under reduced pressure (temp., <80°) and the residue was partitioned between chloroform and water. The chloroform layer was extracted with 100 ml. of 10% sodium hydroxide solution and the aqueous extract was acidified with concentrated hydrochloric acid. The precipitated acid was taken up in chloroform, separated, and concentrated to dryness. The residual solid weighed 3.08 g. (67.5% yield), and its infrared spectrum was qualitatively identical to that of 2,3-dihydro-3-phenyl-3-benzofurancarboxylic acid (III).[4] The neutral chloroform extract was concentrated to dryness. The yellow oil that remained (1.28 g., 25.7% yield) solidified slowly and proved, by its infrared spectrum, to be unchanged ester I. No infrared absorption due to an amide carbonyl group (*i.e.*, V) was detectable in the neutral fraction.

Reaction with *n*-Butylamine.—A mixture of 5 g. of the methyl ester I and 5 ml. of *n*-butylamine (no toluene) was heated at 80° for 24 hr. and worked up by the foregoing procedure. From the acidic fraction there was obtained 0.71 g. (15%) of the carboxylic acid III. The semisolid neutral fraction (4.52 g.) was triturated with pentane and filtered. The solid material, m.p. 105–107°, proved by comparison with an authentic sample (mixture melting point and infrared spectrum), to be N-(*n*-butyl)-2,3-dihydro-3-phenyl-3-benzofurancarboxamide (V, R_2 = HC_4H_8-*n*).[11] It weighed 1.70 g., representing a 29% yield. The pentane filtrate was concentrated to dryness and the residual oil (2.80 g., 56%) soon solidified, m.p. 46–47°. It was recovered ester I.

Acknowledgment.—The authors are indebted to Mr. William Washburn for the infrared spectra and to Mr. Victor Papendick for the pK_a determination.

(11) H. E. Zaugg, R. W. DeNet and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963).

Studies on the Alkaloids of *Securinega virosa* Pax. et Hoffm. II.[1] The Absolute Configuration of C-6 in Virosecurinine and the Stereochemical Interrelationship of Virosecurinine, Securinine, and Allosecurinine[2]

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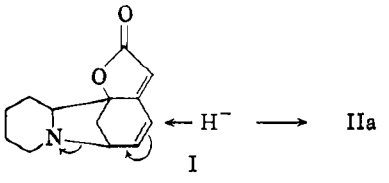
Degradation of virosecurinine (I) has led to the isolation of L-(−)-pipecolic acid and hence to the establishment of the absolute configuration of C-6 in its molecule. The steric relationship of virosecurinine and its related alkaloids, securinine and allosecurinine, has been established.

In part I[1] of this series, it was shown that virosecurinine, an alkaloid of Formosan *Securinega virosa* Pax. et Hoffm. (fam. *Euphorbiaceae*), has structure I (without stereochemical implications) and that it is antipodal with securinine isolated from *S. suffruticosa* by Russian chemists[3] and also by two groups of Japanese workers.[4,5] The present paper describes the establishment of the absolute configuration of C-6 in virosecurinine and also the stereochemical interrelationship of virosecurinine and its related alkaloids.

Virosecurinine, $C_{13}H_{15}NO_2$ (I), when treated with amalgamated aluminum in ether–methanol (4:1), yielded a liquid unsaturated amino lactone, $C_{13}H_{17}NO_2$ (IIa), analyzed as its crystalline picrate. That the allylic C–N bond was reductively cleaved with the formation of a NH group and that the original α,β-unsaturated γ-lactone system was still intact were indicated by its infrared absorption spectrum ($\lambda_{max}^{CHCl_3}$ 2.85, 3.02, and 5.69 μ). The ultraviolet absorption spectrum (λ_{max}^{EtOH} 210.5 mμ) suggested that this compound has no ethylenic double bond[1] extending the conjugation of its α,β-unsaturated γ-lactone system. Acetylation of IIa with acetic anhydride in pyridine provided the acetate, $C_{15}H_{19}NO_3$ (IIb). The presence of its readily reducible ethylenic double bond was demonstrated by the catalytic hydrogenation of IIb with palladized charcoal in alcohol which resulted in the rapid uptake of one molar equivalent of hydrogen and the formation of III which previously had been obtained by a different route.[1] Reduction of I with amalgamated aluminum apparently proceeded by the attack of the hydride ion on the γ-carbon atom which would involve allylic rearrangement by the SN2′ mechanism leading to the formation of IIa, as indicated.



Support for the assignment of the location of this nonconjugated double bond came in the measurement of the nuclear magnetic resonance spectrum[6] of IIb.

Reduction of IIa with lithium aluminum hydride led to a crystalline unsaturated amino diol, $C_{13}H_{21}NO_2$ (IVa), further characterized as the picrate. Benzoylation of IVa with benzoyl chloride and pyridine gave the benzoate (IVb). On oxidation of IVb with potassium permanganate in aqueous acetone in the presence of magnesium sulfate, there was obtained N-benzoyl-L-

(1) T. Nakano, T. H. Yang, and S. Terao, *Chem. Ind.*, 1651 (1962); *Tetrahedron*, **19**, 609 (1963).

(2) For a preliminary communication of this work, see T. Nakano, T. H. Yang, and S. Terao, *Tetrahedron Letters*, 665 (1963).

(3) V. I. Murav'eva and A. I. Ban'kovskii, *Doklady Akad. Nauk, SSSR*, **110**, 998 (1959).

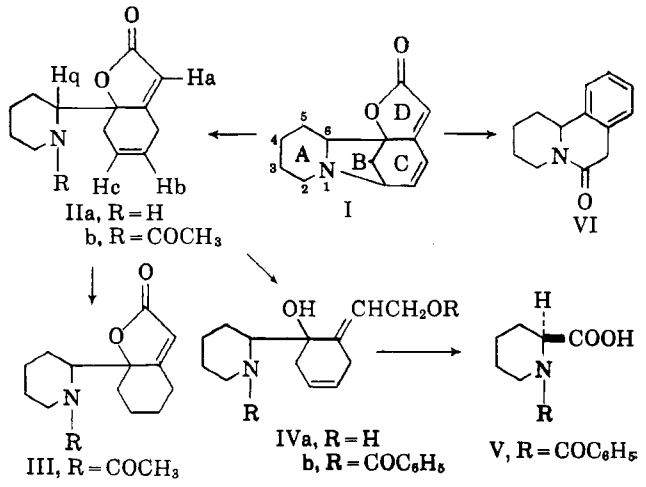
(4) S. Saito, K. Kodera, N. Sugimoto, Z. Horii, and Y. Tamura, *Chem. Ind.*, 1652 (1962).

(5) I. Satoda, M. Murayama, J. Tsuji, and E. Yoshii, *Tetrahedron Letters*, 1199 (1962).

(6) The spectra were measured with a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts in p.p.m. relative to tetramethylsilane equals zero. The three protons, Ha, and Hb and Hc, appeared at 5.88 p.p.m. and at 5.6–5.7 p.p.m., respectively. There was also an additional low-field proton at 5.1 p.p.m. which also was observed in the n.m.r. spectrum of III. This signal can be assigned to a proton in ring A (most likely to Hq). While this is unusually low field for this proton, it seems the proper assignment on the basis of its being coupled to the high-field protons in the rest of the ring, as confirmed by decoupling. Furthermore, the two proton signal at 3.7 p.p.m. has been identified as the other two protons on the carbon next to the amide by the same method. The signal at 3.2 p.p.m. which was not present in III is quite suggestive of protons which are doubly allylic, and this can be taken as evidence in support of structure IIb. These protons were found to be coupled to the olefinic protons Ha and Hb and/or Hc by decoupling.

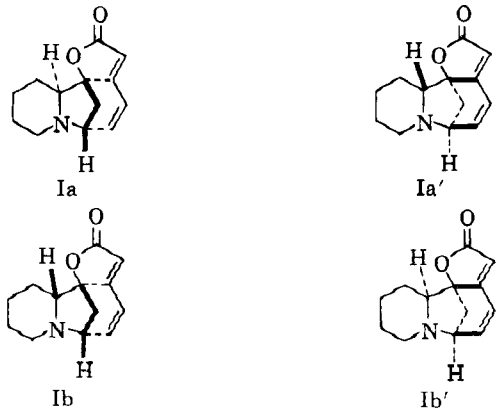
We are indebted to Dr. L. J. Durham of Stanford University, Stanford, Calif., for the measurement of the n.m.r. spectra and many helpful comments.

CHART I



(−)-pipecolic acid (V),[7] m.p. 128–129°, $[\alpha]_D$ −45°, whose infrared spectrum was shown to be identical in chloroform with that of the DL compound.[8]

Turning now to the configuration of virosecurinine (I), inspection of its molecular model permits the following four isomers (Ia and Ib are antipodal with Ia′ and Ib′, respectively).



The isolation of L-(−)-pipecolic acid indicates clearly that virosecurinine corresponds to either Ia or Ib′.

Satoda, *et al.*,[5] reported the isolation of another alkaloid, allosecurinine, from the mother liquor of securinine, and showed that it is a diastereoisomer of securinine. By treatment of these two alkaloids with zinc and sulfuric acid, they obtained two antipodal lactams corresponding to VI. One (from securinine) has m.p. 74–75°, $[\alpha]_D$ +13.9°, and the other (from allosecurinine), m.p. 69°, $[\alpha]_D$ −32.7°. The latter compound corresponds to the lactam (VI),[1] m.p. 75–76°, $[\alpha]_D$ −35.7°, which we previously obtained from virosecurinine by the same reaction,[9] and hence virosecurinine and allosecurinine must have identical absolute configurations at C-6. It follows, therefore, that if virosecurinine is postulated to be Ia, then allosecurinine should be Ib′, or *vice versa*. Since securinine and virosecurinine are mirror images of each other, securinine should be either Ia′ or Ib dependent upon whether virosecurinine is Ia or Ib′, respectively. The absolute configurations of these related alkaloids are now being studied.

(7) Reported m.p. 133° and $[\alpha]_D$ −72° [J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1961)].

(8) N-Benzoyl-DL-pipecolic acid was prepared according to the method of F. E. King, T. J. King, and A. J. Warwick, *ibid.*, 3590 (1950).

Experimental[10]

Reductive Cleavage of the Allylic C–N Bond in Virosecurinine (I).—Virosecurinine (2.40 g.) in ether–methanol (4:1) (80 ml.) was reduced while cooling with water with amalgamated aluminum foil (1.2 g.) until the solution became colorless. Filtration and evaporation of the solution *in vacuo* gave an unsaturated amino lactone (IIa) as a colorless oil (2.42 g.); $\lambda_{max}^{CHCl_3}$ 2.85, 3.02 (NH), 5.69 (α,β-unsaturated γ-lactone CO), 6.04 (C=C), 11.86 μ (C=CHCO); λ_{max}^{EtOH} 210.5 mμ.

Treatment of IIa (40 mg.) with picric acid (45 mg.) in acetone and crystallization from acetone–hexane furnished a picrate (73 mg.), m.p. 217° dec.; $[\alpha]_D$ −86° (*c* 0.81, in acetone); λ_{max}^{Nujol} 3.11 (NH), 5.73 μ (α,β-unsaturated γ-lactone CO); λ_{max}^{EtOH} 211 mμ (log ϵ 4.57).

Anal. Calcd. for $C_{13}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 51.05; H, 4.52; N, 12.54. Found: C, 51.32; H, 4.72; N, 12.75.

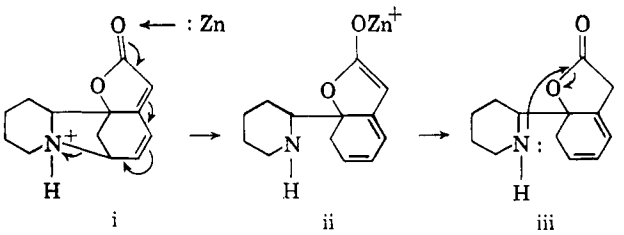
Acetylation was effected by treating IIa (150 mg.) with acetic anhydride (0.5 ml.) and anhydrous pyridine (2 ml.) at room temperature overnight. Crystallization from acetone–ether gave the acetate (IIb) (146 mg.), m.p. 135–136°; $[\alpha]_D$ −227° (*c* 1.75); λ_{max}^{EtOH} 205.5 mμ (log ϵ 4.16), 230 (3.94) (sh); $\lambda_{max}^{CHCl_3}$ 5.71 (α,β-unsaturated γ-lactone CO), 6.06 (C=C), 6.13 (NCOCH$_3$), 11.74 μ (C=CHCO).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 69.02; H, 7.34; N, 5.37. Found: C, 68.80; H, 7.40; N, 5.57.

Catalytic Hydrogenation of the Acetate (IIb).—A solution of IIb (52.2 mg., 0.2 mmole) in 95% ethanol (20 ml.) was hydrogenated in the presence of prehydrogenated palladized charcoal (10 mg.) at 13° and atm. pressure. Within about 20 min. the uptake of hydrogen (5 ml., 0.2 mmole) ceased, and the product was isolated in the usual manner. Crystallization from acetone–hexane yielded a N-acetyl amino lactone (III) as prisms, m.p. 168°; $[\alpha]_D$ −130° (*c* 0.64). The identity was established by direct comparison (infrared, rotation, ultraviolet, and mixture melting point) with the sample obtained previously by a different route.[1]

Reduction of the Unsaturated Amino Lactone (IIa) with Lithium Aluminum Hydride.—To a suspension of lithium aluminum hydride (1.5 g.) in absolute ether (20 ml.) was added with stirring at room temperature a solution of IIa (1.42 g.) in absolute ether (30 ml.), and stirring was continued overnight. The excess reagent was decomposed with ethyl acetate and a saturated aqueous solution of sodium sulfate was added to precipitate inorganic salts followed by the addition of anhydrous sodium sulfate. The solution was filtered and the filtrate was evaporated *in vacuo*. The product was crystallized from acetone–hexane to give an unsaturated amino diol (IVa) as plates (1.44 g.), m.p. 94°; $[\alpha]_D$ +152° (*c* 1.06); $\lambda_{max}^{CHCl_3}$ 2.77, 2.95 (broad) (OH), 6.03

(9) This process may involve attack of zinc on the oxygen atom of the lactonic carbonyl group (i, arrows). The formation of the unstable β,γ-unsaturated lactone on discharge of the resulting complex enolate (ii), under essentially irreversible conditions, is expected. For a similar reference, see R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 10 (1958). The attack of nitrogen on the lactonic carbonyl carbon atom and subsequent dehydration of the liberated hydroxyl, as implied in iii (arrows), may lead to the formation of VI.



(10) Ultraviolet absorption spectra were recorded on a Shimazu self-recording UV spectrophotometer "SV-50" in 95% ethanol. Infrared spectra were taken on a Hitachi infrared spectrophotometer "EPI-S." Rotations were measured with a Kreis polarimeter "0.01°" (Carl Zeiss Co., Ltd.) in 95% ethanol at 10–15°, unless otherwise stated. Melting points were determined by use of a micro-melting point apparatus (Yanagimoto Co., Ltd., Kyoto) and are uncorrected. The elementary analyses were carried out by Miss S. Tomita and Miss Y. Saito of the Microanalytical Laboratory of this faculty.

(C=C), 6.22 μ (C=C). Its ultraviolet spectrum exhibited no selective absorption down to 203 mμ.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.11; H, 9.61; N, 6.33.

A small amount of Va was treated with a solution of picric acid in a minimum amount of acetone. Addition of hexane precipitated the picrate, which, after recrystallization from acetone–hexane at room temperature, showed m.p. 168–169°; $[\alpha]_D$ +22.5° (*c* 1.2).

Anal. Calcd. for $C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 50.44; H, 5.35; N, 12.39. Found: C, 50.17; H, 5.63; N, 12.88.

Benzoylation of the Unsaturated Amino Diol (IVa).—A mixture of IVa (1.67 g.), anhydrous pyridine (20 ml.,) and benzoyl chloride (3 ml.) was kept at room temperature for 3 days. After acidification with 3% hydrochloric acid, the solution was extracted with ether, the ether solution was washed with 3% aqueous sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. Filtration and evaporation of the solution left an oily product (3.37 g.) which was chromatographed in ether on alumina (90 g.) ("Woelm" neutral, activity grade I). Elution with ether–ethyl acetate (30:1) afforded the benzoate IVb as an oil (1.52 g.); $\lambda_{max}^{CHCl_3}$ 2.93 (OH), 5.87 (C_6H_5CO–O), 6.17 μ (N–CO).

Oxidation of the Benzoate (IVb) with Potassium Permanganate.—A mixture of the benzoate IVb (580 mg.) and magnesium sulfate (2.5 g.) in acetone (10 ml.) was cooled at −10 to −2° with ice–salt, and a solution of potassium permanganate (1.2 g.) in aqueous acetone (80 ml.) was added dropwise while stirring over a period of 2.5 hr. During the addition, the temperature of the reaction mixture was maintained at −10 to −2°. Stirring was continued for 4.5 hr., and the solution was poured into methanol (20 ml.) and kept at room temperature overnight. After concentration of the solution *in vacuo*, the manganese dioxide was decomposed with sodium sulfite and 3% hydrochloric acid, and the solution was extracted with chloroform. The chloroform solution was washed with water and extracted with 3% sodium hydroxide. The alkaline solution was then acidified with 3% hydrochloric acid and extracted with chloroform. Washing of the extract with water, drying over anhydrous sodium sulfate and evaporation *in vacuo*, yielded a crystalline mass (250 mg.). This mixture of acids was subjected to sublimation at 65–70° (0.04 mm.) to remove benzoic acid, and the residue (124 mg.) was chromatographed in chloroform on Mallinkrodt's silicic acid (20 g.). Evaporation of the first eluate fraction and crystallization from ethyl acetate–hexane afforded N-benzoyl-L-(−)-pipecolic acid, m.p. 128.5–129°; $[\alpha]_D$ −45.5° (*c* 1.22); $\lambda_{max}^{CHCl_3}$ 5.84 (COOH), 6.16 μ (N–CO).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.85; H, 6.56; N, 6.12.

The infrared spectrum of this compound was identical in chloroform solution with synthetic N-benzoyl-DL-pipecolic acid.[8]

Acknowledgment.—We thank Professor M. Tomita of this faculty for his encouragement throughout this work. This work was supported by grant no. GM 09362-01 from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

Conversion of Morphine Alkaloids and Galanthamine to 1-Methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-epoxyoctahydroindole

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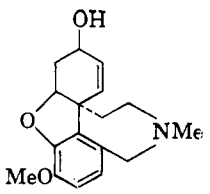
Received March 8, 1963

Cleavage of the B-ring of 14-hydroxydeoxydihydrocodeine (**2**) was achieved on its methine base **3** with loss of C-9 by a modified Prévost reaction, yielding the norseco compound **4**. The compound **4** was finally transformed to two isomers of 1-methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-epoxyoctahydroindole (**15** and **17**), which has a carbon skeleton of mesembrane, one of the type of *Amaryllidaceae* alkaloids. The remaining isomer **24** was obtained by a multiple-step transformation from galanthamine (**1**). The stereochemistry of these isomers and their related compounds are discussed.

The structure of galanthamine (**1**) has been investigated by many workers.[1] Recently, Barton and Kirby[2] achieved its total synthesis. However, no direct evidence has been provided for its stereochemistry. In this paper, the authors' attempt was to confirm an absolute configuration of galanthamine by converting it to 1-methyl-3a-(3′-methoxy-6-methylphenyl)-4,2′-epoxyoctahydroindole, a compound which can be obtained from morphine alkaloids of known configuration.[3] Although we did not accomplish our purpose, the results obtained might be of some interest.



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Hofmann degradation of 14-hydroxydeoxydihydrocodeine (**2**)[4] gave the methine base **3**, which showed absorption bands at 274, 300, and 313 mμ characteristic for the isoeugenol chromophore. A norseco compound **4** was obtained when **3** was treated under the condition of the Woodward modified Prévost reaction,[5] and the reaction mixture was made alkaline with potassium hydroxide. On the other hand, when aqueous ammonia was employed in place of potassium hydroxide, product **5** of composition $C_{21}H_{27}O_5N$[6] was afforded, which on treatment with potassium hydroxide was converted to **4**. The ultraviolet spectrum of **4** showed absorption bands at 231, 279, and 327 mμ which closely coincided with that of 3,4-dihydroxybenzaldehyde. Moreover, the infrared spectrum of **4** exhibited absorption bands at 1710 (six-membered cyclic ketone) and 1690 cm.$^{-1}$ (conjugated aldehyde). Therefore, it follows that **3** was not oxidized first to the

(1) W. C. Wildman, "The Alkaloids," Vol. VI, R. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p. 289.

(2) D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 392 (1960); *J. Chem. Soc.*, 806 (1962).

(3) M. Mackay and D. C. Hodgkin, *ibid.*, 3261 (1955); J. Kalvoda, P. Buchschacher, and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).

(4) A. C. Currie, J. Gillon, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 773 (1960); I. Seki, *Ann. Takamine Lab.* (Tokyo), **13**, 67 (1960).

(5) R. B. Woodward and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 209 (1958).

(6) Its molecular formula agrees with the addition of an acetyl group to the methine base **3**, and its infrared and n.m.r. spectra exhibit the characteristic absorption bands due to acetyl group.