Syntheses of Velbanamine and Catharanthine

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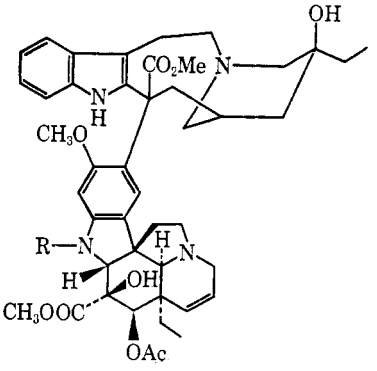
Abstract: The total synthesis of velbanamine (**3**), a degradation product of the oncolytic alkaloids vinblastine (**1**) and vincristine (**2**), is described. An intermediate in this synthesis, namely the pentacyclic lactam **18** has been transformed to the racemate of the naturally occurring alkaloid catharanthine (**33**).

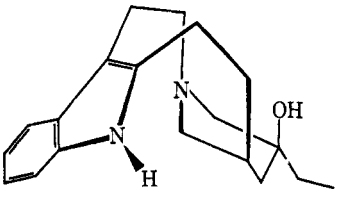
Of the numerous alkaloids isolated from the pantropical plant *Vinca rosea* Linn., vinblastine[3] (VLB) and vincristine (VCR)[4,5] have antitumor activity[6] and are being used in the treatment of Hodgkin's disease and leukemia. Two-dimensional structures for VLB and VCR were proposed in 1964.[7,8] An X-ray diffraction study of a single crystal of vincristine methiodide confirmed the assignment and provided conclusive evidence for the relative and absolute configuration shown in structure **2**.[9] The structure of VLB (**1**) followed from its known relationship to VCR.[10]



1, R = CH_3
2, R = CHO

Reductive cleavage of both alkaloids gave the indole derivative velbanamine (**3**)[7,10,11] and its dehydration product cleavamine (**4**) whose structure has been confirmed by X-ray analysis.[12]

Studies on the synthesis of velbanamine (**3**) were prompted by its potential role as an intermediate[13] in the preparation of the dimeric alkaloids VLB and VCR.



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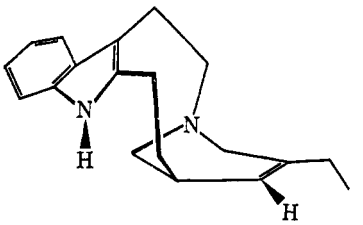

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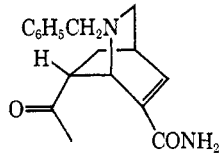
In this paper a total synthesis confirming the previously proposed structure[7,10] is described.[14]

As starting material we chose the isoquinuclidine **5** which previously served in the total synthesis of iboga alkaloids.[15] Oxygenation in *t*-butyl alcohol–monoglyme saturated with potassium *t*-butoxide at −20° gave the crystalline hydroxy ketone **6** in approximately 50% yield. The proton spectra of both the amine **6** and the corresponding hydrochloride indicate the presence of a single epimer and exhibit methyl signals at 2.08 ppm (DMSO-d_6) and 2.20 ppm (D_2O–DCl), respectively. The corresponding signals in the precursor **5** and its hydrochloride appear at 2.08 and 2.18 ppm, respectively, suggesting tentatively that the configuration of the acetyl group in the α-hydroxyketone **6** is the same as that in the precursor **5**. It should be recalled that oxidation of 20-ketosteroids under similar conditions gives 17 α-hydroperoxy-20-ketones.[16] The unusual, direct formation of the ketol in the present case can be attributed to the amine function because tertiary amines are known to reduce hydroperoxides to the corresponding alcohols.[17] To suppress the amine–hydroperoxide interplay we studied the oxygenation in the presence of added reducing agents and found that

(1) National Institutes of Health Predoctoral Fellow, 1965–1967.
(2) National Institutes of Health Predoctoral Fellow, 1965–1968.
(3) N. Neuss, M. Gorman, G. H. Svoboda, G. Maciak, and C. T. Beer, *J. Am. Chem. Soc.*, **81**, 4754 (1959).
(4) G. H. Svoboda, *Lloydia*, **24**, 173 (1961).
(5) A. M. A. approved generic names for vincaleucoblastine and leurocristine, respectively.
(6) R. N. Noble, *Can. Cancer Conf.*, **4**, 333 (1961); and references cited in *Llyodia, Symp.*, **27**, 275 (1964).
(7) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.*, **86**, 1440 (1964).
(8) P. Bommer, W. McMurray, and K. Biemann, *ibid.*, **86**, 1439 (1964).
(9) J. W. Moncrief and W. N. Lipscomb, *ibid.*, **87**, 4963 (1965); *Acta Crystallogr.*, **21**, 322 (1966).
(10) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *J. Am. Chem. Soc.*, **84**, 1509 (1962).
(11) There is no experimental evidence available concerning the conformation of the nine-membered ring in velbanamine and it is assumed that it corresponds to that of cleavamine.
(12) N. Camerman and J. Trotter, *Acta Crystallogr.*, **17**, 384 (1964); *Chem. Ind.* (London), 648 (1963).
(13) G. Büchi, *J. Pure Appl. Chem.*, **9**, 21 (1964).
(14) G. Büchi, P. Kulsa, and R. L. Rosati, *J. Am. Chem. Soc.*, **90**, 2448 (1968). Substances containing the carbon skeleton present in velbanamine were synthesized earlier: J. P. Kutney, W. J. Cretney, P. LeQuesne, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966); J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); J. Harley-Mason and Atta-ur-Rahman, *ibid.*, 208, 1048 (1967).
(15) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, **88**, 3099 (1966).
(16) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).
(17) C. W. Capp and E. G. E. Hawkins, *ibid.*, 4106 (1953).

addition of triethylphosphite[18] raised the yield of hydroxyketone **6** to 96.3%. Before closing the discussion of this substance we should add that efforts to purify the crude product by chromatography on silica gel resulted in conversion to the cyclopentanone **8**. This change seems to be initiated by acid-catalyzed ring opening (**6**, arrows) to give the iminium salt **7** and terminated by cyclization (**7**, arrows) to the new ketone **8**.



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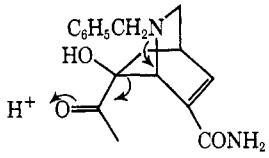

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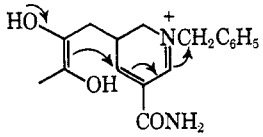

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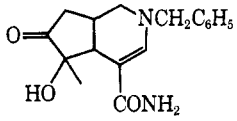

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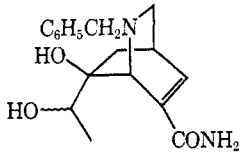
To continue the synthesis of velbanamine the ketone **6** was reduced with sodium borohydride to a mixture of diastereomeric diols (**9**) which was cleaved to the piperidone **10** with sodium metaperiodate. Oxidation of the α-hydroxyketone **6** with the same reagent also gave the ketone **10** but yields were inferior.

Attempts to perform a Hofmann reaction on the α,β-unsaturated amide **10** in methanol solution were not very promising. The methoxyurethan **11** was produced in low yield but efforts to hydrolize it to the β-diketone **12** were fruitless.



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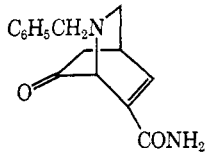

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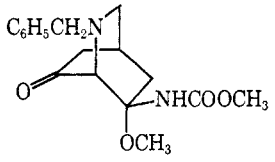

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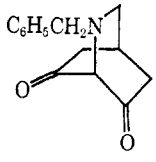

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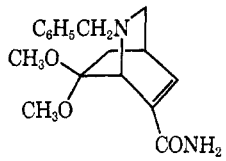
Clearly, the interfering carbonyl group had to be protected. Dimethylketal **13** was prepared from the ketone in hot methanol containing trimethylorthoformate and some *p*-toluenesulfonic acid. Facile reconversion to the ketone **10** excluded skeletal rearrangement in the course of ketalization. Oxidation of the protected amide **13** with sodium hypochlorite[19] gave a mixture of products. Chromatography afforded the enamine **14**, the desired ketone **16**, and very minor amounts of a third substance tentatively assigned the imine structure **15**. In preparative runs it was not necessary to separate these products because hydrolysis of the crude reaction mixture with sodium carbonate in methanol–water furnished the ketone **16** in 79% yield.



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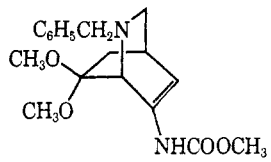

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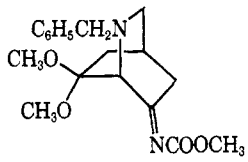

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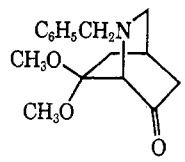

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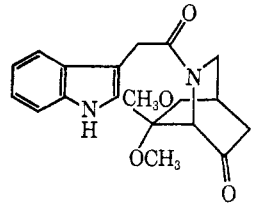
Hydrogenolytic debenzylation of the hydrochloride of the amine **16** followed by condensation with sodium indoleacetate in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[20] gave the amide **17**. Its proton spectrum measured in $CDCl_3$ solution, at room temperature, reveals the presence of two conformers due to restricted rotation about the amide bond.[21] Cyclization of the amide **17** with *p*-toluenesulfonic acid in hot benzene[22] for 7 min produced the pentacyclic methoxyketone **18** in 66% yield. The nonequivalence of the methylene protons situated between the indole ring and amide carbonyl group and the appearance of a one-proton singlet at 4.83 ppm in the proton spectrum strongly suggest that the product of cyclization is the isoquinuclidine **18** rather than its isomer **20**, resulting from a Wagner–Meerwein rearrangement.[23] In the case at hand such a rearrangement is unlikely anyhow because the hypothetical intermediate **21** contains a positive charge next to a carbonyl group.



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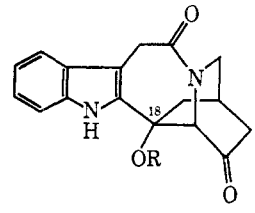
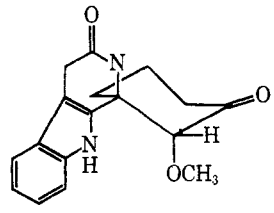


18, R = CH_3
19, R = H



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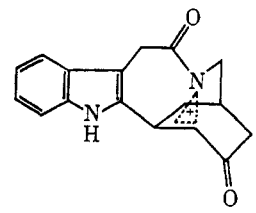


21

When submitted to the action of perchloric acid in acetic acid solution[24] the methoxylactam **18** afforded

(18) *Cf.* J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, **33**, 3294 (1968).

(19) S. Archer and M. R. Bell, *J. Am. Chem. Soc.*, **82**, 4642 (1960).

(20) J. C. Sheehan, J. Preston, and P. A. Cruickshank, *ibid.*, **87**, 2492 (1965).

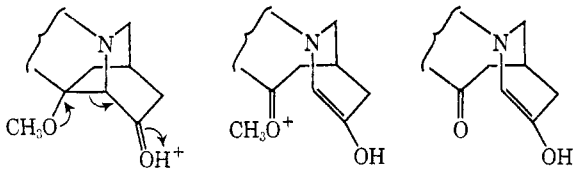
(21) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 161.

(22) Method of W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967).

(23) For the rearrangement of isoquinuclidines to azabicyclo[1.2.3]-octanes see ref 15 and J. W. Huffman, T. Kamiya, and C. B. S. Rao, *J. Org. Chem.*, **32**, 700 (1967).

(24) A. J. Birch and J. S. Hill, *J. Chem. Soc., C*, 419 (1966).

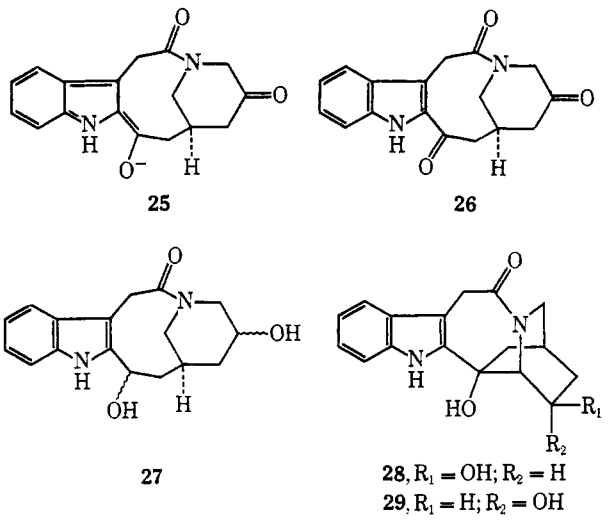
the hydroxylactam **19**. In agreement with the presence of a tertiary alcohol the hydroxy proton appears as a sharp singlet in the nmr spectrum when measured in DMSO-d_6.[25] The mechanism of this ether cleavage is unknown. Evidence in favor of a simple C_{18}–O cleavage is provided by the facile interconversions of 18-hydroxy- and 18-methoxyibogaine[26] but an equally plausible course of events is presented by the sequence **22** → **23** → **24** → **19**.



22 **23** **24**

We were now ready to create the crucial nine-membered ring by retroaldol cleavage of the β-hydroxyketone **19**. Formation of the highly conjugated 2-acylindole **26** was expected to provide the driving force for this change. Treatment of the aldol **19** in *t*-butyl alcohol with potassium *t*-butoxide afforded a solution with intense ultraviolet absorption at 350 mμ attributable to the anion **25**.[27] Upon addition of glacial acetic acid this absorption was replaced by two others at 320 and 293/284 mμ, respectively.[28] Thin-layer chromatography revealed the presence of the diketone **26** in addition to minor amounts of the hydroxyketone **19**. All attempts to isolate the former in pure form failed and we soon discovered that the diketone **26** is extremely unstable with respect to its precursor **19** in the presence of weak base and only moderately stable in the presence of weak acid. Our next experiments were concerned with *in situ* transformations of the anion **25** and the corresponding diketone to products no longer capable of recyclization to isoquinuclidines. We hoped that one of the carbonyl groups in the anion **25** would be protected as an enolate while the other would retain its electrophilic properties but efforts to add acetylene in the presence of potassium *t*-butoxide led to recovery of starting material. Reduction of a buffered solution of the diketone **26**, prepared by adding acetic acid to the enolate **25**, with excess sodium borohydride gave three crystalline diols. Elemental composition and spectroscopic properties left no doubt that the major product (47% yield) was the desired tetracyclic diol **27**. The two minor products turned out to be the epimeric pentacyclic diols **28** and **29**, also available by sodium borohydride reduction of the hydroxyketone **19** under identical conditions. The less polar of the pair was tentatively assigned stereostructure **29**.

When the tetracyclic diol **27** was reduced in glacial acetic acid with stannous chloride and tin[10] in the presence of *p*-toluenesulfonic acid the alcohol **30** and the corresponding acetate **31** were formed. Separation could be avoided by treating the crude reaction mixture with methanolic ammonia. The resulting alcohol **30** was oxidized to the ketone using dimethyl sulfoxide and

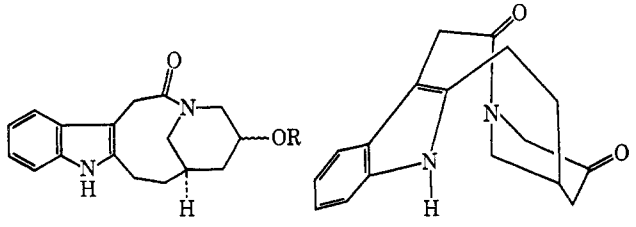


25 **26**

27

28, R_1 = OH; R_2 = H
29, R_1 = H; R_2 = OH

dicyclohexylcarbodiimide.[29] An examination of molecular models indicated that the ketolactam **32** should be most stable in the conformation already indicated. Consequently an organometallic reagent should attack the carbonyl group equatorially producing an ethylcarbinol with the desired stereochemistry. In fact treatment of the ketone **32** successively with ethylmagnesium bromide and with lithium aluminum hydride gave racemic velbanamine (**3**). Identity with natural material[30] was established by comparison of ultraviolet, infrared, and mass spectra as well as behavior on thin-layer chromatoplates. Furthermore racemic velbanamine gave a di-*p*-toluoyl l-tartrate identical with the corresponding salt of optically active velbanamine as judged by mixture melting point determination.



30, R = H
31, R = $COCH_3$

32

While pursuing the synthesis just described it was realized that the pentacyclic methoxylactam **18** might serve as an intermediate in a total synthesis of catharanthine, a major constituent of *Vinca rosea* Linn. Structure **33** was proposed in 1961[31] and although there was no reason to doubt its correctness confirmatory evidence was nevertheless desirable because all experimental information on the biogenesis of iboga alkaloids has been secured with catharanthine.[32]

The first step in the synthesis of catharanthine involved transformation of the cyclic ketone **19** to the ethylcarbinol **36**. This seemingly trivial change did pose some difficulties. Addition of ethyllithium to the

(25) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(26) G. Büchi and R. E. Manning, *ibid.*, **88**, 2532 (1966).

(27) Vobasine, a typical 2-acylindole alkaloid, absorbs at 350 mμ in the presence of a strong base.

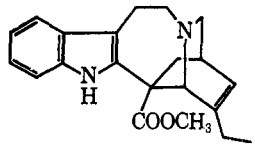
(28) Indole alkaloids show a complex band between 280 and 292 mμ (ε 7000) while 2-acylindoles absorb at 239 (ε 16,000) and 316 mμ (ε 18,500): A. W. Sangster and K. L. Stuart, *Chem. Rev.*, **65**, 69 (1965).

(29) K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.*, **87**, 5670 (1965).

(30) We are indebted to Dr. N. Neuss, Eli Lilly and Co., for samples of velbanamine and natural catharanthine.

(31) N. Neuss and M. Gorman, *Tetrahedron Lett.*, 206 (1961); N. Neuss, M. Gorman, and N. J. Cone, *J. Am. Chem. Soc.*, **87**, 93 (1965).

(32) (a) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc., C*, 1193 (1969); (b) R. Loew and D. Arigoni, *Chem. Commun.*, 137 (1968); (c) A. A. Qureshi and A. I. Scott, *ibid.*, 945, 947, 948 (1968) and other references cited.



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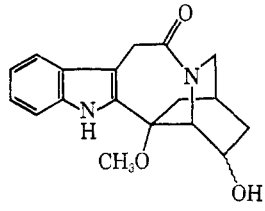
ketone resulted in a mixture of several products owing to attack of the reagent on both ketone and lactam groups. Ethylmagnesium bromide caused reduction to a secondary alcohol **34**. Fortunately this latter difficulty was easy to overcome. Vinylmagnesium bromide afforded a single vinylcarbinol **35** which for steric reasons should have the configuration indicated. Catalytic reduction of the olefin **35** proceeded smoothly and gave the ethylcarbinol **36**. Reduction of the lactam group and hydrogenolysis of the methoxy function were effected in a single operation using a hydride prepared from equimolar quantities of lithium aluminum hydride and aluminum chloride in tetrahydrofuran solution.[33] The desired amine **37** was obtained in 90% yield and this method is clearly superior to that using lithium aluminum hydride alone which in the case of seven-membered lactams yields mostly carbinolamines[34] or enamines[35] due to incomplete reduction.



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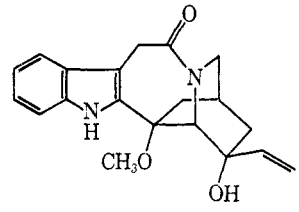

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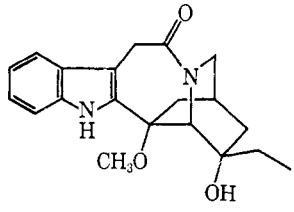

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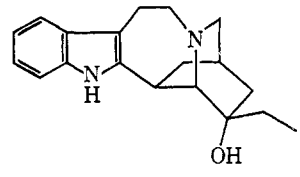

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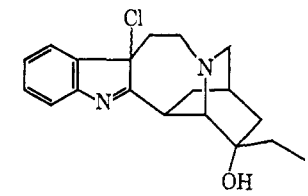
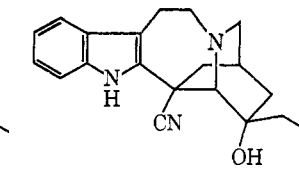
To complete the synthesis of catharanthine the carbomethoxy group needed to be introduced and the alcohol had to be dehydrated. The first objective was achieved by applying a method we had developed earlier.[26] The crude 3-chloroindolenine **38** prepared from the indole **37** with *t*-butylhypochlorite[36] on treatment with potassium cyanide in dimethylacetamide afforded the hydroxynitrile **39**. Dehydration of this alcohol in 100% sulfuric acid at room temperature gave a mixture of the unsaturated nitrile and the corresponding primary amide. Both proved to be very resistant to hydrolysis and potassium hydroxide in diethylene glycol at 150° was needed for complete conversion to the corresponding acid which, again was not purified and directly transformed to the crystalline methyl ester **33** by treatment with diazomethane.



38



39

Infrared, ultraviolet, and nuclear magnetic resonance spectra of the methyl ester were indistinguishable from those of natural catharanthine (**33**).[30] Furthermore synthetic and natural material had identical mass spectra and exhibited identical mobility on thin-layer chromatoplates. Finally, Professor A. I. Scott, Yale University, established identity (letter of January 24, 1969) of a sample of our racemic catharanthine with material prepared in his laboratory from naturally occurring alkaloids.[32c]

Experimental Section

Microanalyses were performed at the M.I.T. Microchemical Laboratory and at Midwest Microlab., Inc., Indianapolis, Ind. Melting points and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (peaks reported in parts per million downfield from tetramethylsilane as internal standard); infrared (ir), Perkin-Elmer Model 237; ultraviolet (uv), Cary Model 14; and mass spectra, Hitachi RMU6D and CEC 21-104 using the direct inlet system. Only the most intense peaks are listed. High-resolution mass spectra were obtained on a CEC 21-110B instrument. Thin-layer chromatograms (tlc) were prepared with Merck Silica Gel PF 254. Merck acid-washed alumina was used for column chromatography unless indicated otherwise. The drying agent used throughout was anhydrous sodium sulfate.

Oxidation of the Isoquinuclidine 5 to the Hydroxyketone 6. A solution of 50 g (0.446 mol) of potassium *t*-butoxide in *t*-butyl alcohol, (300 ml), was mixed with 12 g (72.3 mmol) of triethyl phosphite in monoglyme (100 ml) and cooled to −20° (Dry Ice–carbon tetrachloride bath). Isoquinuclidine **5**, 12.9 g (45.6 mmol) in methylene chloride (150 ml), was added and dry oxygen was bubbled through the stirred reaction mixture for 2.5 hr at −20°. Acetic acid (30 ml) was added to the reaction mixture and the *t*-butyl alcohol and monoglyme were removed under high vacuum (bath below 50°). The pale yellow concentrate was dissolved in cold 6 *N* sulfuric acid and the mixture was washed with benzene (2 × 50 ml). The acid layer was made alkaline with saturated sodium carbonate solution and extracted with methylene chloride and washed with saturated NaCl solution. Evaporation of the dried extract afforded a white crystalline residue, which after recrystallization from benzene give 13.2 g (96.3%) of hydroxyketone, **6**, mp 155–157°. An analytical sample recrystallized from chloroform–benzene exhibited mp 160–161°; ir (Nujol) 3350, 1705, 1670, 1630, and 1580 cm^{-1}; nmr (DMSO-d_6) δ 1.60 (m, 2), 2.08 (s, 3), 2.30–2.80 (m, 3), 3.09 and 3.75 (AB q, 2, J = 15 Hz), 4.25 (s, 1), 5.25 (s, 1, exchanged with D_2O), and 7.22 (s with broad base, 8); nmr (D_2O–DCl, TMS external) δ 1.30–2.00 (m, 2), 2.20 (s, 3), 2.58–2.80 (m, 1), 3.30 (m, 2), 3.69 and 4.75 (AB q, 2, J = 13 Hz), 4.52 (d, 1, J = 2 Hz), 7.37 (s, 5), and 7.60 (q, 1, J = 2 Hz, J = 7 Hz). Cooling the sample to 0° displaced the signal arising from DOH and allowed the signal at 4.52 ppm to be observed.

Anal. Clacd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.87; H, 6.63; N, 8.93.

Rearrangement of the Hydroxyketone 6 to the Cyclopentanone 8. An attempt to purify the hydroxyketone **6** by chromatography on Silica Gel PF_{254}, using 5% methanol–95% chloroform as eluent, resulted in isomerization to the cyclopentanone **8** which crystallized from methanol–chloroform and had mp 202–206°; uv max (EtOH) 293 mμ (ε 21,000);[37] ir (Nujol) 3420, 3340, 1725, 1630, 1560, 1220, and 930 cm^{-1}; nmr (DMSO-d_6) δ 1.25 (s, 3), 4.40 (s, 1), 4.80 (s, 1, exchanged with D_2O), 6.35 (s, 2), 7.25 (s, 5), and 7.60 (s, 1); mass spectrum *m/e* 300 (M), 282, 214, 213, 91.

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Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.69; H, 6.79; N, 9.16.

Reduction of the Hydroxyketone 6 to the Diastereomeric Diols 9. To a stirred solution of hydroxyketone **6**, 4.00 g (13.3 mmol), in 50 ml of methanol at 0° was added 1.5 g (40 mmol) of sodium borohydride. After stirring at 0° for 1 hr, the clear solution was poured into saturated NaCl solution and extracted with methylene chloride. Evaporation of the dried extracts gave a white foam, 4.10 g (100%). Tlc showed a major and a minor component with slightly lower R_f value. An analytical sample of the major diol recrystallized from ethyl acetate–methanol had mp 182–183°; ir (Nujol) 3375, 3200, 1675, 1650, 1630, 1575, 1220, 1140, and 1080 cm^{-1}; nmr (D_2O–DCl, TMS external), δ 1.10 (d, 3, J = 7 Hz), 3.73 and 4.10 (AB q, 2, J = 13 Hz), 4.32 (d, 1, J = 2 Hz), 7.38 (s, 5), and 7.58 (broad d, 1, J = 7 Hz).

Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.20; H, 7.09; N, 9.15.

Periodate Cleavage of the Diastereomeric Diols 9 to the Ketone 10. A stirred solution of crude **9**, 8.0 g (26.5 mmol), in 52 ml of methanol was cooled to 0°, and treated with a 0° solution of 5.66 g (26.5 mmol) of sodium metaperiodate in 52 ml of water. A white precipitate formed immediately. After 5 min, 104 ml of ice water was added and stirring at 0° was continued for 15 min. After standing at 25° for 24 hr, the reaction mixture was treated with 25 ml of saturated sodium carbonate solution and extracted with chloroform. Concentration of the dried extracts gave a white crystalline solid, which after recrystallization from ethyl acetate afforded 4.7 g (59%) of ketone **10** (as the ethyl acetate solvate), mp 109–112° (sinters 105–109°). An analytical sample was recrystallized from ethyl acetate: mp 109–112°; ir (Nujol) 3500, 3300, 1750 (EtOAc solvate), 1720, 1650, 1600, 1500, 1240, 1130, 820, 775, and 700 cm^{-1}; mass spectrum m/e 256 (M), 228, 213, 184, 151, 137, 119, 108, and 91.

Anal. Calcd for $C_{15}H_{16}N_2O_2 \cdot {}^1/_2$ EtOAc: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.24; H, 6.53; N, 9.33.

An analytical sample recrystallized from chloroform had mp 106–109°; ir (Nujol) 3500, 3300, 1720, 1650, 1600, and 1500 cm^{-1}; nmr (DMSO-d_6) δ 2.09 (broad s, 2), 2.15–2.45 (m, 1), 2.65–3.30 (m, 2), 3.58 (s, 2), 4.10 (d, 1, J = 2 Hz), 7.31 (s, 5), and 7.15–7.50 (m, 3).

Anal. Calcd for $C_{15}H_{16}N_2O_2 \cdot {}^1/_2\ CHCl_3$: C, 58.92; H, 5.26; N, 8.86. Found: C, 59.17; H, 5.32; N, 8.58.

Hofmann Rearrangement of the Amide 10 to the Methoxyurethan 11. To a stirred solution of amide **10**, 3.35 g (11.2 mmol), in 160 ml of methanol cooled to 0° was added dropwise 13.9 ml of an aqueous solution 0.8 M in sodium hypochlorite and sodium hydroxide (11.1 mmol of NaOCl and 11.1 mmol of NaOH). After stirring for 0.5 hr at 0°, 0.5 hr at 25°, and 0.5 hr at 45°, the reaction mixture was poured into saturated NaCl solution and extracted with methylene chloride. Evaporation of the dried extracts gave the crude product which was chromatographed on alumina to give 392 mg (11%) of methoxyurethan **11** as an oil; ir (thin film) 3600, 1740, 1530, and 1500 cm^{-1}; nmr ($CDCl_3$) δ 2.00–2.50 (m, 2), 3.08 (s, 3), 3.05 (s, 1), 3.60 (s, 2), 3.63 (s, 3), 5.32 (broad s, 1), and 7.25 (s, 5); mass spectrum m/e 318 (M).

Preparation of the Dimethylketal 13. A solution of 4.26 g (14.2 mmol) of ketone **10**, 3.07 g (16.1 mmol) of p-toluenesulfonic acid monohydrate, and 4.68 g (44.1 mmol) of freshly distilled trimethylorthoformate in 370 ml of absolute methanol was allowed to reflux for 24 hr. After cooling to 25°, the reaction mixture was treated with 4.0 g of solid anhydrous sodium carbonate and concentrated to approximately 90 ml under vacuum. The mixture was diluted with saturated sodium bicarbonate solution and extracted with chloroform. Concentration of the dried extracts and trituration of the resulting residue with hexane–benzene on a steam bath gave 3.70 g (86%) of crystalline dimethylketal **13**, mp 160–163.5°. An analytical sample recrystallized from benzene–cyclohexane: mp 163.5–165.5°; ir (Nujol) 3500, 3400, 1665, 1620, 1580, 1150, 1115, 1085, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.96 (d, 2, J = 3 Hz), 3.36 (s, 3), 3.44 (s, 3), 3.68 and 3.93 (AB q, 2, J = 12 Hz), 4.15 (d, 1, J = 2 Hz), 5.98 (m, 2), and 7.02 (q, 1, J = 7 Hz, J = 2 Hz).

Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.83; H, 7.45; N, 9.03.

A sample of **13** was heated with 6 N sulfuric acid on a steam bath for 8 min. Basic work-up gave a product identical with the ketone **10** (infrared spectrum, melting point and mixture melting point).

Hofmann Rearrangement of the Dimethylketal 13. To a stirred solution of 1.176 g (3.9 mmol) of dimethylketal **13** in 28 ml of methanol maintained at −19° (Dry Ice–carbon tetrachloride bath) was added dropwise 5.36 ml of an aqueous solution 0.8 M in sodium hypochlorite and sodium hydroxide (4.3 mmol of NaOCl and 4.3 mmol of NaOH) at such a rate as to maintain the reaction temperature at −18°. After addition the solution was allowed to stand at 0° for 0.5 hr, 25° for 0.5 hr, and 60° for 10 min. The reaction mixture was poured into saturated NaCl solution and extracted with chloroform. Evaporation of the dried extracts gave 1.2 g of an oil, which was a mixture (tlc) of **16**, **15**, and **14** (major component). The crude reaction mixture was allowed to reflux on the steam bath with 40 ml of 10% aqueous sodium carbonate solution and 23 ml of methanol. Cooling afforded 750 mg of crystalline ketone **16**, mp 121–123°. Concentration of the mother liquors afforded an additional crop of 100 mg (79% total). An analytical sample was recrystallized from cyclohexane: mp 121–123°; ir (Nujol) 1725, 1260, 1150, 1110, 1075, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.08 (s, 3), 3.13 (s, 4), 3.70 (s, 2), and 7.31 (s, 5); mass spectrum, m/e 275 (M), 244, 232, 215, 200, 184, 173, 158, 124, 110, 91.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.80; H, 7.75; N, 5.00.

A sample of **14** isolated by chromatography on silica gel had nmr ($CDCl_3$) δ 3.09 (s, 7), 3.58 (s, 2), 3.72 (s, 3), 6.20 (m, 1), and 7.32 (s with broad base, 6).

Amide 17 from Tertiary Amine 16. A solution of 2.06 g (7.5 mmol) of amine **16** in 60 ml of dry methyl acetate was treated with a solution of dry HCl in methyl acetate until acidic. Evaporation of the solvent under vacuum left the crystalline hydrochloride of **16** which was dissolved in 30 ml of methanol and stirred with 300 mg of 10% Pd/C at 25° under hydrogen at atmospheric pressure. The theoretical quantity of hydrogen (168 ml) was consumed in 20 min and after filtration to remove the catalyst the methanol was evaporated under vacuum. The residue was treated with 2.98 g (15.1 mmol) of sodium indole 3-acetate, 5.75 g (32.4 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 40 ml of water. After standing for 1 hr at 25° the reaction mixture was extracted with chloroform. The extracts were rapidly washed with ice cold dilute aqueous HCl followed immediately by saturated sodium bicarbonate solution, dried and concentrated to an oil which was crystallized from a small volume of benzene to yield 2.6 g (83%) of amide **17** (as the benzene solvate), mp 98–105°. An analytical sample was recrystallized from benzene: mp 106–112°; uv max (EtOH) 220, 274, 282, 291 mμ (ϵ 44,000, 6150, 6600, 5800); ir (Nujol) 3225, 1735, 1630, 1260, 1225, 1125, 1035, 750, and 680 cm^{-1}; nmr ($CDCl_3$) δ 1.83 (m, 2), 2.23 (m, 3), 3.07–3.16 (four singlets, 6), 3.44 (m, 2), 3.71 and 3.82 (two singlets in 2:1 ratio, 2), 4.38 and 5.16 (two singlets in 1:2 ratio, 1), and 6.80–7.70 (m, 6); nmr ($CDCl_3$, 80°) δ 1.75 (m, 2), 2.20 (m, 3), 3.10 (s with broad base, 6), 3.40 (m, 2), 3.70 (m, 2), and 6.80–7.60 (m, 6); mass spectrum, m/e 342 (M), 327, 311, 299, 295, 285, 212, 157, 130.

Anal. Calcd for $C_{19}H_{22}N_2O_4 \cdot C_6H_6$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.21; H, 6.56; N, 6.75.

Cyclization of the Amide 17 to the Lactam 18. In a 500-ml round bottomed flask, 750 mg (3.95 mmol) of p-toluenesulfonic acid monohydrate was fused under high vacuum. Dry benzene (320 ml) was added and the flask was equipped with a fraction-cutting distillation head. After distillation of approximately 40 ml of benzene to remove a small amount of water, 1.60 g (3.81 mmol) of amide **17** was added. The reaction mixture was stirred and allowed to reflux under nitrogen for 7 min, (negative Ehrlich test). Evaporation of the solvent afforded an oil which was dissolved in chloroform and filtered through neutral alumina (activity I). Crystallization from benzene gave 783 mg (66%) of methoxylactam **18**, mp 282–284°. An analytical sample recrystallized from chloroform in colorless crystals: mp 283–284° (sublimes at 225°); uv (EtOH) 222 (ϵ 39,500), 283 (8500), and 292 mμ (7500); ir (Nujol) 3125, 1740, 1635, 1270, 1130, 1110, 1100, 1085, 1070, and 750 cm^{-1}; nmr ($CDCl_3$) δ 2.15 (m, 2) 2.60 (m, 3), 3.09 (s, 3), 3.77 and 4.11 (AB q, 2, J = 15 Hz), 4.83 (s, 1), 7.00–7.70 (m, 4), and 8.30 (broad s, 1); mass spectrum m/e 310 (M), 295, 278, 267, and 186.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.51; H, 6.10; N, 8.94.

Hydroxylactam 19 from Methoxylactam 18. The methoxylactam **18**, 310 mg (1.0 mmol), was dissolved in a solution containing 9.4 ml of anhydrous glacial acetic acid and 0.6 ml of 70% aqueous perchloric acid solution and the mixture was allowed to stand at 25° for 24 hr. After dilution with water, the solution was made basic by the addition of solid sodium carbonate and was extracted with chloroform. Evaporation of the dried extracts afforded the crude product which was crystallized from chloroform to yield 222 mg (62%) of hydroxylactam **19** (as the chloroform solvate), mp 262–267° (sublimes at 250°). An analytical sample recrystallized from chloroform had mp 272–275° (sublimes at 250°); uv max (EtOH) 218, 275, 283, 292 mμ (ϵ 45,000, 8550, 9000, 8250); ir (Nujol) 3300, 1750, 1650, 1315, 1270, 1240, 1190, 1180, 930, and 760

cm^{-1}; nmr (DMSO-d_6) δ 3.50 and 4.12 (AB q, 2, J = 15 Hz), 4.52 (s, 1), 6.00 (s, 1, exchanged with D_2O), 6.92–7.60 (m, 4), and 10.54 (s, 1); mass spectrum, *m/e* 296 (M), 278, 267, 253, 239, 225, 223, 199, 172, 130.

Anal. Calcd for $C_{17}H_{16}N_2O_3 \cdot {}^1/_2\ CHCl_3$: C, 59.04; H, 4.67; N, 7.87. Found: C, 59.09; H, 5.21; N, 8.43.

Retrograde Aldol Cleavage of the Hydroxylactam 19 to the Diketolactam 26. To a stirred solution of 30 mg of **19** in 3.5 ml of dry *t*-butyl alcohol was added in one portion 300 mg of potassium *t*-butoxide. The qualitative ultraviolet spectrum of the reaction mixture at this point showed a maximum at 350 mμ due to the anion **25**. After 5 min the reaction was added dropwise to 50 ml of a stirred 2 *N* HCl solution cooled in an ice bath. After addition was complete the solution was saturated with solid NaCl and extracted with chloroform. Evaporation of the dried extracts afforded 28 mg of a powder which contained two components on tlc. A qualitative ultraviolet spectrum (EtOH) of the mixture indicated the presence of normal indole (uv max 285 and 292 mμ) and 2-acylindole (uv max 316 mμ). Preparative tlc of the two component mixtures afforded the compound with lower R_f in pure form. It was identified as the hydroxyketone **19** by its infrared spectrum (Nujol). Attempts to isolate the other component **26** by preparative tlc failed. In its place the isomer **19** was obtained.

Addition of 2 *N* NaOH solution to a mixture of **19** and **26** in ethanol resulted in the rapid loss of absorbance at 316 mμ. The resulting spectrum was that of the indole **19**.

Similarly a solution of **19** and **26** in acetic acid containing 6% perchloric acid showed a rapid conversion of the 2-acylindole chromophore to that of indole.

Preparation of the Tetracyclic Diol 27. To a stirred, deoxygenated solution of 200 mg (0.562 mmol) of hydroxylactam **19** in 40 ml of dry *t*-butyl alcohol was added under nitrogen 2.24 g (20 mmol) of potassium *t*-butoxide in one portion. After 2 min the reaction was cooled by means of an 18° water bath and 2.4 ml (42 mmol) of anhydrous glacial acetic acid was added rapidly from a syringe that extended beneath the surface of the reaction mixture. The ultraviolet spectrum of the reaction mixture at this point displayed a strong band at 320 mμ and weak bands at 284 and 293 mμ. Without delay ice was added to the water bath and a steady flow of carbon dioxide was passed through the stirred reaction mixture. In quick succession the reaction was treated with 20 ml of pH 6 phosphate buffer (previously cooled to 0°), 1.68 g (20 mmol) of solid sodium bicarbonate, and 800 mg of sodium borohydride. After 20 min an additional 800 mg of sodium borohydride was added. After 45 min at 0°, the reaction mixture was diluted with saturated sodium bicarbonate solution and extracted with chloroform. Concentration of the dried extracts gave 200 mg of a mixture of three compounds (tlc). The tetracyclic diol **27** isolated by preparative tlc was crystallized from chloroform–methanol: 80 mg (47%), mp 266–270°. An analytical sample was recrystallized from ethanol: mp 272–275°; uv max (EtOH) 223, 276, 283, 292 mμ (ϵ 30,800, 5750, 6140, 5400); ir (Nujol) 3250, 1615, 1375, 1350, 1260, 1190, 1135, 1075, 1035, 980, 880, and 750 cm^{-1}; nmr (DMSO-d_6) δ 3.32 and 4.35 (AB q, 2, J = 14 Hz), 3.75 and 4.22 (AB q, 2, J = 16 Hz), 5.23 (d, 1, J = 5 Hz), 5.85 (d, 1, J = 4 Hz), and 7.10–7.80 (m, 4); mass spectrum, *m/e* 300 (M), 282, 207, 159, 158, 156, 143, 130, 112.

Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.07; H, 6.86; N, 9.24.

Diol **29** (32 mg) isolated by preparative tlc of the crude reaction mixture was crystallized from chloroform–methanol, mp 288–292° dec. An analytical sample recrystallized from chloroform–methanol had mp 291–293° dec; uv max (EtOH) 224, 276, 284, 292 mμ (ϵ 33,700, 6760, 7350, 6470); ir (Nujol) 3500, 3300, 3200, 1650, 1625, 1090, 975, 925, and 760 cm^{-1}; nmr (DMSO-d_6) δ 4.95 (broad unresolved band, 1, exchanged with D_2O), 6.00 (s, 1, exchanged with D_2O), 6.90–7.60 (m, 4), and 11.00 (s, 1); mass spectrum, *m/e* 298 (M), 280, 223, 172, 159, 130.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.21; H, 6.12; N, 9.02.

Preparative tlc afforded 22 mg of diol **28**, uv max (EtOH) normal indole; ir (Nujol) 3250, 1635, 1080, 1010, and 730 cm^{-1}; nmr (DMSO-d_6) δ 3.43 and 3.95 (AB q, 2, J = 15 Hz), 4.35 (s, 2), 4.90 (broad unresolved band, 1, exchanged with D_2O), 5.60 (s, 1, exchanged with D_2O), 6.90–7.50 (m, 4), and 11.00 (s, 1); mass spectrum, *m/e* 298 (M), 223, 172, 158, 130, 97. High-resolution mass spectral data for the major ions of **28** are: Calcd for $C_{17}H_{18}N_2O_3$: 298.13173. Found: 298.1314. Calcd for $C_{14}H_{11}N_2O$: 223.08713. Found: 223.0891. Calcd for $C_{11}H_{10}NO$: 172.07624. Found: 172.0772. Calcd for $C_{10}H_8NO$: 158.06058. Found: 158.0595. Calcd for C_9H_8N: 130.06566. Found: 130.0650. Calcd for C_5H_7NO: 97.05275. Found: 97.0517.

Reduction of Tetracyclic Diol 27. Tetracyclic diol **27**, 100 mg (0.33 mmol), was allowed to reflux with 200 mg of anhydrous stannous chloride, 200 mg of powdered tin metal, and 10 mg of *p*-toluenesulfonic acid monohydrate in 10 ml of anhydrous glacial acetic acid for 1.5 hr. The acetic acid was removed under high vacuum. Treatment of the resulting mixture of **30** and **31** (tlc) with methanol saturated with ammonia resulted in the conversion of the acetate **31** to the alcohol **30**. Isolation by preparative tlc gave 48 mg (51%) of tetracyclic alcohol **30**. A sample recrystallized from chloroform had mp 270–273°; uv max (EtOH) 224, 277, 284, 291 mμ (ϵ 27,200, 5570, 5600, 5130); ir (Nujol) 3300, 1605, 1580, 1230, 1165, 1120, 1065, and 760 cm^{-1}; nmr (DMSO-d_6) δ 2.23–3.00 (m, 2), 3.00–5.00 (m, 10), 6.90–7.30 (m, 4), and 10.90 (s, 1); mass spectrum, *m/e* 284 (M), 266, 156, 144, 143, 112, 98. High-resolution mass spectrum data for major ions of **30** are: Calcd for $C_{17}H_{20}N_2O_2$: 284.15248. Found: 284.1529. Calcd for $C_{17}H_{18}N_2O$: 266.14190. Found: 266.1415. Calcd for $C_{11}H_{10}N$: 156.08131. Found: 156.0807. Calcd for $C_{10}H_{10}N$: 144.08132. Found: 144.0801. Calcd for $C_{10}H_9N$: 143.07349. Found: 143.0730. Calcd for $C_8H_{10}NO$: 112.07623. Found: 112.0759. Calcd for C_5H_8NO: 98.06059. Found: 98.0610.

A sample of acetate **31** isolated by preparative tlc before treatment with ammonia in methanol had ir ($CHCl_3$) 3460, 1735, 1635, and 1200 cm^{-1}; mass spectrum *m/e* 326 (M), 266, 182, 156, 154, 143.

Oxidation of the Tetracyclic Alcohol 30 to the Ketone 32. To a stirred solution of 4.31 mg (0.044 mmol) of anhydrous phosphoric acid and 72.5 mg (0.351 mmol) of dicyclohexylcarbodiimide in 0.2 ml of dry dimethyl sulfoxide was added 25 mg (0.088 mmol) of tetracyclic alcohol **30** (at 25°). The reaction mixture was allowed to stir for 19 hr and was then evaporated to dryness under high vacuum at 80°. The crude reaction mixture was separated by preparative tlc to give 12.4 mg (50%) of ketone **32**. A sample was crystallized from methanol: mp 250–252°; uv max (EtOH) 223, 276, 283, 291 mμ (ϵ 30,200, 5640, 6430, 5300); ir (Nujol) 3200, 1710, 1620, 1230, 1175, 975, 745, and 735 cm^{-1}; nmr (DMSO-d_6) δ 2.60–3.00 (m, 2), 3.10–3.70 (m, 5), 4.10–5.20 (m, 3), 6.90–7.70 (m, 4), and 10.90 (s, 1); mass spectrum, *m/e* 282 (M), 182, 156, 143, 130, 110. High-resolution mass spectrum data for major ions of **32** are: Calcd for $C_{17}H_{18}N_2O_2$: 282.1368. Found: 282.1385. Calcd for $C_{13}H_{12}N$: 182.0969. Found: 182.0970. Calcd for $C_{11}H_{10}N$: 156.0813. Found: 156.0826. Calcd for $C_{10}H_9N$: 143.0734. Found: 143.0740. Calcd for C_9H_8N: 130.0656. Found: 130.0666. Calcd for C_6H_8NO: 110.0605. Found: 110.0605.

Racemic Velbanamine (3). To a stirred solution of 10 mg (0.0355 mmol) of tetracyclic ketone **32** in 4 ml of dry tetrahydrofuran at 25° was added under nitrogen 2 ml of saturated ethereal magnesium bromide solution and 1 ml of 3 *M* ethylmagnesium bromide in ether solution. After 10 min saturated ammonium chloride solution was added to destroy excess Grignard reagent and the reaction mixture was extracted with ethyl acetate. Concentration of the dried extracts afforded an oil which contained some unreacted ketone **32**. The last traces of ethyl acetate were removed by the addition of benzene and subsequent evaporation under vacuum. The residue was dissolved in 4 ml of tetrahydrofuran and treated with the magnesium bromide–Grignard reagent as described above. After the excess ethylmagnesium bromide was destroyed with 0.25 ml of isopropyl alcohol, a large excess of lithium aluminum hydride was added and stirring was continued at 25° for 3 hr. Excess hydride was destroyed by the careful addition of saturated aqueous sodium sulfate solution and the reaction mixture was extracted with ethyl acetate. The dried extracts were concentrated to an oil which contained (tlc) racemic velbanamine as the major component. Racemic velbanamine, 2.2 mg (21% from **32**), isolated by preparative tlc, had infrared, ultraviolet, and mass spectra indistinguishable from those of natural velbanamine as well as identical R_f values on tlc: silica gel G (EtOAc and 10% MeOH–90% $CHCl_3$) and alumina G ($CHCl_3$).

Another sample of racemic velbanamine was resolved by conversion to the two diastereomeric di-*p*-toluoyl l-tartrates, which were separated by fractional crystallization using acetone as the solvent; only one salt, mp 140–140.5°, crystallized from acetone and it was shown to be identical with the di-*p*-toluoyl l-tartrate of natural velbanamine, mp 140–140.5° (mixture melting point undepressed).

Vinylcarbinol 35 from the Methoxylactam 18. Methoxylactam **18**, 800 mg (2.58 mmol), was dissolved in 40 ml of dry tetrahydrofuran. The solution was stirred under nitrogen and cooled to 0°.

A tetrahydrofuran solution of vinyl magnesium bromide (40 ml of a 1 *M* solution, 40 mmol of vinyl magnesium bromide) was added. After stirring for 0.5 hr at 0° the reaction mixture was treated with a large excess of saturated ammonium chloride solution and the organic layer drawn off in a separatory funnel. The aqueous solution was extracted with ethyl acetate. Evaporation of the dried extracts gave an oil which was crystallized from benzene to yield 800 mg of vinylcarbinol **35** (92%), mp 279–282° (sublimes at 250°). An analytical sample was recrystallized from methanol–benzene–heptane: mp 284–285° (sublimes at 250°); uv max (EtOH) 223, 278, 284, 293 mμ (ε 37,800, 8370, 9000, 8270); ir (Nujol) 3480, 3140, 1640, 1130, 1070, 1055, 990, 930, and 750 cm^{-1}; nmr (DMSO-d_6) δ 1.80–2.30 (m, 5), 3.00 (s, with broad base, 4), 3.38 and 4.20 (AB q, 2, J = 16 Hz), 4.40 (s, 1), 4.68 (s, 1, exchanged with D_2O), 5.00–6.40 (m, 3), 7.00–7.60 (m, 3), and 11.50 (s, 1); mass spectrum, *m/e* 338 (M), 295, 223, 195, 186.

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.91; H, 6.63; N, 8.13.

Hydrogenation of the Vinylcarbinol 35. To a solution of 1.80 g (5.3 mmol) of vinylcarbinol **35** in 50 ml of dry tetrahydrofuran was added 180 mg of platinum oxide. The mixture was stirred under hydrogen at atmospheric pressure at 25° until the hydrogen required for reduction of the catalyst and the vinyl group was consumed (20 min). The catalyst was removed by filtration and the filtrate was evaporated to give an oil which was crystallized from benzene to yield 1.80 g of ethylcarbinol **36** (99%), 260–265°. An analytical sample recrystallized from ethanol–hexane had mp 275–277°; uv max (EtOH) 223, 278, 284, 293 mμ (ε 34,800, 7080, 7730, 7030); ir (Nujol) 3480, 3140, 1640, 1060, and 750 cm^{-1}; nmr (DMSO-d_6) δ 0.80–1.10 (poorly resolved t, 3, J = 7 Hz), 1.50–2.20 (m, 7), 3.00 (s with broad base, 5), 3.40–3.70 (m, 2), 4.10 (s, 1, exchanged with D_2O), 4.40 (s, 1), 6.95–7.40 (m, 4), and 11.50 (s, 1); mass spectrum, *m/e* 340 (M), 325, 297, 223, 156.

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.60; H. 7.15; N, 8.09.

Reduction of the Lactam 36 to the Amine 37. A solution of 300 mg (0.883 mmol) of **36** in tetrahydrofuran (20 ml) was added dropwise at room temperature under nitrogen to a stirred solution containing 30 mmol of lithium aluminum hydride and 30 mmol of aluminum chloride in tetrahydrofuran (60 ml). After addition the reaction mixture was stirred for 1 hr at room temperature. Saturated Rochelle salt solution was added and then concentrated ammonium hydroxide was added to make the reaction mixture basic. Extraction with methylene chloride and concentration of the dried extracts afforded a crystalline residue which was recrystallized from methylene chloride to yield 235 mg of the amine **37** (90%), mp 195–198°. An analytical sample crystallized from methylene chloride in colorless crystals: mp 203–205°; uv (EtOH) 230 (ε 31,300), 284 (6800), and 292 mμ (6600); ir (Nujol) 3500, 3260, 1175, and 745 cm^{-1}; nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz), 1.00 (s, 1, exchanged with D_2O), 1.30–2.30 (m, 7), 2.20–380 (m, 7), 7.00–7.60 (m, 4), and 7.98 (s, 1); mass spectrum *m/e* 296 (M), 239, 224, 194, 156, and 140.

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.13; H, 8.30; N, 9.49.

Hydroxynitrile 39. To a solution of 108 mg (0.365 mmol) of the indole **37** in methylene chloride (3 ml) was added 1.25 ml of 0.292 *M* triethylamine in methylene chloride solution. After being cooled to −20° under nitrogen, the stirred reaction mixture was treated dropwise with 1.25 ml of 0.322 *M* *t*-butyl hypochlorite in carbon tetrachloride solution. After the addition was complete, stirring was continued for 1 hr at −20°. The cold reaction mixture was washed with ice water, dried, and concentrated under vacuum to a foam. Tlc revealed the absence of starting material. The mass spectrum of the resulting chloroindolenine **38** showed a weak parent ion peak at *m/e* 330 and strong $[M - Cl]^+$ and $[M - HCl]^+$ fragments. Crude chloroindolenine **38** was dissolved in dimethylacetamide (3 ml) and powdered potassium cyanide (240 mg) was added, and the reaction mixture was stirred under nitrogen for 24 hr at 70°. Dimethylacetamide was removed under high vacuum (warm water bath) and xylene was added twice and evaporated under the same conditions. Hydroxynitrile **39**, 26 mg (22%), was isolated from the crude reaction mixture by preparative tlc, mp 225–230°. An analytical sample crystallized from ethanol–hexane in colorless crystals: mp 260–263°; uv (EtOH) 222 (ε 37,700), 275 (7540), 283 (8260), and 290 mμ (7700); ir (Nujol) 3410, 3220, 2225, 1070, and 745 cm^{-1}; nmr (DMSO-d_6) δ 0.85 (t, 3, J = 7 Hz), 7.00–8.00 (m, 4), and 11.00 (s, 1); mass spectrum *m/e* 321 (M), 294, 264, 181, 154, and 140.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 73.64; H, 6.94; N, 12.91.

High-resolution mass spectral data for the major ions: Calcd for $C_{20}H_{23}N_3O$: 321.18410. Found: 321.1855. Calcd for $C_{19}H_{22}N_2O$: 294.17320. Found: 294.1722. Calcd for $C_{17}H_{18}N_3$: 264.15006. Found: 264.1506. Calcd for $C_{12}H_9N_2$: 181.07657. Found: 181.0776. Calcd for $C_{11}H_8N$: 154.06568. Found: 154.0667. Calcd for $C_8H_{14}NO$: 140.10754. Found: 140.1083.

Racemic Catharanthine (33). To 300 mg (3.06 mmol) of 100% sulfuric acid was added at 0° with stirring 20 mg (0.0623 mmol) of hydroxynitrile **39**. After standing for 0.5 hr at room temperature, the reaction mixture was treated with methanol (2 ml). The mixture was made basic with solid sodium carbonate, saturated NaCl solution was then added, and the mixture was extracted with methylene chloride. Evaporation of the dried extracts gave 10 mg of an oil containing the unsaturated nitrile and the corresponding amide. The ir spectrum ($CHCl_3$) of the mixture possessed bands at 2220 and 1670 cm^{-1}; the nmr spectrum ($CDCl_3$) exhibited a vinyl proton signal at 5.40 ppm while the uv spectrum (EtOH) was that of a normal indole. The crude reaction mixture was dissolved in 20% KOH in a diethylene glycol solution (0.25 ml), and heated to 150° for 16 hr under nitrogen. After dilution with methanol, the reaction mixture was cooled to 0° and made acidic with a solution of HCl in methanol. An excess of ethereal diazomethane was added and after 15 min the solution was reacidified with HCl in methanol. Excess ethereal diazomethane was now added again. After 1 hr the reaction mixture was concentrated under vacuum and saturated sodium bicarbonate was added and the solution was extracted with benzene. Combined extracts were washed with saturated NaCl solution, dried, and concentrated to an oil which consisted of only one major compound (tlc). Preparative tlc followed by filtration through neutral alumina (activity I) in chloroform afforded 6 mg (29% from hydroxynitrile **39**) of racemic catharanthine, which crystallized from absolute methanol in colorless crystals: mp 61–63°. Synthetic and natural catharanthine had superimposable ir, uv, nmr, and mass spectra and also identical R_f value on tlc: silica gel G (EtOAc and 5% methanol–95% $CHCl_3$) and alumina G (50% $CHCl_3$–50% benzene). High-resolution data for the major ions of racemic catharanthine: Calcd for $C_{21}H_{24}N_2O_2$: 336.18377. Found: 336.1844. Calcd for $C_{14}H_{15}NO_2$: 229.11026. Found: 229.1098. Calcd for $C_{17}H_{10}N$: 228.08133. Found: 228.0829. Calcd for $C_{13}H_{12}NO_2$: 214.08680. Found: 214.0885. Calcd for $C_{12}H_{10}N$: 168.08131. Found: 168.0818. Calcd for $C_9H_{18}N$: 135.10478. Found: 135.1042. Calcd for $C_8H_{12}N$: 122.09698. Found: 122.0960.

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