Tetrahedron Vol. 38, No. 2, pp. 223 to 243, 1982
Printed in Great Britain.

0040-4020/82/020223-21$10.50/0
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 120

THE SYNTHESIS OF BIS-INDOLE ALKALOIDS AND THEIR DERIVATIVES

MAURI LOUNASMAA* and ANDRÁS NEMES†
Technical University of Helsinki, Department of Chemistry, SF-02150 Espoo 15, Finland

(*Received* 1 *May* 1981)

CONTENTS

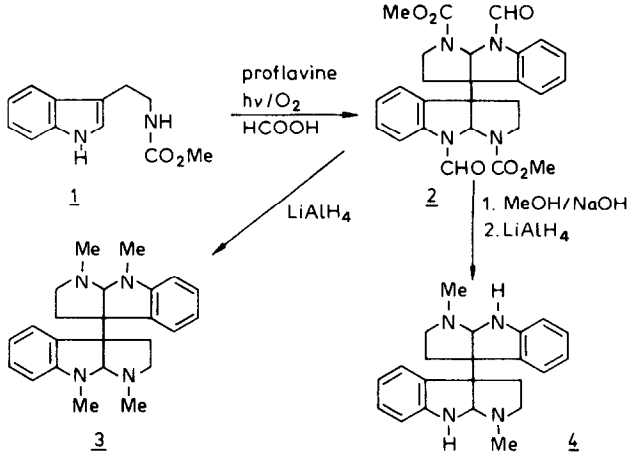
INTRODUCTION

In a relatively short period of time several bis-indole alkaloids, especially those from *Catharanthus roseus* G. Don, have became highly valuable agents in chemotherapy. The generally low concentration of the bis-indole alkaloids in plants and the hope of finding clinically even more favourable ones, have encouraged intensive synthetic research in the field.

Our aim in preparing the present article has been to record recent progress in the synthesis of bis-indole alkaloids and their derivatives. The time period covered extends from June 1972 to December 1980. The earlier publications in the field are only occasionally mentioned since they have been discussed in detail in several review articles, most notably that by Gorman *et al.* in *The Alkaloids.*‡

1. DIMERIZATION FROM TWO MONOMERIC UNITS

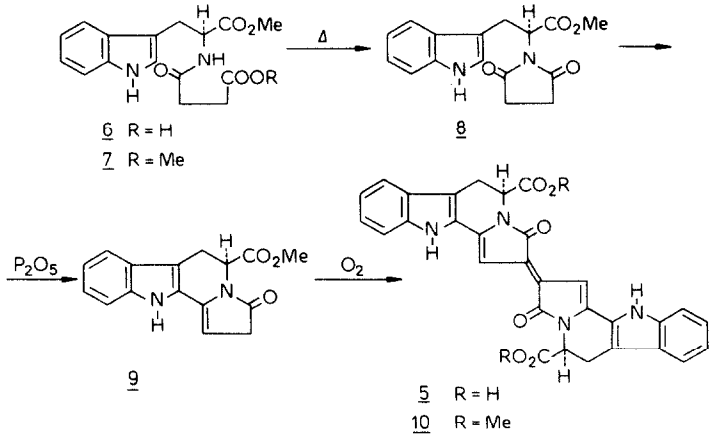
Employing dye-sensitized photo-oxygenation of N_b-methoxycarbonyltryptamine **1**, Hino *et al.* produced an isomeric mixture of dimeric pyrroloindoles **2** (27% yield). $LiAlH_4$ reduction of **2** afforded (±)-folicanthine **3** in 29% yield. The isomeric mixture **2** could also be separated into **2a** (racemic) and **2b** (meso). $LiAlH_4$ reduction of the latter gave meso-folicanthine, a new isomer of folicanthine. Hydrolysis of **2a**, followed by $LiAlH_4$ reduction provided (±)-chimonanthine **4** in 29% yield.[1]



†Permanent address: Gedeon Richter Ltd, 1475 Budapest X, Hungary.

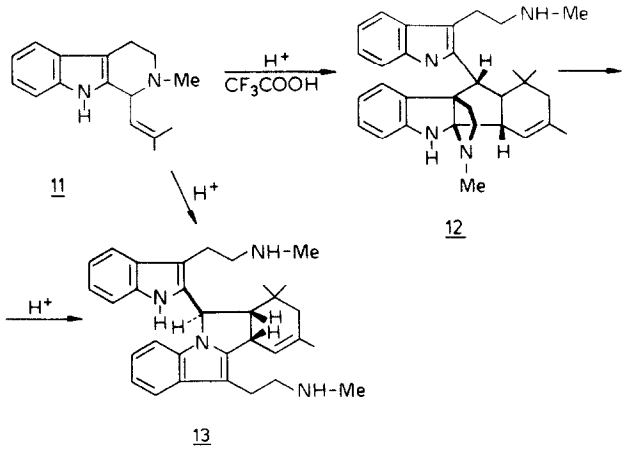
‡J. E. Saxton [Ed.], Specialist Periodical Reports, Vol. 1. The Chemical Society, London (1971).

Trichotomine **5**, a blue pigment from the fruit of *Clerodendron trichotomum*, has been synthesized from L-tryptophan methyl ester and succinic anhydride. The amide **6**, formed by condensation of the starting materials (76% yield), was converted to the dimethylester **7**. On heating **7** under reduced pressure the imide **8** was obtained. Bishler–Napieralski cyclization of **8** provided the tetracyclic lactam **9** in 28% yield and the dimethylester **10** in 5% yield. Oxidative dimerization of **9** to **10** was achieved by passing air into the solution of **9** in n-butanol (35% yield, based on reacted **9**).[2,3] Hydrolysis of **10** gave **5**.[4]



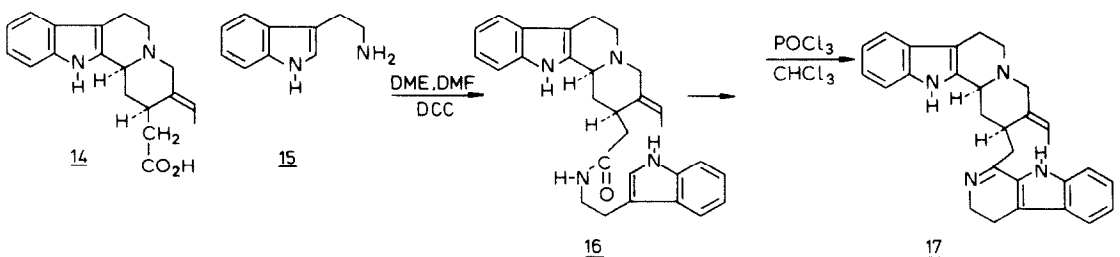
A biomimetic synthesis of **5** from L-tryptophan and α-ketoglutaric acid has also been reported.[5]

The simultaneous occurrence of the monomeric indole alkaloid borrerine **11** and the bis-indoles borreverine **12** and isoborreverine **13** in *Borreria verticillata* suggested a simple chemical relationship between these compounds. Indeed **11** could be dimerized in 80% yield to a mixture of **12** and **13** on heating with acid: **12** was quantitatively transformed to **13** after a longer time under the same conditions.[6]



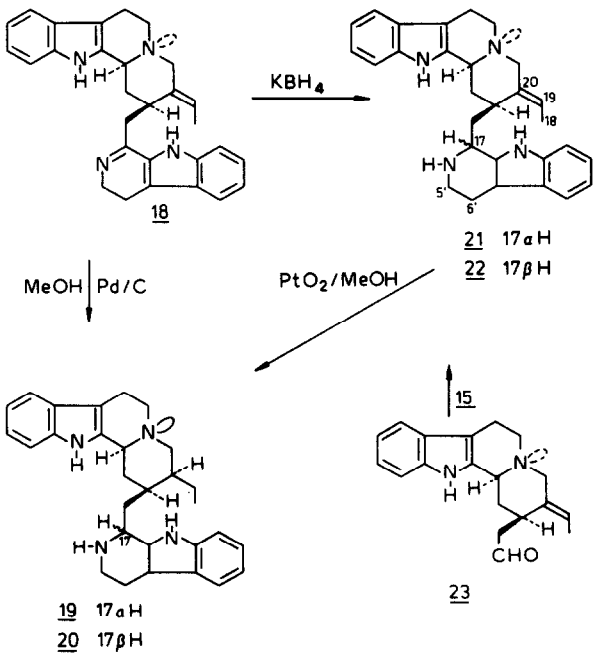
2. SYNTHESIS FROM A CORYNANTHE-TYPE UNIT AND TRYPTAMINE

Yamada *et al.*[7] condensed (±)-geissoschizoic acid **14** with tryptamine **15** to obtain tryptamide **16**. Bishler–Napieralski cyclization of **16** furnished (±)-5′6′-dihydrousambarensine **17**.



Le Men *et al.*[8] have also reported the application of this route. Starting from geissoschizoic acid they obtained **18**, which proved to be identical with the *Strychnos* alkaloid tchibagensine as well as with the 5'6'-dihydrousambarensine alkaloid of *S. usambarensis.*[7] The chemical relationship of **18** to ochrolifuanines C **19** and D **20** has also been demonstrated.

Catalytic reduction of **18** led to **19** and **20**.[9] Reduction of **18** with potassium borohydride, on the other hand, yielded two derivatives epimeric at C(17), **21** and **22**. Geissoschizol **23** and **15** gave Pictet–Spengler reaction products identical with **21** and **22**, which were separated by column chromatography. Ochrolifuanine C **19** was obtained by catalytic hydrogenation of **21** and ochrolifuanine D **20** by similar treatment of **22**.[8]



18

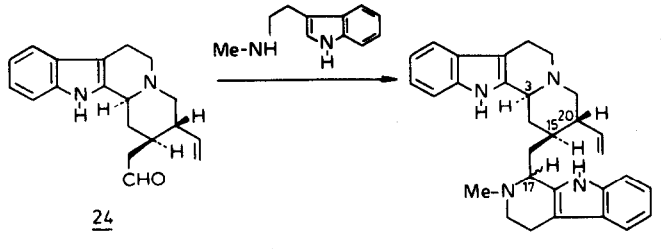
21 17αH
22 17βH

19 17αH
20 17βH

15

23

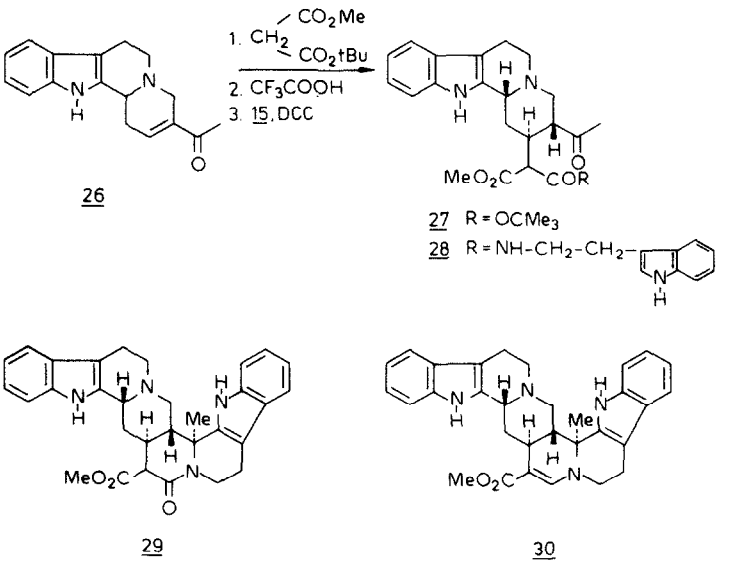
Corynantheal **24**, obtainable from corynantheine by successive saponification, decarboxylation and acidic hydrolysis, and N-methyl tryptamine were condensed giving usambarine **25a** (20% yield) and its C(17) epimer **25b** (40% yield).[10]



24

25a 17αH
25b 17βH

Winterfeldt *et al.*[11,12] have stereoselectively synthesized the octacyclic bis-indole roxburghine D **30**, the main alkaloid of *Uncaria gambir.* Condensation of the hexahydroindoloquinolizine-keton **26** with methyl t-butyl malonate furnished the geissoschizine derivative diester **27**. Selective hydrolysis of **27**, followed by treatment with **15** and dicyclohexylcarbodiimide, gave the tryptamide **28**. The lactam **29** was obtained on treating **28** with acid. Partial reduction of **29** with diisobutyl aluminium hydride yielded roxburghine D **30**.



26

27 R = $OCMe_3$

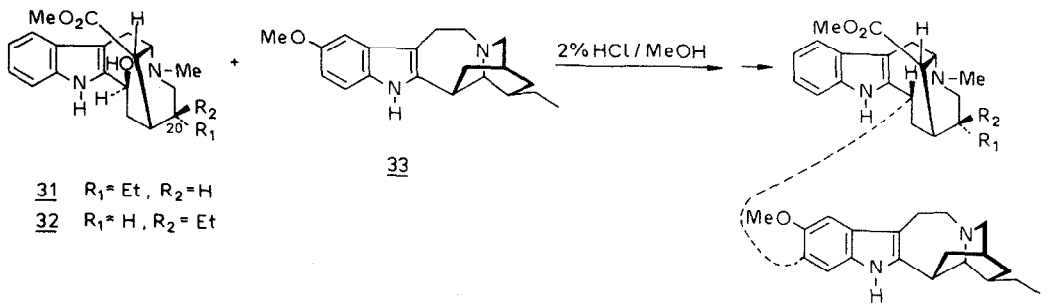
28 R = $NH-CH_2-CH_2-$

29 30

3. SYNTHESIS OF ALKALOIDS OF VOACAMINE-TYPE FROM A VOBASINE AND AN IBOGA UNIT

The original synthesis of Büchi *et al.*[13] for the voacamine has been applied for preparation and structural identification of some dimeric alkaloids.

Knox and Slobbe[14] have reported the coupling of dregaminol **31** and its 20-epimer, tabernaemontaninol **32**, with ibogaine **33** to 16-demethoxycarbonyldihydrovoacamine **34** and its 20′-epimer **35**† in dilute hydrochloric acid/methanol solution. Compounds **34** and **35** are alkaloids of *Ervatamia orientalis*.



31 R_1 = Et, R_2 = H

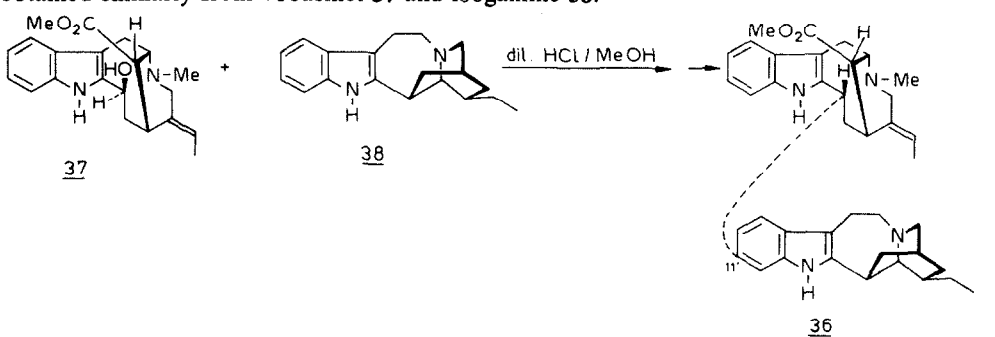
32 R_1 = H, R_2 = Et

33

34 R_1 = Et, R_2 = H

35 R_1 = H, R_2 = Et

Tabernamine **36**, a leukemia inhibitor identified as a bis-indole from *Tabernaemontana johnstonii*, has been obtained similarly from vobasinol **37** and ibogamine **38**.[16]

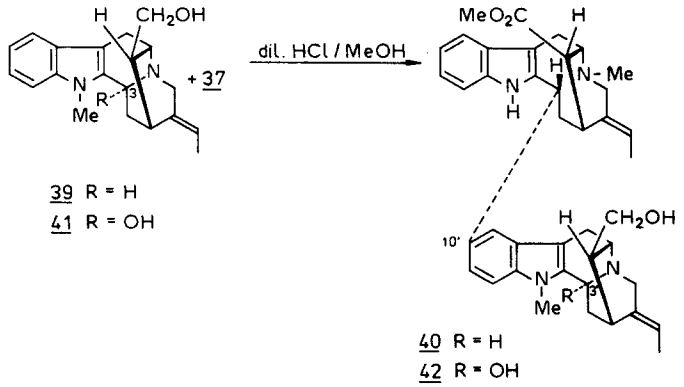


37 38

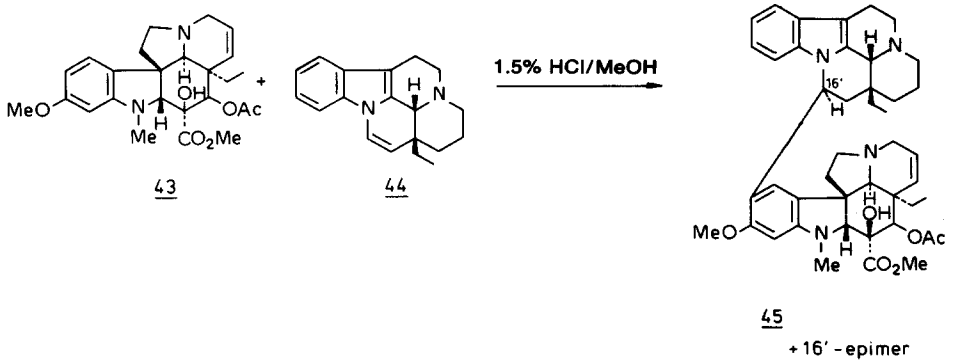
36

Condensation of the tetracyclic compound **37** with a pentacyclic vobasine unit gave bis-indoles of *Tabernaemontana accedens*.[17] Thus, **37** and affinisine **39** gave accedinisine **40**; **37** and accedine (3-hydroxyaffinesine) **41** led to accedinine **42**. When Takano *et al.*[18] applied this same technique to the

†The numbering system employed follows that of Le Men and Taylor.[15]

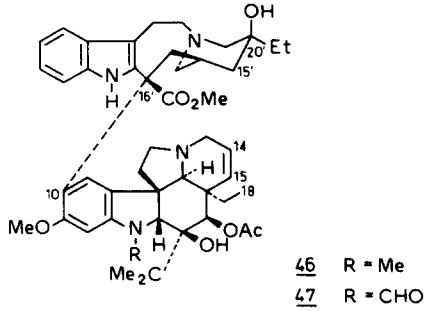


coupling of (−)-vindoline **43** with (±)-eburnamenine **44**, they obtained a mixture of two "non natural" stereoisomeric dimers **45** and its 16′-epimer in 77% yield.



4. SYNTHESIS OF VINBLASTINE TYPE ALKALOIDS

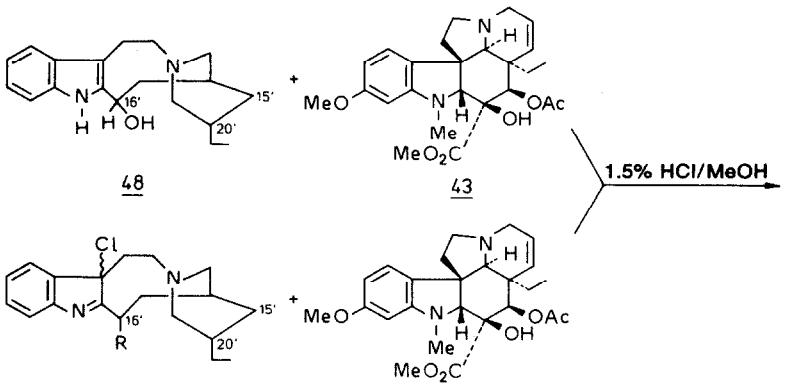
The bis-indole alkaloids of *Catharanthus roseus* G. Don. vinblastine **46** and vincristine **47** have proved to be effective agents in cancer chemotherapy. They are present in the plant only in very low concentration and a considerable amount of effort has been directed towards their synthesis and the synthesis of their natural and synthetic derivatives.



(A) *Starting from tetracyclic ibogane derivatives*

Compounds **46**, **47** and other bis-indole alkaloids of *C. roseus* are composed of an aspidospermane (vindoline) and a tetracyclic ibogane unit. Attempts have been made to condense vindoline **43** with 16-hydroxydihydro-cleavamine **48**[19,20] by Büchi's method. The dimer **49** obtained from this reaction proved to be identical with the compound obtained on coupling chloroindolenine of 20α-dihydrocleavamine **50** and **43**.[21–24]

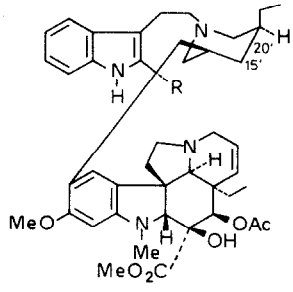
Kutney *et al.*[23,24] have identified **49** by X-ray crystal structure determination, as 16′-epi-16′-decarbomethoxy 20′-deoxy 20′-epi-vinblastine. Similarly, the condensation product of chloroindolenine of 16-carbomethoxy-dihydrocleavamine **51** with **43** is the analogous 16′-epi-20′-deoxy-20′-epivinblastine **53**. On coupling chloroindolenine of 16-carbomethoxycleavamine **52** and **43**, they obtained 16′-epi-15′,20′-anhydrovinblastine **54**, which was identical with a compound synthesized earlier by A-ur-Rahman.[25]



48 43

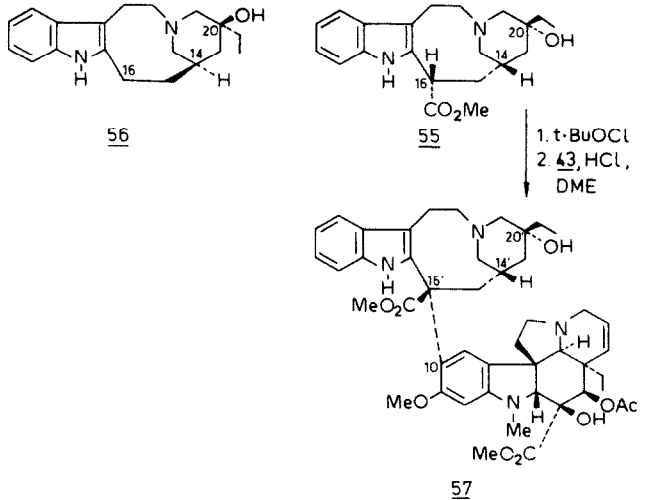
50 R = H
51 R = CO_2Me
52 R = CO_2Me, $\Delta^{15,20}$

43



49 R = H
53 R = CO_2Me
54 R = CO_2Me, $\Delta^{15',20'}$

Recently Kunesch *et al.*[26] have reported the successful employment of chloroindolenine method to obtain a new isomer of vinblastine **46** with the "natural" 16'*S* configuration. The tetracyclic starting compound was secopandoline **55**,[27] which differs from velbanamine **56**, the degradation product of **46**, in the configuration of centers C(14) and C(20) and in bearing a carbomethoxy group at C(16). Unlike the case of cleavamine derivatives **50–52**, the attack of vindoline **43** now takes place from the opposite side of the intermediate carbocation, owing to the opposite configuration of C(14). The product **57** has 16'S, 14'R, 20'S.



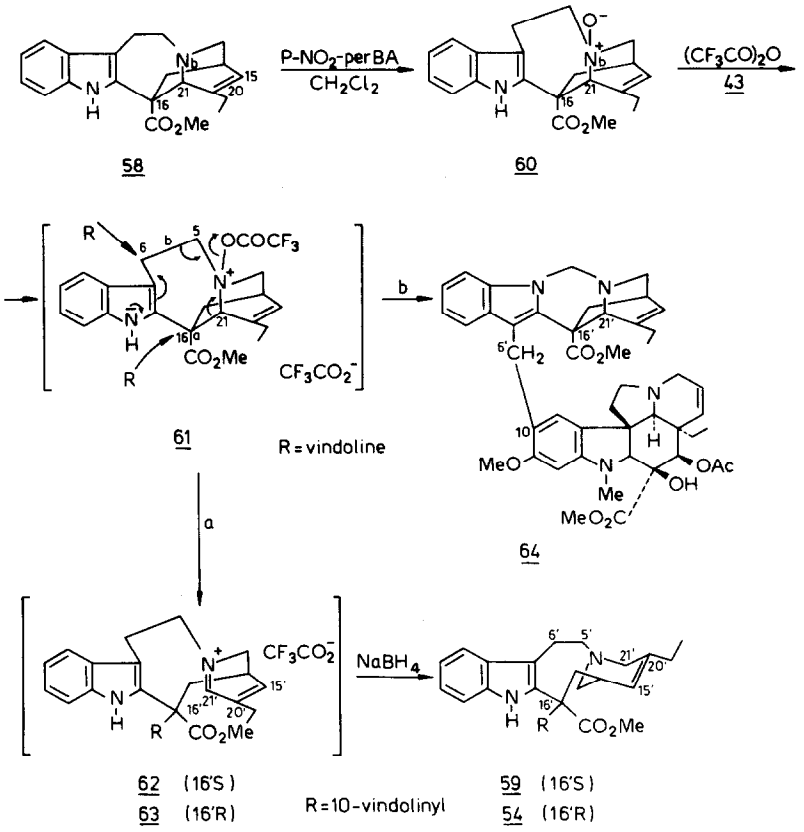
56 55

57

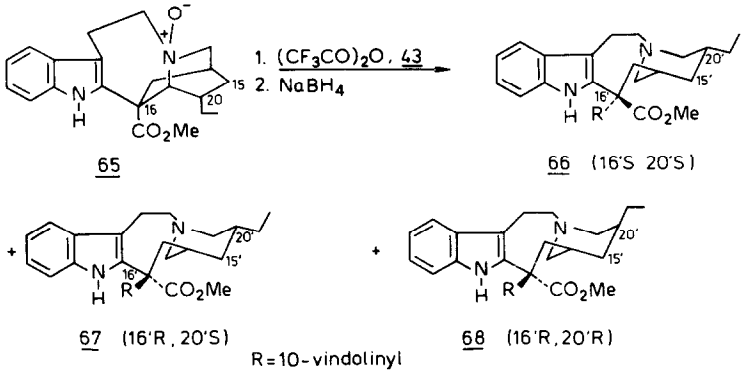
(B) *Starting from pentacyclic ibogane derivatives*

Catharanthine **58**, a pentacyclic iboga alkaloid, and the aspidospermane-type vindoline **43** are the major alkaloidal components of *C. roseus*. This suggested to A-ur-Rahman[25] that **58** and **43** might be the biological precursors of vinblastine-type alkaloids.

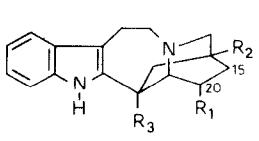
(i) *The Potier*[28,29] *synthesis of anhydro vinblastine* **59** follows a biomimetic pathway. When the C(16)–C(21) skeletal fragmentation of the pentacyclic ibogane skeleton induced by the Polonovski–Potier reaction (modified Polonovski-reaction)[30] occurs conjointly with the attack of the nucleophile vindoline, the resulting bis-indole has the natural, (16′*S*) configuration. A stepwise reaction leads to the isomeric compound with 16′*R* configuration. Catharanthine **58** was converted to its N-oxide **60**. Reaction of **60** with trifluoroacetic anhydride gave the intermediate **61**, where $OCOCF_3$ forms a suitable leaving group. Anhydro vinblastine **59** (50% yield) and its 16′epimer **54** (12% yield) were obtained by direct reduction of the corresponding immonium intermediates **62** and **63** in the reaction medium (Path a). Cleavage of the C(5)–C(6) bond led to the minor product **64** (4% yield) (Path b).



The coupling reaction of 15,20*S*-dihydrocatharanthine N_b-oxide **65** with vindoline **43** led to the formation of three products:[29] deoxyvinblastine **66** (10% yield), 16′-epi-deoxyvinblastine **67** (14% yield) and 16′-epi 20′-epi-deoxyvinblastine **68** (14% yield).



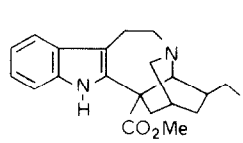
Kutney *et al.*[31-33] have also employed the Polonovski–Potier-reaction for synthesis of vinblastine-type alkaloids. In connection with all the examples they stressed that the relative amounts and the total yields of the products are very sensitive to the experimental conditions and the structure of the starting materials. Other types of starting materials were also used: one side: allocatharanthine **69**, 14,15-dihydroallocatharanthine **70**, coronaridine **71**,[29] and decarbomethoxycatharanthine **72**;[32,34] and other side: vindorosine **73**, N_a-methyl-2,16-dihydrotabersonine **74**, N_a - methyl - 2,16 - dihydro - 11 - methoxytabersonine **75**[29] and vindoline-N-methylamide **76**.[32] Various quantities of **54**-, **59**- and **64**-type bis-indoles were obtained.



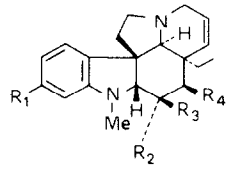
69 $\Delta^{15,20}$, $R_1 = H$, $R_2 = Et$, $R_3 = CO_2Me$

70 $R_1 = H$, $R_2 = Et$, $R_3 = CO_2Me$

72 $\Delta^{15,20}$, $R_1 = Et$, $R_2 = H$, $R_3 = H$



71



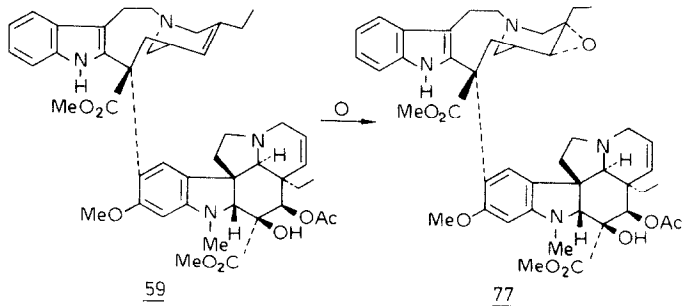
73 $R_1 = H$, $R_2 = CO_2Me$, $R_3 = OH$, $R_4 = OAc$

74 $R_1 = H$, $R_2 = CO_2Me$, $R_3 = H$, $R_4 = H$

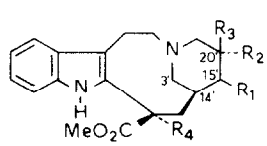
75 $R_1 = OCH_3$, $R_2 = CO_2Me$, $R_3 = H$, $R_4 = H$

76 $R_1 = OCH_3$, $R_2 = CONH\text{-}Me$, $R_3 = OH$, $R_4 = OAc$

(ii) *Synthesis of other bis-indole alkaloids of the vinblastine group.* Because all of the bis-indole alkaloids of the vinblastine group are oxygenated derivatives of anhydrovinblastine **59**,[35] this compound would seem to be an obvious precursor in the biosynthesis of most, if not all members of the vinblastine group deriving from the structural modification of the piperidine group of the indolic part. Further indication of its being such a precursor was provided by enzyme-catalysed formation of leurosine **77**[36] and other vinblastine-type alkaloids.[37] Nevertheless, according to the results of Potier's group,[35,38] enzymic systems are not necessary for the transformation of **59**. Simple agitation of a solution of **59** in an organic solvent solvent led, in different yields, to leurosine **77**, vinblastine **46**, leurosidine **78**, deoxyvinblastine **79**, deoxyleurosidine **80** as well as to small amounts of catharine **81** and catharinine **82**. The last two compounds possess an opened piperidine ring and occur mainly in some other *Catharanthus* species, e.g. *C. ovalis*.



59 → **77**



77 $R_1, R_2 = O$, $R_3 = Et$

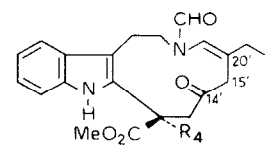
46 $R_1 = H$, $R_2 = Et$, $R_3 = OH$

78 $R_1 = H$, $R_2 = OH$, $R_3 = Et$

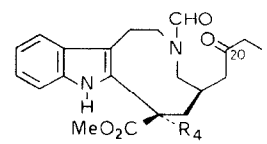
79 $R_1 = H$, $R_2 = Et$, $R_3 = H$

80 $R_1 = H$, $R_2 = H$, $R_3 = Et$

R_4 = 10-vindolinyl



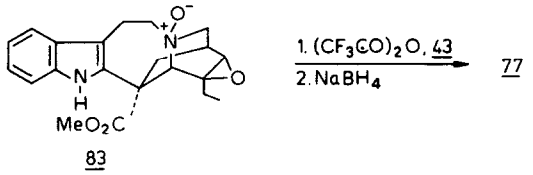
81



82

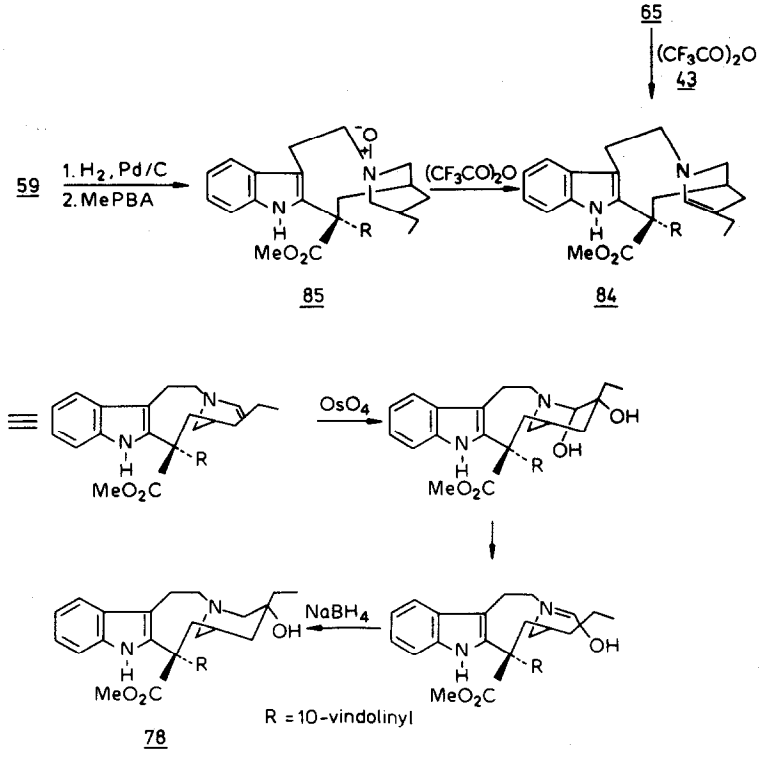
As for the synthesis of the individual vinblastine-type alkaloids, it seems more profitable to follow the biogenetic pathway and to carry out the structural modifications after the Polonovski–Potier-coupling rather than at an earlier stage.

Thus, coupling of 15β-20β-epoxydihydrocatharanthine **83** with vindoline **43** led to leurosine **77** in 20% yield.[40,41]



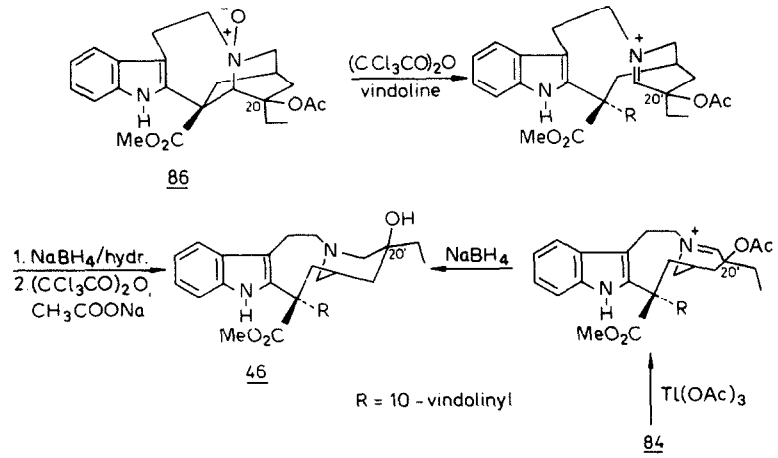
Treating anhydrovinblastine **59** with *p*-nitroperbenzoic acid in HMPT and then with zinc/acetic acid provided **77** in 27% yield.[41,42] Oxidation of **59** with t-butylperoxide or mercuric acetate gave 52% and 62% **77**, respectively.[43,44] With lead tetraacetate as epoxidizing agent, 30% of **59** was transformed to **77** and 35% of unreacted starting material was recovered.[38,45] The expoxidation can also be achieved with air oxygen in the presence of adsorbents. In chloroform or acetone after 72 hr the yield was 40%.[38]

Leurosidine **78** was obtained in low yield when the intermediate **84** of the Polonovski–Potier-coupling of **65** and **43** was subjected to osmylation, followed by $NaBH_4$ treatment.[46] Efforts were directed to the preparation of this enamine **84**. Anhydrovinblastine **59** was hydrogenated (Pd/C), then transformed to N-oxide **85**, quantitatively. This compound 20′-deoxyleurosidine N_b-oxide **85**, led to **84** under modified Polonovski-reaction conditions. Treatment with osmium tetroxide followed by borohydride reduction furnished **78**[47] (25% from 85).



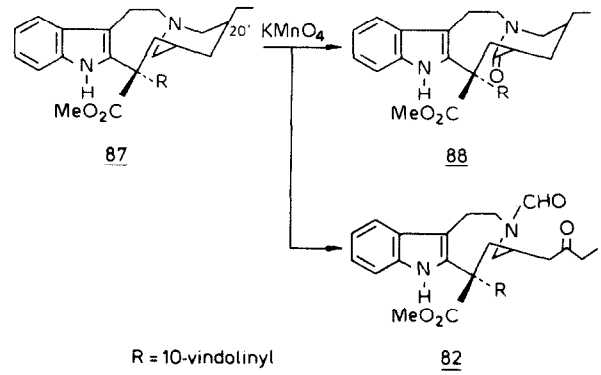
Vinblastine **46** was synthesized from 20-acetoxydihydrocatharanthine-N-oxide **86** by Polonovski–Potier-reaction in the presence of vindoline **43**.[48–50] The intermediate immonium ion was reduced to 20′-acetylvinblastine, deacetylated, and the 17 OH reacetylated (35% overall yield). Treatment of the enamine **84** with thallium triacetate, followed by borohydride reduction afforded **46** in 30% yield from **85**[47] (see also Ref. 20).

Vincristine **47** was obtained from vinblastine **46** by CrO_3 oxidation of **46** sulfate in acetone[51] or by agitation of a formic acid solution of **46** in O_2 atmosphere in the presence of Pd/C[52] in 50–70% yield.



Oxidation of leurosine **77** with t-butyl hydroperoxide in methylene chloride led to catharine **81** (48% yield).[53,54] Air oxidation of anhydrovinblastine **59** in tetrahydrofuran containing 1% aqueous trifluoroacetic acid gave **81** in 34% yield.[54] The latter oxidation was interpreted in terms of the intermediacy of leurosine **77** and a radical mechanism.

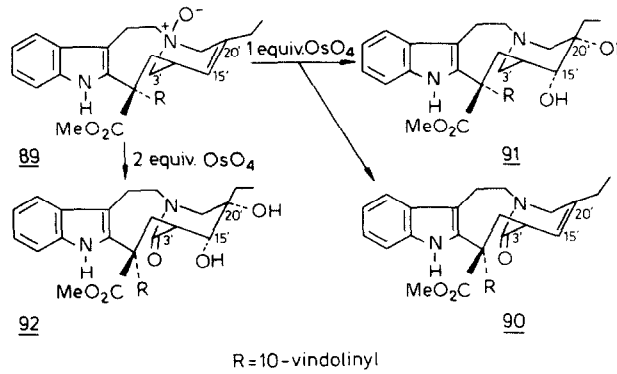
Catharinine (vinamidine) **82** was formed in 22% yield from 20'-deoxy-leurosidine **87** by $KMnO_4$ oxidation in acetone; 3'-oxo-20'-deoxyleurosidine **88**[54,55] was formed as a minor product (11% yield).



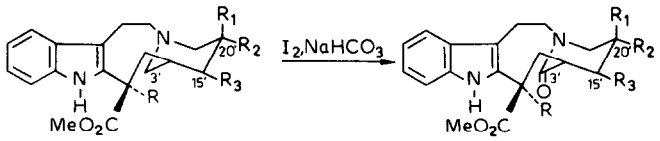
(C) *Other derivatives of vinblastine-type alkaloids*

A number of different derivatives of the vinblastine group were synthesized in the course of studying the synthesis of the naturally occurring compounds and in order to define the structure-activity relationships of bis-indoles with oncolytic potency.

(i) *Changes in functionality of the ibogane unit.* Kutney *et al.*[44,56] have studied the action of oxidizing agents on vinblastine derivatives. Anhydrovinblastine N-oxide **89** with one equivalent of osmium tetroxide in tetrahydrofuran gave 3'-oxoanhydro-vinblastine **90** as major product (53% yield) and 15'-α-hydroxyleurosidine **91** (10% yield). Compound **89** with two equivalents of osmium tetroxide gave 15'-α-hydroxy-3'-oxoleurosidine **92** as the major product (64% yield).



Iodine oxidation under basic conditions provided further 3′-oxo derivatives of vinblastine **46**, leurosidine **78**, and leurosine **77**: 3′-oxovinblastine **93** was obtained in 32% yield, 3′-oxoleurosine **94** in 62% yield and 3′-oxoleurosidine **95** in 56% yield.

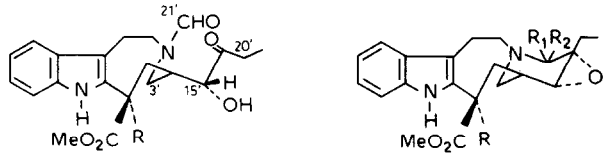


46 R_1=OH, R_2=Et, R_3=H
77 R_1=Et, R_2+R_3=O
78 R_1=Et, R_2=OH, R_3=H

93 R_1=OH, R_2=Et, R_3=H
94 R_1=Et, R_2+R_3=O
95 R_1=Et, R_2=OH, R_3=H

3′-Oxoanhydrovinblastine **90** was also formed from anhydrovinblastine **59** by potassium permanganate oxidation in acetone as a minor product (10% yield). The major product was identified as (15′*R*)-15′-hydroxycatharinine **96** (42% yield).[54,55] Alternatively, $KMnO_4$ oxidation of leurosine **77** led to **94** (19%) and **96** (27%).

Catharine **81**, the peroxidic oxidation product of leurosine **77**, was originally erroneously assigned as 21′-oxo leurosine **97**. However, the synthesis of **97** from leurosine **77** has also been reported.[57] Thus, **77** was oxidized with MnO_2 to 21′-hydroxyleurosine **98**, and with additional MnO_2 to **97**.

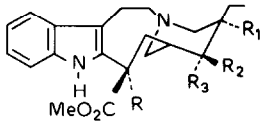


96

97 R_1,R_2=O
98 R_1=H R_2=OH

R=10-vindolinyl

By a combination of oxidative and reductive methods the series of alcohol and glycol derivatives of vinblastine at C(15′)/C(20′) was extended with further possible isomers.[59,60] An optimisation of procedure **89**→**91** was reported by Kutney *et al.*[59] to give a 60% yield of (15′*R*)-15′-hydroxyleurosidine **91**. Moffatt oxidation (DMSO, benzene, pyridine, trifluoroacetic acid, dicyclohexylcarbodiimide) of **91** gave ketol **99** (54% yield), which on reduction with sodium borohydride gave the *trans* glycol, (15′*S*)-15′-hydroxyleurosidine **100** (90% yield). Hydroboration/oxidation (diborane/THF, then NaOH, $MeOH/H_2O_2$) of anhydrovinblastine **59** afforded the secondary alcohol (15′*S*)-20′-deoxy-15′-hydroxyleurosidine **101** in 47% yield. With tributylstannane, the thioxobenzoate of **101** gave 20′-deoxyleurosidine **102**, which was identical with an authentic sample of the natural product. Moffatt oxidation of **101** led to 20′-deoxy-15′-oxoleurosidine **103** (77% yield). (15′*R*)-20′-Deoxy-15′-hydroxyleurosidine **104** was obtained almost quantitatively from **103** by sodium borohydride reduction. Compound **103** was transformed with dimethylamine to an epimeric mixture of **103** and 20′-deoxy-15′-oxovinblastine **105**, from which the compounds were separated by reverse phase hplc.



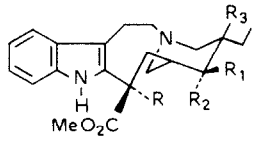
91 R_1=R_3=OH, R_2=H
99 R_1=OH, R_2R_3=O
100 R_1=R_2=OH, R_3=H
101 R_1=R_2=H, R_3=OH
102 R_1=R_2=R_3=H
103 R_1=H, R_2R_3=O

104 R_1=R_3=H, R_2=OH
107 R_1=R_2=H, R_3=OAc
108 R_1=R_3=H, R_3=OAc

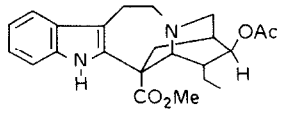
R=10-vindolinyl

Sodium borohydride reduction of **105** produced (15′*R*)-15′-hydroxy-20′-deoxyvinblastine **106** in 47% yield. Compounds **101**, **104** and **106** were transformed to their acetates, **107**, **108** and **109**, respectively.

The fourth possible 15′-acetoxy compound was synthesized by Polonovski–Potier-coupling of (15*R*, 20*S*)-15-acetoxy-15, 20-dihydro-catharanthine **110**[60] with vindoline **43**.[61] The obtained (15′*S*)-15′-acetoxy-20′-deoxyvinblastine **111** was identical with the acetylated minor product of the borohydride reduction of **105**. The naturally occurring vincadiolines **112** and **113** together with the synthetical bis-indoles **91** and **100** provided the four possible C(15′)/C(20′) glycols derived from vinblastine **46** and leurosidine **78**.

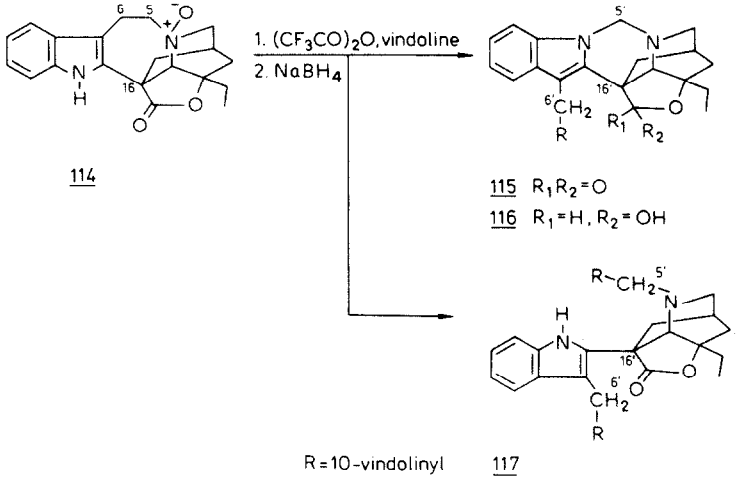


105 $R_1R_2=O, R_3=H$
106 $R_1=OH, R_2=R_3=H$
109 $R_1=OAc, R_2=R_3=H$
111 $R_1=R_3=H, R_2=OAc$
112 $R_2=R_3=OH, R_1=H$
113 $R_1=R_3=OH, R_2=H$



110

Coupling of the 20α-hydroxydihydrocatharanthinic acid lactone **114** with vindoline **43** under Polonovski–Potier-conditions gave the bis-indole compound **115**, result of a C(5)–C(6) bond cleavage, as the main product. The corresponding lactol **116** (by-product of the borohydride reduction) and the trimer **117** (C(5)–C(6) bond fission, followed by nucleophilic attack of vindoline at both 5 and 6 positions) were the

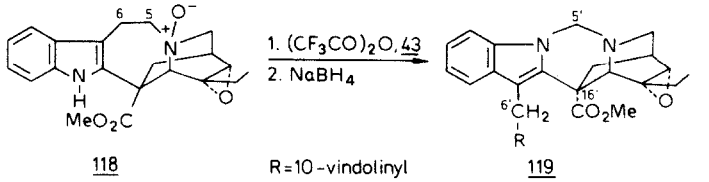


114

115 $R_1R_2=O$
116 $R_1=H, R_2=OH$

R = 10-vindolinyl **117**

minor products.[40,62–64] 15α,20α-Epoxydihydrocatharanthine N-oxide **118** with vindoline **43** gave in turn the bis-indole **119** as a result of the C(5)–C(6) fragmentation.[40] The isomeric 15β,20β-epoxy derivative

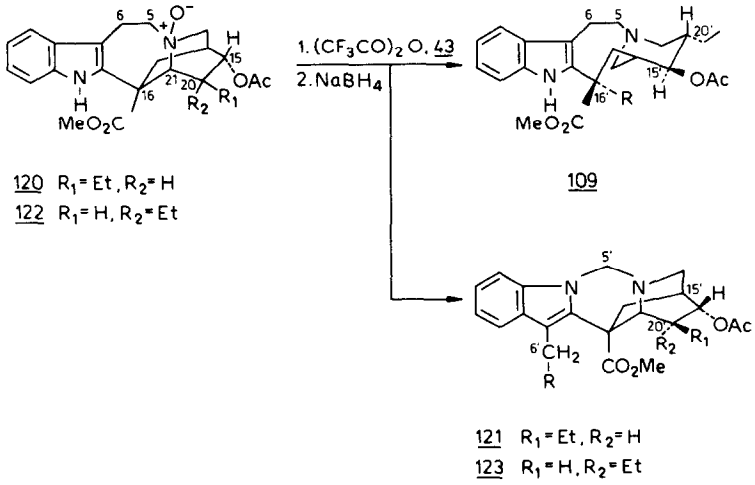


118 R = 10-vindolinyl **119**

was coupled to leurosine (**83** + **43** → **77**), showing that the fragmentation of the relevant bonds in the catharanthine system is sensitive to the stereochemical orientation of the oxygen functionality at C(5) and C(6).

Honma and Ban[63] also studied the effect of the configuration of the oxygen function at C(15) on the

Polonovski–Potier-reaction. On coupling (15*S*,20*S*) - 15 - acetoxy - 15,20 - dihydrocatharanthine N-oxide **120** with vindoline **43** they obtained (15′*R*)-15′-acetoxy-20′-deoxyvinblastine **109** in 6% yield and the bis-indole **121**, a C(5)–C(6) fission product, in 42.5% yield. The same reaction of (15*S*,20*R*) - 15 - acetoxy - 15,20 - dihydrocatharanthine N-oxide **122** afforded **109** in 4% yield and **123**, the C(20) epimer of **121**, in 37% yield.

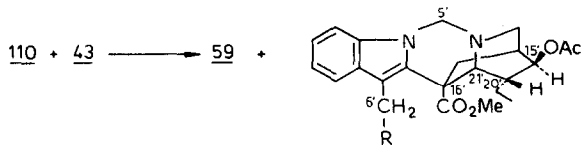


120 R_1 = Et, R_2 = H
122 R_1 = H, R_2 = Et

109

121 R_1 = Et, R_2 = H
123 R_1 = H, R_2 = Et

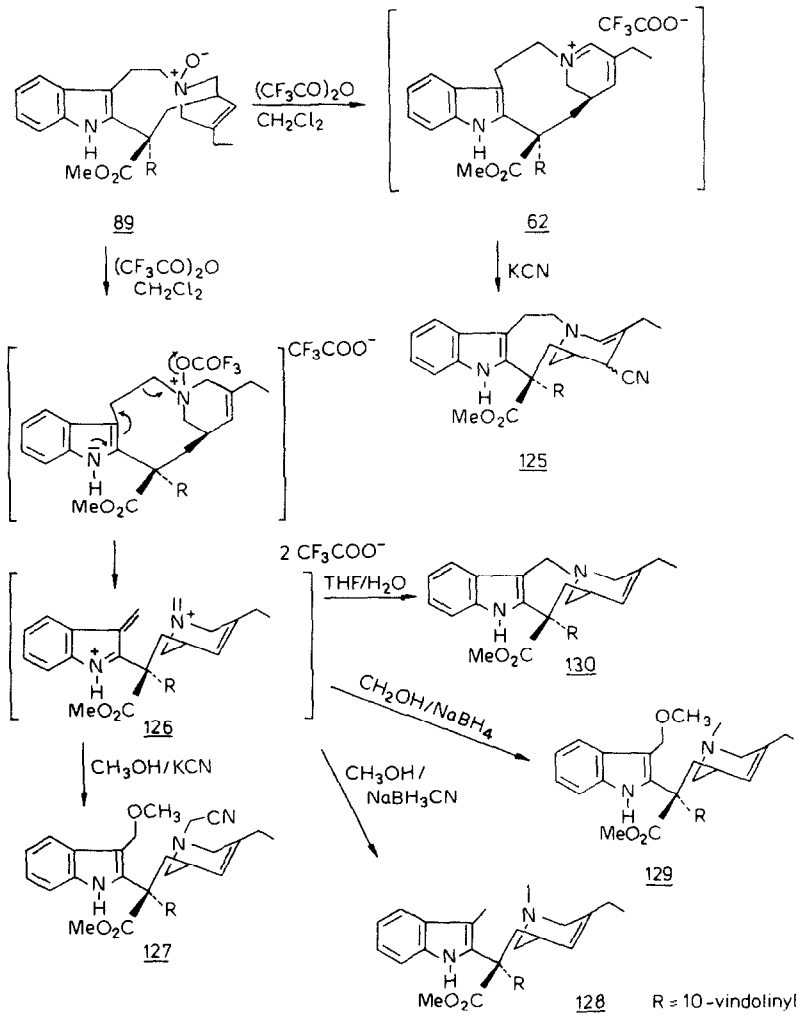
The coupling reaction of **110** and **43** in their hands gave anhydrovinblastine **59** in 22% yield and a new C(5)–C(6) fission product **124**, isomer of **121** and **123**, in 32% yield.



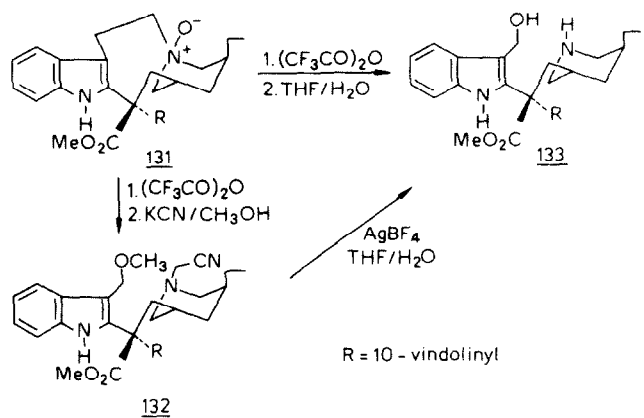
R = 10 - vindolinyl

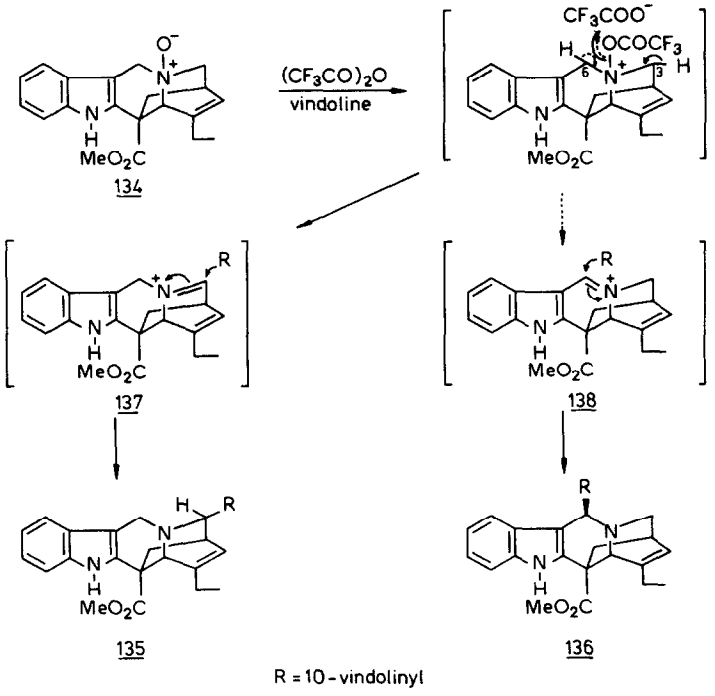
124

Potier *et al.*[65,66] have found that the modified Polonovski-reaction of anhydrovinblastine N_b-oxide **89** in the presence of nucleophiles leads to new 5′ nor and 5′6′ seco derivatives. Treatment of anhydrovinblastine N-oxide **89** with trifluoroacetic anhydride in methylene chloride, and then evaporation with KCN/MeOH produced 15′-cyano-$\Delta^{20',21'}$-deoxyvinblastine **125** in 32% yield and 5′,6-seco bis-indole **127** in 54% yield. Compound **127** was formed by nucleophilic attack of cyanide ion on the conjugated immonium salt **62** (intermediate of the synthesis of anhydrovinblastine **59**). The major product, **127** is a result of the fragmentation reaction of the tryptamine side chain, and attack of both nucleophiles, OCH_3^- and CN^-, on the diimonium salt intermediate **126**. From the common intermediate **126** in the presence of different reductive agents (e.g. sodium cyanoborohydride or sodium borohydride) in methanol, different seco derivatives such as **128** and **129** were isolated. When the product of the modified Polonovski-reaction was evaporated and treated with a mixture of water and tetrahydrofuran, the only bis-indole obtained was 5′-nor anhydrovinblastine **130** (27% yield). Addition of water to the bis-immonium salt **126**, then loss of formaldehyde, followed by a nucleophilic displacement of the substituent on C(6′) led to this new type of bis-indole.

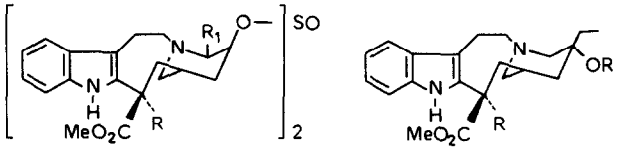


In the case of 20'-deoxyleurosidine N-oxide **131**, fragmentation of the tryptamine chain was the only reaction observed. Thus, treatment of the evaporated reaction mixture from the modified Polonovski-reaction with potassium cyanide in methanol gave rise to the 5'6'-seco derivative **132** (50% field). Another 5'6'-seco derivative, compound **133**, was isolated after treatment with water-tetrahydrofuran. Compound **132** was transformed with silver tetrafluoroborate in tetrahydrofuran to **133**, but cyclization of the latter to a nor derivative did not succeed. On the other hand, on coupling of 5-nor catharanthine N-oxide **134** with vindoline **43** under Polonovski–Potier-reaction conditions (at 0°), the two new dimers **135** and **136** derived from the two possible species of immonium intermediates **137** and **138** were isolated.[67] Potier *et al.*[68] have also shown that 7'-chloro-indolenines from several dimeric alkaloids of vinblastine type are useful intermediates in the preparation of the 5',6'-seco and 5'-nor derivatives of the series.





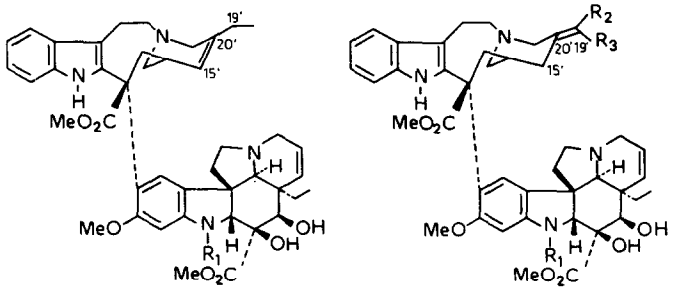
Various synthetic modifications have been carried out with the aim of testing the new derivatives for antitumor activity. Treatment of vinblastine **46** with thionylchloride led to bis 20′ sulfite ester **139**, which was made to react with silver perchlorate in an alcohol to give leurosidine 20′-ethers **140**.[69] Treatment of **139** with $AgClO_4$, followed by acetylation of the 21′ hydroxy compound afforded bis (21′-acetoxyvinblastine)-20′-sulfite **141**.[70]



139 R_1=H
141 R_1=OAc

140 R_1= Me, Et, Pr

R = 10-vindolinyl

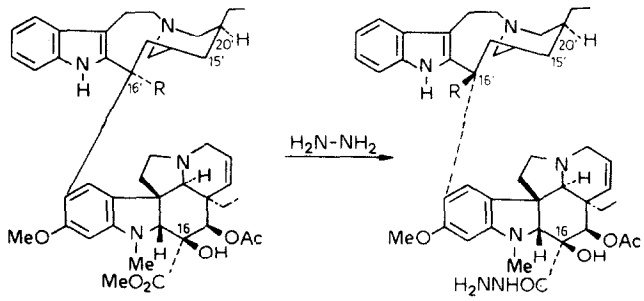


142 R_1=CH_3, CHO

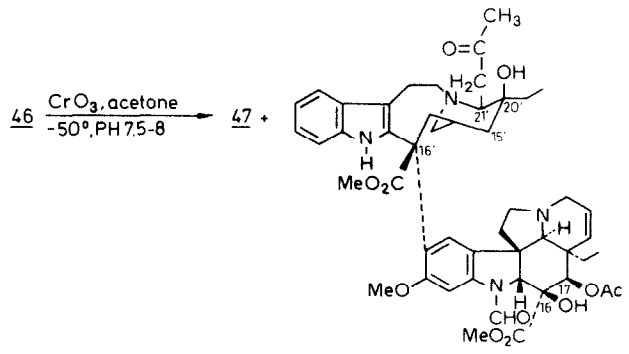
143 R_2= H, R_3=CH_3, or R_2=CH_3, R_3= H
144 R_2= CH_3, R_3= H, R_1=CH_3CHO

Some chemical transformations affected both the ibogane and the vindoline units. Vinblastine **46** and its derivatives were dehydrated by concentrated sulfuric acid to a mixture of three 17-deacetyl isomeric olefins, the 15′,20′-*endo* **142** and the two 19′,20′-*exo* **143** and **144** double bond derivatives.[71]

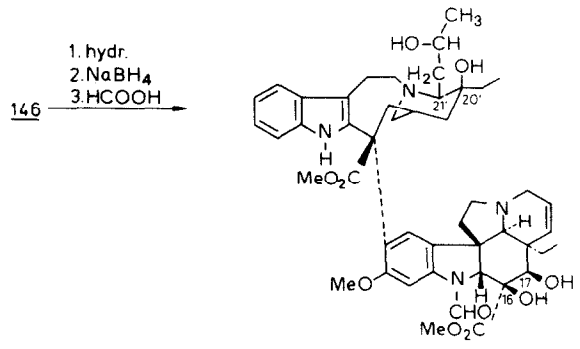
The reaction of vinblastine **46**[72] or 16′ - epi - 16′ - decarbomethoxy - 20′ - deoxyleurosidine **49**[73] with refluxing anhydrous hydrazine led to 16′-decarbomethoxy-17-deacetyl-16-hydrazide derivatives, with retention of the 16′ configuration. The same reaction of 16′-epi-20′-deoxyleurosidine **53** resulted in epimerization.[73] 16′-Decarbomethoxy-20′-deoxyleurosidine 16-hydrazide **145** was obtained in 44% yield, and its C(16′) epimer in 10% yield. 21′-Acetonylvincristine **146** was isolated as a by-product of chromate oxidation of vinblastine **46** to vincristine **47** in acetone. Compound **146** was transformed to 17-deacetyl-21′(2″hydroxypropyl)-vincristine **147** by hydrolysis, borohydride reduction and formylation.[74]



53 R = CO_2Me 145 R = H +16′ epimer

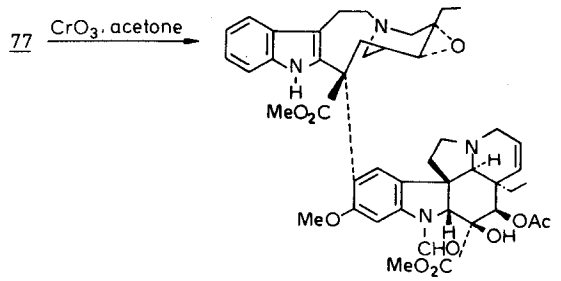


146



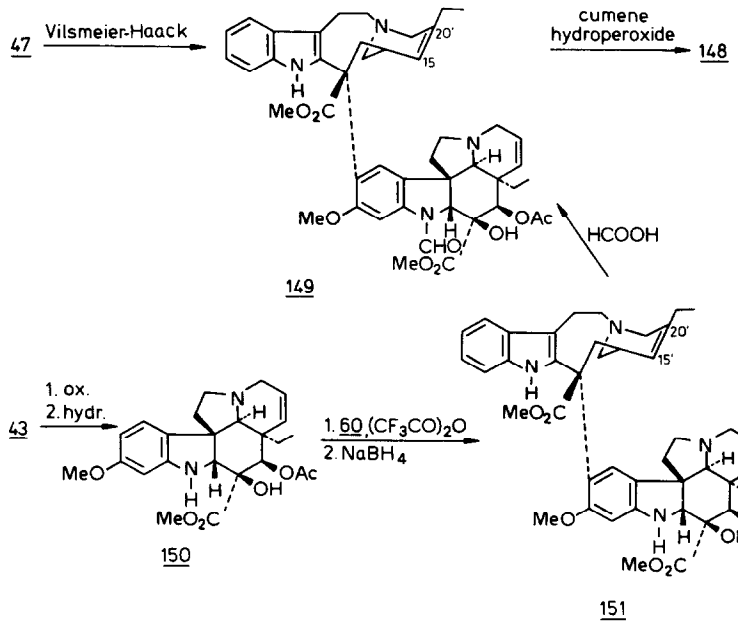
147

(ii) *Functional modifications in the vindoline unit.* The chromate oxidation of various vinblastine derivatives led to different vincristine type compounds of valuable antileukemic potency. Leurosine **77** was transformed with chromic acid in acetone to N_a-demethyl-N_a-formylleurosine **148**.[52]



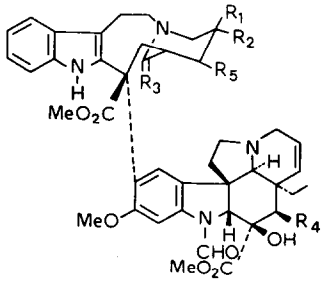
148

An alternative method to obtain **148** is the dehydration of vincristine **47** by Vilsmeier-Haack reagent to 15',20'-anhydrovincristine **149**, followed by epoxidation with cumene hydroperoxide.[75] Compound **148** has also been prepared from N_a-demethylvindoline **150**, obtained from vindoline **43** by oxidation and hydrolysis. Polonovski–Potier-coupling of **150** with catharanthine N-oxide **60** gave N_a-demethyl-15',20'-anhydrovinblastine **151**, which was formylated and epoxidized to give **148**.[75,76]



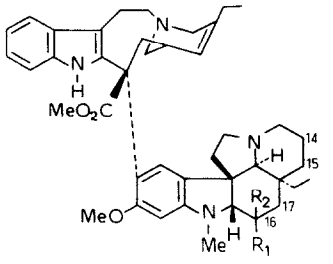
17-Deacetoxyvinblastine[77] was oxidized at room temperature in formic acid by air in the presence of Pt catalyst to 17-deacetoxyvincristine **152** in 75% yield.[78] Chromate oxidation of 20'-deoxyvinblastine **66** gave 20'-deoxyvincristine **153** (60% yield).[79]

A suitable method to oxidize the N_a Me group of vinblastine derivatives is the reaction with large excess of Jones reagent at −78° in acetone–acetic anhydride.[80,81] Thus, **148** was obtained from **77** in 75% yield, and anhydrovinblastine **59** gave an 80% yield of anhydrovincristine **149**. 20'-Deoxyleurosidine **102** led to the corresponding vincristine derivative **154** (68% yield) and 3'-oxoleurosine **94** gave 3'-oxo-N_a-demethyl-N_a-formylleurosine **155** (30% yield).



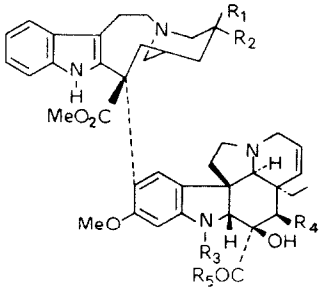
152 R_1 = OH, R_2 = Et, R_3 = H_2, R_4 = R_5 = H
153 R_1 = H, R_2 = Et, R_3 = H_2, R_4 = OAc, R_5 = H
154 R_1 = Et, R_2 = OH, R_3 = H_2, R_4 = OAc, R_5 = H
155 R_1 = Et, R_2, R_5 = O, R_3 = O, R_4 = OAc

New vinblastine derivatives were prepared by Polonovski–Potier-reaction of novel vindoline derivatives.[81,82] 17-Deacetoxyvindoline, 17 - deacetoxy - 16,17 - dehydrovindoline, 14,15 - dihydro - 17 - deacetoxy - 16,17 - dehydrovindoline and their 16-N-methylamides furnished on coupling with catharanthine N-oxide **60** the corresponding anhydrovinblastine derivatives **156–160**.[81,83]



			Yield of the Polonovski-Potier coupling
156	$R_1 = CO_2Me, \Delta^{16,17}$,	R_2 = –	45 %
157	$R_1 = CONH\text{-}Me, \Delta^{16,17}, \Delta^{14,15}$	R_2 = –	36 %
158	$R_1 = CO_2Me, \Delta^{16,17}$	R_2 = –	30 %
159	$R_1 = CONH\text{-}Me, \Delta^{16,17}$	R_2 = –	22 %
160	$R_1 = CO_2Me, \Delta^{14,15}$,	R_2 = OH	32 %

The C(16) carbomethoxy group of vinblastine-type alkaloids was transformed to different esters **161**[84] and hydrazides **162**.[85,86] Compounds **162** were converted to substituted hydrazides **163**,[86] or to acyl azides, which by treatment with NH_3 or an amine yielded new C(16) carboxamides **164**,[85,87] including alkylene-, S-, O- and NH-bridged bis-indole 16-carboxamido dimers.[88] Similarly, leurosine **77** was also transformed to 16-carboxamido derivatives.[89]



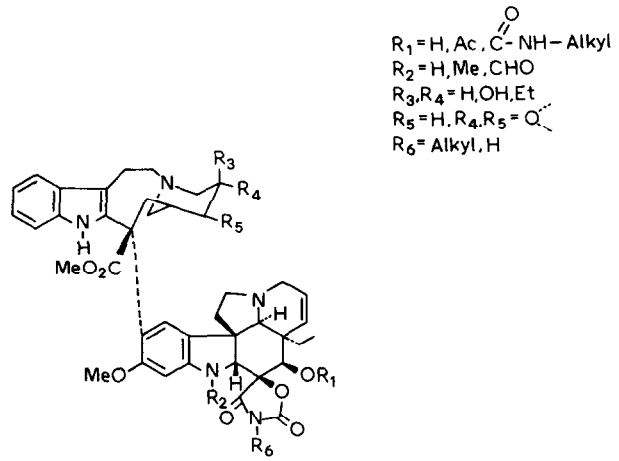
161 R_1=OH, R_2=Et, R_3=Me,CHO, R_4=OH,OAc, R_5=OEt,OBu,OCH_2-CH_2OH

162 R_1=OH,Et, R_2=OH,Et, R_3=Me,CHO, R_4=OH, R_5=NH-NH_2

163 R_1=OH, R_2=Et, R_3=Me, R_4=OH, R_5=NH–N(R_6, R_7) R_6=H, R_7=Me,Et COPr, Bz, CH_2CH_2OH CH_2CH_2OAc, CO_2Et $R_6 = R_7$=Me R_6,R_7=CHMe, $=CMe_2$

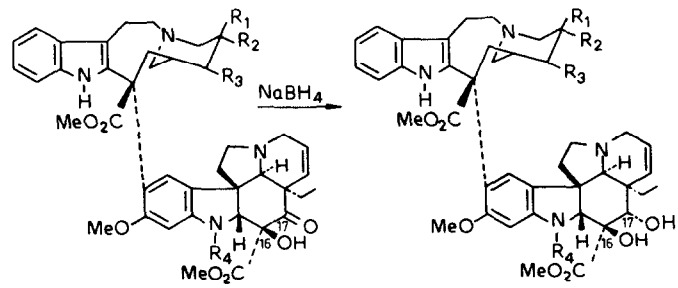
164 R_1=OH, Et, R_2=OH,Et, R_3=Me,CHO, R_4=OH, R_5=NH_2,NH-CH_2-CH_2-OH,NH-Alkyl

N-alkyl-oxazolidinedione derivatives of vinblastine-type alkaloids **165** were synthesized from vinblastine derivatives and alkyl isocyanates.[90] Alternatively, reaction of vinblastine 16-carboxamido derivatives and dimethylcarbonate led to N-unsubstituted vinblastine-spiro-oxazolidine derivatives (R_6 = H).[91]



165

17-Deacetylvinblastine and its derivatives were oxidized with dicyclohexylcarbodiimide and orthophosphoric acid in dimethyl sulfoxide to give 17-deacetoxy-17-oxovinblastine derivatives **166**.[92] Compounds **166** were reduced to give 17-deacetoxy-17-α-hydroxyvinblastine derivatives **167**, which were converted to the 16-carboxyhydrazides.[93]

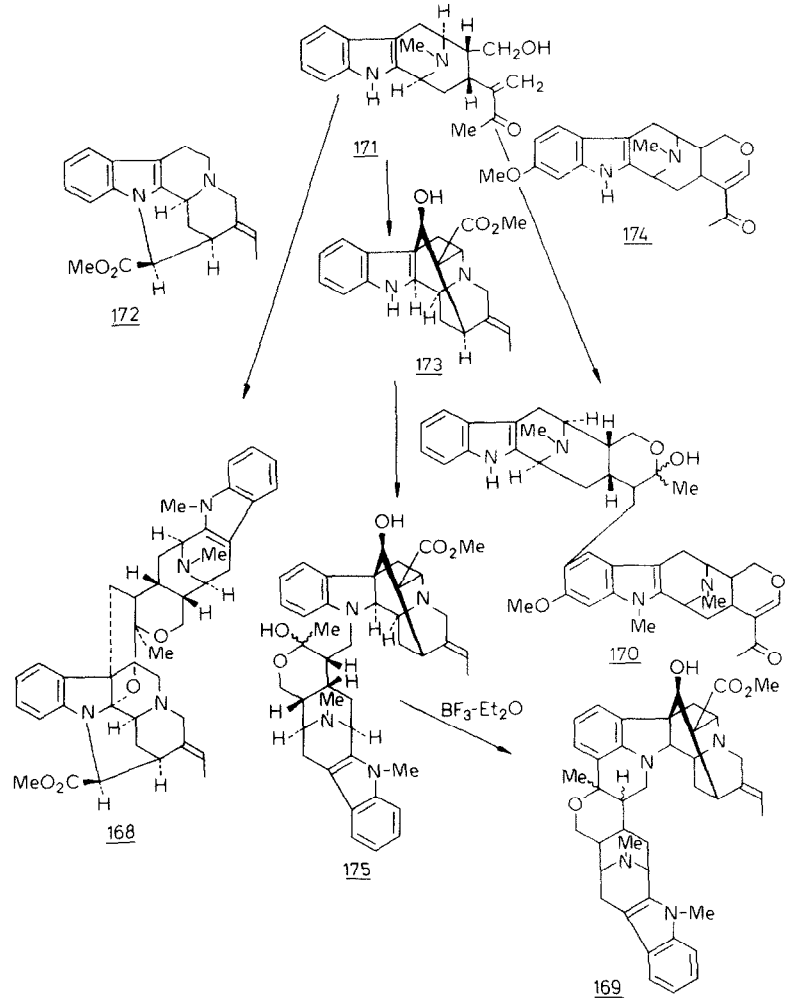


166 R_1, R_2 = H, OH, Et
R_3 = H
R_1 = Et, R_2, R_3 = O
R_4 = Me, CHO

167

5. BIOMIMETIC SYNTHESIS OF ALSTONIA BIS-INDOLES

Villalstonine **168**, alstonisidine **169** and macralstonine **170**, bis-indole alkaloids of *A. muelleriana* and *A. macrophylla*, were synthesized from macroline **171** and pleiocarpamine **172**,[94,95] and quebrachidine **173**[95,96] and alstophylline **174**,[97] respectively. Compounds **171** and **172** in dilute aqueous hydrochloric acid led to **168**, and **171** and **174** under the same conditions to **170**. From the reaction of **171** and **173** a labile amino-hemiacetal **175** was obtained, which on treatment with boron trifluoride etherate was closed to **169**.



REFERENCES

[1]T. Hino, S. Kodato, K. Takahashi, H. Yamaguchi and M. Nakagawa, *Tetrahedron Letters* 4913 (1978).
[2]S. Iwadare, Y. Shizuri, K. Yamada and Y. Hirata, *Ibid.* 1177 (1974).
[3]S. Iwadare, Y. Shizuri, K. Yamada and Y. Hirata, *Tetrahedron* **34**, 1457 (1978).
[4]S. Iwadare, Y. Shizuri, K. Sasaki and Y. Hirata, *Ibid.* **30**, 4105 (1974).
[5]G. J. Kapadia and R. E. Rao, *Tetrahedron Letters* 975 (1977).
[6]F. Tillequin, M. Koch, J. Pousset and A. Cavé, *J. Chem. Soc.* Chem. Comm. 826 (1978).
[7]K. Yamada, K. Aoki and D. Uemura, *J. Org. Chem.* **40**, 2572 (1975).
[8]C. Mirand-Richard, L. Le Men-Olivier, J. Lévy and J. Le Men, *Heterocycles* **12**, 1409 (1979).
[9]C. Richard, C. Delaude, L. Le Men-Olivier and J. Le Men, *Phytochemistry* **17**, 539 (1978).
[10]E. Seguin and M. Koch, *Planta Med.* **37**, 175 (1979).
[11]H. Riesner and E. Winterfeldt, *J. Chem. Soc.* Chem. Comm. 786 (1972).
[12]G. Benz, H. Riesner and E. Winterfeldt, *Chem. Ber.* **108**, 248 (1975).
[13]G. Büchi, R. E. Manning and S. A. Monti, *J. Am. Chem. Soc.* **86**, 4631 (1964). See also J. P. Kutney, A. Horinaka, R. S. Ward and B. R. Worth, *Can. J. Chem.* **58**, 1829 (1980).
[14]J. R. Knox and J. Slobbe, *Aust. J. Chem.* **28**, 1813 (1975).
[15]J. Le Men and W. I. Taylor, *Experientia* **21**, 508 (1965).
[16]G. I. Kingston, B. B. Gerhart and F. Ionescu, *Tetrahedron Letters* 649 (1976).
[17]H. Achenbach and E. Schaller, *Chem. Ber.* **109**, 3527 (1976).
[18]S. Takano, S. Hatakeyama and K. Ogasawara, *Heterocycles* **6**, 1311 (1977). According to other results the coupling of vindoline **43** with eburnamenine **44** gives just one of the two possible 16'-epimers. Pierre Potier, Personal communication.
[19]J. Harley-Mason and A-ur-Rahman, Chem. Comm. 1048 (1967).
[20]J. Harley-Mason and A-ur-Rahman, *Tetrahedron* **36**, 1057 (1980).
[21]N. Neuss, M. Gorman, N. J. Cone and L. L. Huckstep, *Tetrahedron Letters* 783 (1968).
[22]J. P. Kutney, J. Beck, F. Bylsma and W. J. Cretney, *J. Am. Chem. Soc.* **90**, 4504 (1968).
[23]J. P. Kutney, J. Cook, K. Fuji, A. M. Treasurywala, J. Clardy, J. Fayos and H. Wright, *Heterocycles* **3**, 205 (1975).
[24]J. P. Kutney, J. Beck, F. Bylsma, J. Cook, W. J. Cretney, K. Fuji, R. Inhof and A. M. Treasurywala, *Helv. Chim. Acta* **58**, 1690 (1975).
[25]A-ur-Rahman, *Pakistan J. Sci. Ind. Res.* **14**, 487 (1971).
[26]N. Kunesch, P.-L. Vaucamps, A. Cavé, J. Poisson and E. Wenkert, *Tetrahedron Lett.* 5073 (1979). See also R. Z. Andriamialisoa, N. Langlois and P. Potier, *Tetrahedron Lett.* 2849 (1976).
[27]J. Bruneton, A. Cavé, E. W. Hagaman, N. Kunesch and E. Wenkert, *Ibid.* 3567 (1976).
[28]P. Potier, N. Langlois, Y. Langlois and F. Guéritte, *J. Chem. Soc.* Chem. Comm. 670 (1975).

[29]N. Langlois, F. Guéritte, Y. Langlois and P. Potier, *J. Am. Chem. Soc.* **98**, 7017 (1976). See also P. Potier, N. Langlois, Y. Langlois and F. Guéritte, *Ger. Offen* 2, 558, 124 (1976); *Chem. Abstr.* **86**, 29977k (1977).
[30]P. Potier, *Rev. Latinoamer. Quim.* **9**, 47 (1978); P. Potier, In *Stereoselective Synthesis of Natural Products* (Edited by W. Bartmann and E. Winterfeldt), p. 10. Excerpta Medica, Amsterdam–Oxford (1978); P. Potier, In *Indole and Biogenetically Related Alkaloids* (Edited by J. D. Phillipson and M. H. Zenk), p. 159. Academic Press, London (1980); P. Potier, *J. Nat. Prod.* **43**, 72 (1980).
[31]J. P. Kutney, A. H. Ratcliffe, A. M. Treasurywala and S. Wunderly, *Heterocycles* **3**, 639 (1975).
[32]J. P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A. H. Ratcliffe, A. M. Treasurywala and S. Wunderly, *Helv. Chim. Acta* **59**, 2858 (1976).
[33]J. P. Kutney, *U.S. Pat. Appl.* 806, 317 (1977); *Chem. Abstr.* **89**, 43906e (1978).
[34]R. Z. Andriamialisoa, Y. Langlois, N. Langlois and P. Potier, *C.R. Acad. Sci. Paris* **284C**, 751 (1977).
[35]N. Langlois and P. Potier, *J. Chem. Soc.* Chem. Comm. 582 (1979).
[36]K. L. Stuart, J. P. Kutney and B. R. Worth, *Heterocycles* **9**, 1015 (1978).
[37]K. L. Stuart, J. P. Kutney, T. Honda and B. R. Worth, *Ibid.* **9**, 1391, 1419 (1978).
[38]N. Langlois and P. Potier, *J. Chem. Soc.* Chem. Comm. 102 (1978).
[39]J. P. Kutney and B. R. Worth, *Heterocycles* **4**, 1777 (1976).
[40]J. P. Kutney, A. V. Joshua, P. Liao and B. R. Worth, *Can. J. Chem.* **55**, 3235 (1977).
[41]Y. Langlois, N. Langlois, P. Mangeney and P. Potier, *Tetrahedron Letters* 3945 (1976).
[42]P. Potier, N. Langlois, Y. Langlois and P. Mangeney, *Fr. Demand* 2, 357, 249 (1978); *Chem. Abstr.* **89**, 180221s (1978).
[43]J. P. Kutney, J. Balsevich, G. H. Bokelman, T. Hibino, I. Itoh and A. H. Ratcliffe, *Heterocycles* **4**, 997 (1976).
[44]J. P. Kutney, J. Balsevich, G. H. Bokelman, T. Hibino, T. Honda, I. Iton, A. H. Ratcliffe and B. R. Worth, *Can. J. Chem.* **56**, 62 (1978).
[45]P. Potier, N. Langlois and Y. Langlois, Ger. Offen. 2, 815, 822 (1978); *Chem. Abstr.* **90**, 72, 378k (1979).
[46]N. Langlois and P. Potier, *Tetrahedron Letters* 1099 (1976).
[47]P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois and P. Potier, *J. Am. Chem. Soc.* **101**, 2243 (1979).
[48]A-ur-Rahman, A. Basha, H. Ghazala and N. Waheed, *Z. Naturforsch* **31b**, 1416 (1976).
[49]A-ur-Rahman, A. Basha and M. Ghazala, *Tetrahedron Letters* 2351 (1976).
[50]A-ur-Rahman, Ger. Offen. 2, 614, 863, (1977); *Chem. Abstr.* **88**, 7180j (1978).
[51]K. Jovanovics, G. Fekete, E. Bittner, E. Dezséri, J. Éles, K. Szász, (G. Richter Rt.), S. African pat. 7208, 535 (1973); *Chem. Abstr.* **80**, 146401e (1974).
[52]G. Richter Rt., Belg. pat. 823, 560 (1975); *Chem. Abstr.* **84**, 59835p (1976).
[53]J. P. Kutney, J. Balsevich and B. R. Worth, *Heterocycles* **9**, 493 (1978).
[54]J. P. Kutney, J. Balsevich and B. R. Worth, *Can. J. Chem.* **57**, 1682 (1979).
[55]J. P. Kutney, J. Balsevich and B. R. Worth, *Heterocycles* **11**, 69 (1978).
[56]J. P. Kutney, J. Balsevich and G. H. Bokelman, *Ibid.* **4**, 1377 (1976).
[57]G. L. Thompson, G. C. Pascal and R. A. Conrad (E. Lilly and Co.), *U.S. pat.* 4, 122, 081 (1978); *Chem. Abstr.* **90**, 104, 192p (1979).
[58]G. L. Thompson and G. C. Pascal (E. Lilly and Co.), *Ger. Offen.* 2, 813, 286 (1978); *Chem. Abstr.* **90**, 121, 853w (1979).
[59]J. P. Kutney, T. Honda, P. M. Kazmaier, N. J. Lewis and B. R. Worth, *Helv. Chim. Acta* **63**, 366 (1980).
[60]J. P. Kutney, T. Honda, A. V. Joshua, N. G. Lewis and B. R. Worth, *Ibid.* **61**, 690 (1978).
[61]J. P. Kutney and B. R. Worth, *Heterocycles* **6**, 905 (1977).
[62]J. P. Kutney, A. V. Joshua and P. Liao, *Ibid.* **6**, 297 (1977).
[63]Y. Honma and Y. Ban, *Ibid.* **6**, 291 (1977).
[64]P. Mangeney, R. Costa, Y. Langlois and P. Potier, *C.R. Acad. Sci., Paris* **284C**, 701 (1977).
[65]P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois and P. Potier, *J. Org. Chem.* **44**, 3765 (1979).
[66]P. Mangeney, R. Z. Andriamialisoa, J.-Y. Lallemand, N. Langlois, Y. Langlois and P. Potier, *Tetrahedron* **35**, 2175 (1979).
[67]R. Z. Andriamialisoa, N. Langlois, Y. Langlois, P. Potier and P. Bladon, *Can. J. Chem.* **57**, 2572 (1979).
[68]R. Z. Andriamialisoa, N. Langlois, Y. Langlois and P. Potier, *Tetrahedron* **36**, 3053 (1980).
[69]A. S. Kantner, G. E. Gutowski and J. C. Miller (E. Lilly and Co.), *U.S. Pat.* 4, 075, 214 (1978); *Chem. Abstr.* **89**, 43 905d (1978).
[70]A. S. Kantner, G. E. Gutowski and J. C. Miller (E. Lilly and Co.), *U.S. Pat.* 4, 087, 429 (1978); *Chem. Abstr.* **89**, 129 779c (1978).
[71]J. C. Miller, G. E. Gutowski, G. A. Poore and G. B. Boder, *J. Med. Chem.* **20**, 409 (1977).
[72]N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi and R. E. Manning, *J. Am. Chem. Soc.* **86**, 1440 (1964).
[73]J. P. Kutney, E. Jahngen and T. Okutani, *Heterocycles* **5**, 59 (1976).
[74]C. J. Barnett, R. A. Bimm and C. G. Cullinan (E. Lilly and Co.), *U.S. Pat.* 4, 110, 330 (1978); *Chem. Abstr.* **90**, 152 444a (1979).
[75]L. Szabó, K. Nógràdi, K. Honty and C. Szántay, *Symp. Pap.-IUPAC Int. Symp. Chem. Nat. Prod.* 11*th* **3**, 17 (1978); *Chem. Abstr.* **92**, 111 207s (1980).
[76]G. Richter Rt., *Belg. Pat.* 867, 255 (1978); *Chem. Abstr.* **90**, 138 080r (1979).
[77]N. Neuss, A. J. Barnes, L. L. Huckstep, *Experientia* **31**, 18 (1975).
[78]K. Jovanovics, L. Dancsi, S. Eckhardt, C. Lörincz, J. Sugár, Z. Relle, K. Szász, J. Tamás, Á. Szöllösy (G. Richter Rt.), *Ger. Offen* 2, 706, 366 (1977); *Chem. Abstr.* **87**, 201 859g (1977).
[79]G. L. Thompson (E. Lilly and Co.), *Ger. Offen.* 2, 801, 748 (1978); *Chem. Abstr.* **89**, 197 778b (1978).
[80]J. P. Kutney, J. Balsevich, T. Honda, P. Liao, H. P. M. Thiellier and B. R. Worth, *Heterocycles* **9**, 201 (1978).
[81]J. P. Kutney, J. Balsevich, T. Honda, P. Liao, H. P. M. Thiellier and B. R. Worth, *Can. J. Chem.* **56**, 2560 (1978).
[82]J. P. Kutney, K. K. Chan, W. B. Evans, Y. Fujise, T. Honda, F. K. Klein and J. P. Souza, *Heterocycles* **6**, 435 (1977).
[83]J. P. Kutney, W. B. Evans and T. Honda, *Ibid.* **6**, 443 (1977).
[84]G. J. Cullinan (E. Lilly and Co.), *Ger. Offen.* 2, 544, 843 (1976); *Chem. Abstr.* **85**, 94 585z (1976).
[85]G. J. Cullinan and K. Gerzon (E. Lilly and Co.), *Ger. Offen.* 2, 558, 027 (1976); *Chem. Abstr.* **85**, 192 965t (1976).
[86]G. J. Cullinan and K. Gerzon (E. Lilly and Co.), *U.S. Pat.* 4, 166, 810 (1979); *Chem. Abstr.* **92**, 76 761u (1980).
[87]G. J. Cullinan and K. Gerzon ((E. Lilly and Co.), *Ger. Offen.* 2, 739, 443 (1978); *Chem. Abstr.* **90**, 23 367x (1979).
[88]R. C. Allen and K. Gerzon (E. Lilly and Co.), *Eur. Pat. Appl.* 5, 620 (1979); *Chem. Abstr.* **93**, 26 620x (1980).
[89]R. C. Allen, G. J. Cullinan, J. C. Miller and K. Gerzon (E. Lilly and Co.), Fr. Demande 2, 400, 029 (1979); *Chem. Abstr.* **92**, 94 627j (1980).
[90]J. C. Miller and G. E. Gutowski (E. Lilly and Co.), *Ger. Offen.* 2, 753, 791 (1978); *Chem. Abstr.* **89**, 129 7778b (1978).
[91]J. C. Miller (E. Lilly and Co.), *U.S. Pat.* 4, 159, 269 (1979); *Chem. Abstr.* **91**, 157 974x (1979).
[92]I. G. Wright and N. Neuss (E. Lilly and Co.), *U.S. Pat.* 4, 122, 082 (1978); *Chem. Abstr.* **90**, 138 082t (1979).
[93]G. L. Thompson (E. Lilly and Co.), *U.S. Pat.* 4, 195, 022 (1980); *Chem. Abstr.* **93**, 114 803q (1980).
[94]D. E. Burke and P. W. Le Quesne, *J. Chem. Soc.* Chem. Comm. 678 (1972).
[95]D. E. Burke, J. M. Cook and P. W. Le Quesne, *J. Am. Chem. Soc.* **95**, 546 (1973).
[96]D. E. Burke, J. M. Cook and P. W. Le Quesne, *J. Chem. Soc.* Chem. Comm. 697 (1972).
[97]D. E. Burke, C. A. DeMarkey and P. W. Le Quesne, *Ibid.* 1346 (1972).