Total Synthesis of Indole and Dihydroindole Alkaloids. III.[1,2] The Transannular Cyclization of Carbomethoxydihydrocleavamine and Carbomethoxycleavamine Derivatives. An Approach to Vinca and Iboga Alkaloids

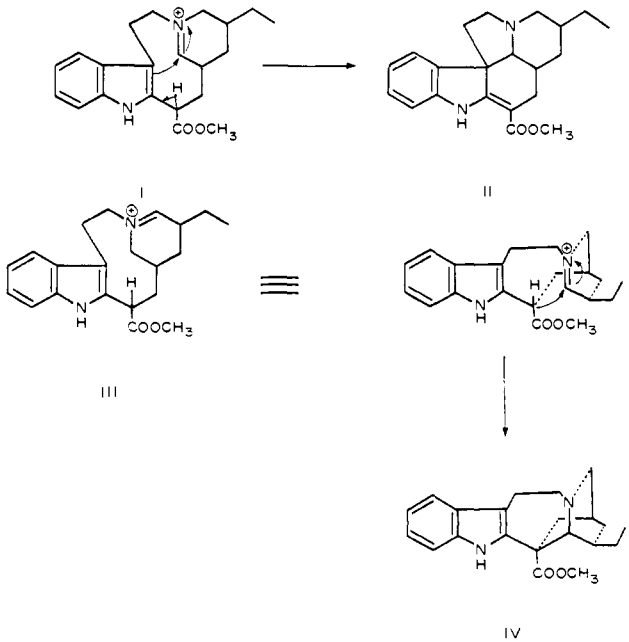
James P. Kutney, Richard T. Brown, Edward Piers, and John R. Hadfield

Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, Canada. *Received April 7, 1969*

Abstract: The transannular cyclization of 18α-carbomethoxy-4α-dihydrocleavamine has been shown to provide three products—pseudovincadifformine (7α-ethyl-5-desethylvincadifformine, V), dihydrocatharanthine (XVI), and the alkaloid, coronaridine (XVII). This cyclization reaction, apart from its interest in the total synthesis of Vinca and Iboga alkaloids, has also been employed to establish the correct absolute configuration of the Iboga family. A similar cyclization of 18β-carbomethoxycleavamine (XVIII) provides 6,7-dehydro-7-ethyl-5-desethylvincadifformine (XX) and the Vinca alkaloid, catharanthine (XIX).

The transannular cyclization of 4β-dihydrocleavamine and (−)-quebrachamine to the corresponding Aspidosperma systems was discussed in the first paper of this series,[3] and the potential of this reaction in the total synthesis of Aspidosperma alkaloids was now apparent. A possible extension of this approach to the Vinca and Iboga alkaloids was of considerable interest, and for this purpose, studies utilizing the ester derivatives of dihydrocleavamine and cleavamine were considered.

It was thought likely that the presence of the carbomethoxy function would alter the course of the transannular cyclization process in a manner which could lead directly to systems inherent in Vinca (I → II), as well as Iboga (III → IV) families.



The major component, 18α-carbomethoxy-4α-dihydrocleavamine, obtained in the reaction of catharanthine with zinc in glacial acetic acid[2,4] was initially employed to test this postulate. Reaction of this compound with mercuric acetate provided three products. The major compound, obtained as an amorphous powder, will be considered presently, while a discussion of the other substances is deferred to a later section of this publication.

This compound, which we have termed pseudovincadifformine (V), was obtained in 25% yield as a white amorphous powder, $[\alpha]^{26}D$ −503°, which analyzed well for $C_{21}H_{26}O_2N_2$. Maxima in the ultraviolet spectrum at 226, 298, and 326 mμ, and absorption bands in the infrared region at 1675 and 1610 cm^{-1} clearly indicated an α,β-unsaturated ester function as part of an α-methyleneindoline chromophore, characteristic of the vincadifformine system.[5] The nmr spectrum exhibited a complex pattern in the aromatic region and a spike at τ 6.23 due to the ester methoxyl protons, while the mass spectrum of pseudovincadifformine[6] was very typical of the vincadifformine fragmentation pattern.[5] The spectral results obtained thus far were sufficient to suggest that the anticipated transannular cyclization (I → II) had indeed occurred.

Chemical evidence in support of the conjugated ester system was provided by acid-catalyzed hydrolysis and decarboxylation of pseudovincadifformine to yield a gummy product (VI) which showed the expected spectral properties of an indolenine system. Subsequent reduction of the latter substance with lithium aluminum hydride afforded a crystalline product for which structure VII was deduced from the following evidence. Elemental analysis and mass spectrometry confirmed the molecular formula, $C_{19}H_{26}N_2$. The spectral data with the typical dihydroindole chromophore in the ultraviolet, a new NH absorption in the infrared, and the characteristic nmr pattern well known in the Aspidosperma alkaloid system, and discussed previously,[3] were in accord with this formulation. Finally, the mass spectrum of this compound,[6] with significant peaks at *m/e* 282 (M^+), 281 (M − 1), 254 (M − 28), 190, 152, 144,

(1) For a preliminary report on a portion of this work, see J. P. Kutney, R. T. Brown, and E. Piers, *J. Amer. Chem. Soc.*, **86**, 2286, 2287 (1964).

(2) Part II. J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and V. R. Nelson, *ibid.*, **92**, 1704 (1970).

(3) J. P. Kutney, E. Piers, and R. T. Brown, *ibid.*, **92**, 1700 (1970).

(4) When the initial investigation was reported (ref 1), the complete stereochemistry of this carbomethoxydihydrocleavamine derivative was not known.

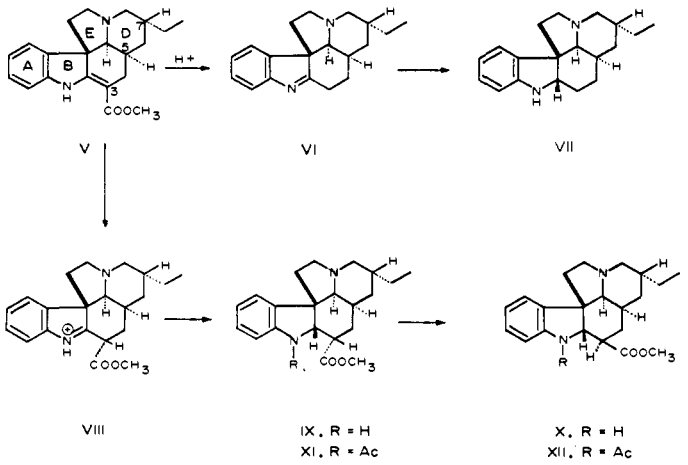
(5) C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men, and M. M. Janot, *Tetrahedron Lett.*, 235 (1962).

(6) J. P. Kutney, R. T. Brown, and E. Piers, *Lloydia*, **27**, 447 (1964).

138, 130, and a very intense peak at 124, was identical with the spectrum of the known 7β-ethyl-5-desethylaspidospermidine.[3] The sequence of reactions described above may, therefore, be expressed by the formulas V → VI → VII. A discussion of the stereochemistry indicated in these formulas will be presented later.

Further evidence for the structure of VII was obtained from the N_a-acetyl derivative, $C_{21}H_{28}O_2N_2$. The ultraviolet spectrum of the latter displayed maxima at 253, 279, and 289 mμ, and the complex multiplet in the aromatic region of the nmr spectrum had now collapsed into a broad three-proton peak centered at τ 2.85 and a one-proton signal at τ 1.87. These spectral data were in excellent agreement with N_a-acetyl-7β-ethyl-5-desethylaspidospermidine obtained previously[3] and with the known Aspidosperma alkaloid, demethoxypalosine.[7]

Additional chemical proof for the chromophoric system present in pseudovincadifformine (V) was provided by reduction of the latter with zinc and sulfuric acid[5,8] to yield two isomeric dihydro derivatives. The major product, dihydropseudovincadifformine (IX), exhibited a characteristic dihydroindole ultraviolet spectrum, while the ester carbonyl band in the infrared had now moved to the saturated region (1725 cm^{-1}). The



mass spectrum of dihydropseudovincadifformine[6] was very instructive and served to confirm the proposed structure for this product. The base peak was seen at *m/e* 124, whereas the second most intense peak was at *m/e* 254. A fragmentation process entirely analogous to that known in the Aspidosperma series and already discussed previously[3] was obviously occurring, except that in this instance the molecular ion eliminated a molecule of methyl acrylate (M]− 86) instead of ethylene to give an identical *m/e* 254 fragment. The latter ion then cleaved as before to afford the abundant fragment at *m/e* 124. The absence of a significant *m/e* 254 peak in the mass spectrum of pseudovincadifformine was due to the presence of the double bond, which prevented any elimination of methyl acrylate (or its equivalent) from the molecular ion. Finally, a comparison of the mass spectra of V and IX with those of vincadifformine and its dihydro derivative[9] revealed that both pairs of spectra were identical.

(7) B. Gilbert, J. A. Brissolese, J. M. Wilson, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Chem. Ind.* (London), 1949 (1962).

(8) P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 152 (1961).

(9) We are very grateful to Professor Carl Djerassi, Stanford University, for providing us with these samples.

The minor product (X) from the zinc–sulfuric acid reduction of pseudovincadifformine (V) also analyzed for $C_{21}H_{28}O_3N_2$ and spectral data indicated the presence of a dihydroindole and a saturated ester function. Acetylation afforded a N_a-acetyl derivative (XII) whose ultraviolet spectrum showed small but distinct differences from that of the acetyl derivative of the major dihydro compound. Moreover, the methoxyl signal in the nmr spectrum of the acetyl derivative was in a more usual position (τ 6.42), while this derivative of IX possessed an unusually high chemical shift (τ 6.83). Molecular models reveal that, in the latter, the ester group is being shielded by the aromatic ring.

Vigorous treatment with sodium methoxide converted the major component IX into a substance which proved to be *identical* with the minor product X. It was thus established that the minor component, which we refer to as isodihydropseudovincadifformine, was stereoisomeric with dihydropseudovincadifformine at the carbon atom bearing the carbomethoxy group.

The isolation and interconversion of the two dihydro compounds in this reduction process could be rationalized by analogy with a similar series of reaction performed by Smith and Edwards[8] in the akuammicine series. Thus, the first step in the reduction would involve protonation at C_3 to give the ion VIII. Addition of the proton to the β face of the molecule would occur in order to allow the carbomethoxy group to take up the more stable equatorial orientation, with ring C in the boat conformation. Reduction of the immonium system would then proceed with addition of hydrogen at C_2, again from the β face to give IX in which the B–C ring junction was the more stable *cis* form with rings C and D in chair conformations. This conversion, however, forces the carbomethoxy group into an unfavorable axial orientation. Epimerization of IX to X is then readily understood as involving a change of orientation of the carbomethoxy group from axial to equatorial.

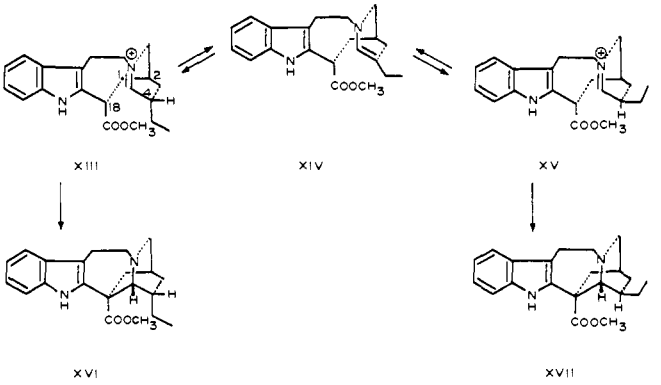
The remaining question of stereochemistry of the cyclization product (V) will be discussed only briefly, since it follows directly from the evidence already presented in previous publications. Thus, the stereochemistry at C_5 and C_7 (Aspidosperma numbering system), which correspond, respectively, to C_2 and C_4 in the starting material, 18α-carbomethoxy-4α-dihydrocleavamine, was established previously[2] as depicted in V. Furthermore, we have also established by X-ray analysis, the absolute configuration of 7β-ethyl-5-desethylaspidospermidine[3]—a cyclization product obtained from 4β-dihydrocleavamine, the latter having the same absolute configuration at C_2 as the above starting material. Therefore, with the exception of C_7, pseudovincadifformine must possess the *same* stereochemistry at the other asymmetric centers as the aspidospermidine derivative. A further confirmation of this result is available from the optical rotatory dispersion curve of pseudovincadifformine. This measurement is in excellent agreement with that published by Klyne, Schmid, *et al.*[10] for the (−)-vincadifformine series. The complete stereoformula for pseudovincadifformine is, thereby, depicted in V, and this product can now be termed as 7α-ethyl-5-desethylvincadifformine.

(10) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *Helv. Chim. Acta*, 48, 443 (1965).

The chromatography of the mixture resulting from mercuric acetate oxidation of 18α-carbomethoxy-4α-dihydrocleavamine yielded, in addition to pseudovincadifformine, small amounts of two other compounds. One of these was an amorphous alkaloid which afforded a crystalline hydrochloride, mp 221–223°. The ultraviolet spectrum of the base indicated the normal indole chromophore, while the presence of an ester carbonyl absorption at 1705 cm^{-1}, and the absence of the strong Bohlmann bands in the region between 2700 and 2800 cm^{-1} displayed by the starting material, suggested that this alkaloid was perhaps a member of the Iboga series. This suggestion was supported by the stability of the ester group to acidic hydrolysis. For example, conditions previously employed for the removal of the ester group in pseudovincadifformine had little effect in this instance. Indeed, comparison of this product with an authentic sample of coronaridine (XVII)[11,12] showed these to be identical. The other compound isolated was crystalline, mp 143–145.5°, and showed similar spectral data to those mentioned for coronaridine. The other possible transannular cyclization product, dihydrocatharanthine (XVI), was prepared in the published manner[13] and compared with our product. We were able to confirm that both compounds were identical.

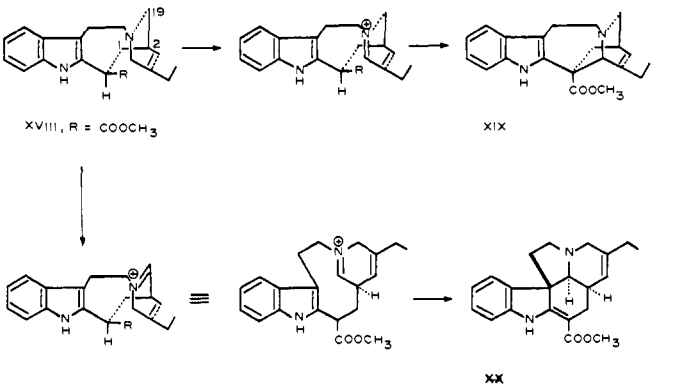
The isolation of both coronaridine and dihydrocatharanthine from this reaction indicated that an isomerization of the ethyl group at C_4 (Iboga alkaloid numbering) in the dihydrocleavamine derivative was occurring prior to the cyclization reaction. A rationalization for these results, utilizing the well-known mobility of the enamine–iminium system,[14,15] is portrayed in the scheme, XIII → XVI and XIII → XIV → XV → XVII.

The stereochemistry of the transannular cyclization in the Iboga series as shown in XVI and XVII has already been discussed elsewhere[16] and need not be dealt with here. It is sufficient to point out that this reaction was not only of value in the synthesis of the Iboga alkaloids, but it served to establish the correct absolute configuration of this alkaloid family.



XIII XIV XV XVI XVII

The obvious extension of this cyclization reaction to the carbomethoxycleavamine series was then considered. The success of this approach would provide a partial synthesis of catharanthine (XIX), the major alkaloid in *Vinca rosea* Linn.[13,17] It was also of interest to see whether the presence of the 3,4 double bond in the cleavamine derivative (XVIII) would alter the course of the transannular cyclization process. In other words, would the relative proportions of the pseudovincadifformine type product (XX) and Iboga product (XIX) remain similar to those observed in the dihydrocleavamine series or would one of these become substantially predominant.



XVIII, R = $COOCH_3$ XIX XX

A solution of 18β-carbomethoxycleavamine (XVIII)[2] in glacial acetic acid was oxidized with mercuric acetate at room temperature. The resultant amorphous product, $C_{21}H_{24}N_2O_2$, obtained in the earlier fractions of the chromatographic separation (29% yield) was examined first. The spectroscopic data quickly revealed that this product was undoubtedly 6,7-dehydro-7-ethyl-5-desethylvincadifformine (XX). Conclusive evidence was obtained from the catalytic hydrogenation of this substance which provided the known 7α-ethyl-5-desethylvincadifformine (pseudovincadifformine) (V) as shown by infrared and thin layer chromatography comparisons.

The second component (5% yield) isolated from the reaction mixture was crystalline and direct comparison with an authentic sample of catharanthine (XIX) established its complete identity.

It was, thus, established that the 3,4 double bond in the cleavamine system still allows transannular cyclization in both possible directions, one of these being of interest for the synthesis of alkaloids such as tabersonine,[18] a relative of vincadifformine, but possessing the 6,7 double bond, and the other providing a synthetic entry into the catharanthine system.

In conclusion, the results presented in this publication serve to exemplify the versatility of the transannular cyclization reaction when applied to appropriate nine-membered ring compounds of the cleavamine and quebrachamine series. The complete stereospecificity of the cyclization emphasizes its potential in the total synthesis of indole and dihydroindole alkaloids.

(11) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Amer. Chem. Soc.*, 82, 1142 (1960).

(12) We are very grateful to Dr. M. Gorman, Lilly Research Laboratories, for providing us with an authentic sample of this alkaloid.

(13) N. Neuss and M. Gorman, *Tetrahedron Lett.*, 206 (1961).

(14) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, 77, 439 (1955).

(15) N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Choudhury, *J. Org. Chem.*, 21, 344 (1956).

(16) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 44, 637 (1966).

(17) M. Gorman. N. Neuss, and N. J. Cone, *J. Amer. Chem. Soc.*, 87, 93 (1965).

(18) M. Plat, J. Le Men, M. M. Janot, J. M. Wilson, H. Budzikiewicz, L. H. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Lett.*, 271 (1962).

Experimental Section[19]

Mercuric Acetate Oxidation of 18α-Carbomethoxy-4α-dihydrocleavamine. A solution of 18α-carbomethoxy-4α-dihydrocleavamine[2,4] (4.5 g, 13.2 mmol) and mercuric acetate (10.5 g, 33 mmol) in glacial acetic acid (150 ml) was stirred at room temperature under an atmosphere of nitrogen for 40 hr. The mixture was filtered, producing 8.2 g of mercurous acetate, and the filtrate was heated under reflux (nitrogen atmosphere) for 5 hr. The acetic acid was then removed under reduced pressure, and the residue was made basic with dilute aqueous ammonia (50 ml). The resulting mixture was extracted thrice with methylene chloride. The combined extracts were washed once with water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure. The brown gummy residue was subjected to chromatography on alumina (200 g).

(a) 7α-Ethyl-5-desethylvincadifformine (Pseudovincadifformine). Elution with benzene afforded from the initial fractions 1.15 g (25%) of an amorphous white powder, which showed one component by tlc (silica gel, 1:9 ethyl acetate–chloroform). This material, 7α-ethyl-5-desethylvincadifformine (pseudovincadifformine) (V), exhibited the following physical and spectral properties: $[\alpha]^{26}D$ −503° (ethanol); λ_{max} 226, 298, 326 mμ (log ε 4.07, 4.12, 4.24, respectively); $\nu_{max}^{CCl_4}$ 3380 (NH), 2780 (Bohlmann band), 1675 (conjugated, $COOCH_3$), 1610 (C=C) cm^{-1}; nmr τ 1.05 (broad signal, 1 H, NH), 2.35–3.35 (diffuse, 4 H, aromatic), 6.23 (singlet, 3 H, $COOCH_3$), and 9.07 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28; O, 9.46. Found: C, 74.48; H, 7.80; N, 8.27; O, 9.62.

(b) Coronaridine (XVII). The later benzene fractions from the above chromatography yielded an amorphous material (450 mg); one spot on tlc (silica gel, 1:9 ethyl acetate–chloroform): λ_{max} 226, 285, 293 mμ; $\nu_{max}^{CCl_4}$ 3400 (NH), 1705 ($COOCH_3$) cm^{-1}; nmr τ 2.01 (broad signal, 1 H, NH), 2.30–3.30 (diffuse, 4 H, aromatic), 6.30 (singlet, 3 H, $COOCH_3$), and 9.10 (triplet, 3 H, CH_2CH_3). The R_f value on tlc and the infrared spectrum of this compound were identical with those of authentic coronaridine (XVIII).[12,13]

The amorphous material was taken up in anhydrous ether and dry hydrogen chloride was passed into the solution. The crystalline material was collected and recrystallized twice from acetone–ether, affording 430 mg (9.5%) of colorless needles of coronaridine hydrochloride, mp 221–223° dec; ν_{max}^{Nujol} 3160 (NH), 2530 (N^+H), 1715 ($COOCH_3$) cm^{-1}. An authentic sample of coronaridine hydrochloride,[12,13] mp 221–223° dec, did not depress the melting point of the above material, and the infrared spectra of the two samples were identical.

(c) Dihydrocatharanthine (XVI). Further elution in the above chromatography with 1:1 benzene–ether eluted a crystalline compound (400 mg) which was recrystallized from petroleum ether (bp 60–80°). The resulting material as colorless prisms (390 mg, 8.8%) showed the following properties: mp 143–145.5°; $[\alpha]^{23}D$ +49° ($CHCl_3$); λ_{max} 225, 286, 293 mμ; ν_{max}^{KBr} 3350 (NH), 1700 ($COCH_3$) cm^{-1}; nmr τ 2.00 (broad signal, 1 H, NH), 2.30–3.30 (diffuse, 4 H, aromatic), 6.38 (singlet, 3 H, $COOCH_3$), and 9.04 (triplet, 3 H, CH_2CH_3). This compound was identified as dihydrocatharanthine (XVI) by comparison (mp and mmp 143–145.5°, tlc, infrared spectra) with an authentic sample prepared by hydrogenation of catharanthine.[20]

7α-Ethyl-5-desethylaspidospermidine (VII). 7β-Ethyl-5-desethylvincadifformine (pseudovincadifformine) (V) (100 mg, 0.3 mmol) was dissolved in 2 *N* hydrochloric acid (3 ml) and the resulting solution was heated in a sealed tube at 110° for 6 hr. The cooled solution was made basic with ice-cold aqueous ammonia and then extracted thoroughly with ether. The combined ether extracts were washed once with cold water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure. The gummy residue (VI) clearly exhibited spectral properties characteristic of an indolenine: λ_{max}^{MeOH} 221, 250 (broad) mμ; $\nu_{max}^{CCl_4}$ 1605, 1575 cm^{-1}, no NH or C=O absorption. The gum was dissolved in dry tetrahydrofuran (2 ml), and the resulting solution was added to a stirred solution of lithium aluminum hydride (100 mg) in dry tetrahydrofuran (3 ml). After heating for 3 hr under reflux, the excess hydride was destroyed by careful addition of saturated aqueous sodium sulfate (10 ml). The mixture was diluted with methylene chloride and filtered, the inorganic salts being washed thoroughly with further volumes of methylene chloride. The combined filtrate and washings were washed with cold water, dried (anhydrous potassium carbonate), and evaporated under reduced pressure. The residual crystalline material was recrystallized from acetone, giving 75 mg (94%) of colorless needles of 7α-ethyl-5-desethylaspidospermidine (VII), mp 89–90°, $[\alpha]^{26}D$ −60° ($CHCl_3$), one spot on tlc (silica gel, 1:1 ethyl acetate–chloroform); λ_{max} 243, 295 mμ (log ε 3.81, 3.45, respectively); λ_{min} 223, 269 mμ (log ε 3.53, 2.69, respectively); ν_{max}^{Nujo} 3230 (NH), 1600 (aromatic C=C) cm^{-1}; nmr τ 2.75–3.55 (diffuse, 4 H, aromatic), 6.34–7.10 (diffuse, 4 H), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 81.00; H, 9.38; N, 9.86.

N_a-Acetyl-7α-ethyl-5-desethylaspidospermidine. To a solution of 7α-ethyl-5-desethylaspidospermidine (VII) (100 mg, 0.35 mmol) in dry pyridine (1 ml) was added acetic anhydride (2 ml) and the resulting solution was heated on a steam bath for 1 hr. The cooled solution was poured into ice-cold dilute aqueous ammonia and the resultant mixture was extracted thoroughly with ether. The combined ether extracts were washed thrice with cold water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure. The residual crystalline material was recrystallized from petroleum ether (bp 60–80°), affording 105 mg (91%) of the N_a-acetyl compound as colorless needles, mp 108–109°; λ_{max} 212, 253, 279, 289 mμ (log ε 4.35, 4.13, 3.58, 2.89, respectively); λ_{min} 226, 276, 287 mμ (log ε 3.51, 3.56, 3.45, respectively); ν_{max}^{KBr} 1655 ($NC(=O)CH_3$), 1595 (aromatic C=C) cm^{-1}; nmr τ 1.87 (unresolved multiplet, 1 H, C-17 proton), 2.70–3.10 (diffuse, 3 H, aromatic), 6.00 (quartet, 1 H, C-2 proton), 6.67–7.07 (diffuse, 2 H, "aspidospermine fingerprint,") 7.78 (singlet, 3 H, $NC(=O)CH_3$), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63; O, 4.93. Found: C, 77.14; H, 8.64; N, 8.97; O, 5.07.

Reduction of 7α-Ethyl-5-desethylvincadifformine (Pseudovincadifformine) (V) with Zinc and Sulfuric Acid. To a solution of 7α-ethyl-5-desethylvincadifformine (V) (1.0 g, 3 mmol) in 10% methanolic sulfuric acid (500 ml) was added zinc dust (150 g). After the resultant mixture had been heated under reflux for 30 min it was filtered and the filtrate was evaporated under reduced pressure. The residue was made basic with ice-cold aqueous sodium carbonate and the mixture was then thoroughly extracted with ether. The combined ether extracts were washed with water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure. The residual gum, which was shown to be a mixture of two components by tlc (silica gel, 1:9 ethyl acetate–chloroform), was subjected to column chromatography on alumina (40 g).

(a) 7α-Ethyl-5-desethyldihydrovincadifformine (Dihydropseudovincadifformine) (IX). Elution with 1:1 benzene–petroleum ether (bp 30–60°) afforded 640 mg (64%) of an amorphous powder (from ether). This material (IX) showed one component by tlc (silica gel, 1:9 ethyl acetate–chloroform), $[\alpha]^{24}D$ −16° (ethanol); λ_{max} 244, 299 mμ (log ε 3.82, 3.45, respectively); $\nu_{max}^{CCl_4}$ 3380 (NH), 1720 ($COOCH_3$), 1605 (aromatic C=C) cm^{-1}; nmr τ 2.70–3.60 (diffuse, 4 H, aromatic), 6.33 (singlet, 3 H, $COOCH_3$), and 9.12 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.97; H, 8.13; N, 8.32.

Acetylation of the above material with acetic anhydride in pyridine gave amorphous N_a-acetyl-7α-ethyl-5-desethyldihydrovincadifformine (N_a-acetyldihydropseudovincadifformine) (XI) which showed one spot on tlc (silica gel, 1:9 ethyl acetate–chloroform); $[\alpha]^{23}D$ +28° (ethanol); λ_{max} 253, 282, 291 mμ (log ε 4.01, 3.49, 3.45, respectively); $\nu_{max}^{CCl_4}$ 1725 ($COOCH_3$), 1660 ($NC(=O)CH_3$), 1595 (aromatic C=C) cm^{-1}; nmr τ 2.30 (unresolved multiplet, 1 H, C-17 proton), 2.80–3.20 (diffuse, 3 H, aromatic), 6.83 (singlet, 3 H, $COOCH_3$), 7.75 (singlet, 3 H, $NC(=O)CH_3$), and 9.08 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.26; H, 8.24; N, 7.51.

(b) 7α-Ethyl-5-desethylisodihydrovincadifformine (Isodihydropseudovincadifformine) (X). Further elution in the above chromatography with 1:1 benzene–ether afforded 80 mg (8%) of compound X, which was an amorphous powder and showed one spot on tlc (silica gel, 1:9 ethyl acetate–chloroform); $[\alpha]^{24}D$ −132° (ethanol); λ_{max} 244, 297 mμ (log ε 3.83, 3.45, respectively); $\nu_{max}^{CCl_4}$ 3380 (NH), 1720 ($COOCH_3$), 1605 (aromatic C=C) cm^{-1}; nmr τ 2.85–3.55 (diffuse, 4 H, aromatic), 6.32 (singlet, 3 H, $COOCH_3$), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.38; H, 8.32; N, 8.29.

Acetylation of the above material with acetic anhydride in pyridine afforded amorphous N_a-acetyl-7α-ethyl-5-desethylisodihydrovincadifformine (N_a-acetylisodihydropseudovincadifformine)

(19) For general information, see ref 3.

(20) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **43**, 1545 (1965).

(XII) which showed one spot on tlc (silica gel, 1:9 ethyl acetate–chloroform) and gave $[\alpha]^{24}D$ +3° (ethanol); λ_{max} 250, 278, 296 mμ (log ε 4.09, 3.47, 3.39, respectively); $\nu_{max}^{CCl_4}$ 1725 ($COOCH_3$), 1660 ($NC(=O)CH_3$), 1595 (aromatic C=C) cm^{-1}; nmr τ 2.75–3.20 (diffuse, 4 H, aromatic), 6.42 (singlet, 3 H, $COOCH_3$), 7.86 (singlet, 3 H, $NC(=O)CH_3$), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91. Found: C, 72.57; H, 8.10.

Epimerization of 7α-Ethyl-5-desethyldihydrovincadifformine (Dihydropseudovincadifformine) (IX). To a solution of compound IX (200 mg, 0.6 mmol) in methanol (2 ml) containing sodium methoxide (60 mg) was added saturated methanolic magnesium methoxide (2 ml). The resulting solution was sealed in a glass tube and heated at 100° for 5 hr. The cooled solution was poured into water (20 ml) and extracted immediately with ether (4 × 20 ml). The combined ether extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residual amorphous powder (165 mg, 83%) was identical with 7α-ethyl-5-desethylisodihydrovincadifformine (isodihydropseudovincadifformine) (X), as shown by thin layer chromatography and infrared spectra.

Mercuric Acetate Oxidation of 18β-Carbomethoxycleavamine (XVIII). A solution of compound XVIII (500 mg, 1.5 mmol) and mercuric acetate (1.8 g, 5.7 mmol) in glacial acetic acid (60 ml) was stirred at room temperature under an atmosphere of nitrogen for 75 min. The precipitated mercurous acetate (1.13 g) was filtered off and the filtrate was treated with hydrogen sulfide gas. The resulting mixture was filtered through Celite, the filtrate was evaporated under reduced pressure at room temperature, and the residue was treated with aqueous ammonia (55 ml). The aqueous alkaline mixture was extracted with dichloromethane (3 × 50 ml), the combined extracts were washed once with water, and then dried over anhydrous sodium sulfate. Evaporation of the solvent produced a light brown oily residue (465 mg), which was subjected to column chromatography on alumina (Woelm, activity III, 50 g).

(a) 6,7-Dehydro-7-ethyl-5-desethylvincadifformine (6,7-Dehydropseudovincadifformine) (XX). Elution with petroleum ether (bp 30–60°)–benzene (2:1) (50 ml) afforded a colorless oil (31 mg), which rapidly decomposed in the presence of air to an intensely violet colored gum. The latter was not characterized. Further elution with the same solvent mixture (120 ml) provided 145 mg (29%) of compound XX as an amorphous solid: λ_{max} 222, 298, 327 mμ (log ε 4.09, 4.10, 4.22, respectively); λ_{min} 258, 307 mμ (log ε 3.19, 4.06, respectively); $\nu_{max}^{CHCl_3}$ 3340 (NH), 1660 ($COOCH_3$), 1600 (C=C) cm^{-1}; nmr (100 MHz) τ 1.06 (singlet, 1 H, NH), 2.70–3.36 (diffuse, 4 H, aromatic), 4.57 (multiplet, 1 H, olefinic H), 6.33 (singlet, 3 H, $COOCH_3$), 8.00 (quartet, 2 H, CH_2CH_3), and 9.00 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33; O, 9.51; mol wt 336. Found: C, 74.82; H, 7.21; N, 8.18; O, 9.46; mol wt 336 (high-resolution mass spectrometry).

Hydrogenation (room temperature and atmospheric pressure) of the above amorphous material in ethyl acetate over 10% palladium on charcoal afforded an amorphous product which was shown by infrared spectrum and tlc (silica gel, 1:9 ethyl acetate–chloroform) to be identical with 7α-ethyl-5-desethylvincadifformine (pseudovincadifformine) (V).

(b) Catharanthine (XIX). Further elution in the above column chromatography with petroleum ether (bp 30–60°)–benzene (1:1) afforded 29 mg of a crystalline material which, after recrystallization from methanol (25 mg, 5%), showed mp 56–59°. This material was shown to be identical with catharanthine (XIX) by direct comparison (mp and mmp 56–59°, infrared spectrum) with an authentic sample.

Acknowledgment. We gratefully acknowledge financial support from the National Research Council of Canada, National Cancer Institute of Canada, and the Medical Research Council of Canada. One of us (R. T. B.) is indebted to the Canadian Commonwealth Scholarship and Fellowship Committee for a scholarship during this study.

Total Synthesis of Indole and Dihydroindole Alkaloids. IV.[1,2] The Total Synthesis of *dl*-Dihydrocleavamine, *dl*-Carbomethoxydihydrocleavamine, *dl*-Coronaridine, *dl*-Dihydrocatharanthine, and *dl*-Ibogamine. A General Entry into the Iboga and Vinca Alkaloids

James P. Kutney, Walter J. Cretney, Philip Le Quesne, Bruce McKague, and Edward Piers

Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, Canada. *Received April 7, 1969*

Abstract: The total synthesis of *dl*-dihydrocleavamine, *dl*-carbomethoxydihydrocleavamine, *dl*-coronaridine, *dl*-dihydrocatharanthine, and *dl*-ibogamine is described. The sequence utilizes in its penultimate step a reductive cleavage reaction to generate the nine-membered ring system of the cleavamine molecule.

The general utility of appropriate nine-membered ring intermediates of the cleavamine and quebrachamine series in the partial synthesis of various members of the Aspidosperma, Vinca, and Iboga alkaloids has been demonstrated in previous publications.[2] It was, therefore, clear that the completion of laboratory syntheses of these intermediates would similarly complete the total syntheses of these various alkaloids. It is the purpose of this publication to describe our successful sequence to several relatives of the cleavamine family.

The stereochemical problems associated with the syntheses of such molecules are often considerable, but in this instance these are simplified markedly by the fact that the transannular cyclization process is completely stereospecific. As we have shown previously,[2,3]

(1) For a preliminary report on a portion of this work, see J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, 88, 4756 (1966).

(2) Part III. J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *ibid.*, 92, 1708 (1970).

(3) Part I. J. P. Kutney, E. Piers, and R. T. Brown, *ibid.*, 92, 1700 (1970).