66271-02-1; Boc-L-Ser(Bzl)-OCH_2PhCH_2COOH CHA salt, 66271-04-3; Boc-L-Met-OCH_2PhCH_2COOH CHA salt, 66271-06-5; Boc-L-Lys(Z)-$OCH_2C_6H_4$-*p*-CH_2COOH_2COPh, 66271-07-6; Boc-L-Asp(OBzl)-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-08-7; Boc-L-Ser(Bzl)-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-09-8; Boc-L-Met-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-10-1; Boc-Val-$OCH_2C_6H_4$-*p*-$CH_2CONHCH_2Ph$, 66271-11-2; Boc-L-Val DCHA salt, 16944-17-5; Boc-L-Val-4-$(OCH_2)PhCH_2CO$-4-$(OCH_2)PhCH_2COOH$, 66271-12-3; *N*-hydroxysuccinimide, 6066-82-6; 4-(bromomethyl)-phenylacetic, acid *N*-hydroxysuccinimide ester, 66271-13-4; Boc-Valyl-4-(oxymethyl)phenylacetic acid *N*-hydroxysuccinimide ester, 66271-14-5; 4-(acetoxymethyl)phenylacetic acid, 61165-81-9; Boc-Gly Cs salt, 42538-64-7; Boc-L-Phe Cs salt, 42538-61-4; Boc-L-Val Cs salt, 42538-62-5; Boc-Leu, 13139-15-6; L-Leu-L-Val, 13588-95-9; Boc-Gly, 4530-20-5; Boc-L-Ala, 15761-38-3; Leu-Ala-Gly-Val, 17195-26-5; benzylamine, 100-46-9; *p*-nitrophenyltrifluoroacetate, 658-78-6; butylamine, 109-73-9; Boc-Valine butylamide, 66271-15-6; Boc-Gly-NHBzl, 19811-52-0.

References and Notes

(1) Supported in part by Grant AM 01260 from the U.S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation. M. E. was the recipient of a fellowship from the Deutsche Forschungsgemeinschaft.
(2) Abbreviations used: Boc, *tert*-butyloxycarbonyl; CHA, cyclohexylamine; DCC, dicyclohexylcarbodiimide; DCHA, dicyclohexylamine; DMF, *N,N*-dimethylformamide; KelF-g-styrene, radiation-induced graft polymer of styrene on solid poly(trifluorochloroethylene); NMR, nuclear magnetic resonance; Pam, phenylacetamidomethyl; PLC, preparative layer chromatography; R, resin; TLC, thin-layer chromatography. Other nomenclature and symbols follow the Tentative Rules of the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967); **247**, 977 (1972).
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Synthesis of Oxysanguinarine

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Base-catalyzed condensation of the homophthalate ester **14** with the imine **15** supplied the lactam amide **16.** This compound was saponified to the acid **17** which was homologated by an Arndt–Eistert sequence to the ester **19.** Hydrolysis and acid-catalyzed cyclization provided the keto lactam **21.** Acid dehydration of the lactam alcohol **22,** derived from reduction of **21,** was accompanied by air oxidation to provide the desired alkaloid oxysanguinarine (**23**).

A number of aromatic benzophenanthridine alkaloids possess interesting biological activity. Nitidine (**1**) and fagaronine (**2**) have shown anticancer activity,[1] while sanguinarine (**3**), chelerythrine (**4**), and chelirubine (bocconine) (**5**) are nematocides.[2]

The aim of the present study was to synthesize a naturally occurring aromatic benzophenanthridine, namely oxysanguinarine (**23**),[3] through a route based on the previously reported finding that base-catalyzed condensation of diethyl glutaconate with *N*-benzylidenemethylamine yields lactam **6**.[4] The first hurdle was to prepare the homophthalic ester **14,** which was to be condensed with piperonylidenemethylamine (**15**) to afford such lactams as **16, 17,** or **18.** Homologation of the acid **17** to the acid **20,** followed by intramolecular Friedel–Crafts acylation, would then afford keto lactam **21,** which would be readily convertible into oxysanguinarine (**23**).

An eight-step sequence to the homophthalic ester **14** was developed which parallels to some extent, but is superior to, that recorded by Haworth and co-workers for the construction of the corresponding homophthalic acid **13.**[5] Doebner con-

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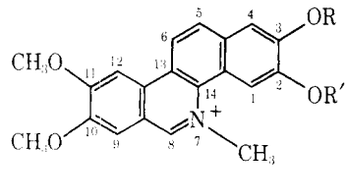
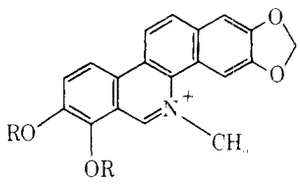
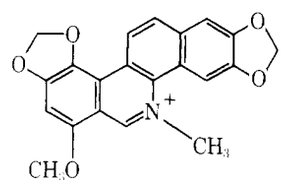


1. R + R′ = CH_2
2. R = H; R′ = CH_3

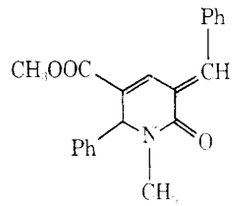


3. R + R′ = CH_2
4. R = CH_3



5

densation of piperonal with malonic acid in refluxing pyridine gave the cinnamic acid **7** in 90% yield. Catalytic hydrogenation of the sodium salt of **7** in water using 5% palladium on carbon furnished, upon acidification, piperonylacetic acid (**8**) in 95% yield. Attempted cyclodehydration of the bromo acid **9**, derived from bromination of **8** in acetic acid, by the Haworth procedure (P_2O_5 in benzene)[5] involved a tedious workup and resulted in a yield of <20% of the hydrindone **10**, so that a



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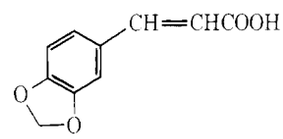

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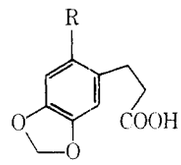
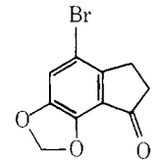


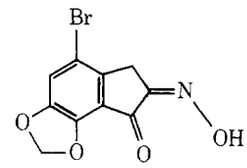
8. R = H
9. R = Br



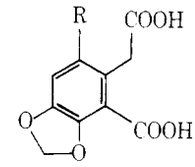
10

method for achieving this transformation in higher yield was sought. Phosphorus oxychloride, polyphosphoric acid, polyphosphate ester,[6] super polyphosphoric acid,[7] and phosphorus oxychloride/zinc chloride[8] were all tried as cyclizing agents and found to be unsatisfactory. However, when the reaction was run using phosphorus pentoxide in refluxing chlorobenzene under conditions of relatively high dilution, the desired hydrindone **10** was obtained in 40% yield. This material was then nitrosated[9] using isoamylnitrite to afford the α-oximino ketone **11** in 85% yield.

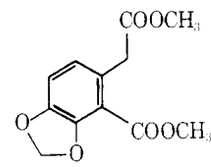
The second-order Beckmann rearrangement of the α-oximino ketone **11** to the bromo diacid **12** had been reported to proceed in 75% yield.[5] However, repeated attempts to duplicate this procedure invariably gave yields on the order of 20%, while the reaction workup was troublesome due to formation of emulsions. Several alternative procedures were investigated, and the best method found involved reaction of **11** in a Schotten–Baumann procedure using *p*-toluenesulfonyl chloride and aqueous sodium hydroxide.[10] The transitory nitrile was immediately hydrolyzed by refluxing the strongly basic reaction mixture until the evolution of ammonia had subsided. Upon acidification, the desired bromo diacid **12** was isolated (51%). Debromination with sodium amalgam then afforded the known 3,4-methylenedioxyhomophthalic acid **13**[5] in 83% yield, or in 8.3% overall yield from piperonal. Fischer esterification of this diacid gave rise to the corresponding diester **14**. The second precursor required for the condensation–cyclization step to the fused lactam was piperonylidenemethylamine (**15**), which was readily prepared



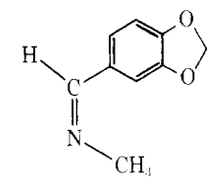
11



12. R = Br
13. R = H



14

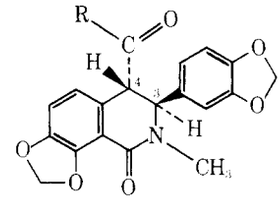


15

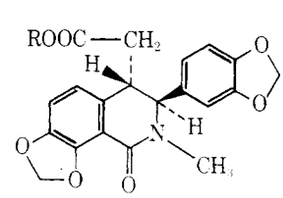
through condensation of piperonal with methylamine.

Condensation of the diester **14** with the Schiff base **15** required refluxing for a week in a sodium methoxide–methanol solution. A requisite added ingredient for this condensation was methylamine gas, which was passed periodically through the mixture. Lactam **16** was thus isolated in 61% yield. The ^1H NMR spectrum of **16** shows the expected signals for two *N*-methyl groups, two methylenedioxys, and five aromatic protons. Present also are two broad peaks at δ 4.17 and 5.42 for the methine protons at C-4 and C-3, respectively. Both of these peaks are resolved into doublets, $J_{3,4}$ = 1 Hz.

Hydrolysis of **16** in 10% aqueous potassium hydroxide afforded the lactam acid **17** in 70% yield. The ^1H NMR spectrum shows only one *N*-methyl signal at δ 3.47, while $J_{3,4}$ = 0 Hz, indicating that the dihedral angle between the hydrogens at C-3 and C-4 must be close to 90°.[11] The corresponding methyl ester **18** exhibits $J_{3,4}$ = 1.5 Hz. Attempts to epimerize the C-4



16. R = $NHCH_3$
17. R = OH
18. R = OCH_3



19. R = CH_3
20. R = H

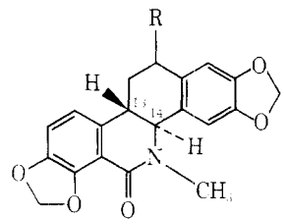
center of **18** with sodium methoxide in methanol gave, as expected, material indistinguishable from **18**, so that the molecule must exist in the thermodynamically more stable trans configuration.

Arndt–Eistert homologation of the lactam acid **17** provided ester **19** (60%), which was saponified to the acid **20**. The C-3 proton in the ^1H NMR spectrum of **20** appears as a broad singlet with no discernible splitting, which corresponds to a 90° angle between the C-3 and C-4 protons, so that these hydrogens also must be trans to each other.[11]

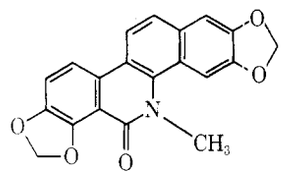
A variety of methods for the cyclodehydration of the acid **20** to the ketone **21** were explored, including phosphorus pentoxide in benzene and in chlorobenzene, polyphosphoric acid by itself and in benzene, super polyphosphoric acid,[7] phosphorus oxychloride, phosphorus oxychloride/zinc chloride,[8] and polyphosphoric ester in chloroform.[6] None of these methods proved satisfactory. The cyclodehydration was then

attempted using a mixture of methanesulfonic acid and phosphorus pentoxide.[12] Under these relatively mild conditions, the desired ketone **21** was generated in 44% yield. The ^1H NMR spectrum of this product shows only four aromatic protons, and the signal for H-14 appears as a doublet, $J_{13,14}$ = 11.5 Hz. This large J value is clearly indicative of a trans diaxial hydrogen relationship.[11]

Sodium borohydride reduction of ketone **21** led to alcohol **22**. Dehydration of this compound using *p*-toluenesulfonic



21, R = =O
22, R = OH



23

acid was accompanied by air oxidation so that oxysanguinarine (**23**) was obtained directly from this step. This material was identical with a sample of oxysanguinarine derived from ferricyanide oxidation of sanguinarine (**3**).[14]

The present synthetic method can be readily adapted to the preparation of such alkaloids as nitidine (**1**) and fagaronine (**2**), since aromatic benzophenanthridine lactams (oxybenzophenanthridenes) are known to be convertible into aromatic benzophenanthridine salts by reduction with lithium aluminum hydride followed by mercuric acetate oxidation.[13]

Experimental Section

Standard Procedures. All melting points were taken on a melting point block and are uncorrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Thin-layer chromatography was on Brinkmann silica gel F-254 plates (0.25-mm thick). Visualization was accomplished by shining UV light on the plates, or by spraying with chromotropic acid reagent. ^1H NMR spectra are in $CDCl_3$ with Me_4Si as internal standard unless specified otherwise.

4-Bromo-6,7-methylenedioxy-1-hydrindone (10). A suspension of 73 g (0.51 mol) of P_2O_5 in 2.1 L of chlorobenzene was refluxed with rapid mechanical stirring. **9**[5] (60 g, 0.22 mol) was added, the mixture turning brown. Refluxing was continued for 2 h. The solution was poured into dilute aqueous NaOH. Workup led to 23 g (40%) of tan prisms: mp 197–199 °C (lit. mp 197–199 °C).[5]

4-Bromo-6,7-methylenedioxy-2-oximino-1-hydrindone (11). To a warm solution of 10 g (39 mmol) of **10** in benzene was added 15 g (0.128 mol) of isoamyl nitrite and 10 mL of concentrated HCl. The mixture was stirred for 2 h at 50 °C. The bright yellow crystals which separated on cooling were collected, washed with methanol, and dried to give 9.48 g (85%) of bright yellow powder: mp 240 °C dec (lit. mp 240 °C dec).[5]

6-Bromo-3,4-methylenedioxyhomophthalic Acid (12). A solution of 14.2 g (0.05 mol) of **11** in 300 mL of cold aqueous NaOH was treated with 55 g (0.26 mol) of *p*-toluenesulfonyl chloride, and the mixture was stirred overnight in a cold water bath. To the resulting black solution, 10 g (0.25 mol) of NaOH was added, and the mixture refluxed 24 h. The cooled reaction mixture was acidifed and extracted with ethyl acetate. The organic extracts were washed with dilute acid, dried, filtered, and evaporated. The dark residue was dissolved in hot methanol, treated with charcoal, and filtered through a Celite pad. The methanol solution was concentrated to 75 mL and 300 mL of hot water was added. Most of the methanol was boiled off. The diacid crystallized upon cooling: 7.73 g (51%); mp 215 °C dec (lit. mp 215 °C dec).[5]

3,4-Methylenedioxyhomophthalic Acid (13). A solution of 6.0 g (20 mmol) of **12** in 200 mL of 1% aqueous NaOH was added to 200 g (0.26 mol of Na metal) of 3% Na/Hg. The temperature was maintained at 90 °C for 16 h. The mixture was filtered, concentrated, and acidified, and the product was collected. The aqueous solution was saturated with NH_4Cl and further extracted with ether. Recrystallization of the combined diacid fractions from hot water gave rise to 3.7 g (83%): mp 201–203 °C (lit. 203–204 °C).[5]

Dimethyl 3,4-Methylenedioxyhomophthalate (14). A solution of 1.0 g (4.4 mmol) of **13** in 50 mL of methanol was saturated with HCl gas and refluxed 16 h. Workup and recrystallization from benzene produced 0.82 g (73%): mp 83–84.5 °C; ν_{max} ($CHCl_3$) 1720 and 1735 cm^{-1}; high-resolution MS calcd for M^+ $C_{12}H_{12}O_6$, *m/e* 252.0623, observed *m/e* 252.0610.

Piperonylidenemethylamine (15). A mixture of 100 g (0.68 mol) of piperonal and 150 g (1.93 mol) of 40% aqueous methylamine was stirred for 3 h and then extracted with ether. The ether solution was dried and evaporated. The residue was placed in a refrigerator where the product crystallized: white needles; 89 g (80%); mp 45–46 °C (lit. mp 46 °C).[15]

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-(*N*-methyl)carboxamide-7,8-methylenedioxy-3,4-dihydroisoquinoline (16).** A sodium methoxide solution was prepared by dissolving 1.5 g (65 mmol) of Na metal in 150 mL of methanol. Addition of 2.5 g (10 mmol) of **14** and 5.2 g (32 mmol) of **15** to this solution gave a pale yellow mixture which was heated to reflux. The mixture was saturated three times a day with methylamine gas, and a mercury seal was used to keep water and air out. Reflux was continued for 7 days, during which time the mixture turned opaque orange, and a yellow solid precipitated.

The solid was filtered off, washed with methanol, and dried. Recrystallization from methanol supplied 2.3 g (61%) of needles: mp 309–311 °C dec; ^1H NMR (TFA) δ 2.93 (3 H, s, NCH_3), 3.37 (3 H, s, NCH_3), 4.17 (1 H, d, $J_{3,4}$ = 1 Hz, H-4), 5.42 (1 H, d, $J_{3,4}$ = 1 Hz, H-3), 5.93 (2 H, s, OCH_2O), 6.22 (2 H, s, OCH_2O), 6.82 (1 H, d, $J_{5,6}$ = 7 Hz, H-6), 7.07 (1 H, d, $J_{5,6}$ = 7 Hz, H-5), and 6.64–6.77 (3 H, m, H-2′, 5′, 6′); ν_{max} (KBr) 1635 and 1655 cm^{-1}; λ_{max} (EtOH) 214 sh, 236 sh, 288, and 321 nm (log ϵ 4.44, 4.17, 3.80, and 3.65).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 63.05; H, 4.94.

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxy-7,8-methylenedioxy-3,4-dihydroisoquinoline (17).** A suspension of 1.4 g (3.66 mmol) of amide **16** in 200 mL of aqueous 10% KOH was refluxed for 48 h under N_2. Workup and recrystallization from methanol supplied 0.95 g (70%): mp 249–254 °C dec; ^1H NMR (TFA) δ 3.47 (3 H, s, NCH_3), 4.25 (1 H, s, H-4), 5.40 (1 H, s, H-3), 5.98 (2 H, s, OCH_2O), 6.27–6.30 (2 H, d, OCH_2O), 6.66–6.95 (3 H, m, H-2′, 5′, 6′), 6.97 (1 H, d, $J_{5,6}$ = 8 Hz, H-6), and 7.17 (1 H, d, $J_{5,6}$ = 8 Hz, H-5).

Anal. Calcd for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09. Found: C, 61.43; H, 4.33.

Methyl Ester of 17. A solution of 0.4 g (1.1 mmol) of **17** in 150 mL of methanolic HCl was refluxed for 12 h. Workup and recrystallization from methanol generated 0.35 g (85%) of ester **18** as prisms: mp 213–214°C; ^1H NMR δ 3.12 (3 H, s, NCH_3), 3.72 (3 H, s, $COOCH_3$), 3.82 (1 H, d, $J_{3,4}$ = 1.5 Hz, H-4), 5.08 (1 H, d, $J_{3,4}$ = 1.5 Hz, H-3), 5.92 (2 H, s, OCH_2O), 6.17 (2 H, s, OCH_2O), 6.60 (1 H, d, $J_{5,6}$ = 7.5 Hz, H-6), 6.83 (1 H, d, $J_{5,6}$ = 7.5 Hz, H-5), and 6.55–6.80 (3 H, m, H-2′, 5′, 6′); ν_{max} (KBr) 1640 and 1730 cm^{-1}; high-resolution MS calcd for M^+ $C_{20}H_{17}NO_7$, *m/e* 383.1004; observed *m/e* 383.1040.

Methyl Ester of *trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxymethyl-7,8-methylenedioxy-3,4-dihydroisoquinoline (19). A solution of 1.18 g (3.20 mmol) of acid **17** in 50 mL of chloroform was treated with 3 mL (35 mmol) of oxalyl chloride and stirred for 18 h in a flask equipped with a $CaCl_2$ drying tube. The solvent was evaporated to dryness, dry benzene was added, and the solvent was again evaporated. The residue was dissolved in chloroform and cooled in an ice bath. This solution was then added slowly to an ethereal diazomethane solution, and the mixture was left standing overnight in an ice bath. The precipitated crystals collected by filtration amounted to 1.05 g (83%) of crude diazoketone. A suspension of this material and 0.5 g of Ag_2O was heated to reflux in 200 mL of methanol for 1 h. The brown mixture was filtered through a Celite pad. The filtrate was evaporated to yield a brown residue. Crystallization from methanol gave 0.76 g (60%) of crystalline ester: mp 199–201 °C; ^1H NMR δ 3.07 (3 H, s, NCH_3), 2.67 (2 H, m, CH_2COOCH_3), 3.68 (3 H, s, OCH_3), 3.35 (1 H, m, H-4), 4.52 (1 H, d, $J_{3,4}$ = 1 Hz, H-3), 5.82 (2 H, s, OCH_2O), 6.05 (2 H, s, OCH_2O), and 6.32–6.77 (5 H, m, ArH); ν_{max} (KBr) 1643 and 1720 cm^{-1}; λ_{max} (EtOH) 215 sh, 235 sh, 286, and 320 nm (log ϵ 4.44, 4.20, 3.77, and 3.64); high-resolution MS calcd for M^+ $C_{21}H_{19}NO_7$, *m/e* 397.1160; observed *m/e* 397.1159.

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxymethyl-7,8-methylenedioxy-3,4-dihydroisoquinoline (20).** A suspension of 750 mg (1.89 mmol) of **19** in 100 mL of 10% aqueous KOH was refluxed for 3 h and the hot brown solution was treated with decolorizing carbon, filtered through a Celite pad, acidified with concentrated HCl, and extracted with chloroform. The extracts were washed with water and dried and the solvent was evaporated. The

residue was recrystallized from methanol: 615 mg (85%) of prisms; mp 244–246 °C dec; ^{1}H NMR (TFA) δ 3.40 (3 H, s, NCH_3), 2.95 (2 H, dd, CH_2COOH), 3.75 (1 H, m, H-4), 4.95 (1 H, br s, H-3), 5.87 (2 H, s, OCH_2O), 6.17 (2 H, s, OCH_2O), and 6.55–7.08 (5 H, m, ArH); ν_{max} (KBr) 1613, 1715, and 2400–3200 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.65; H, 4.47. Found: C, 62.72; H, 4.40.

***trans*-5,8-Dioxohexahydrosanguinarine (21).** A solution of 5 g (35 mmol) of P_2O_5 in 50 g of methanesulfonic acid was warmed to 45 °C. To this solution was added 500 mg (1.31 mmol) of the above acid **20**, and the mixture was stirred for 2 h while the temperature was maintained at 45 °C. The mixture was poured into ice water and extracted with chloroform. The organic solution was extracted with dilute aqueous NaOH and with water and dried, and the solvent was evaporated. The residue crystallized from ethanol: 210 mg (44%) as tan prisms; mp 277–280 °C dec; ^{1}H NMR (TFA) δ 3.38 (3 H, s, NCH_3), 2.55–4.08 (3 H, m, H-6 and H-13), 5.28 (1 H, d, $J_{13,14}$ = 11.5 Hz, H-14), 5.33 (2 H, s, OCH_2O), 5.38 (2 H, s, OCH_2O), 6.85 (1 H, d, $J_{11,12}$ = 8 Hz, H-12), 7.02 (1 H, s, H-1), 7.15 (1 H, d, $J_{11,12}$ = 8 Hz, H-11), 7.53 (1 H, s, H-4); ν_{max} ($CHCl_3$) 1640 and 1675 cm^{-1}; λ_{max} (EtOH) 213, 237, 273, and 317 nm (log ε 4.48, 4.60, 4.02, and 4.07).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14. Found: C, 65.71; H, 4.01.

5-Hydroxy-8-oxohexahydrosanguinarine (22). A suspension of 100 mg (0.27 mmol) of the above keto lactam **21** and 100 mg (13 mmol) of $NaBH_4$ in 100 mL of isopropyl alcohol was stirred at room temperature for 16 h. The solvent was evaporated and water added to the residue. The mixture was acidified with concentrated HCl and extracted with chloroform. The organic extracts were washed with water and dried and the solvent was evaporated. The residue crystallized from methanol: 75 mg (74%) of white prisms; mp 281–283 °C dec; ν_{max} (KBr) 1620 and 3150–3600 cm^{-1}; λ_{max} (EtOH) 219 sh, 236 sh, 290, and 318 nm (log ε 4.40, 4.17, 3.80, and 3.59).

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66. Found: C, 65.20; H, 4.76.

Oxysanguinarine (23). A solution of 50 mg (0.14 mmol) of lactam alcohol **22** and 10 mg of *p*-toluenesulfonic acid in 50 mL of benzene was refluxed for 16 h. The solvent was evaporated and the residue was dissolved in chloroform. The solution was extracted with 5% aqueous $NaHCO_3$ and dried, and the solvent was evaporated. The residue was subjected to preparative TLC using a 3:97 methanol–chloroform solvent system. A compound with an R_f 0.62, which was significantly higher than the R_f (0.29) of the starting lactam alcohol, was obtained. Recrystallization from ether gave 15 mg (30%), mp 347–349 °C dec, spectrally and chromatographically identical with oxysanguinarine: ν_{max} ($CHCl_3$) 1645 cm^{-1}; λ_{max} (EtOH) 241, 281 sh, 289, 331, 348, 370, and 385 nm (log ε 4.27, 4.61, 4.70, 4.17, 4.18, 4.06, and 4.02).

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Chemistry of Chelocardin. 3.[1] Structure and Synthesis of Isochelocardin

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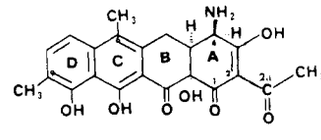
Isochelocardin (**2**), a minor component of the chelocardin fermentation, was shown to be a condensation product of two molecules of chelocardin. Carbobenzoxyisochelocardin acethydrazone (**9**) was synthesized by treatment of carbobenzoxychelocardin with chelocardin acethydrazone, thus confirming the assigned structure. The synthesis of isochelocardin itself is also described.

During the isolation of chelocardin (**1**),[2,3] a potent broad-spectrum antibiotic produced by *Nocardia sulphurea* (NRRL-2822), a contaminant which we designated as isochelocardin, was noted to be present and was subsequently isolated as a hydrochloride salt after chromatographic separation. This compound was present in the isolated chelocardin in proportions ranging from 1 to 3%. In view of the potential



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