Some Observations on the Oxidation of Virosecurinine with Monoperphthalic Acid[1,2]

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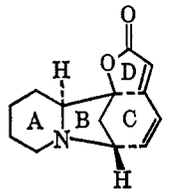
Oxidation of virosecurinine (I) with monoperphthalic acid yielded two products, II and III. These products were formed *via* the intermediate IV by the two routes. One proceeds through path a to yield II, and the other is designated in path b leading to III. The structures of these compounds were deduced from their spectroscopic data and also from an investigation of their respective degradation products.

Virosecurinine (I) is an alkaloid isolated from the leaves of *Securinega virosa* Pax. *et* Hoffm. Its absolute configuration and preferred conformation have already been established in our previous work.[1,5] In an early stage of these investigations, we had found that oxidation of virosecurinine with either hydrogen peroxide or ozone yielded a nicely crystalline, colorless product, $C_{13}H_{15}NO_3$. Because of the complexity of its structure, however, we had not examined it further at that time. In the meantime, we had occasion to investigate this similar oxidation in more detail, and the chemical as well as spectroscopic data on the resulting products have now provided us with some interesting information on their structures and also the mode of their formation.

When virosecurinine (I) was kept at 5° in glacial acetic acid solution with monoperphthalic acid as an



I

organic peracid, there were obtained two kinds of product which exhibited no basicity. They represent the same molecular formula, $C_{13}H_{15}NO_3$, which implies the addition of one oxygen atom to the parent compound. The product with the lower melting point is the 1,2-oxazolactone-A (II) and that of the higher melting point is the 1,2-oxazolactone-B (III), and the ratio of formation is 1:5.5, respectively. As mentioned later, the former undergoes neither ionic[6] nor pyrolytic[7a-d] rearrangement, as would be expected from the N-oxide type of compound IV. Evidence that this compound has structure II was provided by both spectroscopic and chemical data. The ultraviolet [λ_{max} 259 mμ (ϵ 16,000)] as well as infrared spectra[5] [λ_{max} 5.64 (C=O) and 6.07 μ (C=C)] of II showed the presence of the double bond conjugated with the α,β-unsaturated γ-lactone system. Furthermore, a strong infrared absorption band due to the N—O bond[8] appears at 9.80 μ. In its nmr spectrum,[9] the olefinic proton on the α,β-unsaturated lactone ring exhibits a singlet at τ 4.18. Furthermore, there was observed an ABX coupling pattern which is more typical than in the case of virosecurinine (I). The proton H_A appears as a doublet (J_{AB} = 10 cps) at τ 3.05 and the proton H_B, as a quartet (J_{AB} = 10 cps and $J_{BX} \sim 6$ cps) centered at τ 3.76. The proton H_X exhibits a multiplet at τ 5.21, and this proton corresponds to that which occurs at τ 6.18 in the nmr spectrum of I. The great downfield shift of this proton must arise from the paramagnetic effect caused by the introduction of the electronegative oxygen atom in place of the nitrogen on the allylic carbon atom. A similar phenomenon was observed in the nmr spectrum of the bromocyanide (V)[5] obtained by von Braun degradation of I, in which the corresponding proton occurs at τ 5.08.

The 1,2-oxazolactone-B (III) was shown to be identical with the product obtained previously by the oxidation of I with either hydrogen peroxide or ozone. Its ultraviolet spectrum shows an absorption maximum at 213.5 mμ (ϵ 17,700),[10] which indicates the absence of the double bond in conjugation with the α,β-unsaturated lactone grouping. In its infrared spectrum, however, an absorption associated with the out-of-plane deformation of a *cis*-disubstituted olefinic linkage[11] appears at 14.23 μ. Since it shows a strong, sharp infrared band at 3.19 μ,[12] it was at first supposed to be the amino lactone (VI) which possesses a hydroxyl and an imino group. However, this possibility was excluded by the fact that this compound had no basic character, did not undergo acetylation even under

(1) This paper is V in the series, Studies on the Alkaloids of *Securinega virosa* Pax. *et* Hoffm. Part IV: T. Nakano, T. H. Yang, and S. Terao, *J. Org. Chem.*, **29**, 3441 (1964).

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(5) T. Nakano, T. H. Yang, and S. Terao, *Chem. Ind.* (London), 1651 (1962); *Tetrahedron*, **19**, 609 (1962); *Tetrahedron Letters*, 665 (1963); *J. Org. Chem.*, **28**, 2619 (1963); T. Nakano, T. H. Yang, S. Terao, and L. J. Durham, *Chem. Ind.* (London), 1034, 1763 (1963).

(6) J. C. Craig, N. Y. Mary, and L. Wolf, *J. Org. Chem.*, **29**, 2868 (1964).

(7) (a) J. Meisenheimer, *Ber.*, **52**, 1667 (1919); J. Meisenheimer, H. Greeske, and A. Willmersdorf, *ibid.*, **55**, 513 (1922); (b) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960); (c) A. H. Wragg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958); (d) W. Carruthers and R. A. W. Johnstone, *ibid.*, 1653 (1965).

(8) L. D. Quin and G. L. Roof, *J. Org. Chem.*, **27**, 4451 (1962). The N–O peaks observed are a little far from the peaks quoted in ref 8 and elsewhere at 10.3–10.6 μ. The somewhat strained ring system may well account for the hypsochromic shift.

(9) Unless otherwise noted, nmr spectra were obtained with a Varian A-60 spectrometer in deuteriochloroform. All chemical shifts are reported in τ values (parts per million) using tetramethylsilane as an internal reference. We thank Dr. T. Shingu for these determinations.

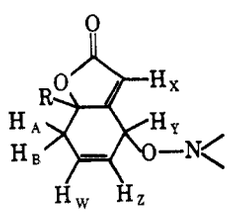
(10) Dihydrovirosecurinine also possesses this absorption maximum. See ref 5.

(11) H. B. Henbest, G. D. Meakins, and G. W. Wood, *J. Chem. Soc.*, 800 (1954).

(12) This absorption may be due to the CH stretching vibration of vinylidene ethers. See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 44.

drastic conditions, and upon column chromatography was easily eluted by nonpolar solvents. In the measurement of its nmr spectrum, no active proton exchangeable with deuterium could be detected. The mass spectrometric molecular weight determination[13] showed a molecular ion peak at *m/e* 233, which precludes the formulation VI for this compound (*m/e* 235). The lack of basicity also eliminates the possibility of the epoxide structure VII, but it is consistent with the formation of the N—O—C linkage of III. The presence of this bond was confirmed by a strong infrared absorption band at 9.60 μ.[8]

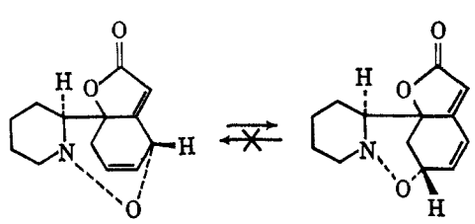
The analysis of the 100-Mc/sec nmr spectrum[14] of III employing double resonance experiments provided more decisive proof on its structure. In the partial formula A, the proton H_X exhibits a singlet at τ 4.29,



A

the proton H_Y, a doublet (J_{YZ} = 6 cps) at τ 4.84, the proton H_Z, a complex multiplet (J_{ZY} = 6 cps, J_{ZW} = 9 cps, $J_{ZA} \sim 2.5$ cps, and $J_{ZB} \sim 1.5$ cps) centered at τ 4.15, the proton H_W, an octuplet (J_{WZ} = 9 cps, J_{WB} = 4 cps, and $J_{WA} \sim 2.5$ cps) centered at τ 3.78, the proton H_B, at τ 6.88 (J_{BA} = 18 cps, J_{BW} = 4 cps, and $J_{BZ} \sim 1.5$ cps), and the proton H_A, at τ 7.77 (J_{AB} = 18 cps and $J_{AW} + J_{AZ} \sim 6$ cps).

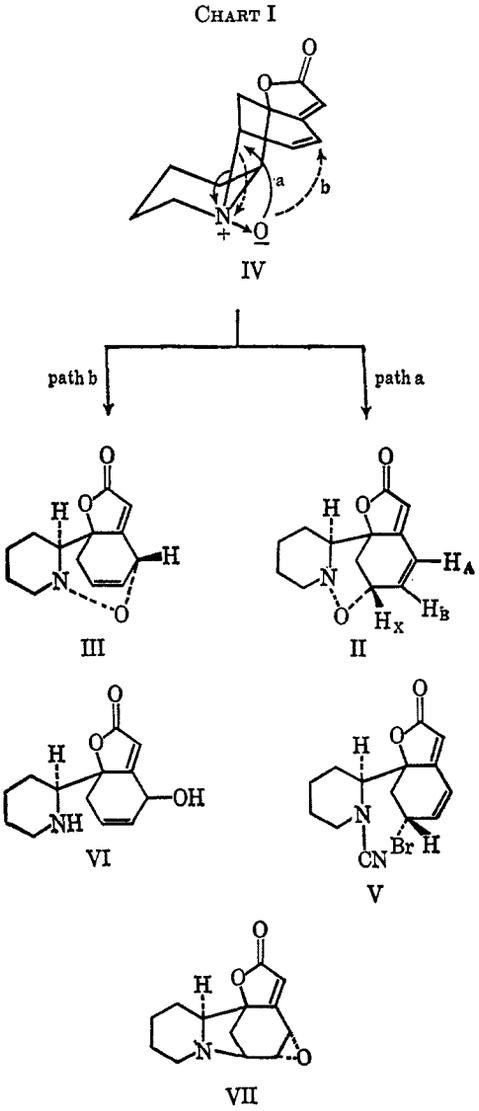
On pyrolysis at 160–170° and 0.04 mm, the 1,2-oxazolactone-B (III) readily rearranges to its isomeric lactone-A (II). However, the reverse course does not follow under this same condition. In the presence of Lewis acids such as boron trifluoride or under the acidic medium as employed for the oxidation, neither II nor III undergoes such rearrangement. Thus, II is thermodynamically a more stable product.



III II

The mechanism for the formation of II and III by the peracid oxidation of I may be explained as follows. The oxidation does not effect epoxidation of the double bond of the ring C, but its initial step may involve the attack of the reagent on the nitrogen atom (N-oxide formation) which leads to the intermediate IV. The attack of the oxidant on the nitrogen must have been made from the sterically less hindered α side of the molecule. The N-oxide IV could not be isolated and it is reasonable to assume that it is so labile and the decrease of the electron density on the nitrogen atom may be so great as to cause immediate cleavage of the allylic C–N bond. Concerted with this bond fission, two types of nucleophilic substitution reaction may take place in competition with each other. One proceeds *via* path a, and, as is apparent from an inspection of Dreiding molecular models, the product II is geometrically forced to assume the same configuration at the allylic carbon atom as the original compound. This reaction is analogous to the rearrangement of N-allyl- and N-benzylamine oxides to O-allyl- and O-benzylhydroxylamines, discovered by Meisenheimer[7a] and studied by Cope and his collaborators[7b] and by Wragg, Stevens, and Ostle.[7c] It is an intramolecular process similar to the rearrangement of nicotine 1′-oxide and related compounds.[7d] The other process is designated in path b, which involves the allylic rearrangement leading to the product III. In this case, the formation of the new oxygen linkage is sterically possible only on the α side of the molecule. Since in path a the attack of the oxygen on the allylic carbon atom is made from the same side (α) of the C–N bond

CHART I



IV III II VI V VII

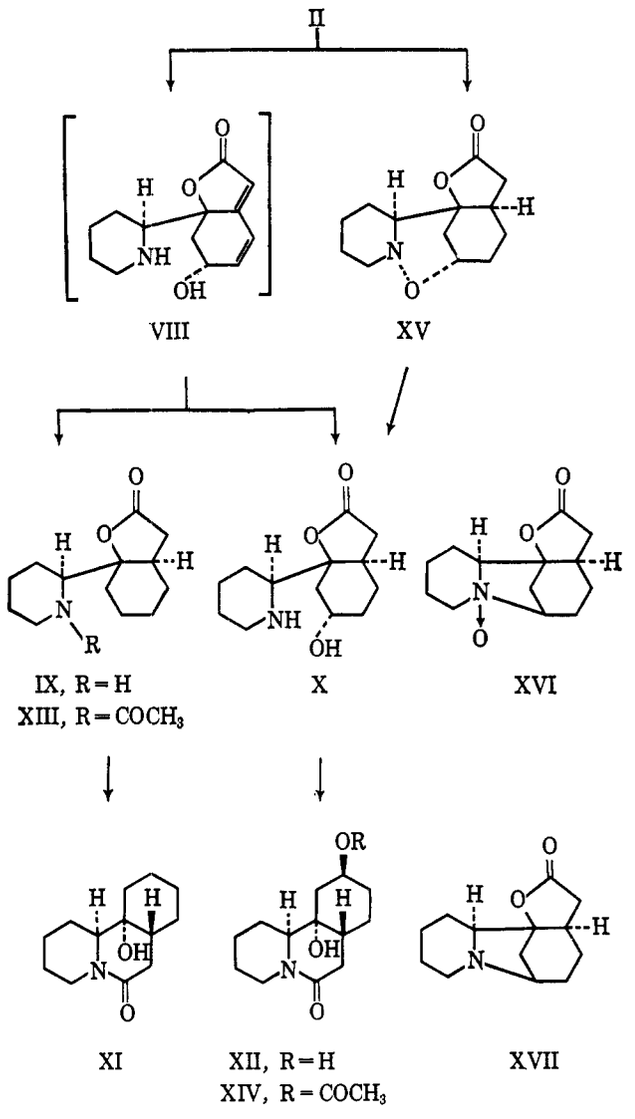
(13) The mass spectrum was obtained on a Hitachi RMU-6D mass spectrometer. We thank Dr. T. Ibuka for this measurement.

(14) The 100-Mc/sec nmr spectra and double resonance experiments were carried out on a Varian Model V-4300D HR-100 nmr spectrometer. The double resonance experiments were done using the method of L. F. Johnson (Varian Technical Information Bulletin, Vol. III, No. 3, Instrument Division, Varian Associates, Palo Alto, Calif., 1962, p 5) which is a modification of the method described by Freeman and Whiffen [*cf.* R. Freeman and D. H. Whiffen, *Mol. Phys.*, **4**, 321 (1961)]. Samples were dissolved in deuteriochloroform containing tetramethylsilane as an internal reference.

to be cleaved, mechanistically path b appears to be more favored than path a, which reflects itself on the result of the formation ratio (1:5.5) of II and III (see Chart I).

On catalytic hydrogenation with platinum oxide in glacial acetic acid, II absorbed 2.66 molar equiv of hydrogen and three kinds of product were obtained. Of these, IX and X have basic properties and must have been produced by the fission of the N–O bond *via* the intermediate VIII (Chart II). In this reduction,

CHART II

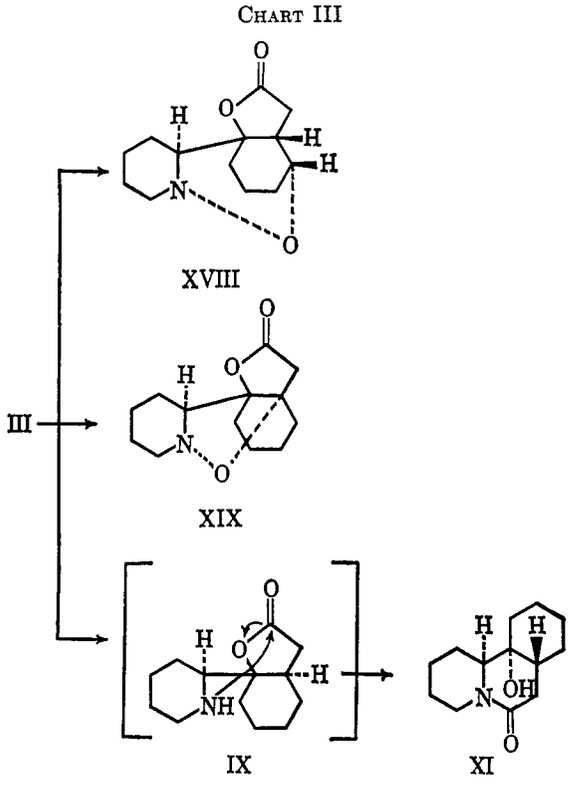


the hydrogenolytic loss of the allylic hydroxyl group may lead to the formation of IX, whereas the retention of its hydroxyl group may produce X. The compounds IX and X were characterized as their crystalline picrates, and, on passage through activated neutral alumina in methylene chloride solution, they were lactamized to the lactam carbinol (XI) and the lactam diol-A (XII), respectively. Acetylation of IX and XII with acetic anhydride–pyridine afforded the N-acetate (XIII) and the O-monoacetate (XIV), respectively. The compounds XIII and XI were shown to be identical with those corresponding derivatives[5] which had been previously prepared by degradation of virosecurinine (I) and whose absolute configurations[15] had been rigorously established.

The other product in the above catalytic hydrogenation of II is the tetrahydro-1,2-oxazolactone-A (XV). This compound was shown not to be identical with tetrahydrovirosecurinine N-oxide (XVI) and is stable under the same hydrogenation conditions as above. However, on hydrogenation in the presence of a large excess of unreduced platinum oxide catalyst in glacial acetic acid, it underwent the fission of its N–O linkage to yield X. The configuration at the C/D ring junction of XV was deduced from a comparison of its ORD and CD curves[16] with those of the compounds XIII and XVII[5,17] of established *trans* C/D ring configuration. The compound XV shows a negative Cotton effect [in cyclohexane: $[\phi]_{238}$ −4042° (trough) and $[\theta]_{220}$ −4743°].[18] Since XIII and XVII also exhibit negative Cotton effects [XIII, in cyclohexane: $[\phi]_{244.5}$ −4542° (trough) and $[\theta]_{230}$ −4240°; XVII, in methanol: $[\phi]_{244}$ −2863° (trough) and $[\theta]_{230}$ −3081°], XV must possess the same *trans* C/D ring configuration as XIII and XVII. These results are consistent with those predicted from the lactone rule proposed by Klyne, *et al.*[19] Since X is derived from XV, X must also have the *trans* C/D ring system as shown in the formula.

On hydrogenation with platinum oxide in ethanol, the 1,2-oxazolactone-B (III) (Chart III) took up ap-

CHART III



(15) Z. Horii, Y. Yamawaki, M. Hanaoka, Y. Tamura, S. Saito, and H. Yoshikawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 22 (1965).

(16) The ORD and CD curves were measured on a Jasco ORD/UV-5 instrument (Japan Spectroscopic Co., Ltd.). We thank Dr. K. Kuriyama of the Research Laboratory, Shionogi and Co. for these determinations and also helpful discussion of the results.

(17) Z. Horii, M. Hanaoka, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, and K. Kotera, *Chem. Pharm. Bull.* (Tokyo), **13**, 27 (1965).

(18) For nomenclature, see C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963).

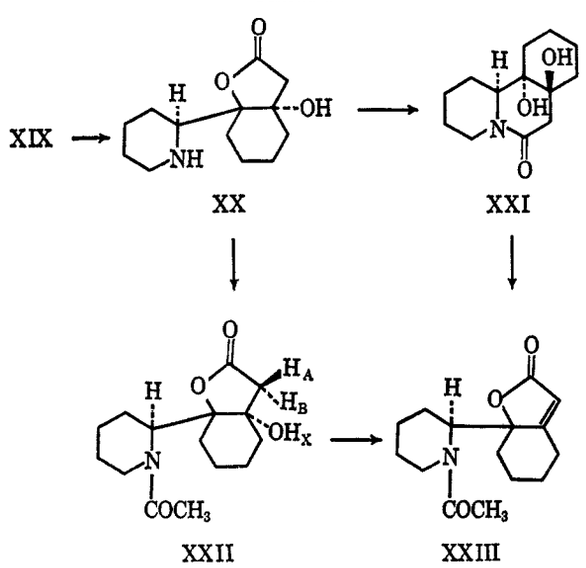
(19) J. P. Jennings, W. Klyne, and P. M. Scopes, *ibid.*, 412 (1964).

proximately 2.2 molar equiv of hydrogen, and, on separation of the resulting products on activated alumina, there were isolated the tetrahydro-1,2-oxazolactone-B (XVIII), the rearranged tetrahydro-1,2-oxazolactone (XIX), and the lactam carbinol (XI). The compounds XVIII and XIX are both nonbasic, and at first they were assumed to be isomers which differ from each other merely in the configuration of the C/D ring junction. However, we might reasonably speculate that the compound XIX arises from hydrogenolysis to the hydroxylamine which adds across the double bond of the unsaturated lactone. As described later, the chemical degradation disclosed that this compound has in fact the structure shown.

The compounds XVIII and XIX had infrared bands at 9.65 and 9.68 μ, respectively, which arise from the N–O absorption.[8] In the nmr spectrum of XVIII, a multiplet peak due to the >C*H*—O grouping appears at τ 5.76, whereas in that of XIX, the corresponding signal was not observed. In XIX, the two protons on the carbon atom adjacent to the lactonic carbonyl group occur as a singlet[20] at τ 7.28, indicating the absence of the neighboring proton. In XVIII, however, the corresponding protons exhibit a complex coupling pattern because of the presence of the proton on the C/D ring junction.

On hydrogenation with platinum oxide in glacial acetic acid, XIX (Chart IV) absorbed 1 molar equiv

CHART IV



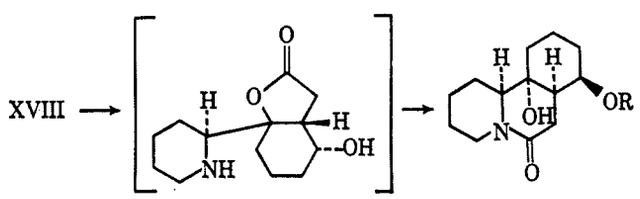
of hydrogen and the product XX was formed, which was isolated as a crystalline styphnate. The compound XX, in contact with activated neutral alumina in methylene chloride solution or in the presence of pyridine as a base catalyst, readily lactamized to the lactam diol-B (XXI). Acetylation of XX with acetic anhydride afforded the hydroxy N-acetate (XXII), which resisted chromic acid oxidation. Attempts to acetylate XXII resulted in the dehydration of the tertiary hydroxyl group to yield the known compound XXIII.[5] Heating of XXI with acetic anhydride–pyridine also gave rise to XXIII.

(20) These protons are magnetically equivalent, or nearly so, thus no coupling was observed between them.

A very interesting example of the ABX coupling pattern is seen in the nmr spectrum of XXII, in which the tertiary hydroxylic proton H_X is in the long-range coupling with the proton H_B, on the carbon atom adjacent to the lactonic carbonyl group. The proton H_A occurs as a doublet (J_{AB} = 17.5 cps) at τ 7.62, the proton H_B, as a quartet (J_{AB} = 17.5 cps and J_{BX} = 2.2 cps) at τ 7.15, and the proton H_X, as a doublet (J_{BX} = 2.2 cps) at τ 4.18. Upon addition of deuterium oxide, the signal of the proton H_X disappears, owing to the exchange of the hydroxylic proton with deuterium. Furthermore, the two protons H_A and H_B now appear as an AB quartet. This spectral evidence also favors the assignment of the location of the tertiary hydroxylic group in XXII.

The configuration of the C/D ring junction both in XVIII (Chart V) and XIX was made on the basis

CHART V



of their respective ORD[19] and CD curves. The compound XIX gives a negative Cotton effect curve[21] (in cyclohexane: $[\theta]_{224}$ −3383°), confirming the *trans* C/D ring system for XIX and hence XX. In contrast to XIII, XV, and XIX, XVIII exhibits a positive Cotton effect (in cyclohexane: $[\phi]_{239}$ +5174° (peak) and $[\theta]_{229}$ +2340°), which suggests a *cis* stereochemistry for the C/D ring junction.

The tetrahydro-1,2-oxazolactone-B (XVIII) is stable under the same conditions as employed for the hydrogenation of XIX. In the presence of a large excess of unreduced platinum oxide in glacial acetic acid, however, XVIII yielded *via* the intermediate XXIV the lactam diol-C (XXV). Acetylation of XXV afforded the O-monoacetate (XXVI).

Experimental Section

All melting points were taken on a Kofler block and are uncorrected. Unless otherwise specified, optical rotations were measured in chloroform, ultraviolet spectra in 95% ethanol, infrared spectra in potassium bromide disks, and optical rotatory dispersion curves in methanol. Alumina for chromatography referrs to Woelm neutral, activity grade I. Elemental analyses were carried out by Dr. K. Konobu and his associates of the Microanalytical Laboratory of this Faculty. Identity of compounds was established by melting point, mixture melting point, and infrared spectra.

Oxidation of Virosecurinine (I) with Monoperphthalic Acid.—An ethereal solution of monoperphthalic acid[22] (150 ml, 0.16 mole) was added slowly with stirring to a solution of I (30 g, 0.14 mole) in glacial acetic acid (120 ml, distilled from potassium permanganate) cooled below 5°. The mixture was allowed to stand below 5° for 20 hr, poured into ice–water (600 ml), made

(21) This compound gives an anomalous ORD curve (in cyclohexane: $[\phi]_{400}$ +584°, $[\phi]_{280}$ +2145°, $[\phi]_{245}$ +2050°, $[\phi]_{225}$ +6940°) arising from the contribution by a large background rotation, which hides a negative Cotton effect. This is uncovered by the CD measurement.

(22) Monoperphthalic acid was prepared according to the method of *Org. Syn.*, **42**, 77 (1962).

alkaline with aqueous ammonia, and extracted with methylene chloride. The organic layer was washed with water, dried over anhydrous sodium sulfate, and distilled off *in vacuo*, leaving a crystalline product (21.3 g). Recrystallization from methanol–methylene chloride gave III (7.23 g) as colorless needles: mp 195–196° dec, $[\alpha]_D$ +14° (*c* 1.20). From the mother liquor, the second crop (2.93 g) of the same compound, mp 182–192°, was obtained. This compound showed infrared bands at 3.19 (CH stretching vibration of vinylidene ether), 5.70 (α,β-unsaturated γ-lactonic carbonyl), 6.12 (conjugated double bond), 9.60 (N–O vibration), and 14.23 μ (CH out-of-plane deformation of *cis*-disubstituted ethylene).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.98; H, 6.57; N, 6.11.

The mass spectrum exhibited *m/e* peaks at 55, 78, 83, 100 (base peak), 106, 134, and 233 (molecular ion peak).

The mother liquor from the above isolation was concentrated to dryness and the residue (8.1 g) was chromatographed in methylene chloride on silicic acid (240 g, Mallinckrodt). Elution was effected in 120-ml fractions with the same solvent. Fractions 1–5 were combined and crystallized from ethanol, giving II as pale yellow needles (2.38 g): mp 142–144°, $[\alpha]_D$ +370° (*c* 0.73). The infrared spectrum showed peaks at 5.74 (α,β-unsaturated γ-lactone), 6.10 (double bond), and 9.80 μ (N–O). The ultraviolet spectrum showed an absorption maximum at 259 mμ (ϵ 16,000).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.94; H, 6.59; N, 5.96.

Fractions 6–10 were combined and crystallized from methanol to give III (3.1 g).

From fractions 11–15 there was recovered I (1.3 g) after crystallization from ethanol.

Attempted Pyrolysis of 1,2-Oxazolactone-A (II).—When II (100 mg) was heated at 0.04 mm, crystals began to sublime at 130° (air bath). Heating was continued for a further 30 min, leaving a small amount of a brown residue. Recrystallization of the sublimate from ethanol gave unchanged material (II) (66 mg).

Attempted Acid-Catalyzed Rearrangements of 1,2-Oxazolactone-A (II) and 1,2-Oxazolactone-B (III). A.—Each of the samples (100 mg) of II and III was dissolved in a mixture of 40% ethereal acetic acid (10 ml) and phthalic acid (100 mg), and the solution was allowed to stand at room temperature for 2 days. Usual working-up recovered the respective starting material (90–95 mg).

B.—Each of the samples (100 mg) of II and III in dry ether (10 ml) was treated with boron trifluoride etherate (0.5 ml). The solution was kept at room temperature for 2 days, poured into ice water, made alkaline with solid sodium carbonate, and extracted with ether. Evaporation of the ether afforded the respective starting material (90–95 mg).

Pyrolysis of 1,2-Oxazolactone-B (III) to 1,2-Oxazolactone-A (II).—Compound III (100 mg) was heated at 0.04 mm. At *ca.* 160°, a reaction set in, and the temperature of the bath was gradually raised to 170°. After 30 min, the distillate (83 mg) was dissolved in ether and filtered on a short column of alumina (2 g) to afford II (75 mg).

Catalytic Hydrogenation of 1,2-Oxazolactone-A (II).—Compound II (1.085 g) in glacial acetic acid (100 ml) was hydrogenated in the presence of prereduced platinum oxide (250 mg) at room temperature and atmospheric pressure. The uptake of hydrogen ceased after 4 hr (2.66 molar equiv). After removal of the catalyst, the filtrate was concentrated *in vacuo* and the residue was chromatographed on Merck's standardized alumina (30 g). Elution was effected in 50-ml fractions with benzene and benzene–ether. Fraction 1 (benzene), after evaporation of the solvent, left a semicrystalline residue (0.2 g). Fraction 2 (benzene) was obtained as an oil (0.27 g), which was treated in ethanol with picric acid. The picrate (50 mg) was obtained: mp 225–226° dec (from acetone–ethylacetate), $[\alpha]_D$ −14° (*c* 2.08, acetone). Its infrared spectrum showed bands at 3.21 (NH) and 5.69 μ (saturated γ-lactonic carbonyl), and was shown to be identical with that of the picrate of IX, prepared previously from I by a different route.[5]

Anal. Calcd for $C_{19}H_{24}N_4O_9$: C, 50.44; H, 5.35; N, 12.39. Found: C, 50.33; H, 5.72; N, 12.35.

The above picrate (30 mg) in a minimum amount of acetone was adsorbed on a column of alumina (3 g) in methylene chloride and the product was eluted with methylene chloride–methanol (9:1). Crystallization from acetone afforded XI (10 mg), obtained previously.[5] On the other hand, the picrate (10 mg) was heated under reflux with a mixture of acetic anhydride (0.5 ml) and pyridine (1 ml) for 1 hr. After evaporation of the solvent *in vacuo*, the product was purified in methylene chloride by passing through a column of alumina (2 g) to give the N-acetate (7 mg): mp 156–156.5°, $[\alpha]_D$ −127° (*c* 0.51). Its infrared spectrum was identical with that of XIII, prepared previously from I by a different route.[5]

Fractions 3–7 (benzene–ether, 3:1 to 1:1) were evaporated *in vacuo* and X was obtained as an oil (0.6 g), which was treated with picric acid in ethanol. Crystallization from acetone–ethyl acetate yielded a picrate (200 mg): mp 221–222° dec, $[\alpha]_D$ −10° (*c* 2.06, acetone).

Anal. Calcd for $C_{19}H_{24}N_4O_{10}$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.83; H, 5.61; N, 11.64.

The above picrate (179 mg) in a minimum amount of acetone was adsorbed on a column of alumina (18 g) in methylene chloride and elution with methylene chloride–methanol (9:1) afforded XII (50 mg), mp 242–243° (from ethyl acetate–methanol), $[\alpha]_D$ −29° (*c* 0.94, ethanol), showing bands at 2.91 and 3.20 (OH), and 6.26 μ (amide) in the infrared.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.19; H, 8.86; N, 5.64.

Fraction 1 (0.2 g) was rechromatographed on Merck's standardized alumina (12 g). The benzene eluate fraction (60 mg) was crystallized from hexane to give XV as needles: mp 166–167°, $[\alpha]_D$ −85° (*c* 0.32). The infrared spectrum showed bands at 5.67 (saturated γ-lactonic carbonyl) and 9.66 μ (N–O). The nmr spectrum exhibited a multiplet at τ 5.55, corresponding to one proton on the carbon atom attached to the oxygen.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.23; H, 8.19; N, 5.82.

Elution with benzene–ether (1:1) yielded XII (60 mg), obtained above.

Acetylation of Lactam Diol-A (XII). Compound XII (30 mg) was treated with a mixture of acetic anhydride (1 ml) and pyridine (2 ml) at room temperature overnight. Usual working-up afforded XIV as plates (28 mg): mp 233–237° (from acetone), $[\alpha]_D$ −43° (*c* 0.95). The infrared spectrum showed bands at 2.92 (OH), 5.79 (O-acetyl), and 6.24 μ (amide). The nmr spectrum exhibited signals at τ 7.97 (3 H, $OCOCH_3$), 6.81 (1 H, OH), and 4.84 (1 H, multiplet, $>CH$–$OCOCH_3$). The peak at τ 6.81 disappeared upon addition of deuterium oxide.

Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.16; H, 8.19; N, 5.01.

Catalytic Hydrogenation of Tetrahydro-1,2-oxazolactone-A (XV).—Compound XV (20 mg) in glacial acetic acid (10 ml) was hydrogenated in the presence of unreduced platinum oxide (100 mg) at room temperature and atmospheric pressure. After 6 hr, the catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The product X (26 mg) was isolated as a picrate (35 mg). The picrate (22 mg) was dissolved in acetone (2 ml) and poured onto a column of alumina (10 g) in methylene chloride, and the product was eluted with methylene chloride–methanol (9:1), giving XII (8 mg), obtained above by hydrogenation of II.

Tetrahydrovirosecurinine N-Oxide (XVI).—Tetrahydrovirosecurinine[6] (XVII) (600 mg) in glacial acetic acid (10 ml) was treated with 30% aqueous hydrogen peroxide (0.2 ml). After standing at room temperature for 1.5 hr, the mixture was poured into water and the product was extracted with methylene chloride. Washing of the extract with water, drying over anhydrous sodium sulfate, and evaporation *in vacuo* left a residue (450 mg). This was chromatographed in methylene chloride on silicic acid (15 g, Mallinckrodt) and elution with the same solvent gave XVI as plates (120 mg): mp 127–129° (from hexane), $[\alpha]_D$ +83° (*c* 0.92). The infrared spectrum showed peaks at 5.63 (saturated γ-lactone) and 9.69 μ (N–O).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.77; H, 8.15; N, 5.86.

Catalytic Hydrogenation of 1,2-Oxazolactone-B (III).—Compound III (10 g) in ethanol (200 ml) was hydrogenated with prereduced platinum oxide (500 mg) at room temperature and atmospheric pressure. *Ca.* 2.2 molar equiv of hydrogen were rapidly absorbed. After filtration from the catalyst, the solution was evaporated *in vacuo* to dryness, giving a residue (10.2 g). The thin layer chromatographic analysis on silica gel G (Merck) (methylene chloride as the developing solvent) showed that it consisted of three products. This mixture was chromatographed on alumina (300 g) and elution with benzene afforded a mixture

of XVIII and XIX in a ratio of 1:9, respectively, as determined by the thin layer chromatography on silica gel G (Merck) using ether as the developing solvent. Recrystallization from acetone–hexane gave XIX as needles (6.23 g): mp 110–111°, $[\alpha]D$ +50° (*c* 0.75). This compound showed infrared bands at 5.60 (saturated γ-lactone) and 9.68 μ (N–O). Its nmr spectrum exhibited a singlet at τ 7.29, corresponding to two protons on the carbon atom adjacent to the lactone carbonyl group.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.69; H, 8.22; N, 5.86.

From the mother liquor of XIX there was obtained XVIII as needles (563 mg) after recrystallization from hexane: mp 135–136°, $[\alpha]D$ +63° (*c* 1.00). Its infrared spectrum showed bands at 5.61 (saturated γ-lactone) and 9.65 μ (N–O). The nmr spectrum exhibited a peak at τ 5.76 characteristic of the >CH–O grouping.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.72; H, 7.93; N, 5.84.

Further elution with methylene chloride–methanol (9:1) gave XI (3.24 g).

Catalytic Hydrogenation of Rearranged Tetrahydro-1,2-oxazolactone (XIX).—Compound XIX (5 g) in glacial acetic acid was hydrogenated with prereduced platinum oxide (500 mg) at room temperature and atmospheric pressure. Hydrogen (1 molar equiv) was taken up in 5 hr. Removal of the catalyst and evaporation of the solvent *in vacuo* gave an amorphous product (XX) (5.37 g). Part (50 mg) of this product in ethanol (1 ml) was treated with styphnic acid (50 mg) to yield a styphnate as fine crystals (72 mg): mp 214° dec (from acetone–ethanol), $[\alpha]D$ −21° (*c* 1.00, acetone). The infrared spectrum showed a band at 5.62 μ (saturated γ-lactone).

Anal. Calcd for $C_{19}H_{24}N_4O_{11}$: C, 47.11; H, 4.99; N, 11.57. Found: C, 47.37; H, 4.89; N, 11.42.

The amorphous product XX (200 mg) was dissolved in acetic anhydride (5 ml) and the solution was set aside at room temperature for 3 hr. Then pyridine (1 ml) was added and the mixture was allowed to stand at room temperature overnight. After acidification with 3% hydrochloric acid (100 ml), the product was isolated by extraction with methylene chloride. Crystallization from ethanol gave XXII as needles (153 mg): mp 237°, $[\alpha]D$ −125° (*c* 1.00). The infrared spectrum showed peaks at 2.95 (OH), 5.60 (saturated γ-lactone), and 6.16 μ (N-acetate).

Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found C, 63.84; H, 8.25; N, 4.82.

The mother liquor of XXII was concentrated *in vacuo* and the residue (70 mg) was chromatographed on alumina (5 g). Elution with methylene chloride yielded the N-acetate (20 mg), mp 170°, identified by direct comparison of an authentic sample of XXIII.

Elution with methylene chloride–methanol (95:5) gave XXII (24 mg), obtained above.

Elution with methylene chloride–methanol (from 9:1 to 1:1) afforded XXI as plates (18 mg): mp 251° (from methanol), $[\alpha]D$ −32° (*c* 1.00, methanol). This compound showed peaks at 2.95 (OH) and 6.15 μ (amide) in the infrared.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 64.93; H, 8.80; N, 5.71.

This compound was very sparingly soluble in the usual organic solvents except methanol and ethanol.

Base-Catalyzed Formation of Lactam Diol XXI.—The amorphous product XX (200 mg) obtained above was heated with pyridine (10 ml) at 100° for 1 hr. Evaporation of the solution *in vacuo* and crystallization of the residue from methanol afforded XXI (187 mg).

Dehydration of Hydroxy N-Acetate XXII.—Compound XXII (100 mg) was heated with pyridine and acetic anhydride (1:1, 5 ml) at 80° for 1 hr. The crude product (90 mg) obtained in the usual way was purified by chromatography on alumina (3 g). Elution with ether gave XXIII (78 mg).

Conversion of Lactam Diol-B XXI into N-Acetate XXIII.—Compound XXI (100 mg) was refluxed with pyridine–acetic anhydride (1:1, 5 ml) for 30 min. Removal of the solvent left a crystalline mass (98 mg), which, after crystallization from acetone, afforded XXIII (76 mg).

Catalytic Hydrogenation of Tetrahydro-1,2-oxazolactone-B (XVIII). A. Compound XVIII (150 mg) in glacial acetic acid (10 ml) was hydrogenated with prereduced platinum oxide (100 mg) at room temperature and atmospheric pressure for 7 hr. The uptake of hydrogen did not take place and the starting material (145 mg) was recovered.

B.—Compound XVIII (130 mg) in glacial acetic acid (10 ml) was hydrogenated in the presence of unreduced platinum oxide (500 mg) at room temperature and atmospheric pressure for 7 hr. During the hydrogenation, the mixture was vigorously stirred. The product (145 mg), isolated in the usual way, was acetylated by heating with acetic anhydride (3 ml) at 100°. After 1 hr, the mixture was poured into water and extracted with methylene chloride. The organic layer was washed with 3% aqueous sodium carbonate and water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*, leaving a crystalline mass (155 mg). This was chromatographed on alumina (30 g) and elution with benzene afforded the starting material (15 mg). Elution with methylene chloride–methanol (9:1) yielded XXVI as plates (80 mg): mp 220–223° (from acetone), $[\alpha]D$ +28° (*c* 1.00). The infrared spectrum showed bands at 2.94 (OH), 5.77 (O-acetyl), 6.21 (amide), and 9.70 μ (C—O).

Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.21; H, 8.15; N, 5.01.

The nmr spectrum exhibited signals at τ 7.98 (3 H, O—$COCH_3$), 7.53 (2 H, singlet, CH_2 adjacent to the amide carbonyl group), 6.84 (1 H, OH), and 4.70 (1 H, multiplet, >CH—O). The signal at τ 6.84 disappeared upon addition of deuterium oxide.

Citrus Bitter Principles. VI.[1] Ichangin

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The isolation and structure determination of ichangin, a new C_{26} terpenoid bitter principle from a hybrid of *Citrus ichangensis*, are described. Ichangin is assigned structure **3** and is closely related structurally to limonin.

From the viewpoint of their limonoid content, the genus *Citrus* (Rutaceae) is a very homogeneous group.[1] Examination of the bitter principles in the seed extracts of different species revealed that one of the most abnormal members of this genus was *Citrus ichangensis* and its hybrids.[1,3] *C. ichangensis* and its hybrids showed a remarkable ability to accumulate relatively large amounts of limonin (**1**) intermediates. Seed extracts from these sources on thin layer chromatography (tlc)[4] showed a much more complex pattern of components, containing four to five other limonoid spots, in addition to the usual obacunone,[5,6] limonin,[6] nomilin,[6,7] and deacetylnomilin.[4]

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