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APPROACHES TO THE SYNTHESIS OF ASPIDOSPERMA ALKALOIDS. PART I. PRELIMINARY STUDIES IN THE VINCADIFFORMINE GROUP.

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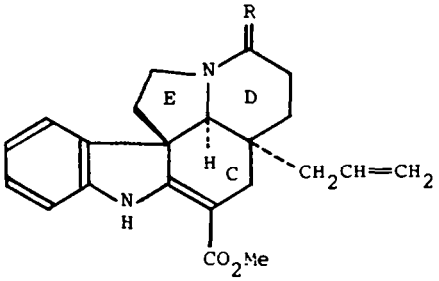
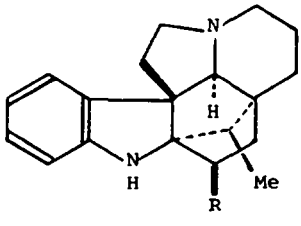
Summary: As a preface to work leading to the total synthesis of 18,19-dehydrotabersonine, described in the following paper, some older work on the synthesis of (±)-3-oxo-20-desethyl-20-allylvincadifformine, its C-20 epimer, and (±)-3-oxo-19-vinylvincadifformine is reported. Attempts to convert these compounds, by appropriate manipulation of the isolated double bond, into a wide range of anilinoacrylate alkaloids, e.g. minovincine, tuboxenine, and pseudokopsinine, are described. Methods for the functionalisation of the double bond at an earlier stage in the synthesis, e.g. using 3,18-dioxo-1-demethylvincatine, have also been investigated.

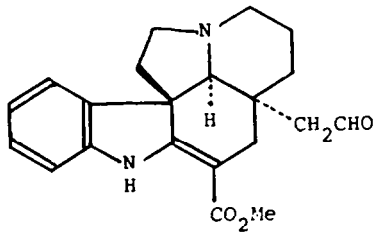
Following our earlier work[1] on the synthesis of Aspidosperma alkaloids containing a functionalised two-carbon substituent attached to C-20, i.e. the cylindrocarpine series, we turned our attention to the synthesis of analogous alkaloids in the vincadifformine group. As in the cylindrocarpine series it was hoped that attachment of an allyl group at C-20, as in (1), would provide a suitable intermediate which could later be transformed into a wide variety of alkaloids by appropriate modification of the allyl group. For example, the intermediate (1) should be susceptible of conversion into tuboxenine (2) and pseudokopsinine (3) by oxidative fission of the terminal double bond, and obvious transformations on the aldehyde (4) so produced. Although it was anticipated that oxidation of the anilinoacrylate double bond might supervene when attempts were made to remove the terminal methylene group it was hoped to find a selective method that would preferentially attack the isolated double bond. In order to stabilise N_b and render it and the adjacent methylene group resistant to oxidation we decided to incorporate N_b in a lactam function. Our initial target, therefore, was the pentacyclic lactam ester (5), which we prepared by adaptation of Levy's synthesis.[2]



(1) R = H_2
(5) R = O

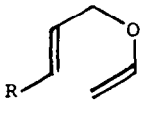


(2) R = H
(3) R = CO_2Me

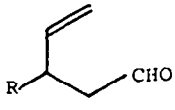


(4)

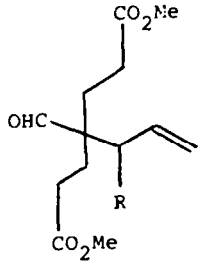
Pent-4-enal (6), prepared by the Claisen rearrangement of allyl vinyl ether (7), was converted into its pyrrolidine enamine, and exhaustively alkylated with methyl acrylate, to give the unsaturated aldehyde diester (8),[4] together with some of the monoalkylated product. Condensation of (8) with 2-hydroxytryptamine hydrochloride in buffered aqueous ethanol gave a mixture of tetracyclic lactams (9), which were separated by chromatography into two mixtures, each of which consisted of two diastereoisomeric racemates. Under the conditions used the more polar fraction constituted approximately 60% of the total product. These four racemates are presumably those derived from the two diastereoisomers (10), which differ in the configuration at C-20, and the two diastereoisomers (11), which also differ at C-20. Following the convention used[5a] in the oxindole alkaloid series in which N_b is basic, we propose to designate diastereoisomers (10a) and (10b) as the A series, and (11a) and (11b) as the B series. In contrast to the situation in the alkaloids equilibration of all four C-7 and C-21 stereoisomers in these N_b lactams is not possible; it is, however, possible in the intermediate tricyclic aminoester (12), but under the experimental conditions used we were unable to influence significantly the relative proportions of the A(10) and B(11) lactams in the product. Because of the uncertainties in the assignment of stereochemical configuration to these stereoisomers both mixtures were converted by means of Meerwein's salt into their iminoethers (13a), then treated with dimsyl sodium in dimethylsulphoxide, in an attempt to cyclise them to the desired pentacyclic lactams (14).



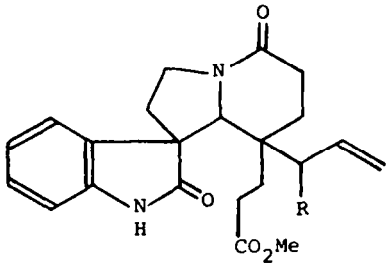
(7) R = H
(25) R = Me



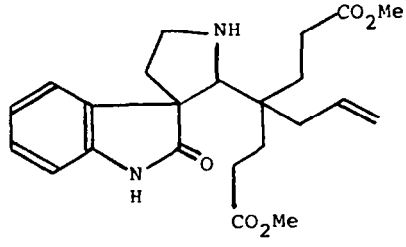
(6) R = H
(26) R = Me



(8) R = H
(27) R = Me

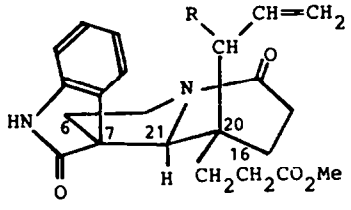


(9) R = H
(29) R = Me

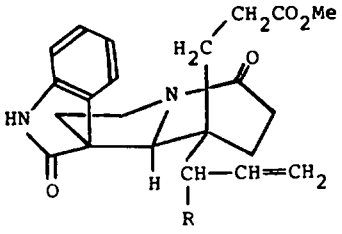


(12)

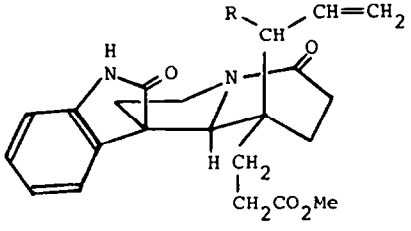
Inspection of the tetracyclic lactams (10) and (11) reveals that only in the case of iminoethers derived from the B series (11a) and (11b) are the iminoether and the future C-16 methylene group sufficiently close to allow cyclisation to take



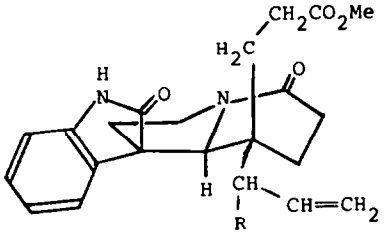
(10a) R = H
(30a) R = Me



(10b) R = H
(30b) R = Me

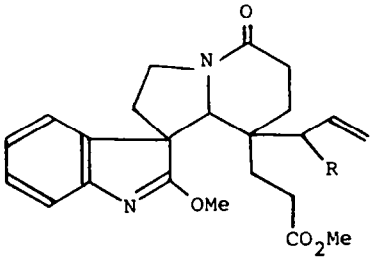


(11a) R = H
(31a) R = Me

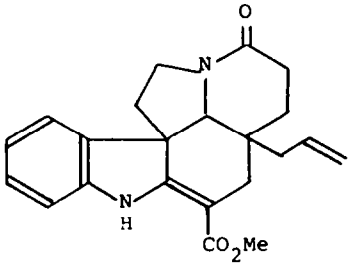


(11b) R = H
(31b) R = Me

place. In the A series (10a and 10b) cyclisation, if it were possible, would lead to a cis disposition of C-6 and the hydrogen at C-21, and the 2,16 double bond would be very severely strained. In contrast, cyclisation of the B isomers (11a and 11b) leads to (5) and its C-20 epimer (15). In the event it was found that the less polar mixture of stereoisomeric lactams could not be cyclised under any conditions, and we therefore conclude that these are the racemates represented by (10a) and (10b). However, the more polar mixture of stereoisomers cyclised relatively smoothly at 65-70 °C to give the pentacyclic lactam esters (5) (39%) and (15) (44%). At 100 °C, only the cis C/D isomer (5) was obtained (in 23% yield), together with a sulphoxide to which we assign the structure (16).



(13a) R = H
(13b) R = Me



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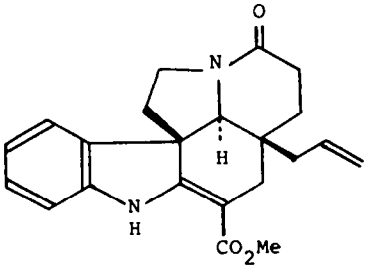
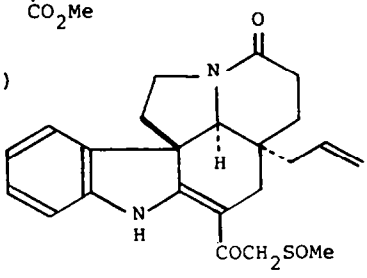
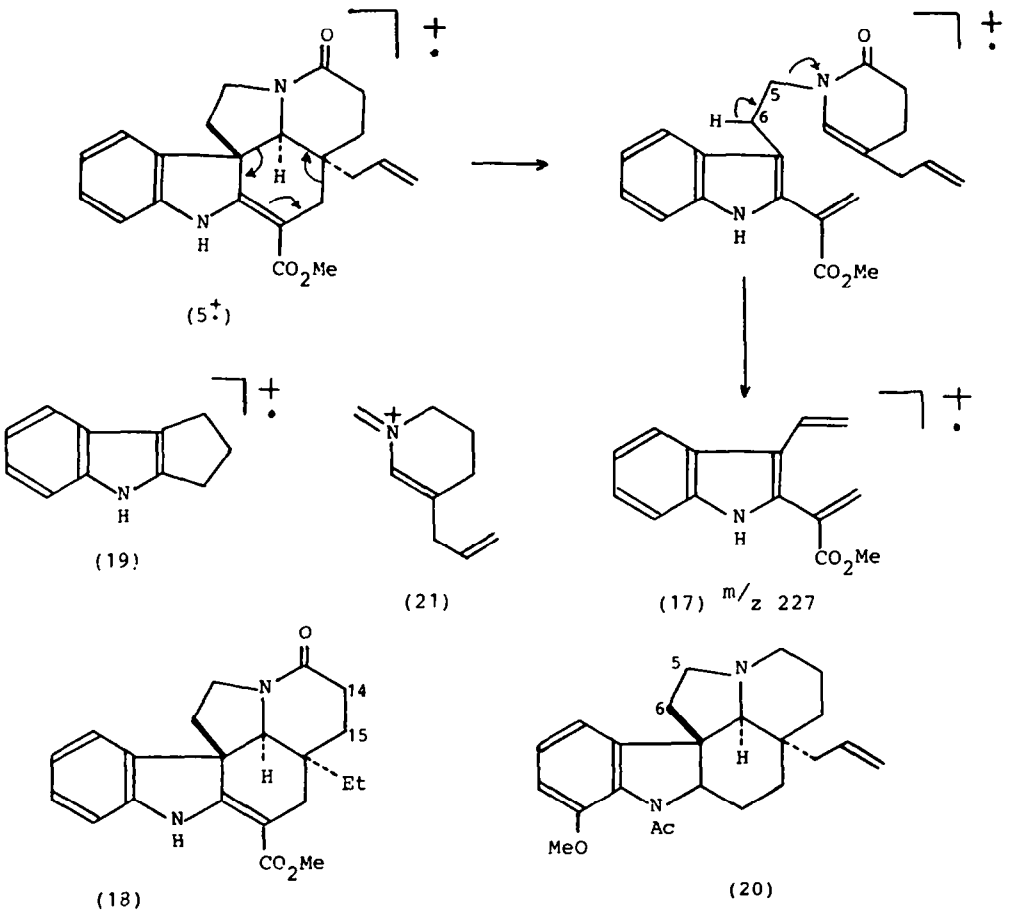


(15)

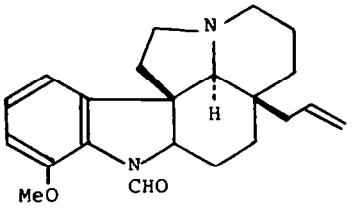


(16)

The stereochemistry of the isomers (5) and (15) follows from their mass spectral fragmentation. Thus, the non-crystalline product (5) exhibited in its mass spectrum important ions at $^{m}/_{z}$ 364 (M^{+}), 227 (base peak, 17), and 195, corresponding to ions at $^{m}/_{z}$ 352 (M^{+}), 227 (17) , and 195 in the spectrum of 3-oxovincadifformine (18).[6] This behaviour may be explained by a reverse Diels-Alder fragmentation of ring C followed by fission of the N_b to C-5 bond with simultaneous loss of hydrogen from C-6, and is consistent only with a cis C/D ring junction. In contrast, the less polar isomer of m.p. 217-219 °C is regarded as the trans C/D isomer (15); in the mass spectrometer it did not give a fragment ion at $^{m}/_{z}$ 227. Instead, the base peak occurred at $^{m}/_{z}$ 157 ($C_{11}H_{11}N^{+}$), possibly owing to the ion (19). Although there appear to be no examples in the literature of the mass spectra of both cis and trans C/D isomers in the vincadifformine series our own earlier experience[1] in the aspidospermidine series is parallel, i.e. 20-allyl-20-desethyl-12-methoxyaspidospermidine (20) gives a base peak at $^{m}/_{z}$ 136 (21) by reverse Diels-Alder fission of ring C followed by fission of the 5,6-bond, but



the trans relative (22) of vallesine gives a base peak at $^{m}/_{z}$ 180, of unknown origin; there is no peak at $^{m}/_{z}$ 136 of significant intensity. For similar reasons the sulphoxide (16) is also believed to have the cis C/D stereochemistry depicted, since its mass spectrum shows the molecular ion at $^{m}/_{z}$ 410, the base peak occurs at $^{m}/_{z}$ 347, owing to loss of SOMe, and there are important peaks at $^{m}/_{z}$ 197 and 150, which are presumably the result of reverse Diels-Alder fission of ring C, followed by rupture of the 5,6-bond.

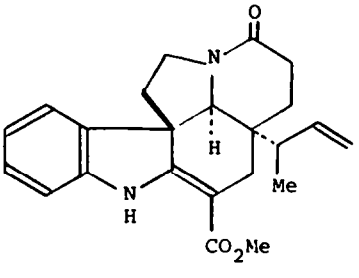


(22)

The desired pentacyclic lactam (5) having been obtained, attempts were made to manipulate the allyl double bond, but without significant success. Oxidative fission by the Lemieux method, successful in the aspidospermine series,[1] failed to give any identifiable product. A mixture of products was obtained, none of which possessed the anilinoacrylate chromophore; clearly, attack had occurred at the 2,16 double bond, as well as the allyl double bond. A similar result was obtained following ozonization at -78 °C.

In subsequent experiments oxidation of the lactam (5) was attempted as a two-stage process, involving hydroxylation by means of osmium tetroxide, followed by glycol cleavage with sodium metaperiodate. This gave a colourless amorphous product which contained the appropriate chromophores ($\nu_{max.}$ 2720, 1720, 1675, 1650, and 1610 cm^{-1}), but it decomposed on attempted crystallisation.

An attempt was next made to convert the allyl group in (5) and (15) into an acetonyl group by the method of Rodeheaver and Hunt.[7] The product appeared from its i.r. absorption at 1710 cm^{-1} to be possibly the desired methyl ketone, but insufficient material was obtained for further study. This reaction is one that merits further investigation.



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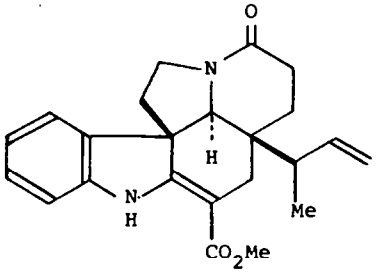
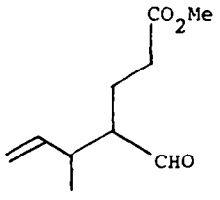


(24)

In parallel experiments an analogous synthesis of the homologues (23) and (24) of the pentacyclic lactams (5) and (15) was carried out, in the hope that isomerization of the double bond to the ethylidene position would give a C-20 side chain

which could be oxidatively cleaved to an acetyl group, and thereby lead to minovincine.[8] For this purpose crotyl vinyl ether (25)[9] was converted into 3-methylpent-4-enal (26)[10] by Claisen rearrangement at 145–150 °C. Pyrrolidine enamine formation and reaction with methyl acrylate in methanol gave the desired aldehyde diester (27), together with the aldehyde monoester (28). Condensation of (27) with 2-hydroxytryptamine hydrochloride in buffered aqueous ethanol gave a mixture of stereoisomers of structure (29) which, like the analogues of structure (9), were separated into two pairs of stereoisomeric racemates by chromatography. That these fractions each consisted of two racemates was shown by the presence of two methyl doublets in their n.m.r. spectra. The less polar mixture (41% yield), which we assign to the A series (30a and 30b), exhibited methyl doublets at δ 0.93 and 1.08, and the more polar mixture, which we regard as the B isomers (31a and 31b) doublets at δ 0.63 and 0.84. Similarly the aldehydo monoester (28) gave with 2-hydroxytryptamine a mixture of stereoisomers (32), separable into the less polar A isomers (33a and 33b) (methyl doublets at δ 0.69 and 0.87), and the more polar B isomers (34a and 34b), which exhibited methyl doublets at δ 0.55 and 0.83 ppm. We do not regard the methyl doublets in these isomers as being due to the presence of C-19 epimers since the methyl group in (28) and the cyclisation product (23) appears as one doublet only (at 60 MHz), which indicates that the C-19 epimers in these compounds give coincident methyl signals.



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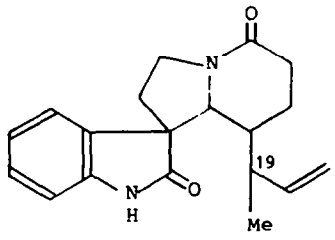

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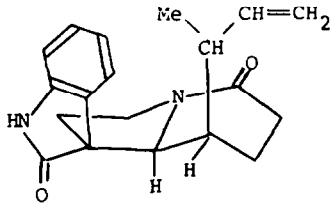
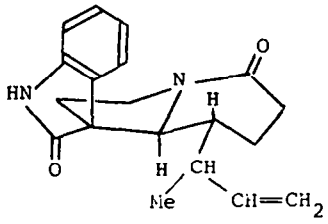
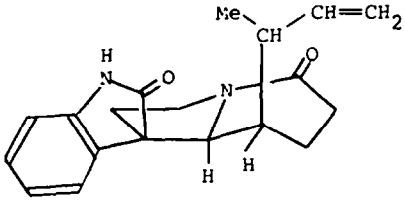


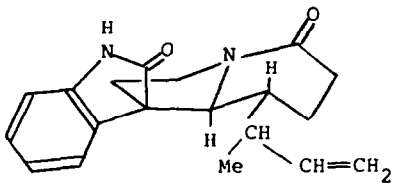
(33a)



(33b)



(34a)

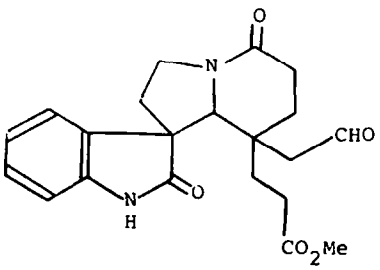


(34b)

In accordance with experience in the series exemplified by (9) only the iminoethers (13b) derived from the more polar tetracyclic lactams of the B series (31a and 31b) cyclised in the presence of dimsyl sodium, with formation of the pentacyclic lactam esters (23) and (24). At the temperature used for the cyclization (75-80 °C) the predominant product was the more polar isomer, which was assigned the cis C/D stereochemistry (23), since its mass spectrum resembled those of 3-oxotabersonine (35) and 3-oxovincadifformine (18), in which reverse Diels-Alder fission of ring C provides the major fragmentation pathway.

Having thus obtained the desired stereoisomer (23) an attempt was made to isomerise the double bond in the methylallyl side chain into the ethylidene position. However, the use of Wilkinson's catalyst, which has been used successfully in an analogous isomerization by other workers,[11] failed, in spite of the use of longer reaction times. Similarly, rhodium trichloride trihydrate[12] was also unsuccessful. Further model experiments in this area were conducted on the more readily available, and less valuable synthetically, tetracyclic lactam (32). However, neither rhodium chloride trihydrate, nor acidic (TsOH) or basic conditions (N-lithio-ethylenediamine)[13] proved effective; hence this approach to the anilinoacrylate alkaloids was not further pursued.

In view of the difficulties encountered in attempts to manipulate the double bond in the pentacyclic lactams containing the anilinoacrylate chromophore the possibility of carrying out the desired transformations at an earlier stage in the synthesis was explored. Initial experiments with this aim were performed on the tetracyclic dilactam (9). The more polar mixture of stereoisomeric lactams (9) was oxidised by means of osmium tetroxide and sodium paraperiodate to give the desired aldehyde (36) in 91% yield; this contrasts with the failure to oxidise the pentacyclic lactam esters (5) under the same conditions. Not surprisingly, an iminoether could not be obtained from the aldehyde (36), but neither could one be obtained from the dimethyl acetal nor the enol acetate derived from (36).



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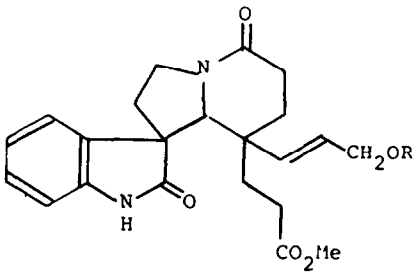
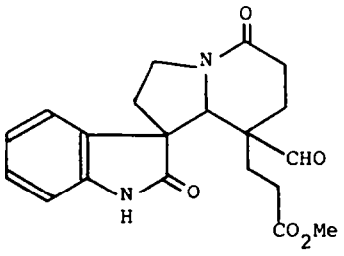


(37) R = Ac
(38) R = H

An alternative method of functionalising the double bond was via allylic acetoxylation by means of mercuric acetate in glacial acetic acid.[14] When the less polar mixture of isomers (10a and 10b) was used as model in this procedure a satisfactory conversion into the trans acetate (37) was achieved, from which the corresponding alcohol (38) was readily obtained. Oxidative fission of the double bond in (38) by means of osmium tetroxide-sodium paraperiodate occurred very

slowly, and was never observed to go to completion, presumably owing to steric hindrance, but a low yield of the desired aldehyde (39) was eventually isolated.

Consideration of the results outlined above led us to conclude that the most fruitful approach to our target molecule would be via the aldehyde (36), which was available in acceptable yield. Reduction of (36) by means of sodium borohydride



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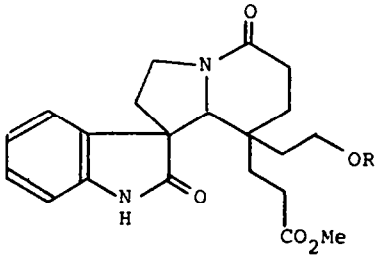

(40) R = H
(41) R = CO_2Me

gave the corresponding primary alcohol (40), which was protected as its methyl carbonate derivative (41). Reaction of (41) with Meerwein's reagent gave the required iminoether, but the yield was comparatively low, possibly owing to cleavage of the carbonate ester protecting group by the reagent. However, the inimoether could not be cyclised by dimsyl sodium, which resulted in the formation of several polar products, from which the required cyclisation product could not be isolated. At this stage further work on this route to the C-19 functionalised anilinoacrylate alkaloids was discontinued in favour of a different approach, which is discussed in the following paper.

This work demonstrated the difficulty of oxidising an isolated double bond in the presence of the anilinoacrylate function, which is itself susceptible to oxidation, as was shown in work contemporary with the above and in work reported subsequently.[5b]

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultraviolet absorption spectra were measured on a Unicam SP800A spectrometer using ethanol as solvent. Infrared absorption spectra were determined on Perkin-Elmer 157G and 297 spectrometers using chloroform as solvent unless otherwise stated.

Nuclear magnetic resonance spectra were measured using Perkin-Elmer R12 and R32 spectrometers.

Mass spectra were determined on an Associated Electrical Industries MS902 instrument.

Pyrrolidine enamine of pent-4-enal. — Pent-4-enal (39.8 g, 0.47 mol) was added dropwise during 0.5 h to a stirred, ice-cold suspension of anhydrous potassium carbonate (33.0 g, 0.24 mol) in pyrrolidine (75.6 g, 0.94 mol). Stirring was continued at room temperature for a further 3 h and the mixture filtered through

sintered glass. The residue was washed thoroughly with dry ether (400 ml) and the ether removed under reduced pressure. Distillation of the residue under reduced pressure gave the pyrrolidine enamine of pent-4-enal, (52.6 g, 81%) as a colourless oil, b.p. 48-52°/0.5 mm; $\nu_{max.}$ (film) 1653 (C=C-N) cm^{-1}.

Methyl 4-formyl-4-(2-methoxycarbonylethyl)hept-6-enoate (8). — To a solution of the pyrrolidine enamine of pent-4-enal (14.75 g, 0.168 mol) in methanol (100 ml), cooled below 5 °C, was added methyl acrylate (23.6 g, 0.275 mole) during 30 min. The mixture was stirred at room temperature for 5 h and then refluxed for 36 h. Glacial acetic acid (20 ml) in water (20 ml) was added and the mixture refluxed for 8 h. Excess methyl acrylate and methanol were removed *in vacuo* and ether (250 ml) was added to the residue. The ether layer was washed with 2M HCl (2 x 100 ml) and then 2M Na_2CO_3 (2 x 100 ml), and dried ($MgSO_4$). Removal of the ether left an oil which was distilled and three fractions were collected. The first fraction was identified as methyl 4-formylhept-6-enoate (2.23 g, 12.1%), b.p. 86-90°/2 mm; $\nu_{max.}$ (film) 2720, 1720 (CHO), 1730 (ester), 1640, 995, 920 ($CH=CH_2$) cm^{-1}; δ (in $CDCl_3$) 1.62-2.65 (7H, m), 3.66 (3H, s, CO_2Me), 4.82-6.10 (3H, m, $CH_2\underline{CH}=\underline{CH}_2$), 9.88 (1H, d, $\underline{J}$ 1.5 Hz, CHO). Following a mixed fraction (0.89 g), methyl 4-(2-methoxycarbonylethyl)-4-formylhept-6-enoate (11.8 g, 47%) was collected as a colourless liquid, b.p. 132-136°/0.3 mm. A small sample was redistilled for analysis (Found: C, 61.20; H, 7.95. $C_{13}H_{20}O_5$ requires C, 60.9; H, 7.9%); $\nu_{max.}$ (film) 2730, 1720 (CHO), 1730 (ester), 1640, 995, 920 ($CH=CH_2$) cm^{-1}; δ (in $CDCl_3$) 1.60-2.48 (10H, m), 3.50 (6H, s, $CO_2\underline{Me}$), 4.85-6.07 (3H, m, $CH_2\underline{CH}=\underline{CH}_2$), 9.73 (1H, s, $\underline{CH}O$).

3-Oxo-1-demethyl-20-desethyl-20-allylvincatine (9). — Methyl 4-formyl-4-(2-methoxycarbonylethyl)hept-6-enoate (7.2 g, 28.1 mmol) and 2-hydroxytryptamine hydrochloride (5.3 g, 25.0 mmol) were dissolved in ethanol (350 ml) containing water (50 ml) and sodium acetate (7.0 g). The mixture was refluxed under nitrogen for 18 h, the solvents were removed under reduced pressure and the residue was partitioned between chloroform and water. The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed on Kieselgel G (400 g). with 4% ethanol in chloroform as eluting agent to give four fractions:

The first fraction contained unreacted aldehyde (780 mg), as verified by i.r., t.l.c., and p.m.r.

The second fraction contained a stereoisomeric mixture of tetracyclic oxindoles (10a and 10b), (3.4 g, 36%) as a pale yellow foam. Recrystallisation

of a small sample from methanol gave the oxindoles as white needles, m.p. 176-214 °C (Found: C, 68.8; H, 6.8; N, 7.55. $C_{22}H_{24}N_2O_4$ requires C, 69.11; H, 6.81; N, 7.33%); $\lambda_{max.}$ (ε) 216 (17,900), 253 (6,620), 264 infl. (4,670), 285 nm (1,300); $\nu_{max.}$ 3440, 3220 (N-H), 1720 br (ester and oxindolyl carbonyls), 1630 br (lactam carbonyl and allyl double bond) cm^{-1}; δ ($CDCl_3$) 1.05-2.8 (12H, m), 3.57 (3H, s, CO_2Me), 3.9-4.2 (2H, m, -N-C$\underline{H}_2$), 4.17 (1H, s, -N-C$\underline{H}$-), 4.7-5.1 (2H, m, $\underline{H}_2$C=CH-), 5.25-5.8 (1H, m, H_2C=C$\underline{H}$-), 7.1-7.4 (4H, m, aromatic C-$\underline{H}$), 9.29 (1H, s, exchanges with D_2O, N-$\underline{H}$); m/z (%) (383 (27), 382 (100), 341 (29), 267 (11), 224 (16), 196 (52), 159 (27), 150 (11), 130 (11), 94 (14).

The third fraction contained both sets of stereoisomers (0.2 g, 2%).

The fourth fraction contained the more polar stereoisomeric mixture of tetracyclic oxindoles (11a and 11b) (5.2 g, 55%) as a whitish foam. Recrystallisation of a sample from methanol gave the oxindoles as heavy white rods, m.p. 186-203 °C (Found: C, 68.85; H, 6.75; N, 7.45. $C_{22}H_{24}N_2O_4$ requires C, 69.11; H, 6.81; N, 7.33%); $\lambda_{max.}$ (ε) 217 (18,900), 254 (6,480), 265 infl. (4,490), 286 nm (1,190); $\nu_{max.}$ 3440, 3220 (N-H), 1725 br (ester and oxindolyl carbonyls), 1630 br (lactam carbonyl and allyl double bonds) cm^{-1}; δ ($CDCl_3$) 0.85-1.2 (1H, m), 1.4-2.9 (11H, m), 3.54 (3H, s, CO_2Me), 3.8-4.2 (2H, m, -N-C$\underline{H}_2$), 4.13 (1H, s, -N-C$\underline{H}$-), 4.9-5.2 ($\underline{H}_2$C=CH-), 5.4-5.95 (1H, m, H_2C=C$\underline{H}$-), 7.1-7.4 (4H, m, aromatic C-H), 9.39 (1H, s, exchanges with D_2O, N-$\underline{H}$); m/z (%) 383 (26), 382 (100), 341 (34), 267 (10), 237 (11), 224 (23), 196 (70), 168 (12), 164 (17), 160 (19), 159 (38), 158 (16), 150 (15), 149 (43), 144 (15), 130 (15), 94 (11).

Methyl iminoether of 3-oxo-1-demethyl-20-desethyl-20-allylvincatine (13a). — The more polar tetracyclic allyl lactam (1.4 g, 3.7 mmol) was dissolved in dry dichloromethane (100 ml) and trimethyloxonium tetrafluoroborate (3.6 g, 24.1 mmol) added. The suspension was stirred at room temperature under nitrogen for 3 days and then poured into ice-water (200 ml). Addition of 10% sodium carbonate solution with vigorous stirring removed the red/brown colour and any solid particles remaining. The organic phase was then separated, washed with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellowish gum which was chromatographed on Kieselgel G (150 g) eluting with 3% methanol in chloroform to give the tetracyclic allyl iminoether (1.2 g, 83%). A small sample was recrystallised from benzene/light petroleum and obtained as colourless prisms, m.p. 171-193 °C; (Found: C, 69.45; H, 7.1; N, 6.9. $C_{23}H_{28}N_2O_4$ requires C, 69.7; H, 7.1; N, 7.1%); $\lambda_{max.}$ (ε) 220 (19,200), 261 (4,900), 272 infl. (3080), 285 infl. nm (1,270); $\nu_{max.}$ 1730 (ester carbonyl), 1625 br (lactam carbonyl),

1578 (C=N) cm^{-1}; δ ($CDCl_3$) 1.1-2.7 (12H, m), 3.5 (3H, s, CO_2Me), 3.99 (3H, s, N=C-OMe), 3.8-4.3 (3H, m, N-C<u>H</u>- and N-C<u>H_2</u>-), 4.7-5.3 (2H, m, <u>H_2</u>C=CH-), 5.6 (1H, m, H_2C=C<u>H</u>-), 6.9-7.5 (4H, m, aromatic C-H); m/z (%) 396 (73), 365 (17), 196 (100), 173 (69), 160 (30), 158 (18).

Treatment of the less polar tetracyclic allyl lactam (1.7 g, 4.45 mmol) in a similar manner gave the desired <u>iminoether</u> (1.5 g, 85%) as a pale yellow gum; (Found: <u>M^+</u>, 396.20432. $C_{23}H_{28}N_2O_4$ requires <u>M</u>, 396.204894); $\lambda_{max.}$ 218, 257, 271 (infl.), 293 (infl.) nm; $\nu_{max.}$ 1730 (ester carbonyl), 1630 br (lactam carbonyl), 1586 (C=N) cm^{-1}; δ ($CDCl_3$) 1.2-2.8 (12H, m), 3.67 (3H, s, CO_2Me), 4.10 (3H, s, C=N-OMe), 3.7-4.3 (3H, m, N-C<u>H</u>- and N-CH_2-), 4.7-5.2 (2H, m, <u>H_2</u>C=CH-), 5.6 (1H, m, H_2C=C<u>H</u>-), 6.9-7.5 (4H, m, aromatic C-H).

3-<u>Oxo</u>-20-<u>desethyl</u>-20-<u>allylvincadifformine</u> (5). — (a) The more polar iminoether (2.04 g, 5.15 mmol) was added to a stirred solution of dimsyl sodium, prepared from sodium hydride (170 mg, 7.09 mmol) in dry dimethyl sulphoxide (40 ml), under nitrogen at 65-70 °C. This mixture was stirred at that temperature for 2.5 h, cooled, and poured into saturated brine (250 ml) and extracted with dichloromethane (3 x 100 ml). The organic layer was washed again with brine (250 ml), water (200 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a dense, pale yellow gum. This was chromatographed on Kieselgel G (160 g), with 3% methanol in chloroform as eluting agent, to give two isomers of the desired compound and a small mixed fraction.

3-<u>Oxo</u>-20-<u>desethyl</u>-20-<u>epiallylvincadifformine</u> (15) (835 mg, 44%), was obtained as a white foam. Recrystallisation of a small sample from methanol gave coarse white crystals, m.p. 214-219 °C (Found: <u>M^+</u>, 364.1785. $C_{22}H_{24}N_2O_3$ requires <u>M</u>, 364.178682); $\lambda_{max.}$ 232, 290, 328 nm; $\nu_{max.}$ 3370 (N-H), 1680 (ester carbonyl), 1640 br (lactam carbonyl), 1610 (2,16-double bond) cm^{-1}; δ 1.3-2.75 (9H, m), 2.96 (1H, d, <u>J</u> 16 Hz), 3.53 (1H, m), 3.76 (4H, s, CO_2Me and N-C<u>H</u>-), 4.1 (1H, m), 5.3-4.97 (2H, m, <u>H_2</u>C=CH-), 5.82 (1H, m, H_2C=C<u>H</u>-), 6.75-7.3 (4H, m, aromatic C-H), 8.86 (1H, s, partial exchange with D_2O, N-<u>H</u>); m/z (%) 364 (39), 363 (20), 265 (16), 264 (23), 208 (34), 180 (33), 179 (25), 178 (23), 157 (100), 144 (13), 110 (14).

A mixed fraction (45 mg, 2.5%) was obtained, then 3-<u>oxo</u>-20-<u>desethyl</u>-20-<u>allylvincadifformine</u> (5) (730 mg, 39%), as a pale yellow foam (Found: <u>M^+</u>, 364.17815. $C_{22}H_{24}N_2O_3$ requires <u>M</u>, 364.178682); $\lambda_{max.}$ 228, 298, 330 nm; $\nu_{max.}$ 3390 (N-H), 1650 br (ester and lactam carbonyls), 1615 (2,6-double bond) cm^{-1}; δ 1.2-2.55 (9H, m), 2.69 (1H, d, <u>J</u> 16 Hz), 3.4 (1H, m), 3.59 (1H, s, N-C<u>H</u>-), 3.77 (3H, s, CO_2Me), 4.2 (1H, m), 4.7-5.2 (2H, m, <u>H_2</u>C=CH-), 5.6 (1H, m, H_2C=C<u>H</u>-),

6.8-7.3 (4H, m, aromatic C-H); m/z (%) 364 (41), 242 (12), 241 (70), 228 (37), 227 (100), 214 (34), 196 (54), 168 (14), 167 (13), 154 (19).

(b) The more polar iminoether (256 mg, 0.7 mmol) was added to a stirred solution of dimsyl sodium, prepared from sodium hydride (85 mg, 3.5 mmol) in dry dimethyl sulphoxide (10 ml), under nitrogen at 95-105 °C, and stirring continued at that temperature for 2 h. The work-up procedure was as above and gave a dark brown gum which was chromatographed on Kieselgel G (40 g), with 2% ethanol in chloroform as eluting agent, to give only one isomer of the desired product (5) (54 mg, 23%), and a mixture of sulphur-containing compounds in a second fraction. This fraction was re-chromatographed on Kieselgel G (20 g) using the same solvent system to give two crude bands. The less polar band was taken up in ethanol and recrystallised four times to give a very small quantity of 3-oxo-16-demethoxycarbonyl-16-(2-methylsulphinylacetyl)-20-desethyl-20-allylvincadifformine (16), m.p. 234-238 °C (Found: C, 67.05; H, 6.2; $\underline{M}^+$, 410.16539. $C_{23}H_{26}N_2O_3S$ requires C, 67.3; H, 6.3%: $\underline{M}$, 410.166404); $\lambda_{max.}$ 210, 241, 293, 301, 360 nm; $\nu_{max.}$ 3340 (N-H), 1650 br (lactam and 16-carbonyl group), 1610 (2,16-double bond), 1015 (sulphoxide) cm^{-1}; m/z (%) 410 (9), 348 (33), 347 (100), 346 (19), 319 (19), 211 (24), 210 (31), 197 (20), 182 (20), 168 (45), 167 (23), 150 (33).

(c) The more polar iminoether (1.4 g, 3.54 mmol) was added to a solution of dimsyl sodium, prepared from sodium hydride (110 mg, 4.58 mmol) and dry dimethyl sulphoxide (20 ml), at room temperature under nitrogen. This mixture was stirred at room temperature for 18 h and then worked up as described above. Chromatography of the residual dark brown gum on Kieselgel G (80 g), with 2% methanol in dichloromethane as eluting agent, gave three major fractions.

The first fraction contained 3-oxo-20-desethyl-20-allylepivincadifformine (380 mg, 30%). An intermediate fraction contained both isomers (45 mg, 4%) and the next fraction contained 3-oxo-20-desethyl-20-allylvincadifformine (271 mg, 22%). The final major fraction contained unreacted starting iminoether (67 mg), as verified by t.l.c., i.r., and n.m.r. spectra.

(d) The less polar iminoether (500 mg, 1.26 mmol) in dry dimethyl sulphoxide (10 ml) was added to a solution of dimsyl sodium, prepared from sodium hydride (50 mg, 2.08 mmol) and dry dimethyl sulphoxide (10 ml), under nitrogen at 65-70 °C and the mixture stirred at this temperature for 3 h. The mixture was worked up as described above to give a dark brown gum which was chromatographed on Kieselgel G (40 g), with 2% methanol in dichloromethane as eluting agent, to give only unchanged starting material, as verified by t.l.c., i.r., and n.m.r. spectra.

Attempted Cleavage of the Allyl Group in 3-Oxo-20-desethyl-20-allylvincadifformine.

3-Oxo-20-desethyl-20-allylvincadifformine (135 mg, 0.37 mmol) was dissolved in an anhydrous mixture of ether (5 ml) and benzene (5 ml), and osmium tetroxide (100 mg, 0.39 mmol) in anhydrous ether (5 ml) was added. The mixture was stirred under nitrogen at room temperature for 15 h and a solution of sodium bisulphite (150 mg, 1.44 mmol) in water (6 ml) added. Stirring was continued for 1 h and the bulk of the solvents removed under reduced pressure. The black residue was partitioned between chloroform and water, the organic layer was separated and dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting pale brown foam was chromatographed on silica gel (25 g) at first with 2% methanol in chloroform as eluting agent and gradually increasing polarity to 15% methanol in chloroform.

The first fraction contained starting material (20 mg) as verified by t.l.c., i.r., and n.m.r. spectra.

The second fraction contained mainly the desired glycol (78 mg, 53%), as a whitish foam; $\lambda_{max.}$ 225, 298, 330 nm; $\nu_{max.}$ 3550-3150 (N-H and glycol O-H), 1640 br (ester and lactam carbonyls), 1610 (2,16-double bond) cm^{-1}; δ ($CDCl_3$) 1.1-4.4 (18H, m, 2 protons exchange with D_2O), 3.74 (3H, s, CO_2Me), 6.7-7.4 (4H, m, aromatic C-H), 8.9 (1H, s, partial exchange with D_2O, N-H).

The crude glycol (40 mg, 0.1 mmol) was dissolved in methanol (3 ml) and a solution of sodium metaperiodate (22 mg, 0.1 mmol) in water (3 ml) was added. This mixture was stirred at room temperature overnight, then diluted with water (10 ml), and extracted with chloroform (3 x 15 ml). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a white foam. This was chromatographed on Kieselgel G (20 g), with 4% methanol in chloroform as eluting agent. The first fraction contained a colourless gum (23 g, 63%), with $\nu_{max.}$ 3490 (N-H), 2740 (aldehyde C-H), 1720 (aldehyde carbonyl), 1675 (ester carbonyl), 1650 br (lactam carbonyl), 1610 (2,16-double bond) cm^{-1}. Attempted trituration with a little methanol rapidly led to formation of a reddish coloured solution and, as seen on t.l.c., decomposition of this product.

There were two other polar products which were eluted together as a second fraction (8 mg). The i.r. spectrum of this fraction showed $\nu_{max.}$ 3460 br (N-H), 2740 (aldehyde C-H), 1740 br, 1640 br, 1575 cm^{-1}.

Action of Mercuric Acetate on 3-Oxo-20-desethyl-20-allylvincadifformine. — An isomeric mixture of 3-oxo-20-desethyl-20-allylvincadifformine and its 20-epimer (76 mg, 0.21 mmol) was dissolved in methanol (5 ml) and mercuric acetate (68 mg,

0.21 mmol) added. The mixture was stirred at room temperature under nitrogen for 2 h and then added to a stirred suspension of cupric chloride (85 mg, 0.63 mmol) and lithium tetrachloropalladate (13 mg, 0.05 mmol) in methanol (5 ml). The mixture was refluxed, under nitrogen, for 10 h and then dilute sodium bicarbonate solution (10 ml) added and stirred for 0.5 h. The resulting suspension was filtered through celite and the solvent removed under reduced pressure and the resulting yellowish solid partitioned between chloroform and water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a pale yellow solid. T.l.c. on Kieselgel GF_{254}, with 3% methanol in dichloromethane as eluting agent, showed two major components, both more polar than starting material. Chromatography on Kieselgel G (20 g), with 2% methanol in chloroform as eluting agent, gave two fractions. The first fraction was a pale yellow foam (11 mg) which contained a trace of another component. Attempts to recrystallise the solid from methanol gave a brown solution which showed extensive decomposition on t.l.c. The second fraction contained mainly one compound in a grey/white solid (24 mg). Recrystallisation of this solid from methanol three times gave a small quantity of a white granular solid, m.p. 297-302 °C (Found: $\underline{M}^+$, 380.17505. $C_{22}H_{24}N_2O_4$ requires $\underline{M}$, 380.173596): $\nu_{max.}$ 3430, 3250, 1710, 1630 cm^{-1}; m/z (%) 381 (23), 380 (100), 348 (29), 235 (13), 187 (23), 179 (16), 160 (20), 159 (18).

3-Methylpent-4-enal (26). — Crotyl vinyl ether (37.6 g, 0.38 mol) was placed in three glass tubes which were cooled in liquid nitrogen and sealed under reduced pressure. The sealed tubes were heated in a Carius furnace at 150 °C for 4 h. The resulting liquid was fractionally distilled to give 3-methylpent-4-enal (31.4 g, 84%), b.p. 112-118°.

Pyrrolidine Enamine of 3-Methylpent-4-enal. — 3-Methylpent-4-enal (31.0 g, 0.32 mol) was added dropwise over 1 h to a stirred ice-cooled suspension of anhydrous potassium carbonate (35 g) in pyrrolidine (47 g, 0.66 mol). The mixture was allowed to come to room temperature and stirred for a further 2 h, the solution filtered under suction and the residual solid washed well with dry ether (250 ml). Removal of the solvent and excess pyrrolidine under reduced pressure gave a green/brown oil which was distilled under reduced pressure to give the pyrrolidine enamine of 3-methylpent-4-enal (39.1 g, 89%), b.p. 70-75°/0.8mm; $\nu_{max.}$ 1650 C=N-N) cm^{-1}; δ ($CDCl_3$) 1.07 (3H, d, $\underline{J}$ 7 Hz, 3-Me), 1.6-2.0 (4H, m), 2.5-3.2 (5H, m), 4.04 (1H, dd, $\underline{J}$ 14, 7 Hz, -C$\underline{H}$=CH-N), 4.7-5.2 (2H, m, $\underline{H}_2$C=CH-), 5.8 (1H, m, H_2C=C$\underline{H}$-), 6.17 (1H, d, $\underline{J}$ 14 Hz, C=C$\underline{H}$N).

Methyl 4-formyl-4(2-methoxycarbonylethyl)-5-methylhept-6-enoate (27). — The pyrrolidine enamine of 3-methylpent-4-enal (39.0 g, 0.26 mol) in dry methanol (200 ml) was cooled in an ice-bath and dry methyl acrylate (38.6 g, 0.52 mol) added dropwise under nitrogen, with stirring, over 0.5 h. The solution was then stirred at room temperature for 5 h and refluxed, under nitrogen, for 36 h. Glacial acetic acid (55 ml) and water (55 ml) were added to the cooled reaction mixture and the whole refluxed for a further 8 h under nitrogen. Excess methyl acrylate and methanol were then removed under reduced pressure and ether (400 ml) added to the remaining solution. The ether layer was separated and washed with dilute hydrochloric acid (2 x 150 ml), dilute sodium carbonate solution (2 x 150 ml), water (150 ml), and dried ($MgSO_4$). Removal of the ether left a yellow/red oil which was fractionally distilled under reduced pressure to give three fractions.

The first fraction contained methyl 4-formyl-5-methylhept-6-enoate (28) (11.9 g, 25%), b.p. 99-104°/1.0 mm; (Found: C, 64.5; H, 8.9. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.7%); $\nu_{max.}$ (film) 2720 (aldehyde C-H), 1735 br (aldehyde and ester carbonyls), 1640 C=C) cm^{-1}; δ ($CDCl_3$) 1.08 (3H, d, J 7 Hz, 5-Me), 1.6-2.8 (6H, m), 3.68 (3H, s, CO_2Me), 4.9-5.25 (2H, m, H_2C=CH), 5.8 (1H, m, H_2C=CH-), 9.66 (1H, t, J 1.5 Hz, CHO).

The second fraction (1.1 g) contained a mixture of the aldehyde esters, boiling range 104-105°/1.0 mm.

The third fraction was collected between 160-165°/0.1 mm and subsequently redistilled to give methyl 4-formyl-4-(2-methoxycarbonylethyl)-5-methylhept-6-enoate (27) (9.8 g, 14%), b.p. 124-130°/0.01 mm; (Found: C, 62.35; H, 8.35. $C_{14}H_{22}O_5$ requires C, 62.22; H, 8.15%); $\nu_{max.}$ (film) 2730 (aldehyde C-H), 1740 br (aldehyde and ester carbonyls), 1640 (C=C) cm^{-1}; δ ($CDCl_3$) 1.05 (3H, d, J 7 Hz, 5-Me), 1.6-2.7 (9H, m), 3.66 (6H, s, CO_2Me), 4.9-5.3 (2H, m, H_2C=CH-), 5.8 (1H, m, H_2C=CH-), 9.59 (1H, s, CHO).

3-Oxo-1-demethyl-19-vinylvincatine (29). — Methyl 4-formyl-4-(2-methoxycarbonylethyl)-hept-6-enoate (6.6 g, 24.4 mmol) and 2-hydroxytryptamine hydrochloride (5.1 g, 24.0 mmol) were dissolved in ethanol (300 ml) containing water (40 ml) and sodium acetate (4.5 g) was added. The mixture was refluxed under nitrogen for 36 h, the solvents were removed under reduced pressure and the residue was partitioned between chloroform and water. The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed on Kieselgel G (300 g), with 5% ethanol in chloroform as eluting

agent. Four fractions were collected.

The first fraction contained unreacted aldehyde (0.3 g), as verified by t.l.c., i.r., and n.m.r. spectra.

The second fraction contained the less polar stereoisomeric mixture of 3-oxo-1-demethyl-19-vinylvincatine (30a and 30b) (3.9 g, 41%) as a white foam: (Found: C, 70.4; H, 7.05; N, 7.3. $C_{23}H_{28}N_2O_4$ requires C, 69.7; H, 7.1; N, 7.1%); $\lambda_{max.}$ 218, 255, 265 (infl.), 286 nm; $\nu_{max.}$ 3440, 3220 (N-H), 1726 br (ester and oxindolyl carbonyls), 1625 br (lactam carbonyl and double bond) cm^{-1}; δ ($CDCl_3$) 0.93 and 1.08 (3H, d, J 7 Hz, C-Me of both isomers), 1.3-2.8 (10H, m), 3.1 (1H, m), 3.54 (3H, s, CO_2Me), 3.5-4.3 (3H, m, -N-CH- and -N-CH_2-), 4.75-5.2 (2H, m, H_2C=CH-), 5.8 (1H, m, H_2C=CH-), 6.85-7.35 (4H, m, aromatic C-H), 10.01 and 10.07 (1H, s, exchange with D_2O, N-H of both isomers); m/z (%) 396 (42) 342 (17), 210 (13), 197 (21), 196 (100), 182 (19), 168 (15), 159 (25), 158 (22), 124 (23).

The third fraction contained a mixture of two sets of stereoisomers (0.4 g, 4%).

The fourth fraction contained the more polar stereoisomeric mixture of 3-oxo-1-demethyl-19-vinylvincatine (31a and 31b) (3.4 g, 36%) as a yellow/brown foam. Recrystallisation of a sample from ethanol gave feathery white plates, m.p. 195-203 °C; (Found: M^+, 396.20354. $C_{23}H_{28}N_2O_4$ requires M, 396.204894); $\lambda_{max.}$ (ε) 218 (19,200), 254 (7,050), 266 infl. (4,790), 285 nm (1,410); $\nu_{max.}$ 3440, 3220 (N-H), 1725 br (ester and oxindolyl carbonyls), 1625 br (lactam carbonyl and double bond) cm^{-1}; δ ($CDCl_3$) 0.63 and 0.84 (3H, d, J 7 Hz, C-Me of both isomers), 1.4-2.7 (10H, m), 3.0 (1H, m), 3.49 (3H, s, CO_2Me), 3.5-4.4 (3H, m, -N-CH- and -N-CH_2-), 4.6-5.0 (2H, m, H_2C=CH-), 5.45 (1H, m, H_2C=CH-), 6.86-7.4 (4H, m, aromatic C-H), 9.84 br (1H, s, exchanges with D_2O, N-H of both isomers); m/z (%) 396 (35), 311 (16), 310 (83), 197 (19), 196 (89), 178 (43), 168 (17), 165 (40), 160 (30), 159 (100), 158 (36), 152 (47), 150 (76), 146 (33), 144 (24), 130 (31), 124 (30), 110 (66).

3-Oxo-1-demethyl-19-vinylvincatine Methyliminoether (13b). — The less polar stereoisomeric mixture of 3-oxo-1-demethyl-19-vinylvincatine (1.65 g, 4.14 mmol) was dissolved in dry dichloromethane (50 ml) and trimethyloxonium tetrafluoroborate (3.23 g, 21.7 mmol) added. This mixture was stirred at room temperature, under nitrogen, for 3 days and then poured into water, the organic layer separated and washed with 10% sodium carbonate solution (20 ml), water (25 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a red/brown gum which was chromatographed on basic alumina (50 g), with chloroform as eluting agent, to give the iminoether (1.36 g, 79%) as a pale yellow gum, $\lambda_{max.}$ 220, 260, 272 (infl.), 286 nm (infl.);

$\nu_{max.}$ 1735 br (ester carbonyl), 1630 br (lactam carbonyl and double bond), 1586 (C=N) cm^{-1}; δ ($CDCl_3$) 0.91 and 1.04 (3H, d, J 7 Hz, C-Me of both isomers), 1.1-2.8 (11H, m), 3.54 (3H, s, CO_2Me), 4.10 and 4.12 (3H, s, N-OMe of both isomers), 3.7-4.3 (2H, m, -N-C<u>H</u>$_2$-), 4.22 (1H, s. -N-C<u>H</u>-), 4.7-5.2 (2H, m, <u>H</u>$_2$C=CH-), 5.64 (1H, m, H_2C=C<u>H</u>-), 6.9-7.5 (4H, m, aromatic C-H).

The same procedure was used to convert the more polar stereoisomeric mixture of 3-oxo-1-demethyl-19-vinylvincatine (2.02 g, 5.1 mmol) in dry dichloromethane (50 ml), using trimethyloxonium tetrafluoroborate (2.81 g, 18.9 mmol), into the desired iminoether. Chromatography on basic alumina (100 g), with chloroform as eluting agent, gave the more polar iminoether (1.89 g, 90%) as an almost colourless gum, $\lambda_{max.}$ 217, 260, 271 (infl.), 285 nm (infl.); $\nu_{max.}$ 1735 (ester carbonyl), 1625 br (lactam carbonyl and double bond), 1580 (C=N) cm^{-1}; δ ($CDCl_3$) 0.61 and 0.85 (3H, d, J 7 Hz, C-Me of both isomers), 1.3-2.8 (11H, m), 4.00 (3H, s, N-OMe), 3.5-4.4 (3H, m, -N-C<u>H</u>- and -N-C<u>H</u>$_2$), 4.6-5.0 (2H, m, <u>H</u>$_2$C=CH-), 5.5 (1H, m, H_2C=C<u>H</u>-), 6.9-7.45 (4H, m, aromatic C-H).

3-<u>Oxo</u>-19-<u>vinylvincadifformine</u> (23). — (a) The more polar methyl iminoether of 3-oxo-1-demethyl-19-vinylvincatine (1.93 g, 4.7 mmol) in dry dimethyl sulphoxide (5 ml) was added to a solution of dimsyl sodium, prepared from sodium hydride (210 mg, 8.7 mmol) and dry dimethyl sulphoxide (20 ml), with rapid stirring under nitrogen at 75-80 °C. Stirring was continued at this temperature for 4 h and then the reaction mixture poured into a saturated brine solution (150 ml). The aqueous solution was extracted with dichloromethane (3 x 50 ml) and the organic layer washed with brine (150 ml), water (150 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a dark brown gum which was chromatographed on Kieselgel G (100 g), with 2% methanol in chloroform as eluting agent. T.l.c. of the second fraction revealed a two-component mixture, the more polar component being the major.

Trituration of this pale brown gum (814 mg, 46%) with ethanol and recrystallisation of the resulting solid from ethanol gave 3-<u>oxo</u>-19-<u>vinylvincadifformine</u> (23) as pale yellow plates, m.p. 160-162 °C; (Found: C, 72.7; H, 6.85; N, 7.1. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%); $\lambda_{max.}$ (ε) 228 (11,500), 299 (13,200), 330 nm (17,200); $\nu_{max.}$ 3350 (N-H), 1650 br (ester and lactam carbonyls), 1615 (2,16-double bond) cm^{-1}; δ ($CDCl_3$) 0.92 (3H, d, J 7 Hz, C-Me), 1.1-1.5 (2H, m), 1.7-2.9 (6H, m), 3.4 (1H, m), 3.73 (3H, s, CO_2Me), 3.9-4.4 (3H, m, -N-C<u>H</u>- and -N-C<u>H</u>$_2$-), 4.5-5.0 (2H, m, <u>H</u>$_2$C=CH-), 5.55 (1H, m, H_2C=C<u>H</u>-), 6.8-7.3 (4H, m, aromatic C-H), 9.08 br (1H, s, partial exchange with D_2O, N-H); m/z (%) 378 (30), 228 (18),

227 (100), 214 (24), 195 (50), 154 (13).

(b) The less polar iminoether (960 mg, 2.34 mmol) in dry dimethyl sulphoxide (5 ml) was added to a solution of dimsyl sodium, prepared from sodium hydride (100 mg, 4.17 mmol) and dry dimethyl sulphoxide (10 ml), under nitrogen at 65-70 °C. The mixture was stirred at this temperature for 3 h and then worked up as described above. The resulting dark brown gum was chromatographed on Kieselgel G (50 g), eluting with 2% methanol in dichloromethane, to give only unchanged starting material, as verified by t.l.c., i.r., and n.m.r. spectra.

3-Oxo-1-demethyl-20-de(2-methoxycarbonylethyl)-19-vinylvincatine (32). — Methyl 4-formyl-5-methylhept-6-enoate (28) (6.1 g, 33.2 mmol) and 2-hydroxytryptamine hydrochloride (6.5 g, 30.6 mmol) were dissolved in ethanol (400 ml) containing water (50 ml) and sodium acetate (8.0 g). The mixture was refluxed under nitrogen for 18 h and then worked up as described above. The yellow/brown gum which resulted was chromatographed on Kieselgel G (500 g), with 3% methanol in chloroform as eluting agent, to give three fractions.

The first fraction contained unchanged aldehyde (0.9 g), as verified by t.l.c., i.r., and n.m.r.

The second fraction contained the less polar stereoisomeric mixture of (33a and 33b) (3.3 g, 35%) as a yellowish foam. A sample was recrystallised from ethanol, as colourless prisms, m.p. 210-219 °C: (Found: M^+, 310.16869. $C_{19}H_{22}N_2O_2$ requires M, 310.168118); $\lambda_{max.}$ 217, 253, 264 infl., 283 nm; $\nu_{max.}$ 3345, 3230 (N-H), 1725 br (oxindolyl carbonyl), 1625 br (lactam carbonyl and double bond) cm^{-1}; δ ($CDCl_3$) 0.69 and 0.87 (3H, d, J 7 Hz, C-Me of both isomers), 1.2-2.8 (8H, m), 3.5-4.25 (3H, m, -N-CH- and -N-CH_2-), 4.4-5.2 (2H, m, H_2C=CH-), 5.6 (1H, m, H_2C=CH-), 6.85-7.45 (4H, m, aromatic C-H), 10.04 and 10.09 (1H, s, exchanges with D_2O, N-H of both isomers), m/z (%) 321 (23), 310 (100), 178 (54), 165 (50), 160 (18), 159 (81), 152 (61), 150 (85), 146 (25), 110 (50).

The third fraction contained the more polar stereoisomeric mixture of (34a and (34b) (3.9 g, 41%) as a white foam. Recrystallisation from methanol gave white plates, m.p. 236-245 °C; (Found: C, 73.6; H, 7.1; N, 8.65. $C_{19}H_{22}N_2O_2$ requires C, 73.5; H, 7.1; N, 9.0%); $\lambda_{max.}$ (ε) 221 (13,200), 234 (6,700), 266 infl. (4,190), 286 nm (1,070): $\nu_{max.}$ 3440, 3210 (N-H), 1720 br (oxindolyl carbonyl), 1630 br (lactam carbonyl and double bond) cm^{-1}; δ ($CDCl_3$) 0.55 and 0.83 (3H, d, J 7 Hz, C-Me of both isomers), 1.3-2.7 (8H, m), 3.5-4.4 (3H, m, -N-CH- and -N-CH_2-), 4.6-5.0 (2H, m, H_2C=CH-), 5.5 (1H, m, H_2C=CH-), 6.9-7.4 (4H, m, aromatic C-H), 9.77 (1H, s, exchanges with D_2O, N-H); m/z (%) 311 (22,), 310 (100), 178 (51), 165 (49),

160 (17), 159 (91), 152 (66), 150 (96), 146 (23), 130 (22), 110 (58).

3,18-Dioxo-1-demethylvincatine (36). — The more polar isomeric mixture of 3-oxo-1-demethyl-20-desethyl-20-allylvincatine (9) (1.04 g, 2.72 mmol) was dissolved in 80% acetic acid (40 ml) and osmium tetroxide (50 mg) added. This mixture was stirred for 0.1 h, then sodium paraperiodate (1.72 g, 5.85 mmol) added in three portions. The mixture was stirred for a further 4 h after which t.l.c. analysis indicated complete reaction to yield one product. The heavy white precipitate of sodium iodate was collected and washed thoroughly with glacial acetic acid. The combined filtrates were evaporated under reduced pressure to give a pale green gum. The residue was taken up in chloroform and washed successively with water, dilute sodium bicarbonate solution, and water again, then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white foam which did not crystallise. Filtration of a chloroform solution through a pad of basic alumina gave an isomeric mixture of 3,18-dioxo-1-demethylvincatine (36) as a foam (956 mg, 91%); (Found: M^+, 384.16899. $C_{21}H_{24}N_2O_5$ requires M, 384.168510); $\lambda_{max.}$ 216, 254, 284 nm; $\nu_{max.}$ 3240, 3200 (N-H), 2720 (aldehyde C-H), 1725 br (aldehyde, ester and oxindolyl carbonyls), 1630 (lactam carbonyl) cm^{-1}; δ ($CDCl_3$) 1.4-2.7 (12H, m), 3.53 (3H, s, CO_2Me), 3.75-4.3 (2H, m, -N-CH_2-), 4.12 (1H, s, -N-CH-), 6.9-7.4 (4H, m, aromatic C-H), 9.75 br (2H, s, 1H exchanges with D_2O, N-H and -CHO); m/z (%) 384 (82), 366 (22), 353 (34), 210 (31), 187 (40), 160 (35), 159 (100), 158 (27), 146 (41), 144 (21), 130 (27), 124 (35).

3-Oxo-18,18-dimethoxy-1-demethylvincatine. — 3,18-Dioxo-1-demethylvincatine (267 mg, 0.7 mmol) was dissolved in trimethyl orthoformate (5 ml) and boron trifluoride etherate (3 drops) added. The mixture was stirred at room temperature under nitrogen for 20 h, then poured into dilute sodium carbonate solution (15 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with water (50 ml) and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a pale green oil which still contained a little trimethyl orthoformate. A dichloromethane solution of this oil was filtered through a small pad of basic alumina and the solvent removed under reduced pressure to give 3-oxo-18,18-dimethoxy-1-demethylvincatine as a yellowish gum (248 mg, 83%); (Found: M^+, 430.21084. $C_{23}H_{30}N_2O_6$ requires M, 430.210372); $\lambda_{max.}$ 220, 254, 283 nm; $\nu_{max.}$ 3430, 3200 (N-H), 2830 (OCH_3), 1725 br (ester and oxindolyl carbonyls), 1625 (lactam carbonyl) cm^{-1}; δ ($CDCl_3$) 1.4-2.7 (12H, m), 3.19 [6H, s, $CH(OMe)_2$], 3.52 (3H, s, CO_2Me), 3.7-4.3 (2H. m, -N-CH_2-), 4.11 (1H, s, -N-CH-), 4.38 [1H, t, J 4 Hz, C$H(OMe)_2$], 6.95-7.4 (4H, m, aromatic C-H), 9.89 (1H, s, exchanges with D_2O, N-H);

m/z (%) 430 (33), 399 (20), 285 (12), 201 (37), 188 (15), 187 (15), 174 (16), 173 (83), 160 (23), 159 (20), 130 (11), 75 (100).

3-Oxo-18-acetoxy-18,19-dehydro-1-demethylvincatine Ethyl Ester. — 3,18-Dioxo-1-demethylvincatine ethyl ester (620 mg, 1.56 mmol) was added to isopropenyl acetate (10 ml) and the mixture stirred, under nitrogen, at room temperature for 0.1 h. Concentrated sulphuric acid (3 drops) was then added and the resulting brown mixture was stirred at room temperature for 18 h and then poured into water (30 ml). The solution was extracted with dichloromethane (2 x 25 ml) and the organic extracts were washed with dilute sodium bicarbonate solution (50 ml) and water (50 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a brown gum. This was taken up in dichloromethane and filtered through a small pad of neutral alumina. Removal of the dichloromethane under reduced pressure gave 3-oxo-18-acetoxy-18,19-dehydro-1-demethylvincatine ethyl ester (549 mg, 83%) as a yellow/brown gum; (Found: M^+, 440.19435. $C_{24}H_{28}N_2O_6$ requires M, 440.194723); $\lambda_{max.}$ 218, 253, 262 infl., 283 nm; $\nu_{max.}$ 3420, 3240 (N-H), 1725 br (ester, oxindolyl and acetate carbonyls), 1630 (lactam carbonyl and enol double bond) cm^{-1}; $\delta(CDCl_3)$ 1.16 (3H, s, Me), 2.2 (3H, s, OCOMe), 1.4-2.8 (10H, m), 4.0 (2H, q, OCH_2Me), 3.5-4.3 (4H, m), 5.15 (1H, d, J 15 Hz, -CH=CH-OAc), 6.9-7.4 (4H, m, aromatic C-H), 9.27 (1H, s, exchanges with D_2O, N-H); m/z (%) 440 (35), 398 (38), 353 (19), 187 (47), 160 (19), 159 (58), 152 (17), 144 (16), 124 (15), 43 (100).

3-Oxo-1-demethyl-20-desethyl-20-(3-acetoxyprop-1-enyl)-vincatine (37). — The less polar isomeric mixture of 3-oxo-1-demethyl-20-desethyl-20-allylvincatine (10a and 10b) (3.4 g, 8.9 mmol) was dissolved in glacial acetic acid (40 ml) and mercuric acetate (11.5 g, 36.1 mmol) added. The mixture was refluxed, under nitrogen, for 48 h, then cooled to room temperature. The resulting suspension was filtered, the solid washed thoroughly with acetic acid and the filtrate evaporated under reduced pressure to give a pale yellow solid. The residue was partitioned between chloroform and dilute sodium bicarbonate solution, the organic layer washed twice with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white solid. This was chromatographed on Kieselgel G (200 g), with 4% methanol in dichloromethane as eluting agent, to give 3-oxo-1-demethyl-20-desethyl-20-(3-acetoxyprop-1-enyl)-vincatine (37) (2.8 g, 72%) as a white powder. A small sample was recrystallised from methanol to give colourless plates, m.p. 165-174 °C; (Found: C, 63.45; H, 6.6; N, 6.0; M^+, 440.19654. $C_{24}H_{28}N_2O_6 . CH_3OH$ requires C, 63.57: H, 6.78; N, 5.9%; M, 440.194723); $\lambda_{max.}$ (ε) 219 (13,200), 255 (6,080), 265 infl. (4,460), 285 nm (1,220); $\nu_{max.}$ 3430, 3200 (N-H), 1725 br (oxindolyl,

ester, acetate carbonyls), 1630 (lactam carbonyl and double bond) cm^{-1}; δ ($CDCl_3$) 1.5-2.9 (10H, m), 2.08 (3H, s, OAc), 3.67 (3H, s, CO_2Me), 3.7-4.2 (2H, m, -N-CH_2-), 4.05 (1H, s, -N-CH-), 4.26 (2H, d, J 5.5 Hz, -CH_2OAc), 5.08 (1H, dt, J 16, 5.5 Hz, -CH=CH-CH_2OAc); 5.53 (1H, d, J 16 Hz, -CH=CH-CH_2OAc), 6.9-7.45 (4H, m, aromatic C-H), 10.03 (1H, s, exchanges with D_2O, N-H); m/z (%) 440 (87), 235 (40), 222 (34), 187 (89), 162 (46), 160 (34), 159 (100), 148 (70), 130 (35).

Attempted Preparation of 3-Oxo-1-demethyl-20-desethyl-20-formylvincatine (39). — 3-Oxo-1-demethyl-20-desethyl-20-(3-acetoxyprop-1-enyl)-vincatine (37) (314 mg, 0.71 mmol) was dissolved in dry methanol (10 ml) and this solution added to a solution of sodium methoxide in dry methanol, prepared from sodium (100 mg) and methanol (10 ml). The mixture was stirred at room temperature, under nitrogen, for 18 h then neutralised with dilute hydrochloric acid. Removal of the solvents under reduced pressure gave a pale brown gum which was partitioned between chloroform and dilute hydrochloric acid. The organic layer was separated and washed with dilute sodium bicarbonate solution, then water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a whitish foam, which showed only one polar component on t.l.c. analysis. The i.r. spectrum showed no evidence of the aldehyde group of the starting material and indicated the presence of a hydroxyl group (3100-3500 cm^{-1}). The alcohol was not purified but used immediately in the next stage.

A solution of the alcohol (38) in 80% acetic acid (10 ml) was stirred at room temperature, under nitrogen, and osmium tetroxide (20 mg) added. The mixture was stirred for 5 h, by which time the solution had become brown, then sodium paraperiodate (706 mg, 2.4 mmol) in 80% acetic acid (20 ml) added. The resulting suspension was stirred for 4 days, during which time a heavy white precipitate was formed. Filtration of the suspension, careful washing of the solid residue with glacial acetic acid, and evaporation of the pale yellow filtrate under reduced pressure gave a brown gum. Chromatography of this gum on Kieselgel G (30 g), with 5% methanol in chloroform as eluting agent, gave an impure first fraction, which was further chromatographed using the same solvent system and adsorbent to give a white foam (85 mg). There was still evidence of some impurity in the compound on t.l.c. analysis and recrystallisations from methanol, aqueous acetone, and benzene/petroleum ether, respectively were attempted without success. Evidence that the foam contained mainly the desired 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (39) was found in the i.r. and n.m.r. spectra which showed: $\nu_{max.}$ 3420, 3220 (N-H), 2720 (aldehyde C-H), 1725 br, 1635 br (lactam carbonyl) cm^{-1}; δ ($CDCl_3$) 1.5-3.0 (10H, m), 3.59 (3H, s, CO_2Me), 3.85-4.2 (2H, m, -N-CH_2-), 4.30 (1H, s, -N-CH-), 6.9-7.5 (4H, m, aromatic C-H), 9.08 (1H, s, CHO), 9.84 (1H, s, exchanges with D_2O,

N-H, respectively).

The remaining fractions contained more polar impure mixtures which were still not separated by further chromatography.

3-Oxo-18-hydroxy-1-demethylvincatine (40). — 3,18-Dioxo-1-demethyl-vincatine (36) (960 mg, 2.5 mmol) was dissolved in methanol (20 ml) and cooled in ice/water. Sodium borohydride (300 mg, 7.9 mmol) was added in portions to the rapidly stirred solution during 0.5 h and the mixture allowed to come to room temperature, then stirred for a further 1 h. T.l.c. analysis of the reaction mixture at this time showed the complete absence of starting material. The mixture was then neutralised with dilute hydrochloric acid and the solvents were removed under reduced pressure. The resulting yellow/green solid residue was taken up in chloroform containing a little methanol and filtered through a small pad of neutral alumina to give 3-oxo-18-hydroxy-1-demethylvincatine (40) (621 mg, 65%) as a white foam; (Found: M^+, 386.18435. $C_{21}H_{26}N_2O_5$ requires M, 386.184159): $\lambda_{max.}$ 220, 255, 284 nm; $\nu_{max.}$ 3460-3100 (N-H and O-H), 1715 br (ester and oxindolyl carbonyls), 1625 br (lactam carbonyl) cm^{-1}; δ ($CDCl_3$) 1.2-2.8 (12H, m), 2.95 br (1H, s, exchanges with D_2O, C-H), 3.56 (3H, s, CO_2Me), 3.4-4.3 (5H, m), 6.85-7.4 (4H, m, aromatic C-H), 9.72 (1H, s, exchanges with D_2O, N-H); m/z (%) 386 (67), 384 (33), 355 (24), 242 (24), 187 (27), 160 (34), 159 (100), 158 (22), 154 (25), 146 (44), 144 (26), 130 (34), 124 (29).

3-Oxo-18-methoxycarbonyloxy-1-demethylvincatine methyl iminoether. — 3-Oxo-18-hydroxy-1-demethylvincatine (40) (610 mg, 1.58 mmol) was dissolved in dry tetrahydrofuran (5 ml) and pyridine (2 ml) added. The mixture was cooled in ice/water and stirred rapidly, under nitrogen, during the addition of methyl chloroformate (200 mg, 2.12 mmol). When the mixture had come to room temperature it was stirred for a further 15 h under nitrogen, then poured into a saturated sodium chloride solution (20 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed successively with dilute hydrochloric acid (2 x 50 ml), dilute sodium bicarbonate solution (50 ml), and water (50 ml), then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a white foam. T.l.c. analysis of this foam showed the presence of one product of much lower polarity than starting material and the i.r. spectrum showed $\nu_{max.}$ 3415, 3200 (N-H), 1745 (carbonate), 1720 br (ester and oxindolyl carbonyls), 1625 (lactam carbonyl) cm^{-1}. The compound appeared to be fairly deliquescent, however, and so was carried directly through to the next stage.

The above foam was dissolved in dry dichloromethane (20 ml) and trimethyloxonium tetrafluoroborate (1.6g, 10.8 mmol) added. This suspension was stirred at

room temperature, under nitrogen, for 3 days and then poured into dilute sodium carbonate solution, the organic layer separated and the aqueous layer extracted twice with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a brown gum, which was chromatographed on Kieselgel G (50 g), with 3% methanol in chloroform as eluting agent, to give 3-oxo-18-methoxycarbonyloxy-1-demethyl-vincatine methyliminoether (340 mg, 47%) as a pale yellow gum; $\lambda_{max.}$ 221, 262, 270 infl. 285 infl. nm; $\nu_{max.}$ 1745 br (carbonate and ester carbonyls), 1630 (lactam carbonyl), 1580 (C=N) cm^{-1}; δ ($CDCl_3$) 0.6-1.1 (1H, m), 1.2-2.7 (11H, m), 3.52 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 4.01 (3H, s, C=N-OMe), 3.4-4.2 (5H, m), 7.05-7.45 (4H, m, aromatic C-H).

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