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METHODS FOR INDOLE ALKALOID SYNTHESIS: REACTIONS OF N-ARYLSULFONYLENAMINES WITH ELECTROPHILES. AN EXPEDITIOUS SYNTHESIS OF (±)-EBURNAMONINE.

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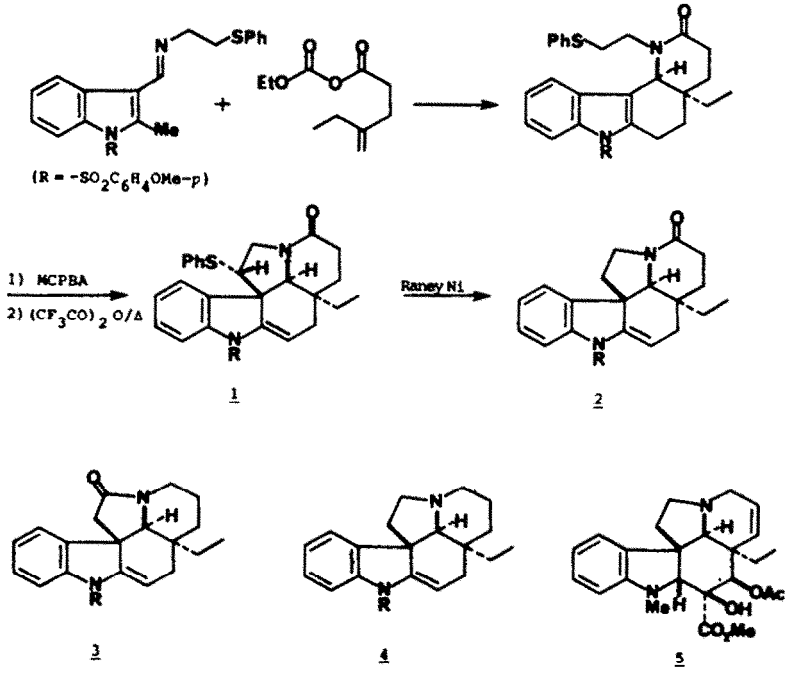
Abstract - Treatment of 4 with MCPBA gave 9. The pentacyclic amide 3 on exposure to cyanogen chloride gave the *cis*-chlorohydrin 20, and the geminal dichloride 21. When 21 was treated with HCl/MeOH it rapidly rearranged to eburnamonine lactam 22.

Dedicated to Professor Ralph Raphael, F.R.S., on the occasion of his 65th birthday.

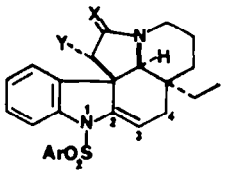
During the last four years we have developed the indole-2,3-quinodimethane strategy for the synthesis of indole alkaloids.[1] As depicted in SCHEME 1, this route enables the central structural core of the Aspidosperma type indole alkaloids to be assembled in an efficient and highly convergent manner. The pentacyclic amide 2 is available as shown, and a complimentary route provides the



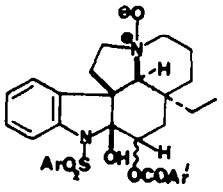
1 2 3 4 5

SCHEME 1

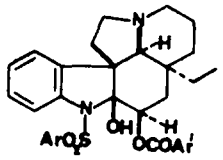
isomeric pentacyclic amide 3.[2] Since the more highly functionalized Aspidosperma alkaloids such as vindorosine 5 have oxygen and carbon substituents at C-3/4, we were concerned with investigating the reactivity of the N-arylsulfonylenamine group in 2, 3, and 4, towards a range of oxygen and carbon electrophiles. In this paper some of the results of this study are described.



3 Y = H, X = O
4 Y = H, X = H,H
6 Y = SPh, X = O
7 Y = SPh, X = S



8
Ar = C_6H_4OMe-*p*
Ar^1 = C_6H_4Cl-*m*



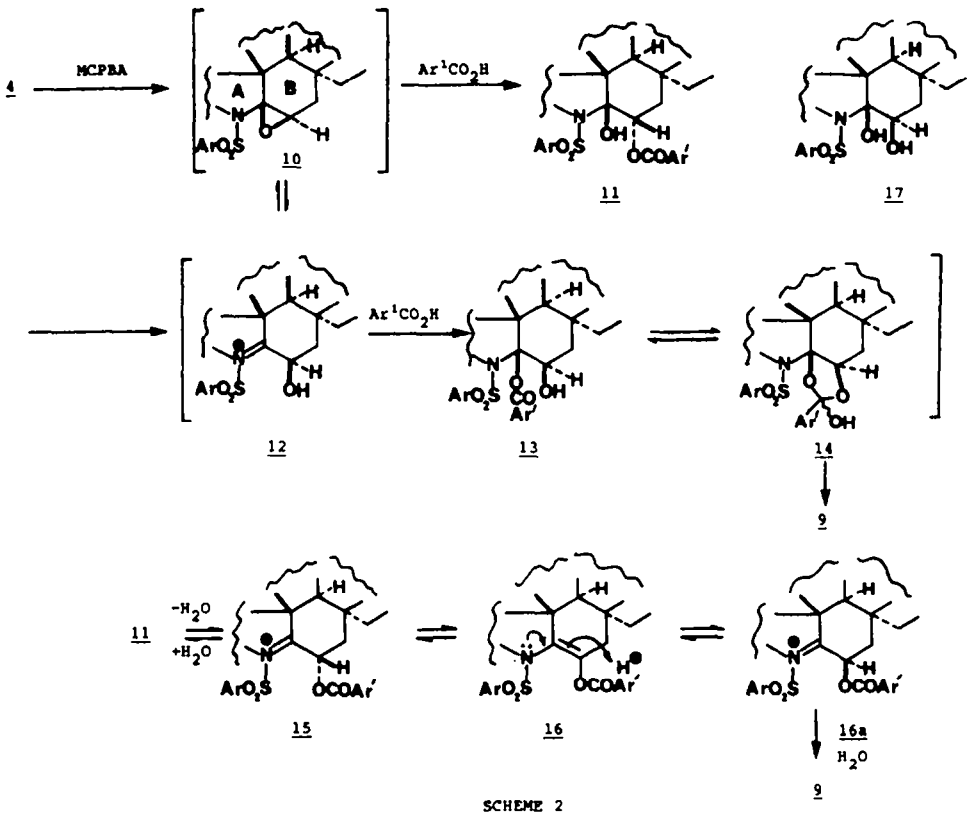
9

The previously described α-thiophenylamide 6,[2] was converted into the thioamide 7 using Lawesson's reagent[3] in toluene, and desulfurized with Raney Nickel to give the *t*-amine 4 in overall 72% yield from 6. Treatment of 4 with MCPBA/CH_2Cl_2/20°C gave 8, which was directly reduced with PPh_3 to give 9 (54%). The axial H atom at C-3 gave rise to double doublets at 5.19 δ (J's = 12.6 and 4.0Hz). Mechanistic considerations predict the 3α-configuration 11, formed through the α-epoxide 10 (maintains a *cis*-AB ring fusion), followed by *trans*-diaxial opening of the strained epoxide 10 with Ar^1CO_2H to give the 3α-benzoate 11, SCHEME 2. This, of course, assumes that there is no participation by the N^1-lone pair. The stereochemical assignment at C-3 and the complete structure of 9 was established by single crystal X-ray crystallography. (See FIGURE 1 for ORTEP representation of 9).[4] The 3-benzoate has the more stable β-equatorial configuration. This implies that the N^1-lone pair has indeed participated, SCHEME 2, to give the iminium ion 12, which adds the *m*-chlorobenzoic acid nucleophile to give 13, that now enters into *ortho*-ester type equilibration with 14 to give 9. An alternative explanation is that the kinetic product 11 (diaxial opening of 10) can equilibrate the 3α-benzoate *via* iminium ion 15 formation, proton loss to give 16, and reprotonation from the α-face (axial) to give 16a, followed by hydration to the observed 3β-benzoate 9.

Other oxidizing agents such as ozone, and osmium tetroxide gave the *cis*-diol 17. Illustrating once again, the marked preference for 4 to add electophiles from the β-face.

We were unable to convert 9 or 16 using a variety of conditions (TFA;TFAA/pyridine/DMAP; MeOH/HCl) into the vincamine/eburnamine skeleton, thus indicating that the N^1-arylsulfonamide must be removed to allow this rearrangement to take place.[5]

The alkaloids of the Eburna species have been the objective of a number of total syntheses and partial syntheses.[6] Vincamine 18 is available by oxidative rearrangement of vincadifformine 19 using a peracid or halogen as the oxidant.[5] Clearly, electron withdrawing groups on the indole nitrogen atom prevent the above rearrangement, and it is known that electron withdrawing substituents (Cl,



SCHEME 2

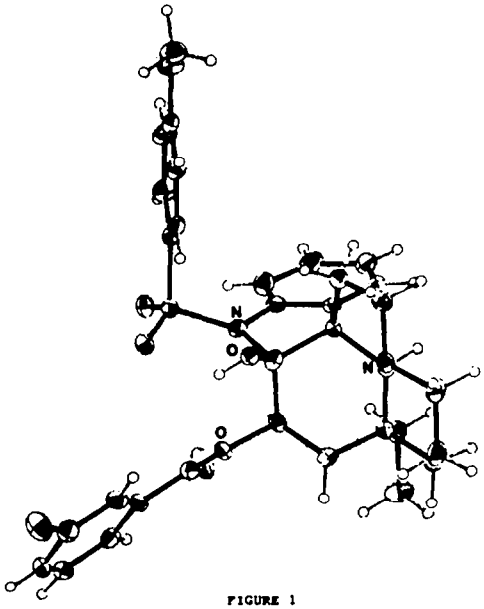
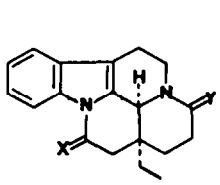
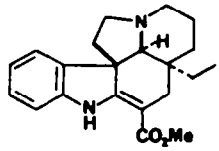


FIGURE 1

Br, NO_2) on the benzenoid ring also prevent the above rearrangement.[7] A similar rearrangement has been used to convert 1,2-dehydroaspidospermidine into eburnamine. More recently, ozone has been used to convert vincadifformine 19 into vincamine 18.[8]

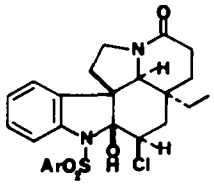


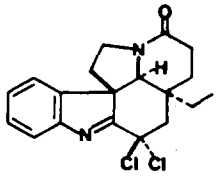


18 X = OH, CO_2Me; Y = H,H
22 X = O ; Y = O
23 X = H,OH; Y = H,H
24 X = O ; Y = H,H

19

The pentacyclic amide 2 was treated with cyanogen chloride[9] in dioxane at 25°C to give the *cis*-chlorohydrin 20 (43%), the *gem*-dichloroimine 21 (56%), a trace of eburnamonine lactam 22 (>1%), and *p*-methoxyphenylsulfonyl cyanide (40%). The structures of 20 and the unusual *gem*-dichloroimine 21 were unambiguously established by single crystal X-ray crystallography, (see FIGURES 2 and 3 respectively for ORTEP representation).[10]





20

21

The dichloroimine 21 proved to be a rather labile compound that rapidly rearranged to eburnamonine lactam 22 (90%) when treated with MeOH/HCl/20°C. Reduction of 22 with $LiAlH_4$/ether/25°C gave (±)-eburnamine 23, which on oxidation with CrO_3/pyridine gave (±)-eburnamonine 24.[6]

The formation of the geminal dichloride 21 by treatment of 2 with cyanogen chloride is unexpected, since this reagent normally functions as a cyanating agent. Treatment of 2, in separate experiments, with Cl_2/dioxane; Cl_2/CCl_4; NCS/dioxane, gave in each case the *cis*-chlorohydrin 20 (20-60%). Whereas, when 2 was exposed to NCS/KCN/dioxane at reflux, a low yield *ca.*10% of 21 was isolated. Also, treatment of the *cis*-chlorohydrin 20 with $SOCl_2$/pyridine gave the geminal dichloride 21 (25%). The propensity of 2 towards chlorination is further illustrated by the formation of the *cis*-chlorohydrin 20, when 2 is treated with NCl_3;

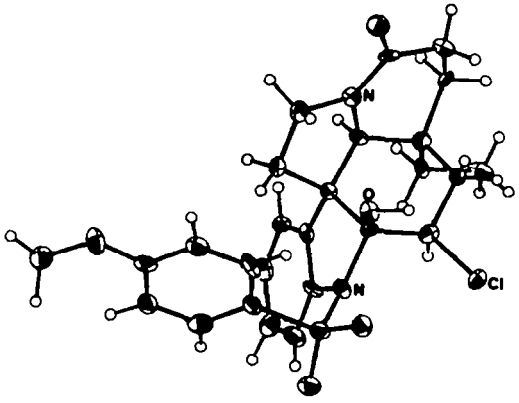


FIGURE 2

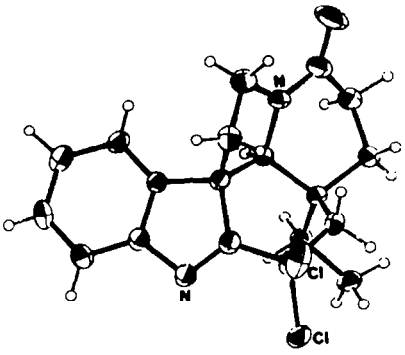
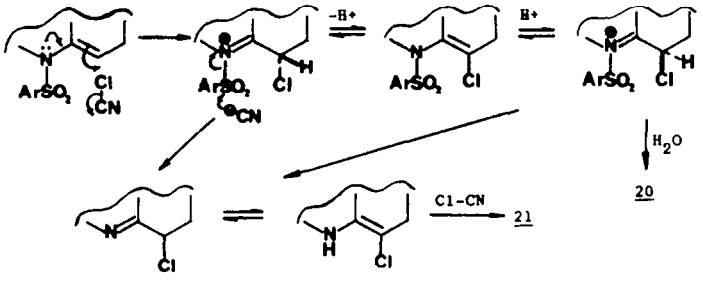
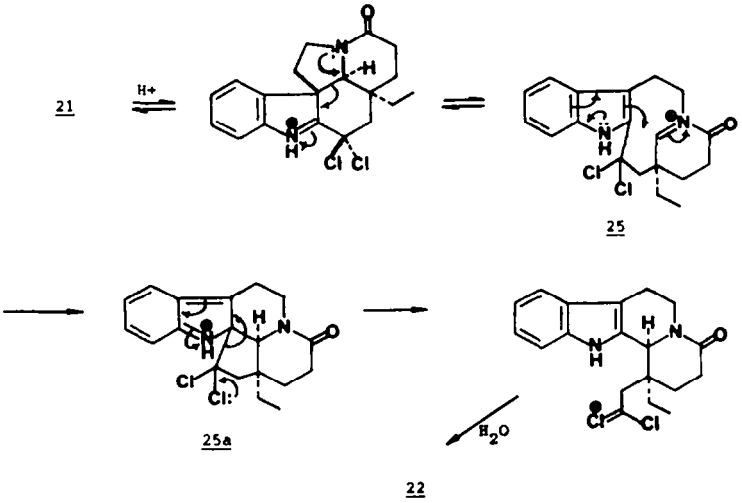


FIGURE 3



SCHEME 3



SCHEME 4

NOCl or Bu^tOCl.

Evidently, the conversion of 2 into 21 requires cyanide ion to remove the N^1-arylsulfonyl group, SCHEME 3. The acid-catalyzed rearrangement of 21 into (±)-eburnamonine lactam 22 presumably involves an acyliminium species such as 25, which is subsequently trapped at the 2-position of the indole to give 25a, which can hydrolyze and regain the indole aromaticity to give 22. The extensive studies of Lévy parallel these observations for 3-carbomethoxy-3-chloro systems.[8]

Finally, treatment of 2 or 3 with a wide range of carbon electrophiles, such as the Vilsmeier reagent; $Cl_2CHOMe/SnCl_4$; sulfonium ions; oxonium ions, and acylating agents/Lewis acids, unfortunately resulted in no reaction. In summary, vicinal oxidation of the 2,3-double bond of 2 and 3 results in *cis*-addition on the β-face. When the N^1-arylsulfonyl group is cleaved by Cl-CN to give 21, the rearrangement of the Aspidosperma skeleton into the Eburna skeleton under acid catalyzed conditions becomes possible.[11]

Acknowledgements: The National Institute of Health (GM 29801) is thanked for financial support.

EXPERIMENTAL

The general details of the various experimental protocols associated with this work have been described in detail.[2]

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-aspidospermidine 4.
To a solution of the amide 6 (137.2mg. 0.24mmol.) in dry toluene (3.5ml.) was treated with Lawesson's reagent (50.3mg.) and heated to 80°C under argon. After 1h. the solution was cooled to 25°C, diluted with benzene (30ml.), washed with water (20ml.) and dried (Na_2SO_4). Evaporation of the filtered solution gave the α-thiophenylamide 7 (140mg.) as an off-white foam, that was sufficiently pure for the next step. The thioamide 7 (140mg.) was dissolved in hot ethanol/THF (8ml. 5:3) and treated with Raney Nickel (2g.). After 45min. the mixture was filtered through a celite pad and washed with $EtOH/CH_2Cl_2$. Evaporation of the filtrate gave 4 (77.5mg. 72% from 6), m.p. 176-177.5°C (from hexane-benzene). ^1H NMR ($CDCl_3$, 90MHz) δ 1.17(3H,t,J = 7Hz), 1.53(2H,m), 1.70(2H,q,J = 7Hz), 2.13(4H,m), 2.60(4H,m), 2.90(2H,m), 3.70(1H,s), 3.72(3H,s), 5.95(1H,q,J's = 9 and 2Hz), 6.76 (2H,d,J = 10Hz), 7.06(2H,m), 7.24(2H,m), 7.77(2H,d,J = 10Hz). Anal. Calcd. for $C_{26}H_{30}N_2O_3S$: C,69.30; H,6.71; N,6.22. Found: C,69.19; H,6.77; N,5.95.

(±)-1-[(*p*-Methoxyphenyl)sulfonyl]-2β-hydroxy-3β-(3-chlorobenzoyloxy)-aspidospermadine 9.
To a solution of 4 (0.368g. 0.82mmol.) in benzene (10ml.) was added MCPBA (387mg.) and the mixture stirred at 20°C for 22h. The solution was diluted with EtOAc (100ml.) and washed with aqueous $NaHSO_3$ (20ml.), aqueous $NaHCO_3$ (2 x 20ml.), brine (20ml.), and dried (Na_2SO_4). The dried extract was filtered and evaporated *in vacuo*; the residue was dissolved in $AcOH/H_2O$ (9:1, 20ml.), Ph_3P(264mg.) added in small portions, and the mixture stirred at 20°C for 72h. The solution was diluted with water (100ml.), basified with 10% aqueous Na_2CO_3 (300ml.), and extracted with dichloromethane (2 x 50ml.). The dried (Na_2SO_4) extract was evaporated, and the residue chromatographed over silica gel eluting with 40% $CHCl_3$/hexane to give 9 (185.6mg., 36.5%), m.p. 201-203°C (from EtOH). IR (Nujol mull.) 3400, 1730, 1600, 1250, 1154cm^{-1} λmax. 230 and 254nm (ε, 17,200 and 8,600) (in acetonitrile). ^1H NMR (360MHz) δ 0.81(3H,t,J = 7.2Hz), 0.90-1.08(2H,m), 1.46(1H,dd,J's = 6 and 11Hz), 1.53-2.08(8H,m), 2.29(1H,s), 2.40(1H,d,J = 12.6Hz), 2.92(1H,m), 3.10(1H,bd,J = 12Hz) 3.79(3H,s), 5.21-5.17(1H,dd,J's = 4.0 and 12.6Hz), 6.79(2H,d,J = 9Hz), 7.09(2H,m), 7.42(1H,t,J = 10Hz), 7.20(2H,m), 7.55(1H,d,J = 10Hz), 7.68(3H,m), 8.10(1H,d,J = 10.5 Hz), 8.16(1H,bs). Anal. Calcd. for $C_{33}H_{35}N_2O_6SCl$: C,63.60; H,5.66; N,4.50. Found: C,63.85; H,5.67; N,4.69.

3,3-Dichloro-1,2-dehydroaspidospermidin-8-one 21, and 3β-Chloro-2β-hydroxy-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidin-8-one 20.
To a solution of the amide 2 (25mg., 0.054mmol.) in dioxane (2ml.) at 0°C was added cyanogen chloride (2ml.) as a neat, colourless liquid. The reaction was sealed and left for 20h. at 25°C. The resulting mixture was evaporated *in vacuo*, and the residue chromatographed on a 0.5mm. silica preparative layer plate eluting with $EtOAc/CHCl_3$ (35/65)(x 4) to give the dichloroimine 21 (10.8mg., 56%), m.p. 164°C (d) (EtOAc-hexane). IR ($CHCl_3$) 1660, 1650, 1640, 1460, 1410, 1125, 1095cm^{-1} ^1H NMR (360MHz) δ 0.86(3H,t,J = 7.2Hz), 1.22(2H,q,J = 7.2Hz), 1.43(1H,m), 1.89(2H, dd,J's = 5.9 and 13.5Hz), 2.32(2H,m), 2.79(1H,m), 2.99(1H,dd,J's = 1.7 and 15.9Hz), 3.09(1H,d,J = 15.9Hz), 3.56(1H,m), 3.66(1H,d,J = 1.3Hz), 4.44(1H,dd,J's = 7.9 and 11.8Hz), 7.39(3H,m), 7.81(1H,d,J = 7.7Hz). MS, m/e Calcd. for $C_{19}H_{20}N_2Cl_2O$,

362.098. Found: 362.097.

The *cis*-chlorohydrin 20 (12.1mg., 43%) was also isolated. It has m.p. 259°C (d) (EtOAc-hexane). IR ($CHCl_3$) 3480, 3475, 1625, 1590cm^{-1} ^{1}H NMR (360MHz) δ 0.76(3H,t,J = 7.4Hz), 1.05(2H,q,J = 7.4Hz), 1.20(2H,m), 1.35(1H,dd,J's = 7.4 and 14.4Hz), 1.64(1H,m), 1.80(1H,m), 2.13(1H,t,J = 13.4Hz), 2.38(2H,m), 3.17(1H,bt), 3.63(1H,dd,J = 6.5 and 10.7Hz), 3.81(3H,s), 3.82(1H,s), 4.15(1H,dd,J's = 3.5 and 13.0Hz), 6.84(2H,d,J = 9.0Hz), 7.03(1H,d,J = 7.0Hz), 7.10(1H,t,J = 7.6Hz), 7.30(1H,m) 7.68(2H,d,J = 9Hz), 7.78(1H,d,J = 8Hz). MS, m/e Calcd. for $C_{26}H_{29}N_2O_5SCl$, 480.1720. Found: 480.1718.

19-Oxoeburnamonine 22.[6]

The dichloroimine 21 (3.5mg.) in methanolic HCl (2ml.) at 0°C was warmed to 25°C. After 22h. the mixture was quenched with 20% aqueous $NaHCO_3$ (5ml.), and extracted with EtOAc (2 x 15ml.). The dried (Na_2SO_4) extract was concentrated *in vacuo*, and the residue purified by PLC eluting with EtOAc/$CHCl_3$ (35/36) to give 22 (3.3mg., ≥95%), m.p. 215-216°C (EtOAc-hexane). IR ($CHCl_3$) 1705, 1650, 1635, 1625cm^{-1} ^{1}H NMR (360MHz) δ 1.02(3H,t,J = 7.6Hz), 1.62(2H,m), 1.72(1H,m), 2.07(1H,m), 2.29 (1H,m), 2.45(1H,m), 2.64(1H,d,J = 13.4Hz), 2.80(2H,d,J = 1.85Hz), 3.05(2H,d,J = 8.5Hz) 4.05(1H,d,J = 1.5Hz), 4.98(1H,m), 7.33(2H,m), 7.43(1H,d,J = 6.5Hz), 8.34(1H,d,J = 7.2Hz).

19-Eburnamonine 24.[6]

To a solution of 22 (5.3mg.) in ether (3ml.) at 25°C was added $LiAlH_4$ (21mg.), and the mixture heated at reflux for 1h. Water (1ml.) was added to the mixture, and the resulting slurry filtered. The filtrate was evaporated and the residue dissolved in dry pyridine (2ml.), and CrO_3 (5mg.) added. The reaction mixture was passed through an alumina packed column, eluting with dichloromethane (20ml.) and the residue purified by PLC to give 24 (1mg., 20%), identical (^{1}H NMR; IR; MS; TLC) with an authentic sample purchase from Aldrich Chemical Company.

REFERENCES AND FOOTNOTES

1. P. Magnus, T. Gallagher, P. Brown and P. Pappalardo, *Acc. Chem. Res.*, 1984,*17*, 35; P. Magnus and P. Brown, *J. C. S. Chem. Comm.*, 1985, 184.

2. C. Exon, T. Gallagher and P. Magnus, *J. Am. Chem. Soc.*, 1983, *105*, 4739; T. Gallagher, P. Magnus and J. C. Huffman, *Ibid.*, 1983, *105*, 4750.

3. S. Scheibye, B. S. Pederson and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, *87*, 229.

4. Details of the X-ray structure determination of 9 are available on microfiche from Indiana University Chemistry Library. Request Structure Report No. 83085.

5. G. Croquolois, N. Kunesch, and J. Poisson, *Tetrahedron Letters*, 1974, 4427; G. Hugel, J. Lévy, and J. Le Men, *C. R. Acad. Sci., Ser. C.*, 1972, *274*, 1350; G. Hugel, B. Gourdier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1974, 1597.

6. For a recent review of eburnamine-vincamine alkaloids see:- *The Alkaloids*, Ed. R.H.F. Manske and R.G.A. Rodrigo, Vol. XX, p. 297, Academic Press, New York, 1981; E. Wenkert, *Pure. Appl. Chem.*, 1981, *53*, 1271; L. Szabó, J. Sápi, G. Kalaus, G. Argay, A. Kálmán, E. Baitz-Gács, J. Tamás and C. Szántay, *Tetrahedron*, 1983, *39*, 3737; G. Kalaus, N. Malkieh, I. Katona, M. Kajtár-Peredy, T. Koritsánszky, A. Kálmán, L. Szabó and C. Szántay, *J. Org. Chem.*, 1985, *50*, 3760, and references cited therein; S. Takano, M. Yonaga, M. Morimoto and K. Ogawawara, *J. Chem. Soc., Perkin Trans. I*, 1985, 305, for an enantiospecific synthesis and compilation of references.

7. G. Lewin, Y. Rolland, and J. Poisson, *Heterocycles*, 1980, *14*, 1915; G. Hugel, G. Massiot, J. Lévy, and J. Le Men, *Tetrahedron*, 1981, *37*, 1369; G. Hugel, J. Y. Laronze, J. Laronze, and J. Lévy, *Heterocycles*, 1981, *16*, 581.

8. B. Danielli, G. Lesma, G. Palmisano, and B. Gabetta, *J. C. S. Chem. Comm.*, 1981, 903; J. Lévy, C. Pierron, G. Kukacs, G. Massiot, and J. Le Men, *Tetrahedron Letters*, 1976, 669; J. Lamotte, L. Dupont, O. Dideberg and G. Lewin, *Acta. Crystallogr. Sect. B.*, 1980, *36*, 196.

9. M. E. Kuehne, *J. Am. Chem. Soc.*, 1959, *81*, 5400; G. H. Coleman, R. W. Leeper, and C. C. Schulze, *Inorg. Synth.*, 1946, *2*, 90.

10. The structures of 20 and 21 have been determined crystallographically. Details are available on microfiche from the Indiana University Chemistry Library. Request Structure Reports No.s 83096 and 83085 respectively.

11. Because of the reluctance of the N-Arylsulfonylenamine functional group to undergo electrophilic substitution by carbon electrophiles, and their general

resistance to allylic oxidation (oxygenation at C-4), we have investigated the use of N-carbomethoxy indoles in the indole-2,3-quinodimethane strategy: see P. Magnus and P. M. Cairns, *J. Am. Chem. Soc.*, in press (1986); and P. M. Cairns, unpublished results from this laboratory.

X-ray Structure determinations were carried out by Dr. John Huffman, Molecular Structure Center, Indiana University, Bloomington, Indiana 47405.