distilled without decomposition even at 50 μ pressure. The yields in subsequent runs, 34, 64, 46, 31, 62, 94 and 74%, varied unaccountably. Jaeger and van Dijk,[7] who gave almost no experimental detail, did not give a yield for this preparation, but did state that the product was an uncrystallizable oil. Other workers[14] have reported their inability to repeat this preparation.

The crude 2-isonitrosocyclohexanone was transformed into 1,2-cyclohexanedionedioxime in yields varying from 22 to 58% by treatment with equivalent amounts of hydroxylamine hydrochloride and sodium methoxide in methanol. After recrystallization from methanol-water it melted at 190–195°

In a typical run 10 g. (0.07 mole) of the dioxime in 560 ml. of boiling absolute ethanol was reduced by the addition of 70 g. of sodium. After cooling and diluting with water the product was steam distilled into hydrochloric acid solution. After concentration under reduced pressure the 1,2-cyclohexanediamine dihydrochloride crystallized (54% yield).

The dihydrochloride was converted to the free amine by dissolving in excess sodium hydroxide solution, extracting with ether, drying over sodium metal and distilling. The product boiled at 79–81° (15 mm.) (82%), reported[7] b.p. 79–81° (15 mm.). Over-all yields based on the starting ethyl 2-ketocyclohexanecarboxylate varied from 0–20%. The free amine absorbed carbon dioxide and water with great avidity.

The configuration of the product as *trans*-1,2-cyclohexanediamine has been established by resolution with *d*-tartaric acid.[8]

Preparation of *trans*-Decahydroquinoxaline from *trans*-1,2-Cyclohexanediamine.—To 0.9 g. (0.008 mole) of the diamine was added 1.5 g. of 30% aq. glyoxal (0.008 mole). After standing 5 min., 10 ml. of absolute ethanol and 0.4 g. of 5% rhodium-on-alumina catalyst were added and the reaction mixture hydrogenated for 4 hr. at 200° and 102 p.s.i. After filtration, evaporation to dryness and vacuum sublimation, 0.25 g. (20%) of authentic *trans*-decahydroquinoxaline, m.p. 147–148°, was obtained. No low melting isomer was obtained. Tar accounted for the balance of the material. The dinitroso derivative and mixed melting point comparisons further identified the product.

Acknowledgments.—This investigation was generously supported by grants from the Eli Lilly Co., 1954–1958, and by a fellowship to L. P. from the Linde Division, Union Carbide Corporation. Especial thanks are due to Dr. Reuben G. Jones, Director of Organic Research, Lilly, for his good offices and to Dr. Harold Boaz, Physicochemical Department, Lilly, for the data on infrared spectra and pK_a's.

PROVO, UTAH

(14) E. G. Rauh, G. F. Smith, C. V. Banks and H. Diehl, *J. Org. Chem.*, **10**, 199 (1945).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, HARVARD UNIVERSITY]

18-Oxostrychnine

BY PAUL J. SCHEUER[1,2]

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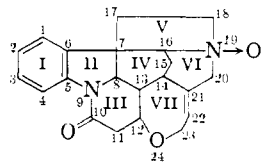
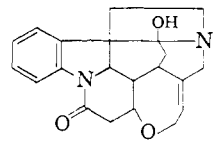
Oxostrychnine, a neutral by-product in the isomerization of strychnine-N-oxide to pseudostrychnine, is shown to be the 18-oxo compound.

The transformation of cyclic tertiary amines to corresponding lactams has frequently been observed in the course of structural studies on alkaloids, particularly among those of the garrya group.[3] An analogous lactam was first observed in the strychnine series by Brehm[4] as a by-product in the isomerization of strychnine-N-oxide (I) to pseudostrychnine (II). In addition to pseudostrychnine, a neutral substance, m.p. 332–334°, of the empirical



I



II

composition $C_{21}H_{20}N_2O_3$ was isolated. Brehm, who named the neutral substance oxostrychnine, obtained pseudo- and oxostrychnine in a yield ratio of 80:20 when catalytic amounts of dichromate were used to effect the decomposition of the N-oxide. It was later found that when equimolar quantities of dichromate are utilized, the two compounds are produced in an approximately equal ratio.

Beside the likely C-16 position which becomes hydroxylated in pseudostrychnine, the two most probable positions for the new oxygen atom in oxostrychnine are C-18 or C-20. That the strychnine skeleton had indeed remained intact during the changes leading to the formation of the oxo compound—thus eliminating the C-16 position from further consideration—was shown by the conversion of oxostrychnine to dihydroöxostrychnine, m.p. 321–324°, by means of catalytic hydrogenation and by further transformation of the dihydro derivative with lithium aluminum hydride to the known dihydrostrychnidine, m.p. 212–215°.

A priori it might be argued that the most likely point of attachment of the new oxygen atom in oxostrychnine is at the allylic position, C-20. It may be noted, however, that the formation of the major reaction product, pseudostrychnine (II), involves placement of a new oxygen atom at the non-allylic C-16. Furthermore, spectral data indicated strongly that the 18-oxo structure is correct. In addition to the infrared band at *ca.* 6 μ (5.97 μ in potassium bromide, 6.03 μ in Nujol), which is also present in strychnine and is assigned to the $>N^a-CO-$grouping, oxostrychnine exhibited a second lactam band at *ca.* 5.87 μ (5.82 μ in

(1) University of Hawaii, Honolulu 14, Hawaii. From the Ph.D. Thesis of P. J. S., Harvard, 1950.

(2) A summary of results of this work was published by H. L. Holmes in R. H. F. Manske and H. L. Holmes, eds., "The Alkaloids," Vol. 2, Academic Press, Inc., New York, N. Y., 1952, pp. 522–524.

(3) K. Wiesner and Z. Valenta in L. Zechmeister, ed., "Fortschritte der Chemie Organischer Naturstoffe," Vol. 16, Springer, Vienna, 1958, p. 26 ff.

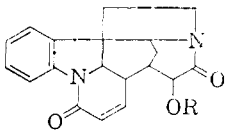
(4) W. J. Brehm, Ph.D. Thesis, Harvard, 1948.

TABLE I

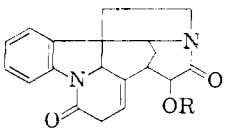
CARBONYL ABSORPTION OF SEVERAL STRYCHNINE DERIVATIVES

	Wave length, μ	
	$CHCl_3$ soln. (6 mg./ml.)	KBr disk
Oxostrychnine	5.88, 5.95	5.82, 5.97
Dihydroöxostrychnine	5.91-5.96	5.85, 5.97
Oxostrychnineglycol monoacetate	5.72, 5.89, 5.97	5.75, 5.85, 6.02-6.07
Strychninolone-*a* acetate	5.76, 5.96-5.98	
Strychninolone-*b*	5.95-5.96	
Strychninolone-*b* acetate	5.76, 5.96-5.98	

potassium bromide, 5.92 μ in Nujol, 5.88 μ in chloroform), which was suggestive of a five-membered lactam. Table I includes available data of oxostrychnine, its dihydro derivative, oxostrychnineglycol monoacetate (Vb), strychninolone-*a* acetate (IIIb),[5] strychninolone-*b* (IVa)[5] and strychninolone-*b* acetate (IVb).[5]



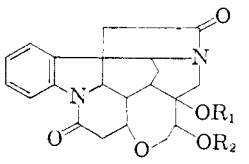
IIIa, R = H
b, R = Ac



IVa, R = H
b, R = Ac

None of the six-membered lactams show a band comparable to the 5.88 μ band of oxostrychnine. Wenkert and co-workers,[6] on the other hand, report lactam absorption of several N-methyloxindoles at 5.82-5.83 μ (in carbon tetrachloride), and Pelletier and Jacobs[7] show that the γ-lactam in α-oxoatisine absorbs at 5.88 μ (potassium bromide). The 5.88 μ band of oxostrychnine is therefore ascribed to a five-membered lactam, thereby providing excellent physical evidence for the 18-oxo structure. A puzzling point in this connection is the infrared spectrum of the simplest five-membered analog, 1-methyl-2-pyrrolidinone, which when measured as a liquid film[8] exhibits a medium band at 5.74 μ and a strong broad band at 5.94-6.04 μ.

In order to obtain chemical evidence for the probable 18-oxo structure, oxostrychnine was subjected to oxidation with potassium permanganate in acetone, a reagent with which Leuchs[9] and later Prelog[10]—to cite only two of the many examples—had cleaved ring VII of strychnine. In the case of oxostrychnine this reaction and more drastic variations thereof led to a neutral compound, m.p. 300–305°, $C_{21}H_{22}N_2O_5$, to which the 21,22-diol structure Va was assigned.



Va, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = Ac$

Attempts to cleave the glycol Va were made with a large variety of cleavage reagents: periodic acid, lead tetraacetate, sodium bismuthate and the perchlorato-cerate complex. All attempts at simple cleavage failed, leading either to recovery of glycol or to intractable resins. The latter course is perhaps not surprising when one considers that the C-22 secondary hydroxyl would be transformed into the reactive $-O-CH_2-CHO$ grouping. Experiments designed to oxidize the secondary hydroxyl group to a carbonyl function, to be followed by cleavage of the ensuing ketol, also failed. The Oppenauer method, oxidation with N-bromosuccinimide or with chromium trioxide in acetic acid, led to glycol recovery. A glycol monoacetate (Vb), m.p. 285–288°, $C_{23}H_{24}N_2O_6$, could be prepared, but this acetate could not be cleaved. Nor would this compound undergo the Serini rearrangement to the 22-oxo compound, as might have been expected from Wagle's work[11] in the steroid field.

The glycol Va was assumed to have the *cis* configuration by virtue of the method by which it was prepared. It was deemed desirable to prepare the *trans*-glycol *via* the epoxide in order to ascertain whether the *trans*-glycol could be cleaved more readily. Perbenzoic acid oxidation afforded oxostrychnine epoxide, m.p. 321–324°, $C_{21}H_{20}N_2O_4$, in good yield, but the epoxide was not affected by prolonged heating under reflux with dilute sulfuric acid in dioxane.

Degradation of oxostrychnine was finally brought about by ozonization, a method which had produced few useful results in previous studies of strychnine and its derivatives.[12] When oxostrychnine was ozonized below 0°, only starting material was recovered. Ozonization in glacial acetic acid, followed by oxidation of the product with hydrogen peroxide, yielded amorphous solid material. The mixture could be separated by chromatography or, as was found subsequently, by fractional crystallization from chloroform. The chloroform-soluble compound, m.p. 321–324°, after recrystallization from ethanol was readily shown to be oxostrychnine epoxide by direct comparison with an authentic sample prepared by perbenzoic acid oxidation (*vide supra*).[13] The major, chloroform-insoluble product of the reaction crystallized from methanol in transparent plates and melted at 288–292° on slow heating or at 314–317° when the capillary was introduced above 250°. The ultraviolet spectrum of this compound (λ_{max} 252 mμ, log Σ 4.11; inflection at 278 mμ, log Σ 3.56) proved that the N-acylaniline system of strychnine was still intact. The infrared spectrum exhibited the two lactam bands of oxostrychnine and a new band in

(5) Spectral data of the strychninolones were kindly supplied by Prof. R. B. Woodward.

(6) E. Wenkert, A. K. Bose and T. L. Reid, THIS JOURNAL, **75**, 5514 (1953).

(7) S. W. Pelletier and W. A. Jacobs, *ibid.*, **78**, 4139 (1956).

(8) S. P. Sadtler and Son, Inc., Infrared Spectrogram 6528.

(9) H. Leuchs, *Ber.*, **41**, 1711 (1908); H. Leuchs and G. Schwaebel, *ibid.*, **46**, 3693 (1913).

(10) V. Prelog and M. Kocór, *Helv. Chim. Acta*, **30**, 360 (1947).

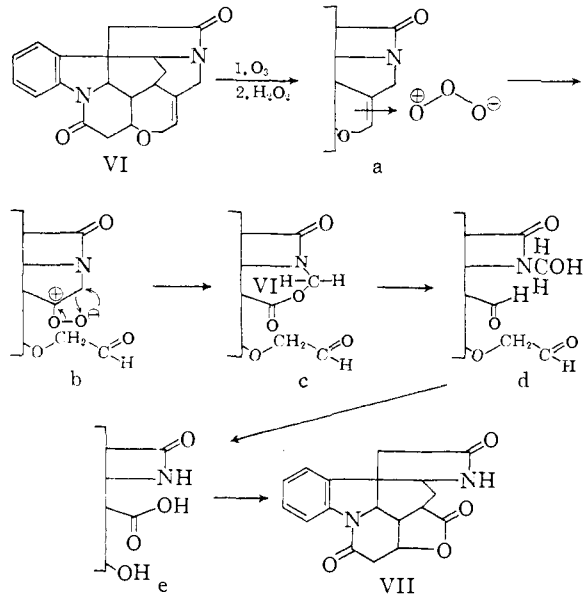
(11) S. S. Wagle, Ph.D. Thesis, Harvard, 1950.

(12) See, for example, H. Leuchs and K. Taube, *Ber.*, **58**, 1729 (1925); M. Kotake, T. Sakan and S. Kusumoto, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **35**, 415 (1939); R. Huisgen and H. Wieland, *Ann.*, **555**, 9 (1943); V. Prelog and M. Kocór, *Helv. Chim. Acta*, **31**, 237 (1948).

(13) The formation of a stable epoxide on ozonization was recently observed with a highly hindered olefin by Bartlett [P. D. Bartlett and M. Stiles, THIS JOURNAL, **77**, 2806 (1955)].

the carbonyl region at 5.65 μ which was indicative of a γ-lactone grouping. Another new band at 3.08 μ indicated the presence of an >NH linkage. The compound was neutral, but dissolved slowly in dilute acid or base. It was saturated to dilute permanganate solution. Its empirical formula was $C_{18}H_{16}N_2O_4$, which corresponds to a formal loss of C_3H_6 and a gain of H_2O from the starting material.

In order to arrive at a reasonable structure for the lactone it is profitable to consider the ozonization reaction in some detail. The possibility that the epoxide might be the primary product which subsequently rearranged with the loss of carbon seems to be without precedent. Bailey in his recent review[14] pointed out that epoxide rearrangements under ozonization conditions have led to ketones, acids or enols *without loss of carbon*. The lactone would therefore have to arise as a separate product of the ozonization for which the following mechanism may be written.



Electrophilic attack of ozone may take place at C-21 or C-22 since both carbons are in β-position to a hetero atom. For the ensuing carbonyl compound and zwitterion according to the Criegee mechanism[15] (b) as shown, rather than an alternate formulation, $>NCH_2CO-$ and $-OCH_2\overset{\oplus}{C}HO\overset{\ominus}{O}$ are chosen since (b) involves a tertiary and the alternate formulation a secondary carbonium ion.[16]

Rearrangement of the zwitterion to form (c) is in accord with the behavior of systems having a β-nitrogen atom. Analogous cases which were studied by Young and co-workers[17] were found to lose carbon monoxide. In the case of intermediate (c) ring VI would be cleaved leading to (d) which then would lose a one-carbon fragment under the influence of hydrogen peroxide. The fate of the glycolic aldehyde (or acid) side chain need not be questioned. While this side chain is commonly lost in basic medium, it was found by Leuchs[18] that it may be cleaved in acid medium as well. Lactone VII would be the observed product of this series of changes.

Thus it appears likely that lactone VII arose from 18-oxostrychnine by ozonization and oxidation with hydrogen peroxide. The alternate possibility that it might have arisen from 20-oxostrychnine cannot be dismissed entirely. Cleavage of ring VI with loss of one carbon would certainly occur with ease. So would the cleavage and loss of the glycolic acid side chain. The C-18 carbonyl function would, and conceivably could, arise from the amine under the oxidative conditions of the reaction.

Additional evidence for the structure of lactone VII was obtained from a series of ring opening experiments. When the lactone was left in contact with sodium methoxide in a large excess of methanol, an unsaturated acid (VIII), m.p. 299–302°, was isolated. On the basis of its ultraviolet spectrum (Fig. 1) as compared with that of strychninolone-*a*

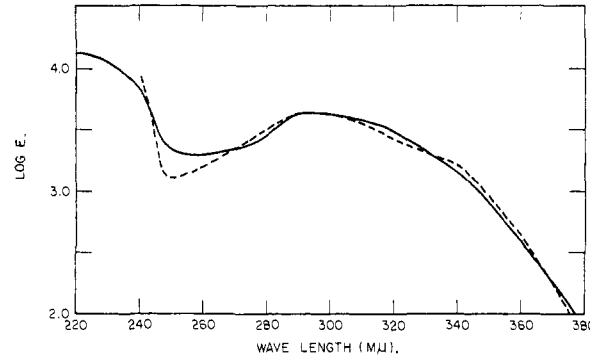
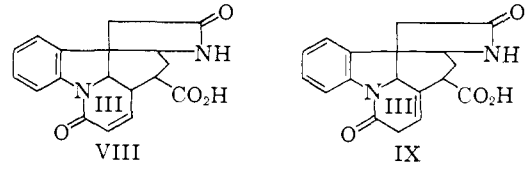


Fig. 1.—Ultraviolet spectra: ———, acid VIII; - - - -, strychninolone-*a* IIIa.

(IIIa),[19] the α,β-unsaturated lactam structure was assigned to it. When the base treatment was



carried out for forty-eight hours, a different acid (IX), m.p. 255–259°, was isolated. The ultraviolet spectrum of this acid is virtually unchanged from that of the parent lactone VII (Fig. 2). This would indicate that the α,β-unsaturated lactam of ring III was isomerized to the sterically more favorable β,γ-isomer. A thorough study by Leuchs[20] showed that in the related strychninolone series the α,β-double bond of the *a*-series is easily shifted to the β,γ-position of the *b*-series.

The mechanism by which 18-oxostrychnine is formed from strychnine-N-oxide is at present obscure. A study which was carried out subse-

(14) P. S. Bailey, *Chem. Revs.*, **58**, 925 (1958).

(15) R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957).

(16) The alternate zwitterion, $-OCH_2\overset{\oplus}{C}HO\overset{\ominus}{O}$, would doubtless be rearranged and cleaved to -OH. In order to account for the loss of carbon from ring VI the oxidation of $>NCH_2CO-$ to $>NCOCO-$ and subsequent cleavage would have to be postulated.

(17) W. G. Young, A. C. McKinnis, I. D. Webb and J. D. Roberts, THIS JOURNAL, **68**, 293 (1946).

(18) H. Leuchs and P. Reich, *Ber.*, **43**, 2417 (1910).

(19) V. Prelog, S. Szpilfogel and J. Battegay, *Helv. Chim. Acta*, **30**, 366 (1947).

(20) H. Leuchs and W. Bendixsohn, *Ber.*, **52**, 1443 (1919).

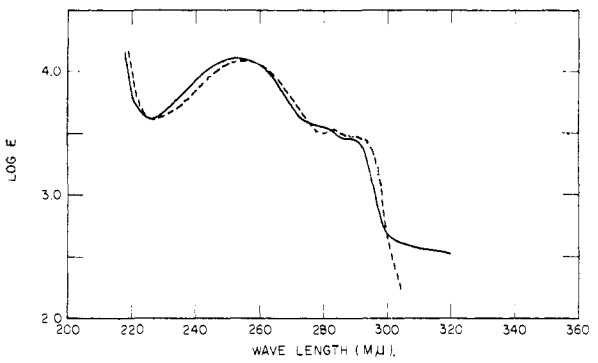


Fig. 2.—Ultraviolet spectra: ———, lactone VII; – – – –, acid IX.

quently by Scheuer and co-workers[21] with a simple model compound failed to shed light on this point. Additional data are needed before a satisfactory mechanism can be presented.

Experimental[22]

Oxystrychnine (VI).—Strychnine-N-oxide was prepared by Brehm's[4] method. The oxidation was carried out by dissolving 14.4 g. (0.0411 mole) of the N-oxide in 80 ml. of boiling water and adding 12.1 g. (0.0411 mole) of potassium dichromate in 110 ml. of boiling water with stirring. Shortly after addition of the oxidant the golden-yellow solution turned dark and a gray-brown solid began to precipitate. Stirring and heating was continued for 30 min. The mixture was cooled to room temperature and filtered. The solid was washed thoroughly with hot water and dried: 14.2 g. of light brown powder.

The powder was treated with 60 ml. of hot 1 *N* HCl and filtered while hot. The precipitate was washed with another 60-ml. portion of hot acid. The acidic filtrate was made alkaline with concd. NH_3 solution and yielded 6.75 g. (46.9%) of crude pseudostrychnine. The neutral precipitate was dried: 6.75 g. (47.2%) of crude oxostrychnine. A pure product was obtained after recrystallization from chloroform–ligroin and then from MeOH; $[\alpha]^{26}D$ −31.9° (3% in $CHCl_3$)[4]; ultraviolet spectrum (absolute EtOH), λ_{max} 256 mμ, log ε 4.03.

Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.22; H, 5.98; N, 8.25.[4]

Dihydrostrychnidine.—Dihydroöxostrychnine, m.p. 321–324°, was prepared from oxostrychnine as described by Brehm.[4] One gram (0.0029 mole) of this compound dissolved in 225 ml. of dry tetrahydrofuran was added during 3 hours to 1 g. (0.026 mole) of $LiAlH_4$ in 100 ml. of dry ether with refluxing and stirring. Stirring and refluxing was continued for 33 hours. The opaque solution was cooled in an ice-bath; water was added dropwise followed by acidification with 6 *N* H_2SO_4. Acidic and/or neutral by-products were extracted with ether. The aqueous acidic phase, which was rapidly assuming the cherry-red color characteristic of strychnidine derivatives, was made alkaline with 10% NaOH solution. The resulting cream-colored suspension was extracted with ether. The ethereal solution was dried over NaOH pellets and concentrated. On scratching, crystallization set in and 240 mg. (26%) of product was collected. Recrystallization from EtOAc brought the m.p. to 216–219° after sintering from 180° on.

A comparison sample was prepared by palladium-on-charcoal hydrogenation of strychnidine[23]: m.p. 212–215° after sintering. The mixed m.p. of the two substances was 210–214° and their infrared spectra were identical.

18-Oxostrychninediol-21,22. Method *a*.—Reagent grade acetone was refluxed for 24 hours with powdered $KMnO_4$ and distilled. Oxostrychnine (1.75 g., 0.005 mole) was dissolved in 675 ml. of acetone. To the solution was added with stirring in 3 portions 1.6 g. (0.01 mole) of finely powdered $KMnO_4$. The first portion was used up within 40 min.; the second after 8.5 hours; and the third was not completely decolorized after 75 hours when the reaction was discontinued. Throughout the reaction the temperature was maintained at 23 ± 1°. Manganese dioxide was filtered off and suspended in 200 ml. of H_2O. Sulfur dioxide was bubbled through the suspension until all MnO_2 was reduced. The white precipitate which became apparent during the reduction was collected and recrystallized from H_2O, 427 mg. Extraction of the aqueous acidic solution with 5 portions of $CHCl_3$ furnished after drying over Na_2SO_4 and removal of the solvent another batch of the solid: 465 mg. after recrystallization from H_2O; total yield, 47%. The compound crystallized in transparent plates with parallel cleavage lines, m.p. 300–305°, after darkening from 180° on.

Method *b*.—Oxostrychnine (3.48 g., 0.01 mole) was dissolved in 200 ml. of pyridine and 200 ml. of water. With stirring and cooling to 0–10°, 3.12 g. (0.02 mole) of finely powdered $KMnO_4$ was added during 1 hour. No MnO_2 precipitated even on warming to 40° for 30 min. Addition of 20 ml. of 6 *N* NaOH finally resulted in precipitation. The precipitate was filtered and was washed well with hot water. The washings were combined with the light brown filtrate and the aqueous pyridine was distilled *in vacuo*. The residual liquid was acidified with 6 *N* HCl. The crystalline precipitate was collected, washed with cold water and dried: 2 g. of glycol (52%), m.p. 290–295°.

Anal.[24] Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 65.74; H, 5.72; N, 7.59.

The glycol was soluble in hydroxylic solvents, insoluble in ether, benzene or acetone. The infrared spectrum showed a hydroxyl band at 3.07 μ (Nujol mull) beside the two unchanged lactam bands.

18-Oxo-21-hydroxy-22-acetoxystrychnine.—Oxostrychninediol (200 mg., 0.00052 mole) was dissolved in 25 ml. of Ac_2O and 4 ml. of pyridine and allowed to stand at room temperature for 28 hours. The solvent was removed *in vacuo* at room temperature. The dry residue was taken up in $CHCl_3$, treated with charcoal and concentrated to a small bulk. On addition of a few drops of ligroin, rosettes of needles appeared. After standing in the cold overnight the material was collected and dried: 168 mg. (75.5%), m.p. 279–282° after sintering to clusters of slender needles *ca.* 250°. Recrystallization from chloroform–ligroin furnished transparent rods, m.p. 285–288°, after sintering to needles.

Anal. Calcd. for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.72; H, 5.87; N, 6.41.

The infrared spectrum ($CHCl_3$ solution) showed a hydroxyl band at 2.87 μ and a carbonyl band at 5.72 μ beside the two unchanged lactam bands at 5.90 and 6.03 μ.

18-Oxostrychnine-21,22-epoxide.—Oxostrychnine (3.48 g., 0.01 mole) was dissolved in 50 ml. of $CHCl_3$ and cooled to 0°. To this solution was added 20 ml. of a chloroform solution containing 0.011 mole of perbenzoic acid. The flask was kept at 6° and the consumption of perbenzoic acid was followed by titration of aliquots. After 55 hours 7.8% of perbenzoic acid remained and the reaction was discontinued. After washing with 25 ml. of 2 *N* NaOH followed by 45 ml. of H_2O in 4 portions, the $CHCl_3$ solution was dried over Na_2SO_4 and the solvent removed almost completely. Scratching of the residual concentrate produced chunky prisms, m.p. 313–316° dec., 2.45 g. (67%). Repeated recrystallization from EtOH raised the m.p. to 321–325°.

Anal. Calcd. for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 68.83, 69.19; H, 5.53, 5.44; N, 7.67.

The compound was saturated to 1% $KMnO_4$ solution and had an infrared spectrum ($CHCl_3$) very similar to that of oxostrychnine. However, the two lactam bands remained unresolved and the γ-lactam band was slightly displaced toward longer wave length. The most prominent new band in the region characteristic for epoxides was at 7.7 μ with only a weak band at 7.9 μ, where most epoxides absorb.[25]

Lactone VII.—Oxostrychnine (1.74 g., 0.005 mole) was dissolved in the minimum amount (85 ml.) of glacial HOAc.

(21) P. J. Scheuer, W. I. Kimoto and K. Ohinata, THIS JOURNAL, **75**, 3029 (1953).

(22) Microanalyses by S. M. Nagy, Massachusetts Institute of Technology, unless otherwise noted. Melting points on a Kofler hot-stage with exceptions noted, and uncorrected.

(23) This sample was generously supplied by Dr. M. S. Simon, who obtained it by electrolytic reduction of strychnine.

(24) Carried out by Mr. W. Manser, Zürich, Switzerland.

(25) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., Ltd., Loudon, 1954, p. 102 ff.

The solution was cooled to 10–15° and oxygen containing ozone (0.0051 mole of ozone per hour by thiosulfate titration of liberated iodine) was bubbled through the solution for 2 hours (100% excess). Two such batches were combined and a solution of 25 ml. of 30% H_2O_2 in 100 ml. of H_2O was added to it. The resulting yellow solution was left at room temperature for 4 hours and was then warmed on the steam-bath for 2 hours. The solvent was distilled *in vacuo* until 25 ml. of yellow oil remained. To this oil was added 45 ml. of H_2O and 5 ml. of 30% H_2O_2. After the solution was allowed to stand overnight at room temperature a solid deposit was formed. The solid was collected, washed well with water containing a little sodium bisulfite and dried, 1.7 g. The filtrate was treated with solid sodium bisulfite until all hydrogen peroxide was reduced and was extracted with 150 g. of $CHCl_3$ in 6 portions. After drying of the $CHCl_3$ extract over Na_2SO_4 and removal of the solvent, there was left 0.2 g. of crystalline solid; combined yield, 1.9 g. (58.5%). The combined solids were treated with a small amount of $CHCl_3$. From these $CHCl_3$ washings there was obtained 0.1 g. of a substance, m.p. 321–325°, which was identified as oxostrychnine epoxide by comparison of its infrared spectrum with that of an authentic sample. The residual solid melted at 285–292°. It was recrystallized 3 times from absolute MeOH, m.p. 288–292°, when heated on a Kofler block, or 314–317° when the capillary was placed in the bath above 250°.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.06, 65.99, 66.29; H, 4.93, 4.93, 4.75; N, 8.26, 8.40.

The substance was saturated to 1% $KMnO_4$, was insoluble in 10% $NaHCO_3$, but dissolved slowly in 10% NaOH or 6 *N* HCl; $[\alpha]^{24}D$ +139 ± 2° (*c* 1.288, glac. HOAc); ultraviolet spectrum (absolute EtOH): λ_{max} 252 mμ, log ε 4.11. The infrared spectrum (Nujol mull) had bands at 3.08 and 5.65 μ in addition to the two lactam bands.

Acid VIII.—To 20 ml. of absolute MeOH containing 0.61 mmole of Na was added 200 mg. (0.62 mmole) of lactone VII. Within a few minutes the lactone dissolved to form a yellow solution. After standing for one hour the solvent was removed *in vacuo* at room temperature. The residual solid was dissolved in 5 ml. of H_2O and extracted with $CHCl_3$. This extract when worked up contained only a slight oily film. The aqueous basic solution was cooled and acidified by dropwise addition of 1 *N* HCl. The resulting white precipitate was filtered off, washed with H_2O and dried. It was crystallized from MeOH, forming fern-like leaves which sintered to fine needles above 200° and melted at 279–285°. After further recrystallization from MeOH the m.p. was raised to 299–302°. The substance liberated CO_2 from 10% $NaHCO_3$ and was unsaturated to 1% $KMnO_4$; mol. wt. calcd. for monobasic acid, 324; found by titration in 50% EtOH against 0.01116 *N* NaOH: mol. wt., 327 ± 5; ultraviolet spectrum (absolute EtOH): λ_{max} 292 mμ, log ε 3.61 (see Fig. 1).

Acid IX.—To a solution of 0.30 mmole of Na in 10 ml. of absolute MeOH was added 100 mg. (0.31 mmole) of lactone VII. The yellow solution was left at room temperature for 46 hours. The solution was worked up as above. No basic or neutral products were isolated and acidification produced only a small amount of yellow gum which was insoluble in $CHCl_3$. Extraction of the aqueous acidic phase with 60 ml. of $CHCl_3$ in 4 portions, followed by drying over Na_2SO_4 and removal of the solvent, left a transparent glassy residue. After drying *in vacuo*, this glass could be crystallized from MeOH furnishing 5.6 mg. of rectangular plates arranged in radial clusters, m.p. 255–259°. The compound dissolved readily in 10% $NaHCO_3$ with evolution of CO_2 and was unsaturated to 1% $KMnO_4$; ultraviolet spectrum (absolute EtOH): λ_{max} 254 mμ, log ε 4.06 (see Fig. 2).

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Structures of Haemanthamine and Crinamine[1]

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Degradative and spectral evidence is presented to show that structures XXVa and XXVIa represent the alkaloids haemanthamine and crinamine, respectively.

The alkaloid haemanthamine (natalensine) ranks second only to lycorine in abundance within the family Amaryllidaceae. It was reported first as a constituent of the *Haemanthus* hybrid "Konig Albert" by Boit.[2] Within the last five years it has been isolated from a number of *Haemanthus*,[3,4] *Narcissus*,[5–8] *Crinum*,[9] *Hippeastrum*,[10,11] *Hymenocallis*[12,13] and *Zephyranthes*[9,10,14] species and from *Calostemma purpureum* R. Br.,[13] *Elisena longipetala* Lindl.,[13] *Galanthus elwesii* Hook. F.,[14] *Sprekelia formosissima* (L.) Herb.,[14] *Urceolina miniata* (Herb.) Benth. and Hook,[13] and *Vallota purpurea* (Ait.) Herb.[11] In contrast, crinamine, which was isolated first by Tanaka[15] from *Crinum asiaticum* var. *japonicum* Bak., occurs in trace amounts in *Ammocharis coranica* (Ker.) Herb.,[16] *Brunsvigia cooperi* Baker,[17] a few *Crinum* spp.[9,14,16] and *Nerine bowdenii* W. Wats.[18]

The quantity of crinamine at our disposal was so limited that degradation was limited to critical experiments which were performed after the struc-

(1) Paper XIII in a series concerning alkaloids of the Amaryllidaceae; previous paper, H. M. Fales and W. C. Wildman, THIS JOURNAL, **80**, 4395 (1958). Part of the present paper has appeared in communication form: (a) H. M. Fales and W. C. Wildman, *Chemistry & Industry*, 561 (1958); (b) W. C. Wildman and H. M. Fales, THIS JOURNAL, **80**, 6465 (1958).

(2) H.-G. Boit, *Chem. Ber.*, **87**, 1339 (1954).

(3) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 1248 (1955).

(4) F. L. Warren and W. G. Wright, *J. Chem. Soc.*, 4696 (1958).

(5) H.-G. Boit, W. Stender and A. Beitner, *Chem. Ber.*, **90**, 725 (1957).

(6) H.-G. Boit and W. Döpke, *ibid.*, **89**, 2462 (1956).

(7) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 163 (1956).

(8) H.-G. Boit, W. Döpke and A. Beitner, *ibid.*, **90**, 2197 (1957).

(9) H.-G. Boit, W. Döpke and W. Stender, *ibid.*, **90**, 2203 (1957).

(10) H.-G. Boit, W. Döpke and W. Stender, *Naturwissenschaften*, **45**, 390 (1958).

(11) H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956).

(12) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).

(13) H.-G. Boit and W. Döpke, *Chem. Ber.*, **90**, 1827 (1957).

(14) H.-G. Boit and H. Ehmke, *ibid.*, **88**, 1590 (1955).

(15) K. Tanaka, *J. Pharm. Soc. Japan*, **57**, 139 (1937).

(16) L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, **77**, 1253 (1955).

(17) L. J. Dry, M. Poynton, M. E. Thompson and F. L. Warren, *J. Chem. Soc.*, 4701 (1958).

(18) The alkaloids of *N. bowdenii* will be discussed in a future paper of this series.