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THE TOTAL SYNTHESIS OF SECURININE AND VIROSECURININE

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Abstract—The total synthesis of securinine (I) and virosecurinine (II) is described.

SECURININE[1] is an alkaloid from *Securinega suffruticosa* Rehd. and its optical antipode, virosecurinine,[2] was isolated from *Securinega virosa* Pax. et Hoffm. The structures, I and II, of securinine[3,4] and virosecurinine[5] were established through the chemical[3,5] and X-ray crystallographic[4] studies, showing the presence of a novel decahydro-6,10-methanopyrido[1,2-a]azepine system fused with a $\Delta^{\alpha,\beta}$-butenolide ring, which is common[6] in many other minor alkaloids[7] from *Securinega* species. The total synthesis of securinine (I) and virosecurinine (II) is now described.

The synthesis consists of four parts; the preparation of the α-ketol (VII) possessing ring A and C of I, the transformation of VII into the butenolide (XII), the cyclization

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

[2] T. Nakano, T. H. Yang and S. Terao, *Chem. & Ind.* 1651 (1962).

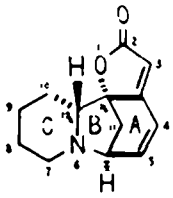
[3a] S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki and Y. Tamura, *Tetrahedron* **19**, 2085 (1963); [b] Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito and K. Kodera, *Ibid.* **19**, 2101 (1963); [c] I. Satoda, M. Murayama, J. Tsuji and E. Yoshii, *Tetrahedron Letters* 1199 (1962); [d] J. Parello, A. Melera and R. Goutarel, *Bull. Soc. Chim. Fr.* 898 (1963); [e] S.-F. Chen, C.-H. Hsieh and H.-T. Liang, *Scientia Sinica* **12**, 1525 (1963).

[4] S. Imado, M. Shiro and Z. Horii, *Chem. Pharm. Bull. Tokyo* **13**, 643 (1965).

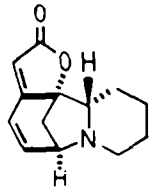
[5] T. Nakano, T. H. Yang and S. Terao, *Tetrahedron* **19**, 609 (1963); Idem., *J. Org. Chem.* **28**, 2619 (1963).

[6] There are two exceptions, norsecurinine and dihydronorsecurinine, possessing octahydro-5,9-methanopyrrolo[1,2-a]azepine system: G. O. Iketubosin and D. W. Mathieson, *J. Pharm. Pharmacol.* **15**, 810 (1963); S. Saito, T. Tanaka, K. Kotera, H. Nakai, N. Sugimoto, Z. Horii, M. Ikeda and Y. Tamura, *Chem. Pharm. Bull. Tokyo* **13**, 786 (1965).

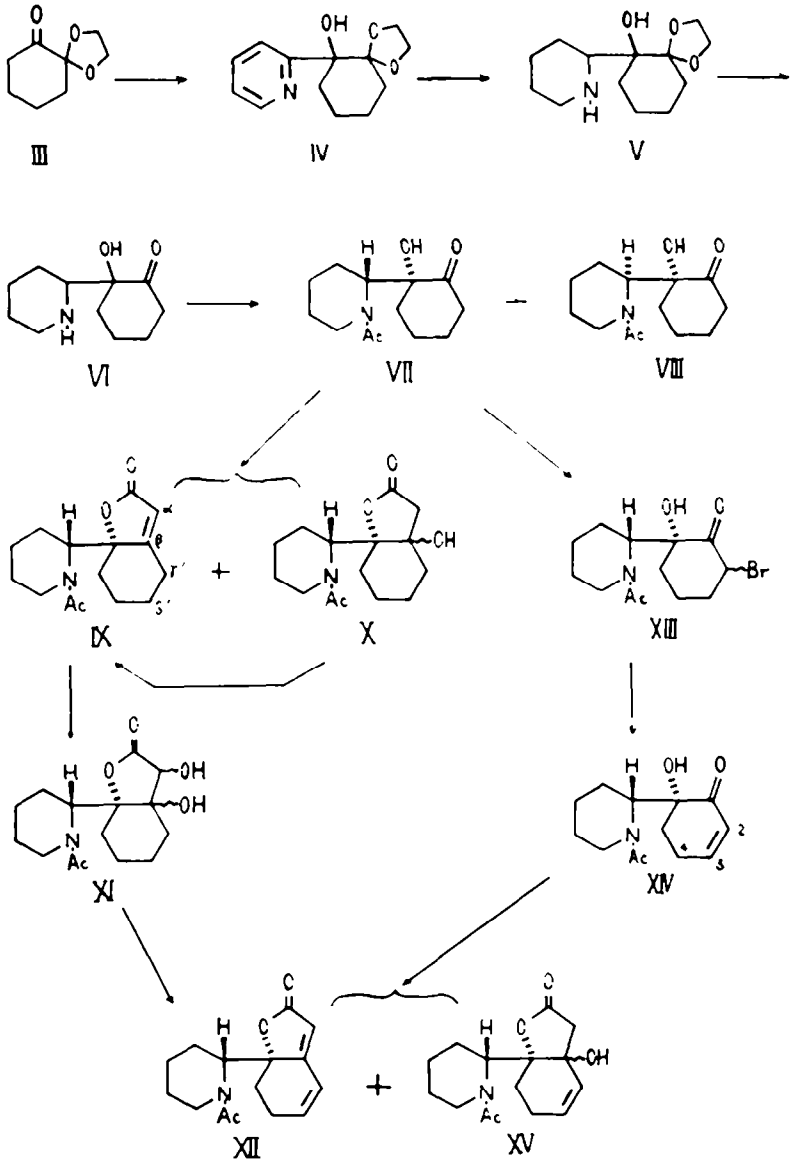
[7a] Allosecurinine:[7a,7d] see also A. Chatterjee, R. Mukherjee, B. Das and S. Ghosal, *J. Indian Chem. Soc.* **41**, 163 (1964); Z. Horii, Y. Yamawaki, Y. Tamura, S. Saito, H. Yoshikawa and K. Kotera, *Chem. Pharm. Bull. Tokyo* **13**, 1311 (1965); [b] viroallosecurinine: S. Saito, T. Iwamoto, T. Tanaka, C. Matsumura, N. Sugimoto, Z. Horii and Y. Tamura, *Chem. & Ind.* 1263 (1964); [c] dihydrosecurinine: S. Saito, N. Shigematsu and Z. Horii, *J. Pharm. Soc. Japan* **83**, 800 (1963); [d] securinol A and B: Z. Horii, M. Ikeda, Y. Tamura, S. Saito, K. Kotera and T. Iwamoto, *Chem. Pharm. Bull. Tokyo* **13**, 1307 (1965); [e] phyllantine: J. Parello and S. Munavalli, *C.R. Acad. Sci., Paris* **260**, 337 (1965); [f] securitinine: Z. Horii, M. Ikeda, M. Hanaoka, M. Yamauchi, Y. Tamura, S. Saito, T. Tanaka, K. Kotera and N. Sugimoto, *Chem. Pharm. Bull. Tokyo* **14**, 917 (1966).



I

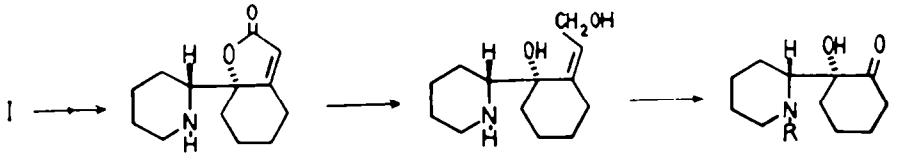


II



of XII to form ring B and the resolution of the resulting racemic alkaloid (XXVI). A part of this work has been reported in previous short communications.[8]

Condensation of 1,4-dioxaspiro[4,5]decan-6-one[9] (III) with pyridyllithium[10] in anhydrous ether gave the pyridyl alcohol (IV) in 66% yield. Hydrogenation of IV with platinum oxide in acetic acid afforded a diastereoisomeric mixture of the piperidyl alcohol (V) in 90% yield. Deketalization of V with 10% hydrochloric acid followed by acetylation gave two diastereoisomers of 2-(1-acetyl-2-piperidyl)2-hydroxycyclohexanone, (VII), m.p. 73·5–74·5°, and (VIII), b.p. 130°/0·2 mm, after chromatographic separation on alumina. The α-ketol (VII) was identical in IR spectrum (CCl_4) with the degradation product (XIX) of securinine, which was obtained by LAH reduction of the lactone[3a] (XVI), derived from securinine, followed by ozonolysis of the resulting diol (XVII) and subsequent acetylation.



XVI XVII XVIII R=H XIX R=Ac

In order to prepare the butenolide (IX) from the α-ketol (VII), several condensation reactions of VII were tried with various reagents, such as triethyl phosphonoacetate,[11] diketene,[12] ethyl acetoacetate,[13] ethyl cyanoacetate[13] and diethyl malonate,[13] but without success. However, lithium ethoxyacetylide,[14] which is known to react with a ketone and rearrange with dilute sulfuric acid to give an α,β-unsaturated ester, was found to react smoothly with VII in anhydrous ether at −30°. Treatment of the resulting crude carbinol with dilute sulfuric acid in tetrahydrofuran gave the butenolide (IX), m.p. 153–154°, and the hydroxylactone (X) in 50% and 21% yields, respectively. The latter (X) could be easily transformed into IX by heating with acetic anhydride. The butenolide (IX) was identical with the degradation product[3a] (the N-acetyl derivative of XVI) of securinine by comparison of their IR spectra (chf) and GLC behaviour. A similar reaction was also performed with VIII to give the corresponding butenolide (XX) and the hydroxylactone (XXI). The IR spectrum (chf) of XX was identical with that of the degradation product[7a] of allosecurinine.[15]

Introduction of a double bond into γ′,δ′-position to the lactone carbonyl group of

[8] S. Saito, N. Shigematsu, H. Yoshikawa, Z. Horii and Y. Tamura, *Chem. Pharm. Bull. Tokyo* **11**, 1219 (1963); Z. Horii, M. Hanaoka, Y. Tamura, S. Saito and N. Sugimoto, *Chem. & Ind.* 664 (1964); S. Saito, H. Yoshikawa, Y. Sato, H. Nakai, N. Sugimoto, Z. Horii, M. Hanaoka and Y. Tamura, *Chem. Pharm. Bull. Tokyo* **14**, 313 (1966); Z. Horii, M. Hanaoka, Y. Tamura, S. Saito and N. Sugimoto, *Ibid.* **14**, 1059 (1966).

[9] R. H. Jeager and H. Smith, *J. Chem. Soc.* 160 (1955).

[10] H. Gilman and S. M. Spatz, *J. Org. Chem.* **16**, 1485 (1951).

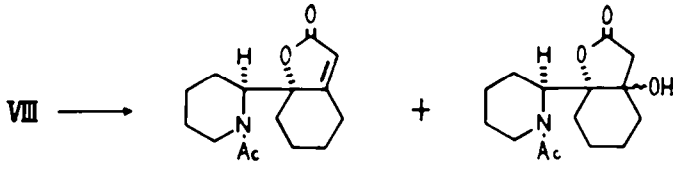
[11] W. S. Wadsworth Jr. and W. D. Emmons, *J. Am. Chem. Soc.* **83**, 1733 (1961).

[12] R. N. Lacey, *J. Chem. Soc.* 816 (1954).

[13] J. Colonge and J. C. Dubin, *Bull. Soc. Chim. Fr.* 1767 (1960).

[14] J. F. Arens, *Advances in Organic Chemistry Methods and Results* Vol. II; p. 203. Interscience, New York (1960).

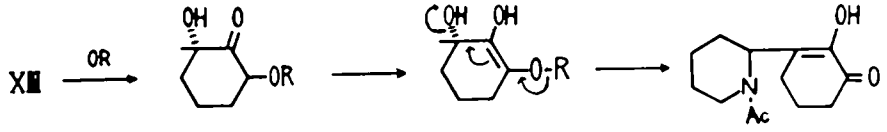
[15] Allosecurinine[7a] is the epimer of securinine at C_{10a}.



XX XXI

the butenolide (IX) could not be realized by allylic halogenation with N-bromosuccinimide, N-chlorosuccinimide and N-bromoacetamide, by allylic oxidation with various oxidizing agents [$Pb(OAc)_4$, $Hg(OAc)_2$, SeO_2, MnO_2, CrO_3, H_2O_2 and $K_3Fe(CN)_6$] and by dehydrogenation with chloranil and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. However, the hydroxylation[16] of IX with potassium permanganate in aqueous acetone afforded a 5·5% yield of the diol XI, which was dehydrated with thionyl chloride in pyridine to give the desired butenolide (XII), m.p. 162–164°, in 4·5% yield. This compound (XII) had absorption at 262·5 mμ (log ε 4·17) in the UV region and at 1739 cm^{-1} in the IR region, characteristic to an $\alpha,\beta,\gamma',\delta'$-unsaturated γ-lactone grouping, and was shown to be identical with 6-(1-acetyl-2-piperidyl) 6-hydroxy-2-cyclohexene-$\Delta^{1,\alpha}$acetic acid γ-lactone,[3a] derived from securinine, by comparison of IR spectra (chf) and GLC behaviour.

Since the yield of XII was too poor for the further reactions, a better method was sought for its preparation. Bromination of VII in acetic acid in the presence of hydrobromic acid afforded the α-bromoketone (XIII), m.p. 169–170°. Treatment of XIII with sodium hydroxide or sodium alkoxide in alcohol or dimethyl sulfoxide gave only the diosphenol (XXII), whose structure was verified by a positive ferric chloride and its spectral evidences; absorptions at 274·7 mμ (log ε 4·16) in the UV region and at 3205 and 1669 cm^{-1} in the IR region, characteristic to a diosphenol grouping. The formation of XXII from XIII was assumed to proceed according to the following schema.[17] The α-bromoketone (XIII), however, when treated with lithium bromide



XXII

and lithium carbonate in dimethylformamide, was converted into the desired α,β-unsaturated ketone (XIV), m.p. 109–111°. In agreement with structure XIV, the product exhibited absorptions at 3436 and 1672 cm^{-1} in the IR region. In the NMR spectrum an olefinic proton at C_3 appeared as a multiplet at 2·95 τ and an olefinic proton at C_2 as an octet at 3·88 τ with coupling constants ($J_{2H,3H} \approx 10$, $J_{2H,4Ha} \approx 3$ and $J_{2H,4Hb} \approx 1$ c/s).

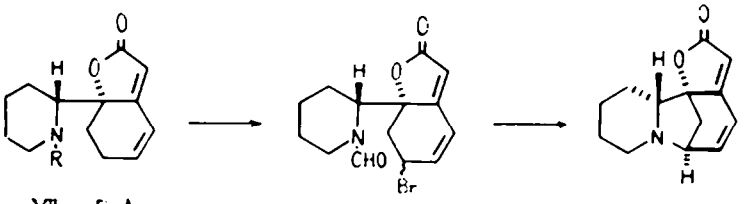
Condensation of XIV with lithium ethoxyacetylide followed by treatment with dilute sulfuric acid gave XII and the hydroxylactone (XV), in overall yields of 37% and 4% from VII, respectively. The result shows the exclusive 1,2-addition of lithium ethoxyacetylide on XIV.

As the final stage of the synthesis, the ring closure of XII was performed to

[16] The starting material was recovered by the reaction with OsO_4.

[17] cf. N. L. Wendler and D. Taub, *J. Am. Chem. Soc.* **82**, 2836 (1960).

construct ring B of I. Allylic bromination of the N-formyl derivative (XXIV), which was obtained from the N-acetyl derivative (XII) on hydrolysis followed by formylation with formic acid, was effected with N-bromosuccinimide to give the N-formyl bromide (XXV). Hydrolysis of XXV with 20% HCl followed by refluxing with potassium carbonate in chloroform gave the racemic securinine (XXVI ≡ I), m.p. 109–111°, in 7·5% yield, which showed absorptions at 250 mμ (log ε 4·27) in the UV region and at 1840 and 1760 cm^{-1} in the IR region. The identity of the synthetic product as the racemic securinine was established by the superposability of the IR and UV spectra with those of the natural securinine.



XII R=Ac
XXIII R=H
XXIV R=CHO

XXV

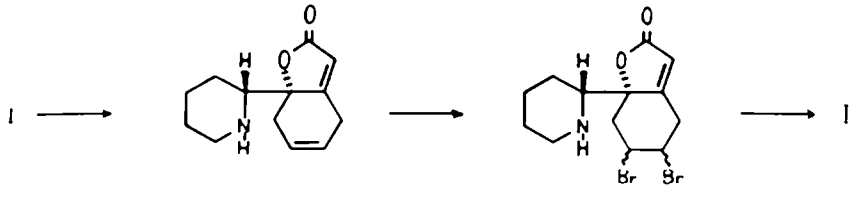
XXVI

The racemic securinine thus obtained was readily resolved by taking advantage of low solubility of securinine *d*-camphor-10-sulfonate in hot acetone. Recrystallization of the material of low solubility from a mixture of methanol and acetone gave securinine *d*-camphor-10-sulfonate, m.p. 211–213°, $[\alpha]_D^{20}$ −186°, and recrystallization of the material of high solubility from acetone gave virosecurinine *d*-camphor-10-sulfonate, m.p. 199–201°, $[\alpha]_D^{20}$ +243°. The synthetic securinine and virosecurinine were identical with the corresponding natural alkaloids in all respects. Their physical data are summarized in Table 1. The total synthesis of securinine and virosecurinine is thus completed.

TABLE 1

	M.p.	$[\alpha]_D^{20}$
rac-securinine	109–111°	—
securinine (natural)	143–144°	−1042°
securinine (synthetic)	143–144°	−1045°
virosecurinine (natural)	144–146°	+1050°
virosecurinine (synthetic)	142–144°	+1049°

Finally, we wish to add the following partial synthesis of securinine, which might provide an alternative route to the total synthesis. Addition of bromine to the unsaturated lactone[2a] (XXVII), derived from securinine, afforded the dibromide (XXVIII), which was refluxed with potassium carbonate in chloroform to give the natural securinine (I) in 15% yield.



XXVII

XXVIII

EXPERIMENTAL

M.ps and B.ps are uncorrected. The extracts were dried over Na_2SO_4. Column chromatography was carried out on alumina (E. Merk's Brockmann grade II–III) and silica gel (Mallinckrodt Chemical Works). GLC analyses were made on Perkin–Elmer gas chromatograph model 800, employing SE-30 column (column temp 175°). NMR spectra were measured on Hitachi Perkin–Elmer H-60 type Spectrometer at 60 mc in $CDCl_3$ with TMS as an internal reference.

6-(2-Pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (IV)

A soln of III[9] (16 g) in anhyd ether (30 ml) was added to a stirred soln of 2-pyridyllithium (prepared from 1·6 g Li, 14 g of n-BuBr and 16 g of 2-bromopyridine) in 50 ml anhyd ether in a stream of N at −30° over a period of 40 min. After the addition was complete, stirring was continued for an additional 3 hr at −20 ~ −30°. The resulting complex was decomposed with sat. NH_4Claq. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried and evaporated. Distillation of the residue gave 16 g (66%) of b.p. 145–150°/2 mm, which solidified immediately and was recrystallized from ether as colorless plates, m.p. 113–114°, ν_{max}^{Chf} cm^{-1}: 3356 (OH), 1595, 1572 (pyridine). (Found: C, 66·61; H, 7·39; N, 6·04. $C_{13}H_{17}NO_3$ requires: C, 66·36; H, 7·28; N, 5·95%.)

6-(2-Piperidyl)-1,-4-dioxaspiro[4,5]decan-6-ol (V)

Compound IV (9·2 g) was hydrogenated in glacial AcOH (40 ml) over PtO_2 (400 mg) at atm press. and room temp. After the theoretical amount of H was absorbed, the catalyst was filtered off and the filtrate was evaporated. The residue was made alkaline with sat. K_2CO_3aq and extracted with chf. Evaporation of the dried extract and recrystallization of the residue from AcOEt gave 8·5 g (90%) of V as colorless needles, m.p. 149·5–150·5°, ν_{max}^{Chf} cm^{-1}: 3534 (OH), 3356 (amine). (Found: C, 64·58; H, 9·52; N, 5·60. $C_{13}H_{23}NO_3$ requires: C, 64·70; H, 9·61; N, 5·80%.)

2-Hydroxy-2-(2-piperidyl)cyclohexanone (VI)

A soln of V (4·0 g) in 10% HCl (70 ml) was warmed at 70–80° under stirring for 4 hr. The cooled soln was made alkaline with conc NaOHaq, saturated with K_2CO_3, and extracted with chf. Evaporation of the dried extract and recrystallization of the residue from pet. ether gave 3·2 g (97%) of VI as colorless needles, m.p. 89–90°, $\nu_{max}^{CCl_4}$ cm^{-1}: 3472 (OH), 3322 (amine), 1706 (CO). (Found: C, 67·02; H, 9·77; N, 7·18. $C_{11}H_{19}NO_2$ requires: C, 66·97; H, 9·71; N, 7·10%.)

2-(1-Acetyl-2-piperidyl)-2-hydroxycyclohexanone (VII) and (VIII)

A mixture of VI (2·0 g) and Ac_2O (25 g) was warmed at 80° for 10 min. Excess Ac_2O was distilled off under reduced press. The residue was made alkaline with sat. K_2CO_3aq and extracted with chf. Evaporation of the dried extract and distillation of the residue gave 2·0 g (82%) of the diastereoisomeric mixture of α-ketols as a yellow viscous oil, b.p. 128–130°/0·2 mm. The product (2·0 g) was chromatographed on alumina (200 g). Chf eluted first 0·7 g of VII as crystals, which were recrystallized from ligroin as colorless prisms, m.p. 73·5–74·5°, $\nu_{max}^{CCl_4}$ cm^{-1}: 3436 (OH), 1704 (CO), 1639 (amide). (Found: C, 65·44; H, 8·89; N, 5·90. $C_{13}H_{21}NO_3$ requires: C, 65·24; H, 8·85; N, 5·85%.) The second chf fraction gave a mixture (1·0 g) of VII and VIII. The third chf fraction gave 0·2 g of VIII as a viscous oil, which was distilled as a colorless viscous oil, b.p. 130°/0·2 mm, $\nu_{max}^{CCl_4}$ cm^{-1}: 3430 (OH), 1704 (CO), 1639 (amide). (Found: C, 65·27; H, 8·75. $C_{13}H_{21}NO_3$ requires: C, 65·24; H, 8·85%.) The second fraction was chromatographed twice on alumina (200 g) using chf as solvent to give 0·6 g of VII and 0·2 g of VIII, respectively. The purity of VII and VIII was checked by TLC on alumina (E. Merk) with chf–benzene (3:2) as solvent.

2-Hydroxy-2-(2-piperidyl)cyclohexane-$\Delta^{1,\beta}$-ethanol (XVII)

A suspension of LAH (2·5 g) in anhyd ether (100 ml) was added dropwise to a stirred soln of XVI[8a] (4·6 g) in anhyd ether (80 ml). After the reaction mixture was refluxed under stirring for 5 hr, excess hydride was decomposed with water (10 ml). The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried and evaporated. Distillation of the residue gave 3·5 g (80%) of XVII, b.p. 145–150°/0·1 mm, which solidified immediately and was recrystallized from ether as colorless needles, m.p. 111–112°, ν_{max}^{Chf} cm^{-1}: 3300 (OH). (Found: C, 69·59; H, 10·35. $C_{13}H_{25}NO_2$ requires: C, 69·29; H, 10·29%.)

2-Hydroxy-2-(2-piperidyl)cyclohexanone (XVIII)

Ozone was passed through a soln of XVII (1·4 g) in 10% HCl (60 ml) at 0° for 5 hr. The soln was warmed at 60° for 1 hr to decompose the ozonide, made alkaline with K_2CO_3, and extracted with chf. Evaporation of the dried extract and distillation of the residue gave 0·65 g (53%) of XVIII, b.p. 150° (bath temp)/2 mm, which solidified immediately and was recrystallized from pet. ether as colorless needles, m.p. 114·5–115·5°, $\nu_{max}^{CCl_4}$ cm^{-1}: 3472 (OH), 3322 (amine), 1706 (CO). (Found: C, 66·71; H, 9·76. $C_{11}H_{19}NO_2$ requires: C, 66·97; H, 9·71%.) The hydrochloride was recrystallized from ether–EtOH as colorless needles, m.p. 202–203°. (dec). (Found: C, 52·66; H, 8·86. $C_{11}H_{20}NO_2Cl \cdot H_2O$ requires: C, 52·43; H, 8·81%.)

2-(1-Acetyl-2-piperidyl)-2-hydroxycyclohexanone (XIX)

A mixture of XVIII (0·5 g) and Ac_2O (10 g) was warmed at 80° for 10 min. The mixture was treated as described for VII. Distillation of the crude product gave 0·34 g (48%) of XIX as a pale yellow viscous oil, b.p. 160° (bath temp)/0·3 mm, $\nu_{max}^{CCl_4}$ cm^{-1}: 3436 (OH), 1704 (CO), 1639 (amide). (Found: C, 64·78; H, 8·81. $C_{13}H_{21}NO_3$ requires: C, 65·24; H, 8·85%.) IR spectrum of this compound in CCl_4 was identical with that of VII.

2-(1-Acetyl-2-piperidyl)-2-hydroxy-$\Delta^{1,6}$-cyclohexaneacetic acid γ-lacetone (IX) *and 2-(1-acetyl-2-piperidyl)-1,2-dihydroxycyclohexaneacetic acid γ-lactone* (X)

A soln of ethoxyacetylene[18] (2·0 g) in anhyd ether (10 ml) was added to a stirred soln of MeLi (prepared from 0·2 g Li and 4·0 g MeI) in anhyd ether (15 ml) in a stream of N at $-10 \sim -15°$ over a period of 10 min. The reaction mixture was stirred for an additional 15 min. To the mixture prepared above was added a soln of VII (1·0 g) in anhyd ether (10 ml) at $-30°$ under stirring over a period of 30 min. After the addition was complete, stirring was continued for 2 hr at $-30°$ and 3 hr at room temp. The resulting complex was decomposed with sat. NH_4Claq. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried and evaporated to give a reddish brown oil (1·4 g). A soln of this oil in THF (14 ml) was refluxed with 15% H_2SO_4 (2·4 ml) for 20 min. The soln was neutralized with $NaHCO_3$, evaporated, and extracted with chf. Evaporation of the dried extract and chromatography of the residue on silica gel (12 g) with chf gave crystals, which were recrystallized from ligroin to give 0·55 g (50%) of IX as colorless needles, m.p. 153–154°, ν_{max}^{Chf} cm^{-1}: 1742 (lactone), 1631 (amide). (Found: C, 68·55; H, 7·99; N, 5·15. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04; N, 5·32%.) This IX was identical with the N-acetyl derivative of XVI in IR spectrum (chf) and retention time on GLC. AcOEt eluted crystals, which were recrystallized from acetone to give 0.2 g (21%) of X as colorless cubes, m.p. 233–235°, ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1764 (lactone), 1616 (amide). (Found: C, 64·26; H, 8·16; N, 5·05. $C_{15}H_{23}NO_4$ requires: C, 64·03; H, 8·24; N, 4·98%.)

A mixture of X (100 mg) and Ac_2O (10 ml) was refluxed for 5 hr. The reaction mixture was evaporated and the residue was made alkaline with K_2CO_3aq and extracted with chf. Evaporation of the dried extract and recrystallization of the residue from ligroin gave 70 mg (75%) of IX, which was identical with the specimen obtained above.

The diastereoisomer (XX) *of* IX *and the stereoisomer* (XXI) *of* X

α-Ketol VIII (400 mg) was condensed with ethoxyacetylene (1·0 g) and the reaction mixture was worked up as described for IX and X. The crude product was chromatographed on silica gel (5 g). Chf eluted crystals, which were recrystallized from n-hexane to give 180 mg (41%) of XX as colorless plates, m.p. 96–97°, ν_{max}^{KBr} cm^{-1}: 1733 (lactone), 1637 (amide). (Found: C, 68·48; H, 8·08; N, 5·53. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04; N, 5·32%). This XX was identical with the degradation product of allosecurinine in IR spectrum (chf) and retention time on GLC. AcOEt eluted crystals, which were recrystallized from acetone to give 50 mg (11%) of XXI as colorless needles, m.p. 220–221·5°, ν_{max}^{KBr} cm^{-1}: 3311 (OH), 1736 (lactone), 1608 (amide). (Found: C, 64·39; H, 8·35; N, 4·84. $C_{15}H_{23}NO_4$ requires: C, 64·03; H, 8·24; N, 4·98%.)

[18] E. R. H. Jones, G. Eglinton, M. C. Whiting and B. L. Shaw, *Organic Syntheses* **34**, p. 46. Wiley, New York (1954).

2-(1-Acetyl-2-piperidyl)-1,2,α-trihydroxycyclohexaneacetic acid γ-lactone (XI)

A soln of $KMnO_4$ (2·05 g) in acetone (100 ml) and water (50 ml) was added under stirring to a soln of IX (1·65 g) in acetone (25 ml) at room temp. After standing for 3 days at room temp, the reaction mixture was filtered. The filtrate was neutralized with dil HCl and evaporated under red. press. The residue was extracted with chf and the extract was washed with water. Evaporation of the dried extract and refluxing of the residue with anhyd ether (50 ml) gave white crystals, which were recrystallized from EtOH to give 105 mg (5·5%) of XI as colorless plates, m.p. 238–240°, ν_{max}^{Nujol} cm^{-1}: 3257 (OH), 1789 (lactone), 1637 (amide). (Found: C, 61·01; H, 7·42; N, 4·94. $C_{15}H_{23}NO_5$ requires: C, 60·59; H, 7·80; N, 4·71%.)

6-Bromo-2-hydroxy-2-(1-acetyl-2-piperidyl)cyclohexanone (XIII)

A soln of VII (1 g) in glacial AcOH (20 ml) was saturated with HBr. A soln of Br (0·8 g) in glacial AcOH (8 ml) was added with stirring at 55–65° over a period of 5 hr. After the addition was complete, the reaction mixture was stirred at the same temp for an additional 2 hr and allowed to stand overnight at room temp. The mixture was made alkaline with sat. $NaHCO_3$aq and extracted with chf. The chf layer was washed with water, sat. $NaHCO_3$aq, and then water. The dried extract was evaporated and the residue was chromatographed on silica gel (12 g). Chf eluted a reddish brown viscous oil, which solidified on standing. Recrystallization from AcOEt gave 1·0 g (75%) of XIII as colorless plates, m.p. 169–170°, ν_{max}^{Chf} cm^{-1}: 3472 (OH), 1718 (CO), 1629 (amide), NMR τ: 4·84 (1H, qu, 10·0, 5·0 c/s, —COCHBr—), 5·10 (1H, t, 5·2 c/s, —N—CH<), 5·85 (1H, s, OH), 7·79 (3H, s, N—$COCH_3$). (Found: C, 49·20; H, 6·24; N, 4·22. $C_{15}H_{24}NO_3Br$ requires: C, 49·04; H, 6·34; N, 4·40%.)

3-(1-Acetyl-2-piperidyl)-2-hydroxy-2-cyclohexenone (XXII)

A soln of XIII (300 mg) in EtOH (15 ml) was refluxed with powdered NaOH (100 mg) for 1 hr. The reaction mixture was evaporated and the residue was taken up in chf, and the soln was extracted with 10% NaOH. The aqueous layer was washed with chf, acidified with 10% HCl and extracted with chf. The dried extract was evaporated and the residue was chromatographed on silica gel (1 g). Chf eluted crystals, which were recrystallized from ligroin to give 87 mg (39%) of XXII as colorless needles, m.p. 118·5–119·5°, ν_{max}^{KBr} cm^{-1}: 3205 (OH), 1669 (CO), 1618 (amide), λ_{max}^{EtOH}: 274·7 mμ (log ε 4·16). (Found: C, 65·66; H, 8·03; N, 5·67. $C_{13}H_{19}NO_3$ requires: C, 65·80; H, 8·07; N, 5·90%.) This compound gave a dark purple color with an ethanolic $FeCl_3$.

6-(1-Acetyl-2-piperidyl)-6-hydroxy-2-cyclohexenone (XIV)

To a soln of XIII (1·1 g) in dimethylformamide (30 ml) was added 1·0 g LiBr and 1·5 g Li_2CO_3, and the mixture was heated at 120° under stirring in a stream of N for 7 hr. The cooled reaction mixture was poured into ice water and extracted with chf. The chf layer was washed with 10% HCl and water. Evaporation of the dried extract and recrystallization of the residue from ligroin gave 585 mg (71%) of XIV as colorless plates, m.p. 109–111°, ν_{max}^{Chf} cm^{-1}: 3436 (OH), 1672 (CO), 1623 (amide), NMR τ: 2·95 (1H, m, C_2—H), 3·88 (1H, o, 10·0, 3·0, 1·0 c/s, C_3—H), 5·08 (1H, t, 5·0 c/s, —N—CH<), 5·91 (1H, s, OH), 7·79 (3H, s, N—$COCH_3$). (Found: C, 65·75; H, 7·33; N, 5·75. $C_{13}H_{19}NO_3$ requires: C, 65·80; H, 8·07; N, 5·90%.)

6-(1-Acetyl-2-piperidyl)-6-hydroxy-2-cyclohexene-$\Delta^{1,3}$-acetic acid γ-lactone (XII)

(a) *From* XI. Thionyl chloride (0·8 ml) was added dropwise to a cooled soln of XI (0·3 g) in anhyd pyridine (6 ml). The reaction mixture was warmed at 60° for 15 min. After standing for 2 days at room temp, the mixture was poured into ice water and extracted with chf. The extract was washed with water, dried and evaporated. The residue was chromatographed on alumina (15 g) using benzene as solvent. The eluate was dissolved in AcOEt and filtered. Evaporation of the filtrate and recrystallization of the residue from AcOEt gave 12 mg (4·5%) of XII as colorless plates, m.p. 162–164°, ν_{max}^{Chf} cm^{-1}: 1739 (lactone), 1634 (amide), λ_{max}^{EtOH}: 262·5 mμ (log ε 4·17). (Found: C, 69·01; H, 6·96; N, 5·45. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%.) This XII was identical with the degradation product of securinine in IR spectrum (chf) and retention time on GLC.

(b) *From* XIV. The XIV (425 mg) was condensed with ethoxyacetylene (1·0 g) and the reaction mixture was worked up as described for IX and X. The crude product was chromatographed on

silica gel (6 g). Chf eluted crystals, which were recrystallized from AcOEt to give 320 mg (69%) of XII as colorless plates, m.p. 162–164°. (Found: C, 69·17; H, 7·40; N, 5·30. $C_{15}H_{19}NO_3$ requires; C, 68·94; H, 7·33; N, 5·36%.) This XII was identical with XII obtained in (a) in all respects. AcOEt eluted crystals, which were recrystallized from acetone to give 40 mg (8%) of *6-(1-acetyl-2-piperidyl)1-hydroxy-2-cyclohexeneacetic acid γ-lactone* (XV) as colorless prisms, m.p. 220·5–222°, ν_{max}^{KBr} cm^{-1}: 3247 (OH), 1776 (lactone), 1618 (amide). (Found: C, 64·62; H, 7·65; N, 4·90. $C_{14}H_{21}NO_4$ requires: C, 64·49; H, 7·58; N, 5·01%.)

6-Hydroxy-6-(2-piperidyl)-2-cyclohexene-Δ$^{1,\alpha}$-acetic acid γ-lactone (XXIII)

A mixture of XII (290 mg) and conc HCl (5 ml) was heated at 130° in a sealed tube for 20 hr. Water (5 ml) was added to the cooled reaction mixture and the soln was washed with chf. The aqueous layer was made alkaline with $NaHCO_3$ and extracted with chf. The dried extract was evaporated and the residue was converted into the picrate, which was recrystallized from MeOH–acetone to give 42 mg of the picrate of XXIII as yellow pillars, m.p. 204–206°, ν_{max}^{Nujol} cm^{-1}: 1770 (lactone), 1640 (double bond). (Found: C, 50·98; H, 4·14; N, 12·69. $C_{19}H_{20}N_4O_9$ requires: C, 50·89; H, 4·50; N, 12·50%.)

6-(1-Formyl-2-piperidyl)-6-hydroxy-2-cyclohexene-Δ$^{1,\alpha}$-acetic acid γ-lactone (XXIV)

A mixture of XXIII (420 mg), 98% formic acid (2 ml) and Ac_2O (2 ml) was heated on a water bath for 4 hr. The reaction mixture was evaporated under reduced press and the residue was taken up in AcOEt containing a small amount of MeOH. The soln was evaporated and the residue was washed with ether and recrystallized from AcOEt to give 360 mg (76%) of XXIV as colorless pillars, m.p. 190–191°, ν_{max}^{Nujol} cm^{-1}: 1750 (lactone), 1650 (amide). (Found: C, 68·04; H, 6·89; N, 5·89. $C_{14}H_{17}NO_4$ requires: C, 67·99; H, 6·93; N, 5·66%.)

4-Bromo-6-(1-formyl-2-piperidyl)6-hydroxy-2-cyclohexene-Δ$^{1,\alpha}$-acetic acid γ-lactone (XXV)

A soln of XXIV (0·38 g) in anhyd CCl_4 (40 ml) was refluxed with N-bromosuccinimide (0·29 g) in the presence of a small amount of benzoyl peroxide for 8 hr. Additional small amount of benzoyl peroxide was added to the mixture during the reaction. The succinimide formed was filtered off and the filtrate was washed with 5% $NaHCO_3$ and water. Evaporation of the dried filtrate and recrystallization of the residue from AcOEt gave 0·33 g (66%) of XXV as colorless pillars, m.p. 165–167° (dec), ν_{max}^{Nujol} cm^{-1}: 1760 (lactone), 1668 (amide). (Found: C, 51·89; H, 4·49; N, 4·54. $C_{14}H_{16}NO_4Br$ requires: C, 51·54; H, 4·94; N, 4·29%.)

Racemic securinine (XXVI)

A mixture of XXV (0·3 g) and 20% HCl (5 ml) was heated on a water bath for 4 hr. The reaction mixture was evaporated under reduced press. To the residue was added K_2CO_3 (0·5 g), water (0·5 ml) and chf (30 ml), and the mixture was refluxed for 4 hr. The cooled reaction mixture was extracted with 10% H_2SO_4 (10 ml). The aqueous layer was made alkaline with NH_4OH and extracted with chf. The dried extract was evaporated and the residue was chromatographed on alumina. Chf eluted crystals, which were recrystallized from *n*-hexane to give 15 mg (7·5%) of XXVI as yellow needles, m.p. 109–111°, $\nu_{max}^{CCl_4}$ cm^{-1}: 1840, 1760 (lactone), λ_{max}^{EtOH} 256 mμ (log ε 4·27). (Found: C, 72·21; H, 6·63; N, 6·58. $C_{13}H_{15}NO_2$ requires: C, 71·86; H, 6·96; N, 6·45%.) IR spectrum (CCl_4) of XXVI was identical with that of natural securinine.

Resolution of racemic securinine

d-Camphor-10-sulfonic acid (110 mg) was dissolved by heating in a soln of *rac* XXVI (100 mg) in acetone (2 ml). After the soln was allowed to stand at room temp overnight, a mixture of crystals, plates and needles, was formed and filtered. Acetone (2 ml) was added to the crystals and refluxed until the needles dissolved. Undissolved plates were separated by filtration, washed with hot acetone, and recrystallized from MeOH–acetone to give 62 mg of securinine *d*-camphor-10-sulfonate as colorless plates, m.p. 211–213°, $[\alpha]_D^{20}$ −186° (*c* = 1, EtOH). This salt was identical with natural securinine *d*-camphor-10-sulfonate, m.p. 210–211° in all respects (IR, mixed m.p., optical rotation). The filtrate and washings were concentrated to 1 ml. Colorless needles separated were recrystallized from acetone to give 59 mg of virosecurinine *d*-camphor-10-sulfonate as colorless needles, m.p.

199–201°, $[\alpha]_D^{20}$ +243° (*c* = 1, EtOH). This salt was identical with natural virosecurinine *d*-campho - 10-sulfonate, m.p. 200–201° in all respects (IR, mixed m.p., optical rotation). Securinine *d*-camphor-10-sulfonate (62 mg) was dissolved in water (4 ml), made alkaline with conc NH_4OH and extracted with chf. The extract was dried and evaporated. Recrystallization of the residue from n-hexane gave 22 mg of I as yellow needles, m.p. 143–144°, $[\alpha]_D^{20}$ −1045° (*c* = 1, EtOH). This was identical with natural securinine in all respects (IR, mixed m.p., optical rotation). The same treatment of virosecurinine *d*-camphor-10-sulfonate (59 mg) as described for securinine *d*-camphor-10-sulfonate gave 20 mg of II as yellow needles, m.p. 142–144°, $[\alpha]_D^{20}$ +1049° (*c* = 1, EtOH). This was identical with natural virosecurinine in all respects (IR, mixed m.p., optical rotation).

4,5-*Dibromo*-2-*hydroxy*-2-(2-*piperidyl*)-$\Delta^{1,\alpha}$-*cyclohexaneacetic acid* γ-*lactone* (XXVIII)

A soln of Br (190 mg) in chf (1·7 g) was added to a soln of the hydrochloride (300 mg) of XXVII in chf (20 ml) under stirring at 5°. The reaction mixture was stood at 20° overnight. Anhyd ether was added to the mixture and resulting crystals were recrystallized from MeOH–ether to give 340 mg (70%) of the hydrochloride of XXVIII as colorless prisms, m.p. 205–206°, ν_{max}^{Nujol} cm^{-1}: 1758 (lactone), 1653 (C=C). (Found: C, 37·36; H, 4·01; N, 3·38. $C_{13}H_{18}NO_3Br_2Cl$ requires: C, 37·57; H, 4·36; N, 3·37%.)

Securinine (I) *from the dibromide* (XXVIII)

A mixture of the hydrochloride (300 mg) of XXVIII, K_2CO_3 (0·5 g), water (0·5 ml) and chf (30 ml) was refluxed for 3·5 hr. The cooled reaction mixture was worked up as described for racemic securinine to give 24 mg (15%) of I, m.p. 142–144°, which was identical with natural securinine in all respects.

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