amounts of nitrosyls under the conditions reported above. Alternatively, these side products may arise from the disproportionation[28] of Ru(III) in alkaline solution into Ru(II) and Ru(IV), with Ru(IV) catalyzing the aquation of $Ru(NH_3)_6^{3+}$ (or $Ru(NH_3)_5NH_2^{2+}$ at pH's >11).

Adding solutions of $Ru(NH_3)_6^{3+}$ (10^{-2} *M*) to oxygen saturated solutions of $^{15}NH_3$ (0.28 M) produced $Ru(NH_3)_5{}^{14}NO^{3+}$, exclusively.[29] This establishes that it is the coordinated ammonia which is oxidized, even in the presence of a large excess of aqueous ammonia. No evidence for ammonia exchange was observed in a similar system by allowing $Ru(NH_3)_6^{3+}$ to stand in the presence of argon saturated 0.3 *M* $^{15}NH_3$ for 20 hr. The hexaammine complex from the latter reaction was collected by ion exchange, and the 4 *M* HCl rinse was concentrated by evaporation to dryness. The product was then converted to $Ru(NH_3)_5NO^{3+}$ using alkaline peroxide. No $Ru(NH_3)_5{}^{15}NO^{3+}$ was observed.[29]

If the aerial oxidation of ammonia is allowed to proceed in 0.1 *M* KOH, the yield of $Ru(NH_3)NO^{3+}$ does not appear to increase appreciably after 15 min, but rather anation of the nitrosyl complex proceeds to produce increasing amounts of *t*-$Ru(NH_3)_4(NO)OH^{2+}$.[21] In our experiments at pH 13, a weak, sharp band appeared at 2095 cm^{-1} in the ir spectrum of the solid product. The source of the latter band can be attributed to $Ru(NH_3)_5N_2^{2+}$ arising from the self-dismutation of $Ru(NH_3)_5NO^{3+}$ in alkaline solution.[30,31]

Variation of the pH of the reaction markedly affects the yield of Ru nitrosyls. The optimum pH at 25° appears to be 13 (KOH). At pH 11 (HPO_4^{2-}–PO_4^{3-} or CO_3^{2-}–HCO_3^- buffers) no nitrosyl product was observed using the sensitive ir method described above. Working at pH 13 permits one to obtain sufficient yields of $Ru(NH_3)_5NO^{3+}$ on the order of minutes instead of hours at pH 12. As expected, lowering the temperature or using an air flow (instead of oxygen) reduces the rate (not the yield) at which the nitrosyls are produced.

The use of HO_2^-–H_2O_2 (pH 11.5) in argon saturated $Ru(NH_3)_6^{3+}$ still produces $Ru(NH_3)_5NO^{3+}$, while $Ru(NH_3)_5Cl^{2+}$ produces little, if any Ru nitrosyl. The nitrosyl is produced rapidly (t = 15 min) at pH 11.5 in yields of >71%. The improved yields of nitrosyl in alkaline peroxide bears a strong resemblance to the persulfate method[32] for preparing $[Ru(NH_3)_5NO]SO_4{\cdot}0.5S_2O_8$. The latter, high yield preparation of the nitrosyl requires an ammonia buffer, $Ru(NH_3)_5Cl^{2+}$ and $(NH_4)_2(S_2O_8)$. This suggests that in cases where oxidants (known to proceed by free-radical processes)[33] are used, the oxidation of ammonia to nitrosyl competes much more favorably than the aquation reaction.

The utility of alkaline solutons in preparing ruthenium complexes from $Ru(NH_3)_6^{3+}$ has only recently been appreciated. Amido[34,35] complexes have been implicated in the reaction of $Ru(NH_3)_6^{3+}$ with $S_2O_3^{2-}$ and SO_3^{2-} (to produce sulfamate)[36] and with NO (to produce $Ru(NH_3)_5N_2^{2+}$).[37,38] The ability of paramagnetic ruthenium(III) in alkaline solution to activate ammonia is now apparent. The facile, aerial oxidation of coordinated ammonia described above suggests that potential homogeneous systems can be devised to catalytically generate NO_x, NH_2OH (coordinated), or even NO_3^- and to incorporate these forms of activated nitrogen into organic substrates. Further extensions of our model system may lead to metal centers requiring less extreme pH's for the controlled, direct oxidation of NH_3.

Acknowledgment. We wish to thank the National Science Foundation (G.P. 38513X) for financial support.

References and Notes

(1) E. Van Tamelen, *Acc. Chem. Res.*, **3**, 361 (1970).
(2) A. E. Shilov, *Russ. Chem. Rev.*, **43**, 378 (1974).
(3) D. R. Safrany, *Sci. Am.*, (Oct) 64 (1974).
(4) G. C. Sweeney, "Technology and Economics of Ammonia Production", presented at Symposium on Nitrogen Fixation, University of Washington, Pullman, Wash., May 1974.
(5) E. E. Van Tamelen and H. Rudler, *J. Am. Chem. Soc.*, **92**, 5253 (1970).
(6) M. E. Volpin, V. B. Shur, R. V. Kudryavtsev, and L. A. Prodayko, *Chem. Commun.*, 1038 (1968).
(7) A. E. Shilov, *Russ. Chem. Rev.*, **43**, 378 (1974).
(8) W. Latimer, "Oxidation Potentials", 2nd ed, Prentice-Hall, Englewood Cliffs, N.J., 1952, p 129.
(9) K. Jockers, *Nitrogen*, **No. 50**, 27 (1967).
(10) F. Steel, *Fortschr. Chem. Forsch*, **4**, 301 (1963).
(11) Reference 8, p 91.
(12) J. Broomhead and H. Taube, *J. Am. Chem. Soc.*, **91**, 1261 (1969).
(13) S. Diamond and H. Taube, to be published, J. Amer. Chem. Soc., 1975; *J. Chem. Soc., Chem. Commun.*, 622 (1974); private communication with S. Diamond.
(14) J. N. Armor, R. Furman, and M. Z. Hoffman, *J. Am. Chem. Soc.*, **97**, 1737 (1975).
(15) J. A. Stanko, C. A. Tollinche, and T. H. Risby, *Can. J. Chem.*, in press, J. A. Stanko, personal communication.
(16) K. R. Grudy, C. A. Reed, and W. R. Roper, *Chem. Commun.*, 1501 (1970).
(17) K. R. Laing and W. R. Roper, *Chem. Commun.*, 1556 (1968).
(18) F. Bottomley and J. R. Crawford, *Chem Commun.*, 200 (1971).
(19) W. L. Bowden, W. F. Little, and T. J. Meyer, *J. Am. Chem. Soc.*, **96**, 5605 (1974).
(20) R. Eisenberg and C. D. Meyer, *Acc. Chem. Res.*, **8**, 26 (1975).
(21) S. D. Pell and J. N. Armor, *Inorg. Chem.*, **12**, 873 (1973).
(22) J. N. Armor, M. Buchbinder, and R. Cheney, *Inorg. Chem.*, **13**, 2990 (1974).
(23) J. N. Armor, Ph.D. Thesis, Stanford University, May 1970.
(24) J. N. Armor and M. Z. Hoffman, *Inorg. Chem.*, **14, 444** (1975).
(25) L. H. Vogt, J. L. Katz, and S. E. Wiberley, *Inorg. Chem.*, **4**, 1157 (1965).
(26) P. Ford and C. Sutton, *Inorg. Chem.*, **8**, 1544 (1969).
(27) S. D. Pell, Ph.D. Thesis, Boston University, Sept 1975.
(28) DeF. P. Rudd and H. Taube, *Inorg. Chem.*, **10**, 1543 (1971).
(29) R. Cheney and J. N. Armor, manuscript in preparation: ν_{NO} for $Ru(NH_3)_5{}^{15}NO^{3+}$ is 1875 cm^{-1}.
(30) F. Bottomley and J. Crawford, *J. Am. Chem. Soc.*, **94**, 9092 (1972).
(31) F. Bottomley, S. G. Clarkson, and E. Kiremire, *J. Chem. Soc., Chem. Commun.*, 91 (1975).
(32) K. Gleu and I. Buddecker, *Z. Anorg. Allg. Chem.*, **268**, 202 (1952).
(33) J. D. White and H. Taube, *J. Phys. Chem.* 7**4**, 4142 (1970).
(34) J. N. Armor, *J. Inorg. Nucl. Chem.*, **35**, 2067 (1973).
(35) D. Waysbort and G. Navon, *Chem. Commun.*, 1410 (1971).
(36) J. N. Armor and H. Taube, *Inorg. Chem.*, **10**, 1570 (1971).
(37) S. D. Pell and J. N. Armor, *J. Am. Chem. Soc.*, **94**, 686 (1972).
(38) S. D. Pell and J. N. Armor, *J. Am. Chem. Soc.*, **95**, 7625 (1973).
(39) Send all correspondence to Central Research Laboratory, Allied Chemical Corporation, P.O. Box 1021R, Morristown, N.J. 07960.

S. D. Pell, J. N. Armor*[39]
Department of Chemistry, Boston University
Boston, Massachusetts 02215

Received April 18, 1975

Absolute Stereochemistry of the Bisindole Alkaloids of the Vinblastine Type. Circular Dichroism Studies

Sir:

A number of bisindole alkaloids have been isolated from *Vinca rosea L.* (*Catharanthus roseus* G. Don). Of particular importance is the antitumor activity possessed by vinblastine (**1**), vincristine (**2**), and some of their analogs.[1,2] In order to provide an opportunity for detailed studies on structure–activity relationships in this area, attempts have been made in recent years to synthesize such "dimeric" substances. The approach selected should ideally provide sufficient versatility to allow preparation of novel synthetic variants as well as the natural systems. In one series of investigations[3] it has been shown that chloroindolenine intermediates can provide such versatility and in more recent studies a family of synthetic dimers has been obtained for biological evaluation. Unfortunately the previous data reported[3] did not allow an unambiguous stereochemical assignment at C_{18}', the chiral center linking the indole and dihydroindole units. In fact, up to this time, no unambiguous method, except for a complete X-ray determination, was available for

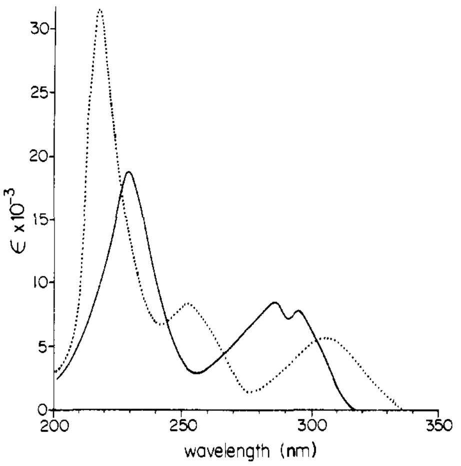
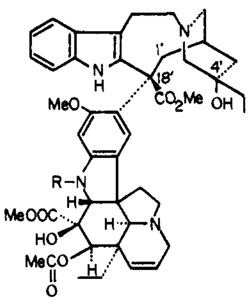
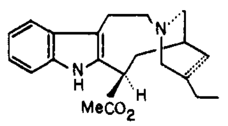


Figure 1. Ultraviolet absorption spectra of 18β-carbomethoxycleavamine (**3**) (—) and vindoline (**4**) (• • •), solvent methanol.

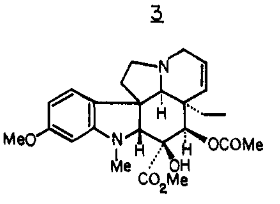


1 R = Me, Vinblastine

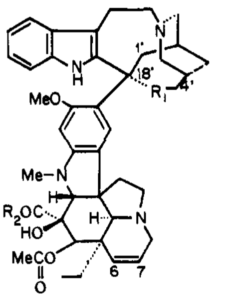
2 R = CHO, Vincristine



3



4

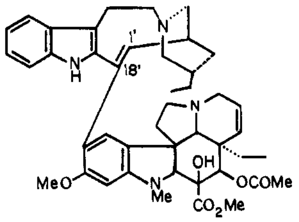


5 R_1 = H, R_2 = OMe

6 R_1 = H R_2 = OMe (6,7-dihydro-)

7 $R_1 = CO_2Me$, R_2 = OMe (6,7-dihydro-)

8 R_1 = H, $R_2 = NHNH_2$



9

determining the configuration at this important center. Recently[4] we have shown by the X-ray technique that the synthetic substances possess the "unnatural" stereochemistry at C_{18}' as shown in structures **5–8**. Since Moncrief and Lipscomb[5] had earlier performed an X-ray analysis of the natural systems it is clear that two families of compounds are now available which differ at the important C_{18}' chiral center. Utilizing the natural and synthetic substances it is now possible to evaluate the application of circular dichroism (CD) for the purpose of determining the configuration at C_{18}' in any dimeric substances which become available from subsequent synthetic studies. The results presented below reveal that this simple method can indeed be employed for the solution of this stereochemical problem.

The ultraviolet (uv) spectrum of the indole chromophore is characterized by two bands at ca. 280 and 225 nm (Figure 1). The long wavelength band, which usually shows some fine structures, has been shown to be composed of two overlapping electronic transitions (^1L_b and ^1L_a).[6] The high intensity band at ca. 225 nm is assumed to be a ^1B_a transition.[7] The indoline chromophore, on the other hand, has a uv spectrum characteristic of benzenoid compounds. Thus vindoline (**4**) has absorption bands at 305, 252, and 217 nm (MeOH), corresponding to the ^1L_b, ^1L_a, and ^1B transitions, respectively (Figure 1). Since bisindole alkaloids of the vinblastine type have a number of asymmetric centers, which can perturb the indole and indoline electronic transitions, one obtains fairly complex CD spectra. To get structural information from these complex data of the long wavelength transitions would be a difficult, if not impossible task. On the other hand, the chiral center at C_{18}' has the unique property in that it controls the relative geometry of the constituent indole and indoline moieties. Thus optical rotation arising from dipolar coupling between electronic transitions of these two chromophores can in turn be correlated to the absolute stereochemistry at this assignment center.

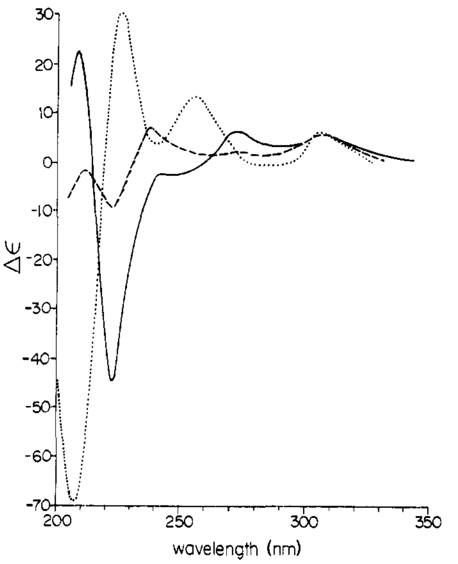


Figure 2. Circular dichroism spectra of vinblastine (**1**) (• • •), (**7**) (—), and (**9**) (- - -), solvent methanol.

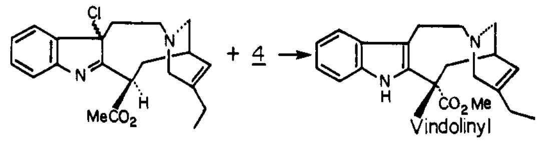
Table I. CD Data (nm) of Some Bisindole Alkaloids at the 200–230-nm Spectral Region

Compounds	1st Cotton effect (Δε)	2nd Cotton effect (Δε)
Vinblastine 1	224 (+30)	207 (−69)
Vincristine 2	229 (+19)	205 (−37)
Leurosine	224 (+32.5)	212 (−64)
Isoleurosine	224 (+31)	211 (−55)
Pleurosine	224 (+44)	211 (−69)
Leurosidine	223 (+23)	210 (−51)
5	221 (−57)	210 (+44)
6	221 (−49)	206 (+38)
7	222 (−45.5)	209 (+23)
8	223 (−33)	210 (+20)
10	220 (−52)	211 (+37)

It is well known that the dipole-coupling mechanism plays a major part in the development of Cotton effects for strong transitions.[8] Thus the two intense absorption bands below 230 nm of the indole and indoline chromophores can most likely interact to give rise to characteristic split Cotton effects. This is in fact observed from the CD of six naturally occurring[9] and four synthetic "dimers"[3,10] (**5–8**, Table I and Figure 2). It can be seen that these two series of compounds, which have opposite stereochemistry at C_{18}' have split Cotton effects of opposite sign. Thus the CD data at this spectral region can be used empirically to determine the absolute stereochemistry at the C_{18}' chiral center.

The naturally occurring and synthetic bisindole alkaloids

5–8 differ also in the stereochemistry at C_4' in that the former compounds have a 4'α-ethyl group while the synthetic dimers have a 4'β-ethyl group. Since the 4'-ethyl group would prefer the equatorial configuration, the conformation of the six-membered ring could be different between these two series of compounds. The relative insignificance of conformational changes in this part of the molecule to the overall effect on the CD data is revealed in the case of synthetic dimer **10** (Table I).[11] Chemical correlation[4] of **10** with **7** established its complete structure and absolute configuration. The signs of the Cotton effects in **10** are as expected for the unnatural stereochemistry at C_{18}'.



11 10

Finally the relative sensitivity of the CD effects to changes in chirality at C_{18}' are seen in the $\Delta^{1',18'}$-dimer **9**.[10] In the latter compound, the C_{18}' trigonal center decreases the angle of twist between the two chromophores and this results in a greatly decreased split Cotton effect.

As mentioned previously, work in this area of importance to the partial or total synthesis of antitumor alkaloids has required the X-ray diffraction for solution of the problem of C_{18}' stereochemistry. As the above results reveal it is now possible to monitor this dimerization reaction through observation of the CD spectrum and thereby provide a simple method for evaluating the chirality of compounds from future studies.

Although the above CD studies are based on an empirical correlation of the synthetic and natural dimers there is a theoretical basis for the observed changes in the CD curves. The "exciton chirality method" of Harada and Nakanishi,[12] which correlates signs of Cotton effects arising from dipolar interaction between aromatic chromophores with absolute configurations, is well documented and is based on molecular exciton theory.[13] In order to apply this method to the present case, however, it is necessary to know the polarization of the electronic transition moments involved. Unfortunately, this information is presently unavailable, so that further studies along this line are desirable.

Acknowledgments. This work was supported by the National Research Council of Canada (J.P.K.), by National Institutes of Health Grant No. CA-11095 (A.I.S), and by Contract NO1-CM-23223 (J.P.K.) from the Divison of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Md.

References and Notes

(1) For a general review of the chemistry, see A. A. Gorman, M. Hesse, and H. Schmid in "The Chemical Society, Specialist Periodical Reports, The Alkaloids", Vol. 1, Chapter 14, 1970.
(2) For a general review of the biological activity see, R. B. Livingstone and S. K. Carter, "Single Agents in Cancer Chemotherapy", IFT/Plenum, New York, N.Y., 1970, pp 279–317.
(3) J. P. Kutney, J. Beck, F. Bylsma, and W. J. Cretney, *J. Am. Chem. Soc.*, **90**, 4504 (1968).
(4) J. P. Kutney, J. Cook, K. Fuji, A. M. Treasurywala, J. Clardy, J. Fayos, and H. Wright, *Heterocycles*, **3**, 205 (1975).
(5) J. W. Moncrief and W. N. Lipscomb, *J. Am. Chem. Soc.*, **87**, 4963 (1965).
(6) G. Weber, *Biochem. J.*, **75**, 335 (1960).
(7) J. R. Platt, *J. Chem. Phys.*, **19**, 101 (1951).
(8) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).
(9) Kindly provided by N. Neuss, Eli Lilly and Company, Indianapolis, Ind.
(10) J. P. Kutney, E. Jahngen, and R. Imhof, unpublished results.
(11) This compound has been prepared at the University of British Columbia by the chloroindolenine method employing HCl in methanol[3,4] and at Yale University employing $ZnCl_2$–CF_3COOH.
(12) N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972).
(13) A. S. Davydov, "Theory of Molecular Excitons", M. Kasha and M. Oppenheimer, Jr., Translators, McGraw-Hill, New York, N.Y., 1962.

James P. Kutney,* Donald E. Gregonis
Rene Imhof, Isamu Itoh, Edwin Jahngen
Department of Chemistry, University of British Columbia
Vancouver, British Columbia, V6T 1W5, Canada

A. Ian Scott,* W. K. Chan
Sterling Chemistry Laboratory, Yale University
New Haven, Conneticut 06520

Received March 24, 1975

Reaction of Lithium Vapor with Alkenes. A New Synthesis for Polylithium Compounds

Sir:

It has recently been reported that at elevated temperatures lithium vapor reacts with chlorocarbons[1] and with carbon vapor[2] to produce novel polylithium organic compounds. The reaction of excess lithium vapor with several alkenes has been studied and it has been found that both substitution of lithium for hydrogen and addition of lithium to the double bonds occur to produce polylithiated alkanes and alkenes.

A large excess of lithium (>15 g) was vaporized at 700–800° in an evacuated stainless steel reactor (Figure 1) with an inconel Knudsen cell (A) which was heated resistively. Simultaneously, the alkene was slowly vaporized into the circular tube (B) above the Knudsen cell. During the 30-min reaction period, products were collected as solids on the liquid nitrogen cooled cold finger (C). The pressure in the reactor during the reaction was approximately 10^{-3} Torr. After the reaction the contents of the reactor were warmed to room temperature and removed under argon.

The very reactive solids obtained from the reaction looked metallic but were very brittle. Frequently portions of the solid were colored, the hue varying from red to black. The products were carefully hydrolyzed by both H_2O and D_2O in a standard vacuum line to yield alkenes and alkanes which were identified by comparing ^1H NMR data, mass spectral fragmentation patterns and, if necessary, GLC retention times to authentic samples. The relative amount of lithiation was determined by low resolution mass spectroscopy (70 eV) of the deuterated alkenes recovered from the

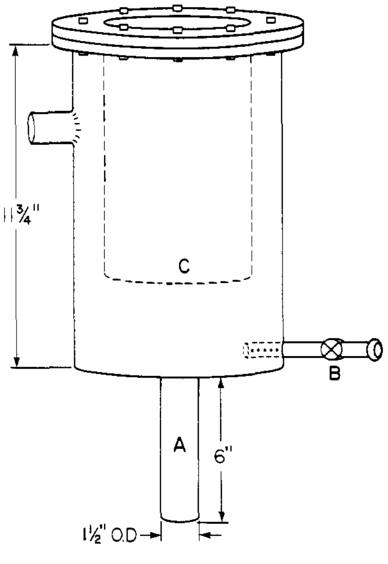


Figure 1. Inverted Dewar type reactor.