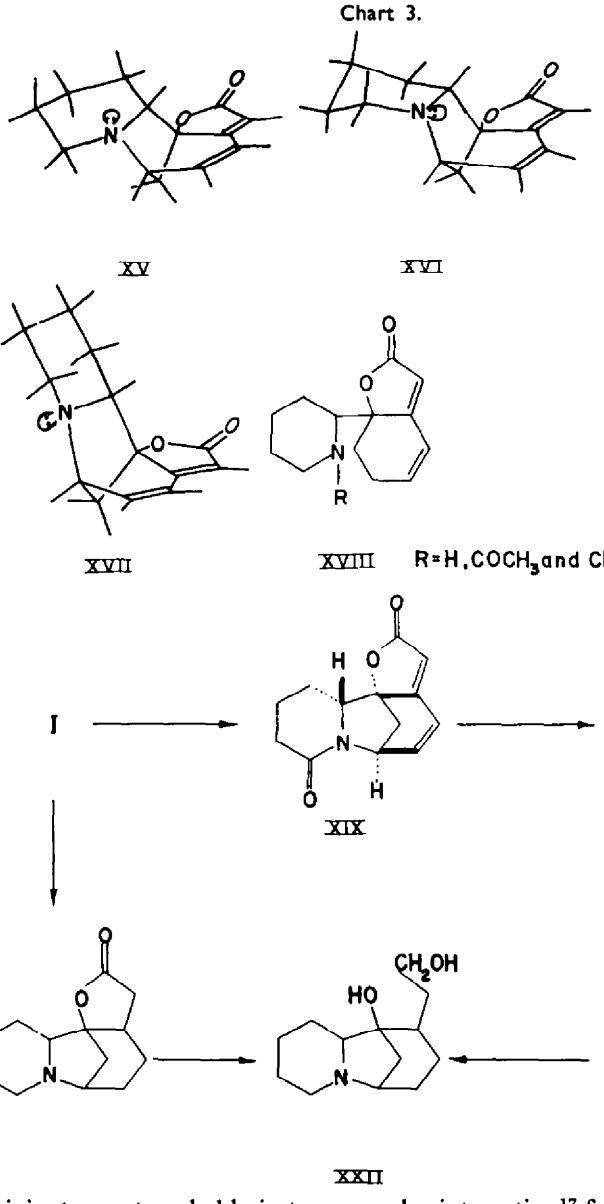
FIG. 3. Ultraviolet spectra of securinine and its hydrochloride in EtOH.
——— securinine
- - - - - securinine hydrochloride

It has been established that the asymmetric center of (+)-N-benzoylpipecolic acid possesses the R-configuration.[14,15] Thus, the absolute configuration (I), presented from the rotatory dispersion curve as well as the molecular rotation, was proved to be correct.

Now, a priori three conformations of structure I due to the stereochemistry of the B/C ring juncture, if we assume that the piperidine ring exists preferably in a chair conformation, are considered: two B/C *cis* forms, (XV and XVI), and one B/C *trans* form (XVII). The UV spectrum and the rotatory dispersion afforded a very interesting information on the choice of a preferable conformation. Securinine showed two absorption bands at 256 mμ (log ε 4·27) and 330 mμ (log ε 3·30) in the UV spectrum (Fig. 3), the latter of which is thought to be the orgin of the Cotton effect in the rotatory dispersion curve[16] of securinine. This UV band was not affected by changing solvents from ethanol to dioxane, chloroform or n-hexane, but disappeared in acidic media. The hydrochloride of securinine (Fig. 3) as well as the degradation products (XVIII and XIX) were all colorless and lacked the absorption at 330 mμ in the UV [the lactam (XIX), $C_{13}H_{13}O_3N$, m.p. 238–240°, $[\alpha]_D$ −700° (in ethanol) was obtained by ozonolysis of securinine, and its structure was established from a series of reactions shown in Chart 3, the elemental and spectral analyses]. Therefore, the characteristic absorption at 330 mμ in the UV spectrum as well as the yellow-coloring of securinine

[15] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 3590 (1950).
[16] Z. Horii, T. Tanaka, Y. Tamura, S. Saito, C. Matsumura and N. Sugimoto, *J. Pharm. Soc., Japan* **83**, 602 (1963).

Chart 3.



would originate most probably in transannular interaction[17] from the nitrogen to the conjugated system in structure I. Thus, the conformer (XVII) is excluded because such interaction between the nitrogen and the conjugated system is impossible. Consequently, the conformation shown by XV or XVI may be concluded as most favorable.

[17] The abnormally intense negative Cotton effect would also be ascribed to this $\ddot{N}\overset{\frown}{}C{=}C{-}C{=}C{-}C{=}O$ system. U. Weiss and H. Ziffer, *Experientia* **19**, 108 (1963); C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Amer. Chem. Soc.* **84**, 870 (1962); A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *Ibid.* **84**, 1945 (1962).

EXPERIMENTAL

M.ps and b.ps are uncorrected. Unless otherwise stated, UV spectra were determined in ethanol solution. Specific rotations were measured with Yanagimoto photomagnetic direct reading polarimeter model OR-20, using 10 cm cell and ethanol, unless otherwise specified. Optical rotatory dispersion curves were measured with Rudolph automatic recording spectropolarimeter, using 1 cm cell and methanol at 19–22°.

1,3,4,6,7,11b-*Hexahydro*-6-*oxo*-2H-*benzo* [a] *quinolizine* (II)

Securinine was reduced by the method of Satoda *et al.*[3] To a stirred solution of 2 g securinine in 40 g conc H_2SO_4 and 100 ml absolute ethanol, 20 g Zn-dust was added during 30 min and the mixture stirred at room temp for 5 hr. The inorganic material was filtered off and washed with ethanol. The filtrate and washings, made alkaline with aqueous ammonia, were evaporated under red. press., KOHaq added to the residue and the resulting solution extracted with ether. The dried extract was evaporated to give a viscous oil which solidified immediately. Recrystallization from pet ether (b.p. 40–60°) gave 1·2 g of pale yellow needles of the lactam (II), m.p. 69–70° (reported 74–75°[3]). λ_{max} 264 mμ (log ε 2·52), 271 mμ (log ε 2·53), ν_{max}^{KBr} cm^{-1}: 1630 (six-membered lactam). (Found: C, 77·50; H, 7·51. Calcd. for $C_{13}H_{15}ON$: C, 77·58; H, 7·51%).

1,3,4,6,7,11b-*Hexahydro*-2H-*benzo* [a] *quinolizine* (III)[4]

To a suspension of 1 g $LiAlH_4$ in 40 ml anhydrous ether, a solution of 1 g II in 10 ml anhydrous ether was added dropwise with stirring. After the mixture had refluxed for 4 hr, the excess hydride was decomposed with 10 ml water. The inorganic material was filtered off and washed with ether. The dried filtrate was evaporated and distilled at 127–128°/7 mm to give 600 mg of colorless oil. A sample for specific rotation and rotatory dispersion was prepared by purification through the perchlorate followed by redistillation. $[\alpha]_D$ +222° (*c*, 0·022 in pyridine). R.D. (*c*, 0·524): $[\alpha]_{700}$ +107°, $[\alpha]_{589}$ +140°, $[\alpha]_{300}$ +750°, $[\alpha]_{281}$ +895°, $[\alpha]_{275}$ +760°, $[\alpha]_{270}$ +1230°, $[\alpha]_{266}$ +1050°, $[\alpha]_{250}$ +2040°. The hydrochloride (IIIa) was recrystallized from isopropanol, m.p. 256–257°. R.D. (*c*, 0·425): $[\alpha]_{650}$ +117°, $[\alpha]_{589}$ +140°, $[\alpha]_{400}$ +300°, $[\alpha]_{300}$ +624°, $[\alpha]_{270}$ +620°. (Found: C, 69·64; H, 8·04. $C_{13}H_{16}NCl$ requires: C, 69·78; H, 8·11%). The perchlorate (IIIb) was recrystallized from isopropanol m.p. 160–161°. $[\alpha]_D$ +81·6° (*c*, 1·03). λ_{max} 264 mμ (log ε 2·59), 272 mμ (log ε 2·59). (Found: C, 54·02; H, 6·30. $C_{13}H_{18}O_4NCl$ requires: C, 54·26; H, 6·31%). The methiodide (IIIc) was prepared by refluxing III with methyl iodide in ether for 3 hr and recrystallized from isopropanol, m.p. 173–174° (decomp.). R.D. (*c*, 0·368): $[\alpha]_{650}$ +43°, $[\alpha]_{589}$ +46°, $[\alpha]_{400}$ +120°, $[\alpha]_{300}$ +250°, $[\alpha]_{275}$ +350°. (Found: C, 50·66: H, 6·11. $C_{14}H_{20}NI$ requires: C, 51·07; H, 6·12%).

Antipode of III

Virosecurinine was subjected to the same series of reactions[4] for III, b.p. 150–160° (bath temp)/8 mm. A sample for specific rotation was prepared by purification through the perchlorate followed by redistillation. $[\alpha]_D$ −209° (*c*, 0·025 in pyridine). The perchlorate was recrystallized from isopropanol m.p. 160–162°. $[\alpha]_D$ −75·3° (*c*, 1·03). λ_{max} 264 mμ (log ε 2·53), 272 mμ (log ε 2·51). (Found: C, 54·05; H, 6·33. $C_{18}H_{18}O_4NCl$ requires: C, 54·26; H, 6·31%).

Ethyl 2-(N-*methyl*-2′-*piperidyl*) *phenylacetate* (IV)

Securinine methiodide[1] was reduced (Zn-dust and H_2SO_4) according to the method described for II to give IV, b.p. 152–153°/5 mm. The perchlorate was recrystallized from isopropanol, m.p. 169–170° (reported 171–172°[3]). λ_{max} 266 mμ (log ε 2·81), 272 mμ (log ε 2·74), ν_{max}^{KBr} cm^{-1}: 1724 (ester). (Found: C, 52·80; H, 6·67. Calcd. for $C_{16}H_{24}O_6NCl$: C, 53·11; H, 6·68%).

N-*Methyl*-2-[o-(2′-*hydroxyethyl*) *phenyl*] *piperidine* (V)

To a suspension of 1·5 g $LiAlH_4$ in 30 ml anhydrous ether was added with stirring a solution of 1·5 g IV in 20 ml anhydrous ether. After the addition was complete, stirring was continued at room temp for 1 hr. The excess hydride was decomposed with ice-water and the resulting solid filtered and washed with ether. The dried filtrate was evaporated and the residue distilled at 175–180° (bath temp)/0·04 mm to give a viscous oil of V. λ_{max} 262 mμ (log ε 2·38), 268 mμ (log ε 2·28), 272 mμ (log ε 2·21), $\nu_{max}^{CCl_4}$ cm^{-1}: 3549, 3400–3280 (hydroxyl).

The acetate of V was prepared by refluxing a solution of 90 mg aminoalcohol (V), 2 ml pyridine and 2 ml acetic anhydride for 30 min. The mixture was poured into ice-water, made alkaline (K_2CO_3 aq) and extracted with ether. The dried ether extract was evaporated and the residual oil converted to the picrate. Recrystallization from ethanol gave 60 mg picrate of the acetate of (V), m.p. 137–138°. (Found: C, 53·65; H, 5·54. $C_{22}H_{26}O_9N_4$ requires: C, 53·87; H, 5·34%).

N-*Methyl*-2-(o-*vinylphenyl*) *piperidine* (VI)

(a) *From* IIIc. A solution of 600 mg IIIc in 5 ml water was passed through a column of Amberlite IR 400 (1·2 × 8 cm) and eluted with 50 ml water. The aqueous solution eluted was evaporated to dryness (red. press.) and the residue heated at 120–130° (bath temp)/10 mm for 30 min. After cooling, 5 ml water was added and the solution extracted with ether. The dried ether extract was evaporated to give 350 mg crude oil of VI. The perchlorate was recrystallized from isopropanol, m.p. 155–157°, $[\alpha]_D$ + 20·4° (*c*, 0·09). λ_{max} 241 mμ (log ε 4·04), 285 mμ (log ε 2·45), ν_{max}^{KBr} cm^{-1}: 1626 (double bond). (Found: C, 55·72; H, 6·70. $C_{14}H_{20}O_4NCl$ requires: C, 55·72; H, 6·68%).

(b) *From* V. A mixture of 200 mg V, 100 mg powdered KOH and a trace of Cu-powder was distilled at 170–180° (bath temp)/5 mm for 3 hr and the colorless oil which distilled over converted to the perchlorate. Recrystallization from isopropanol gave 85 mg of the perchlorate of VI, m.p 155–157°, $[\alpha]_D$ +21·4° (*c*, 0·075). (Found: C, 55·71; H, 6·79. $C_{14}H_{20}O_4NCl$ requires: C, 55·72; H, 6·68%). This compound was identical in m.p., mixed m.p., UV spectrum and IR spectrum with the Hofmann degradation product of IIIc.

N-*Methyl*-2-(o-*ethylphenyl*) *piperidine* (VII)

A solution of 250 mg VI in 10 ml ethanol was hydrogenated (25 mg PtO_2; at atm. press. and room temp until 1 mole H_2 was taken up after 1 hr). The filtered solution was evaporated under red. press. and the residue distilled at 150° (bath temp)/5 mm to give 185 mg colorless oil, which was converted to the perchlorate. Recrystallization from ether-ethanol gave the perchlorate of VII, m.p. 145–146°. λ_{max} 264 mμ (log ε 2·67), 271 mμ (log ε 2·68). (Found: C, 54·98; H, 7·36. $C_{14}H_{22}O_4NCl$ requires: C, 55·35; H, 7·30%).

α-*Ketol* (X)

According to the method of Satoda *et al.*,[3] dihydrosecurinine[1] was converted to X. To a cold suspension of 1 g $LiAlH_4$ in 40 ml anhydrous ether, a solution of 3 g dihydrosecurinine in 15 ml anhydrous ether was added dropwise with stirring. After the mixture had refluxed for 5 hr, 30 ml wet ether and then 10% NaOH aq were added carefully to the ice-cooled reaction mixture to decompose the excess $LiAlH_4$. The inorganic material precipitated was filtered off and washed with ether. The filtrate and washings were dried and evaporated to give 2·3 g dihydrosecurininediol[3] as a viscous oil, which was converted to the hydrochloride, colorless plates from isopropanol–ethyl acetate, m.p. 180–181° (reported m.p. 165°[3]). ν_{max}^{KBr} cm^{-1}: 3226 (hydroxyl), 1647 (double bond). (Found: C, 60·19; H, 8·47. Calcd. for $C_{13}H_{22}O_2NCl$: C, 60·05; H, 8·53%). A slow stream of ozone was passed through a solution of the hydrochloride in 30 ml water at 0° for 2 hr. The solution was warmed at 60° for 30 min to decompose the ozonide, made alkaline (K_2CO_3), extracted with chloroform and dried. Evaporation of the extract gave 400 mg of viscous oil, which distilled at 130–140° (bath temp)/3 mm $\nu_{max}^{CCl_4}$ cm^{-1}: 3472 (hydroxyl); 2778, 2703 (*trans*-quinolizidine band); 1709 (ketone). A sample for rotatory dispersion was prepared by purification through the hydrochloride, followed by redistillation. R.D. (*c*, 0·085): $[\alpha]_{650}$ +47°, $[\alpha]_{589}$ +47°, $[\alpha]_{450}$ +14°, $[\alpha]_{350}$ −94°, $[\alpha]_{303}$ −965° $[\alpha]_{265}$ +3280°, $[\alpha]_{260}$ +3040°. The perchlorate was obtained in the usual way, white needles from ethanol, m.p. 179–181°. ν_{max}^{KBr} cm^{-1}: 3446 (hydroxyl), 1737 (ketone). R.D. (*c*, 0·314): $[\alpha]_{700}$ +6·4°, $[\alpha]_{589}$ +6·4°, $[\alpha]_{400}$ −16°, $[\alpha]_{313}$ −550°, $[\alpha]_{267}$ +1020°, $[\alpha]_{250}$ +920°. (Found: C, 44·67; H, 6·24. $C_{11}H_{18}O_6NCl$ requires: C, 44·67; H, 6·13%). The hydrochloride, m.p. 203° (decomp.) (reported m.p. 213°[3]). ν_{max}^{KBr} cm^{-1}: 3279 (hydroxyl), 1736 (ketone). R.D. (*c*, 0·413): $[\alpha]_{650}$ +24°, $[\alpha]_{589}$ +24°, $[\alpha]_{400}$ +9·7°, $[\alpha]_{313}$ −755°, $[\alpha]_{260}$ +1730°, $[\alpha]_{250}$ +1640°.

Diol (XIII)[13]

To a suspension of 0·7 g $LiAlH_4$ in 10 ml anhydrous ether, a solution of 1·0 g lactone (XII)[1] in 10 ml anhydrous ether was added dropwise with stirring. After refluxing for 3 hr, the mixture was treated in the manner described for III. The dried ether extract was evaporated to give 0·8 g crude XVI, which

was recrystallized from pet ether (b.p. 60–80°), m.p. 93·5–94·5°. ν_{max}^{KBr} cm^{-1}: 3322 (hydroxyl), 1653 (double bond). (Found: C, 70·47; H, 9·60. $C_{13}H_{21}O_3N$ requires: C, 69·92; H, 9·48%).

(+)-N-*Benzoylpipecolic acid* (XIV)[18]

To a cooled solution of 0·8 g XIII in 5 ml benzene and 4 ml 10% NaOH aq, 1·15 g benzoyl-chloride was added dropwise with stirring. After stirring was continued at room temp for 6 hr, the benzene layer was separated, washed with 10% HCl aq and water, dried and evaporated (red. press.). The residual oil (1 g) was dissolved in 10 ml acetone, and 3 g $MgSO_4$ added. To the cooled mixture was added dropwise with stirring a solution of 3 g $KMnO_4$ in 300 ml acetone below 5°. The reaction mixture was stirred at 5° for 6 hr and allowed to stand overnight, until the excess $KMnO_4$ was decomposed by addition of 5 ml ethanol. The precipitated MnO_2 was filtered off and washed with acetone and then with hot water. The combined filtrate and washings were evaporated (red. press.), the residue acidified with 10% HCl aq, extracted with chloroform and the extract dried and evaporated. The residual oil was purified by chromatography employing 3 g silica gel and benzene–chloroform (1 : 1). The first fraction gave benzoic acid and the second N-benzoylpipecolic acid (48 mg). The latter was distilled twice at 130–140° (bath temp)/0·03 mm, crystallized by standing overnight in pet ether (b.p. 60–80°) and recrystallized once from water, m.p. 120–121°, $[\alpha]_D$ +43° (*c*, 0·03). $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712 (carboxylic acid), 1626 (amide). This compound was identical with an authentic specimen of (±)-N-benzoylipipecolic acid,[14] m.p. 131–132°, (Found: C, 66·64; H, 6·66; N, 6·01. Calcd. for $C_{13}H_{15}O_3N$: C, 66·93; H, 6·48; N, 5·76%) by comparison of their IR spectra in chloroform solution.

Ozonolysis of securinine

A slow stream of ozone was passed through a solution of 5 g securinine in 200 ml chloroform at 0° for 7 hr. The solvent was removed (red. press.), the residue dissolved in 50 ml water and heated at 60° for 30 min. After cooling, the aqueous solution was shaken with chloroform. Evaporation of the solvent from the dried chloroform layer gave 3·2 g of crude reddish brown oil (A). The aqueous layer was made alkaline (sat. $NaHCO_3$ soln.), extracted with chloroform and dried. Evaporation of the solvent from the chloroform extract gave 400 mg crystals, which gave securinine, m.p. 142–143°, by chromatographical purification employing silica gel and chloroform.

The crude oil (A) was chromatographed on silica gel with chloroform to give two pure crystalline materials. The first crystals eluted were the lactam XIX (390 mg, colorless needles), m.p. 238–240° from benzene–pet ether (b.p. 60–80°), $[\alpha]_D$ −700° (*c*, 0·1). ν_{max}^{KBr} cm^{-1}: 1815, 1745 (unsaturated γ-lactone); 1630 (six-membered lactam). λ_{max} 256 mμ (log ε 4·31). (Found: C, 67·09; H, 5·57; N, 6·07. $C_{13}H_{13}O_3N$ requires: C, 67·52; H, 5·67; N, 6·06%). The second crystals eluted were 10 mg of colorless needles, m.p. 263–265° (decomp.) from benzene, which were not further characterized. $[\alpha]_D$ −840° (*c*, 0·1). ν_{max}^{KBr} cm^{-1}: 1727, 1667, 1629. λ_{max} 261 mμ (log ε 4·11). (Found: C, 63·71; H, 4·61; $C_{13}H_{11}O_4N$ requires: C, 63·67; H, 4·52%).

Dihydrolactam (XX)

A solution of 170 mg XIX in 20 ml glacial acetic acid was hydrogenated (40 mg Pd-C at atm. press. and room temp; 20 ml H_2 being taken up in 2·5 hr). After removal of catalyst by filtration, evaporation of the filtrate (red. press.) gave 174 mg of viscous liquid, which solidified on cooling. Recrystallization of the solid from benzene–pet ether (b.p. 60–80°) gave 150 mg of colorless needles, m.p. 207·5–208·5°, $[\alpha]_D$ −60° (*c*, 0·1). ν_{max}^{KBr} cm^{-1}: 1812, 1745 (unsaturated γ-lactone); 1631 (lactam). This compound showed no absorption above 220 mμ in the UV spectrum. (Found: C, 66·91; H, 6·62. $C_{13}H_{15}O_3N$ requires: C, 66·93; H, 6·48%).

Tetrahydrolactam (XXI)

A solution of 130 mg XX in 30 ml ethanol was hydrogenated (25 mg PtO_2 at atm. press. and room temp and, after 5 hr, further 10 mg catalyst was added; 16·4 ml H_2 being taken up in 10 hr). The catalyst was removed by filtration, and evaporation of the filtrate gave a viscous liquid, which solidified immediately. Recrystallization from ether–pet ether (b.p. 40–60°) gave 120 mg of colorless needles, m.p. 173·5–175°, $[\alpha]_D$ −48·5° (*c*, 0·2). ν_{max}^{KBr} cm^{-1}: 1773 (γ-lactone), 1637 (lactam). This compound showed no absorption above 220 mμ in the UV spectrun. (Found: C, 66·48; H, 7·36. $C_{13}H_{17}O_3N$ requires: C, 66·36; H, 7·28%).

Tetrahydrodiol (XXII)

(a) *From tetrahydrosecurinine.* To a suspension of 0·3 g $LiAlH_4$ in 20 ml anhydrous ether, a solution of 1·3 g tetrahydrosecurinine[1] in 10 ml anhydrous ether was added dropwise with stirring at 0°. After refluxing for 8 hr, 3 ml 10% NaOH aq was added carefully to the ice-cooled reaction mixture, the inorganic material precipitated was filtered off and washed with ether. The combined ether layer and washings were dried and evaporated. The residual oil was distilled at 180° (bath temp)/0·1 mm to give 1·1 g of colorless vicsous oil, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3534, 3356 (hydroxyl). The hydrochloride crystallized as colorless plates, m.p. 224–226° from ethanol–ether. (Found: C, 60·19; H, 9·04; N, 5·31. $C_{13}H_{24}O_2NCl$ requires: C, 59·64; H, 9·24; N, 5·35%). The methiodide was prepared by refluxing a mixture of 0·8 g XXII, 2 ml methyl iodide and 10 ml acetone for 30 min. After cooling, the precipitates were collected by filtration and recrystallized from methanol to give 1·3 g methiodide in colorless needles, m.p. 252–253°, ν_{max}^{Nujol} cm^{-1}: 3356 (hydroxyl). (Found: C, 45·72; H, 6·97; N, 4·13. $C_{14}H_{26}O_2NI$ requires: C, 45·78; H, 7·13; N, 3·81%).

(b) *From* XXI. To a suspension of 250 mg $LiAlH_4$ in 20 ml anhydrous tetrahydrofuran, a solution of 100 mg XXI in 15 ml anhydrous ether was added dropwise with stirring at 0°. After refluxing for 20 hr, 30 ml wet ether and then 3 ml 10% NaOH aq were added carefully to the ice-cooled reaction mixture and stirring was continued for an additional 30 min. The inorganic material was filtered off. Evaporation of the dried filtrate and subsequent distillation at 165–170° (bath temp)/0·2 mm gave 20 mg of yellowish viscous liquid, which was identical in IR spectrum with the specimen of XXII prepared in (a). The methiodide crystallized as colorless needles m.p. 251–253° from methanol and was identical in m.p., mixed m.p. and IR spectrum (Nujol) with tetrahydrosecurinine diol methiodide prepared in (a).

Acknowledgements—The authors sincerely thank Professor Yoshio Ban, Hokkaido University, for his valuable advice and also to Dr. Kaoru Kuriyama, Shionogi Seiyaku Co. for measurement of the rotatory dispersion curves of compounds (III) and (Xa).