Tetrahedron. Vol. 30, pp. 3003 to 3011 Pergamon Press 1974. Printed in Great Britain

REGIO- AND STEREOSPECIFIC MODELS FOR THE BIOSYNTHESIS OF THE INDOLE ALKALOIDS—II[a]

BIOGENETIC TYPE SYNTHESIS OF *ASPIDOSPERMA* AND *IBOGA* ALKALOIDS FROM A CORYNANTHE PRECURSOR

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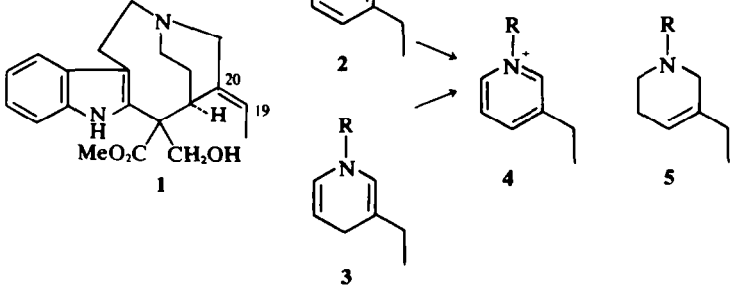
(*Received in USA* 8 *March* 1974; *Received in the UK* 18 *April* 1974)

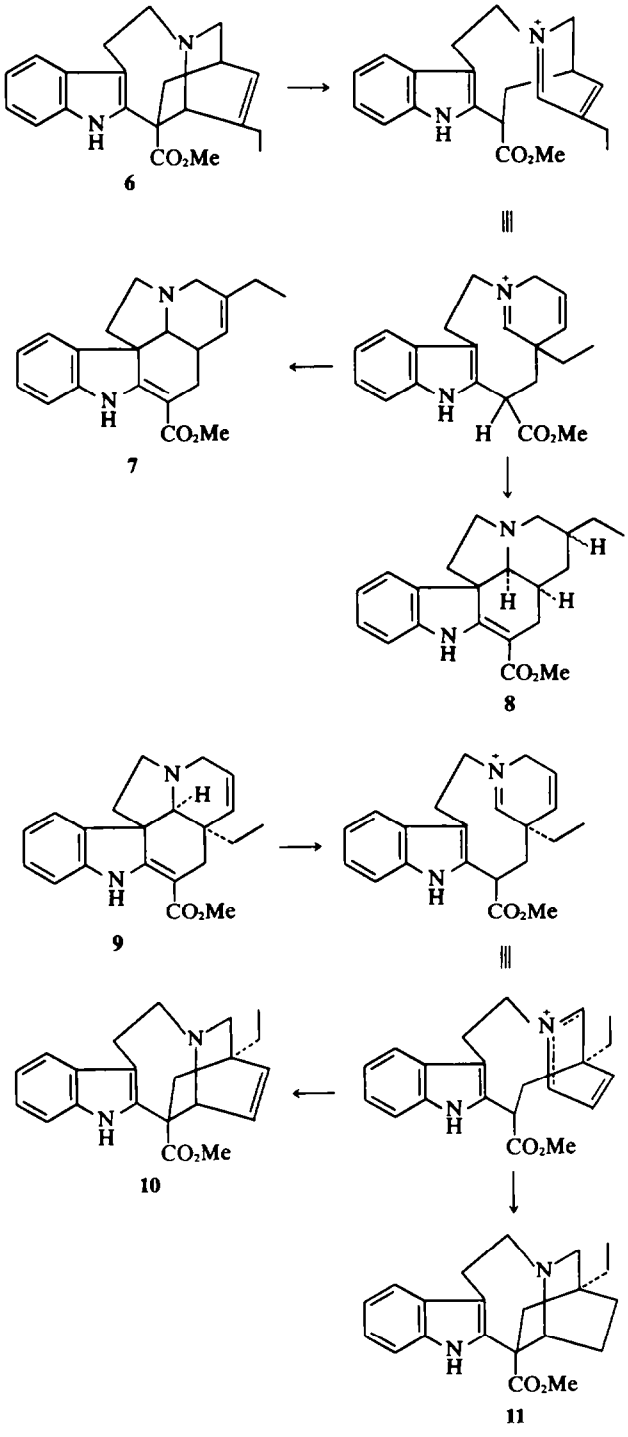
Abstract—The thermal reactivity of dihydro-stemmadenine acetate (**14**) has been investigated as a model for the biochemical conversion of Corynanthe to *Iboga* alkaloids in which the highly reactive achiral ester dehydrosecodine A(**17**) is invoked to rationalize the observed products pseudocatharanthine (**7**) and its 15, 20 dihydro derivative (**8**). Interception of the reactive intermediate from the alcoholysis of dihydropreakuammicine acetate (**15**) has provided further insight into the mechanism of this and related rearrangements. Generation of the isomeric ester dehydrosecodine B(**24**) from stemmadenine (**1**) has been demonstrated in a biogenetic-type conversion to the *Aspidosperma* alkaloids (±)-tabersonine (**9**) and (±) vincadifformine (**27**) by two different processes.

These reactions constitute a separation of the mechanisms operative in the vigorous treatment of stemmadenine acetate on a silica surface which was shown previously to yield a mixture of *Aspidosperma* and *Iboga* alkaloids and also serve to explain the occurrence of racemic and antipodal versions of complex indole alkaloids in Nature.

In 1968 we suggested[1] that, as a result of biosynthetic experiments with the interesting alkaloid stemmadenine (**1**), the more complex *Aspidosperma* and *Iboga* families are produced by a formal dehydration of **1** (m.w. 354) to generate the structural and stereo-isomers of m.w. 336, which include the achiral seco-acrylic ester series. Subsequent chemical and biochemical studies[2,3] have indicated that the latter process could also be effected indirectly by prior reduction of the 19,20-ethylidene double bond of stemmadenine, followed by oxidation at some later stage. Such oxidation-reduction has also been invoked to explain the observed products from reaction of **1** in acetic acid.[4] The low and variable yields of this latter reaction might in part depend on the efficiency of hydrogen transfer system inherent in the dihydropyridines generated, as it is well known[5] that systems such as **2** and **3** readily disproportionate to the pyridinium salt (**4**) and the tetrahydropyridine (**5**). There are also authenticated cases of reduction of isolated double bonds mediated by the disproportionation of reduced pyridine systems *e.g.* in the conversion of catharanthine (**6**) to a mixture of pseudocatharanthine (**7**) and its dihydro derivative (**8**)[6] and the rearrangement of tabersonine (**9**) to a mixture of

[a] Preliminary communication: A. I. Scott and C. C. Wei, *J. Am. Chem. Soc.* **94**, 8263, 8264 (1972).





allocatharanthine (**10**) and dihydroallocatharanthine (**11**).[7]

We therefore examined the thermolysis of 19,20-dihydrostemmadenine (**12**) which took this reductive factor of our earlier experiments into account and also made allowance for the regiospecific (aerial) oxidation of **12** at C_3 to dihydropreakuammicine (**13**). In order to complete the analogy with the earlier work using acetic acid (which has been shown to form the primary acetate), dihydrostem-

madenine was converted to the acetate (**14**). When the latter compound was heated on a silica gel TLC plate at 150° for 45 min the resultant mixture afforded (±) pseudocatharanthine[5,*] **7** (1%)—and its dihydro derivative[6,*] **8** (0·5%). No trace of tabersonine (**9**) was detectable in this experiment. In order to rationalise this result it is necessary to generate a double bond at $C_{3\text{-}14}$ (**15a**→**15b**) so that the extended reverse Mannich chemistry shown in **13**→**16** can operate. The further reaction of the iminium salt (**16**) is seen as a rearrangement to 3,14-dehydrosecodine (**17**), which we have designated dehydrosecodine A. (Scheme 1).

Recombination of the achiral ester (**17**) affords (±)-pseudocatharanthine whereas conjugate reduction of **16** leads to the secodine (**18**) whose cyclisation to (±) dihydropseudocatharanthine (**8**) is unexceptional. A more efficient way of demonstrating this regio- and stereospecific rearrangement was found by preparing 19,20-dihydropreakuammicine acetate (**15**) a known autoxidation product of **14**, by Pt-0_2 oxidation of **14**. Thermolysis of **15** at 150° for 20 min afforded (±) **7** in yields which, although by no means optimised, average 5%. The known equilibrium between **7** and catharanthine (**6**) completes the partial synthesis of the latter member of the *Iboga* family in racemic form.

Further insight into the mechanism of this remarkable reaction was gained by methanolysis of the acetate (**15**) at room temperature for 4 hr, or at 80° for 15 min.† The products of this reaction were now *optically active* and were separated to afford a dextrorotatory 15-methoxydihydropseudocatharanthine (**19**) and the levorotatory diastereomer (**20**) in the ratio 9:1. The combined overall yield of this reaction from dihydrostemmadenine (**12**) was 3·5%. This result is in full accord with the postulate that the immonium species (**16**) is an intermediate in the rearrangement process and that conjugate addiction of methanol affords the diastereomeric mixture (**19, 20**) *via* **21**. The stereospecific preference for the absolute configuration **19** over **20** may well be dictated by the configuration of the OMe group at C_{15} which controls the observed stereochemistry of the cyclisation process. This particular model is also illustrative of the remarkable variation[8] in absolute configuration of the pentacylic *Aspidosperma* alkaloids even within the same plant, which could be mediated by conjugate addition of the appropriate prosthetic group of the synthesizing enzyme to such an immonium species. Another pertinent example is the co-occurrence of (−) coronaridine (**2**) and (+) catharanthine within the same species (*Catharanthus roseus*).[9] This duality of absolute stereochemistry for such complex alkaloids again can be viewed as the result of the timing of the reduction step on the immonium ion (**16**) which can either be reduced and cyclised to give (−) coronaridine or pass through the achiral intermediate (**17**) with protropic loss of C_{20} stereochemistry and thence by enzymic control to the antipodal series represented by catharanthine (**7**). In this connection it is of interest to note that the *in vitro* conversion described above in which **16** is suggested as the first formed *chano* intermediate, the thermal reaction serves to epimerise this center so that the products of the reaction are (±) pseudocatharanthine and the corresponding *racemic* dihydro compound (**8**). The milder conditions used in the methanolysis experiment however give products which on the basis of molecular rotation differences with other members of this series indicate an optical purity of *ca* 70–80%. The configuration of the OMe group at C_{15} in these diastereoisomers is at present unknown. A similar reaction was observed when dihydropreakuammicine acetate was heated in ethanol at 80° for 15 min to yield a separable mixture of the dextrorotatory and levorotatory diastereomers of 15-ethoxy-15,20 dihydropseudocatharanthine (**22, 23**) in the ratio 10:1, in 10% (combined) yield.

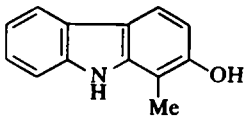
The above experiments indicate that an "*Iboga* synthetase" model in the form of dehydrosecodine A(**17**) has been demonstrated to operate and that not only the regio specific generation and recombination of **17** mediated by the collapse of reduced preakuammicine (**13**) but the stereospecificity of the recyclization process leads to the *Iboga* isomer, (±) pseudocatharanthine (**7**) which in turn is convertible to (±) catharanthine (**6**). Although the yields in this reaction are not yet of preparative value it is our view that the synthesis and reactivity of the dehydrosecodine system is worthy of more detailed study as a new method of preparing quite complex pentacyclic alkaloids from simple starting materials, with full stereospecific control.

The corynanthe-aspidosperma relationship

The reverse Mannich chemistry discussed in a previous hypothesis for *Aspidosperma* biosynthesis[1] differs in regiospecificity for the *Iboga* model described in the preceding section in that the formation of the secodine system now takes place *via* $C_{20,21}$ rather than $C_{3,14}$. The introduction of unsatura-

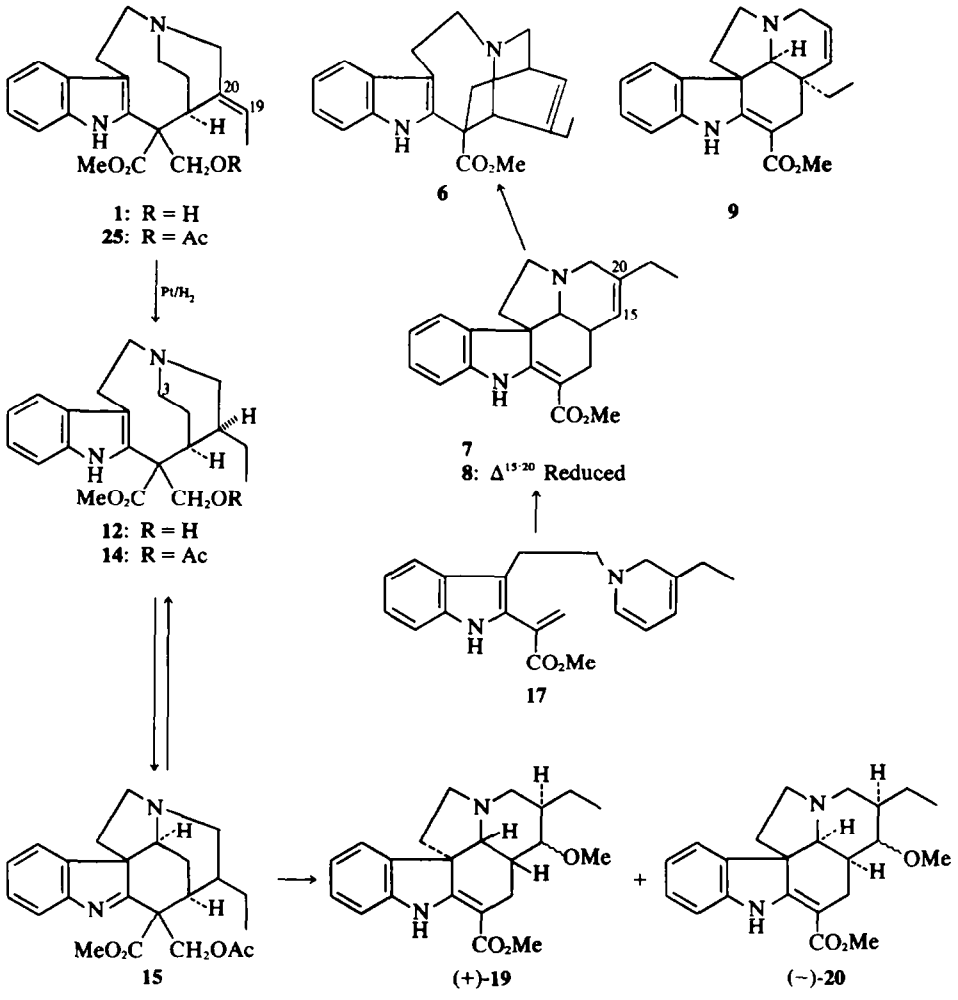
*All of the reaction products were identified by spectroscopic mass spectrometric and TLC comparison with authentic samples. For details of the TLC systems used see Ref 4. The identification of new compounds isolated in these reactions is described in experimental Section.

†The pyrolysis of 15 in ethyl acetate took a completely different course to afford the carbazole (1)



(i)

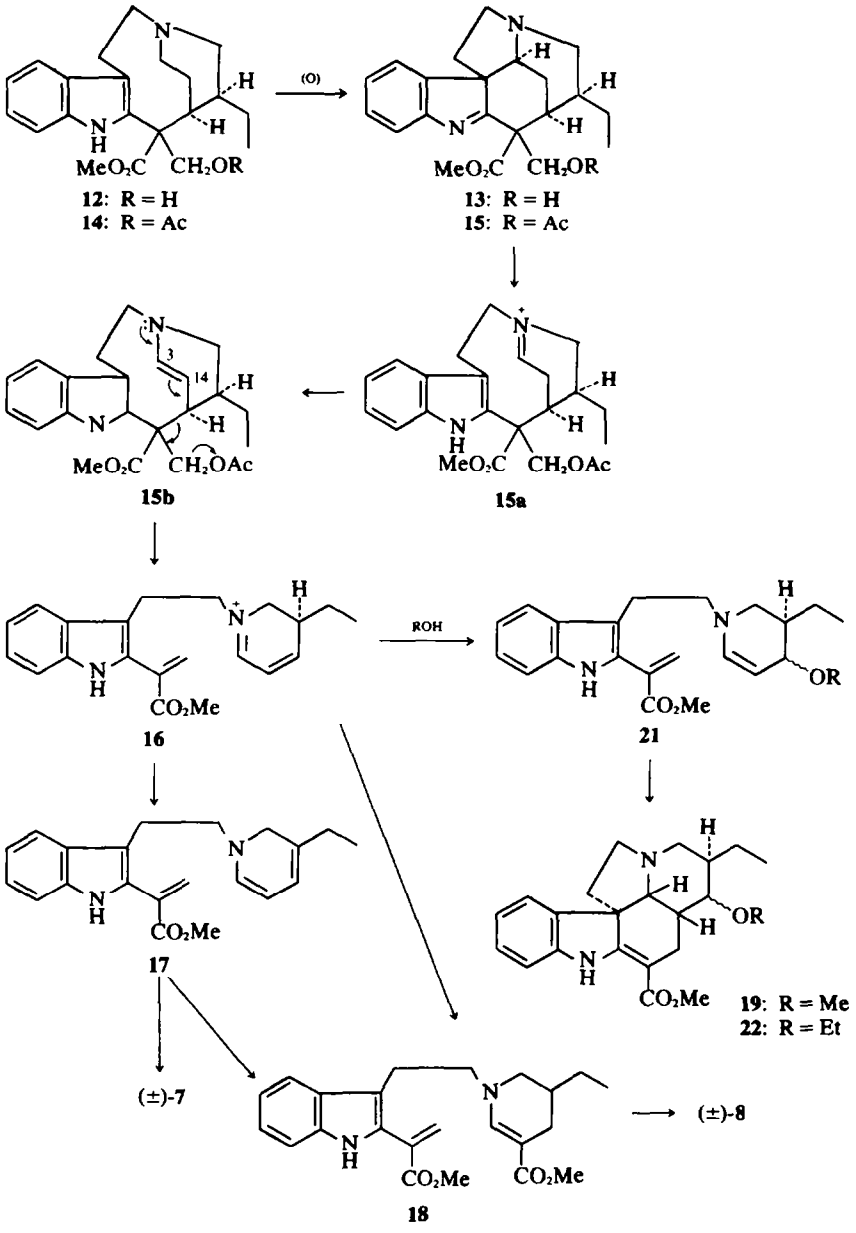
by a mechanism discussed in Ref 16.



tion at C_{21} could in principle be realised by two methods. First it was hoped that the simple isomerization process (Scheme 2) previously adduced for reaction of stemmadenine (acetate) in hot acetic acid solution, might be capable of more rigorous control and thus lead *only* to *Aspidosperma* framework by recombination of the dehydrosecodine B(**24**). We were further encouraged to search for isomerization conditions when it was discovered that whereas stemmadenine (**1**) is hydrogenated unexceptionally to the 19,20-dihydro derivative (**12**) in presence of platinum catalyst, the behavior of stemmadenine acetate (**25**) is quite different towards reduction. Thus at atmospheric pressure, hydrogenation of **25** over platinum in ethanol solution leads to (±)-tetrahydrosecodine (**26**) in 75% yield. The facile cleavage of the 15, 16 sigma bond in **25**, but not in **1** is suggestive that the primary acetoxyl at C_{17} aids the irreversible loss of acetate from the Δ20, 21 isomer (**25a**) which is in equilibrium with the Δ19, 20 exocyclic olefinic group of the starting material. This high yielding partial synthesis of the naturally occurring member of the secodine family also serves as a model for the biosynthesis of these alkaloids from stemmadenine.

Experiments designed to capture the fugitive dihydropyridine (**24**) in the cyclised form corresponding to the *Aspidosperma* alkaloids were therefore developed. In the first of these, direct conversion of stemmadenine acetate (**25**) to (±) vincadifformine* (**27**) was achieved in low yield (0·15–0·20%) by thermolysis at 150° on a silica gel surface for 25 min. The analytical and preparative procedures* used for this and the succeeding experiments left no doubt that tabersonine (**9**) was not a product of the reaction. A plausible reaction pathway is shown in Scheme 2 which suggests that

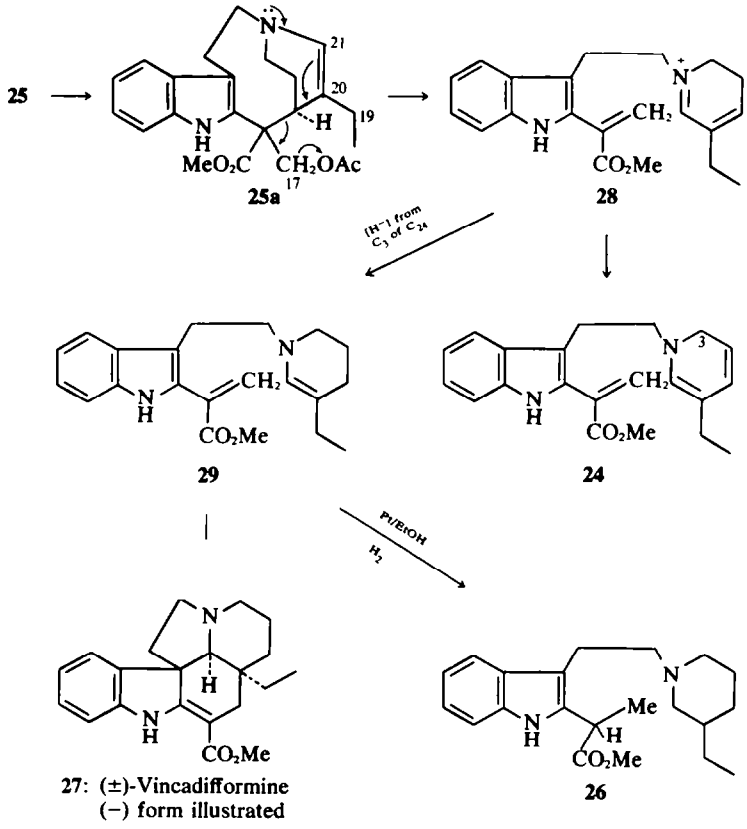
*All of the reaction products were identified by spectroscopic mass spectrometric and TLC comparison with authentic samples. For details of the TLC systems used see Ref 4. The identification of new compounds isolated in these reactions is described in experimental Section.



SCHEME 1.

the intermediate immonium species (**28**) suffers reduction by disproportionative release of hydride to the secodine (**29**) which then cyclises to (±) vincadifformine and that this sequence is favored over the more direct rearrangement (without reduction) to (±) tabersonine (**9**). An alternative method was then studied, which takes into account the ready aerial oxidation in acetic acid solution of **25** to the acetate (**30**) of the naturally occurring pentacyclic alkaloid, precondylocarpine[10]*, a step which can be achieved more efficiently using platinum catalyzed oxidation.[11] Catalytic reduction of the ethylidene group of **30** affords the dihydroacetate (**31**) which is now formally capable of regiospecific collapse to dehydrosecodine B as shown in Scheme 3. When the acetate (**31**) was subjected to thermolysis (150°, silica gel, 25 min) a

*This structure was further confirmed by conversion to condylocarpine (see Experimental Section).



SCHEME 2.

separable mixture of (±) tabersonine **9** (0·2%) and (±)-vincadifformine **27** (0·2%) was produced, while no trace of pseudocatharanthine (**7**) could be detected. We conclude from these results that the generation of the B ester (**24**) takes place *without rearrangement to the A isomer* (**17**) according to Scheme 3. Although the yields in these models for "*Aspidosperma* synthetase" are extremely low the reactions provide a working hypothesis for the complex series of rearrangements which accompany the biochemical conversion of the *Corynanthé* to the *Aspidosperma* and *Secodine* families. At the same time, we believe that the multi-step reaction sequence which was concealed in our earlier model experiments can now be understood in terms of the operation of indiscriminate oxidative and reductive attack on stemmadeine acetate, the first formed product of the reaction between acetic acid and the original substrate, stemmadenine. Depending on the timing of the oxidative and reductive steps, the acetate (**25**) is converted to both the preakuammicine and precondylocarpine skeletons which at the appropriate oxidation level collapse to *Iboga* and *Aspidosperma* alkaloids respectively.

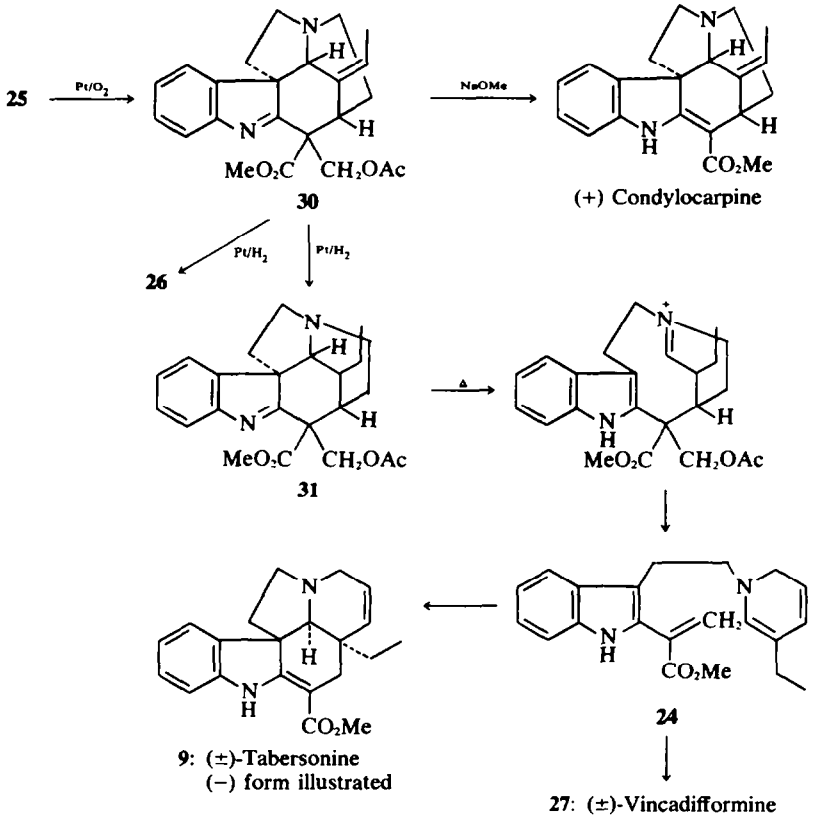
Since the reaction conditions reported herein take place, with the exception of the alcoholysis procedures, under rather vigorous conditions, the conversions are low yielding but it is our view that the controlled synthesis of the acrylic esters **17** and **24** holds considerable promise as a general method of entry to the *Aspidosperma* and *Iboga* series and that in the light of the high yielding stereospecific cyclisation step recently carried out by Ziegler[12] on the synthetic acrylic ester (**32**) to give (**33**), rather facile synthesis of the pentacyclic indole alkaloids is now entirely feasible *via* **17** and **24**.

EXPERIMENTAL

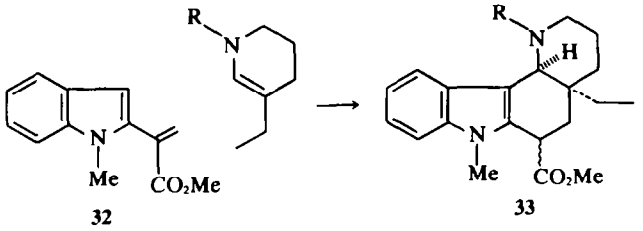
Stemmadenine (**1**). 6·8 Kg of the ground fruits of *Stemmadenia Donnell-smithii** were extracted, following the reported procedure,[13] to yield 1·11 g of crystalline stemmadenine, m.p. 199° (lit. 199 ~ 200°C); λ_{max}^{MeOH} 228, 285, 292 nm; *m/e* 354 (M^+), 336 ($M^+ - H_2O$), 324 ($M^+ - CH_2O$), 323, 123 (base peak), identical in every respect with a sample provided by Dr. D. Stauffacher.[14]

19,20-*Dihydrostemmadenine* (**12**).[15] To a soln of stemmadenine (52 mg), in glacial AcOH, was added platinum oxide (50 mg), and the resulting mixture was hydrogenated (40 psi) on a Parr shaker for 3 hr. The soln was

*Obtained through the generous cooperation of Prof. A. G. Pompa, University of Mexico.



SCHEME 3.



filtered through celite and the filtrate was evaporated under reduced pressure. The residual material was purified by preparative TLC (silica gel, 10% MeOH in $CHCl_3$) affording 40 mg of dihydrostemmadenine (75% yield). It was converted to the hydrochloride salt which crystallized from acetone m.p. 209 ~ 210°; λ_{max}^{MeOH} 226, 278 (sh), 284, 292 nm; *m/e* 356 (M^+), 124 (base peak.)

19,20-*Dihydrostemmadenine acetate* (**14**). Dihydrostemmadenine (40 mg) in 3 ml of Ac_2O-pyridine (molar ratio 1:2) was stirred at room temp under N_2 for 3 hr. After the reaction, the solvent was removed under reduced pressure and the residue was worked-up according to the usual procedure for alkaloids. Purification by preparative TLC (silica gel, 10% MeOH-$CHCl_3$) gave the title compound (25 mg; 45% yield); *m/e* 398 (M^+), 339 ($M^+ - OC\overset{O}{\overset{\|}{C}}CH_3$) 124 (base peak).

Stemmadenine acetate (**25**). Stemmadenine (29 mg) in Ac_2O (2 ml) was heated at 100° with stirring under N_2 for 1 hr. The solvent was evaporated and the crude product was crystallized from benzene to give crystalline stemmadenine acetate (25 mg, 80%), m.p. 157–160°; *m/e* 396 (M^+), 337 ($M^+ - O\overset{O}{\overset{\|}{C}}CH_3$), 123 (base peak). NMR: δ ($CDCl_3$) 1·63 (d, 3H, C=C–CH_3), 1·80 (s, 3H, –$\overset{O}{\overset{\|}{C}}CH_3$), 3·54 (s, 3H, –$OCH_3$), 5·22 (m, 1H, C–CH=C), 6·84 (m, 4H, ArH), 8·2 (broad, 1 H, NH).

Hydrogenation of stemmadenine acetate: *Tetrahydrosecodine* (**26**). Stemmadenine acetate (80 mg) in 20 ml of abs EtOH was hydrogenated over Pt (from 80 mg of PtO_2) under 1 atom of H_2 for 24 hr. The soln was filtered through celite and purified *via* preparative TLC (silica gel; 15%

MeOH-$CHCl_3$) to give tetrahydrosecodine[16] (52 mg) (75% yield), λ_{max}^{MeOH} 225, 278 (sh) 286 and 292 nm; *m/e* 342 (M^+) 126 (base peak); NMR δ ($CDCl_3$) 0·9 (t, 3H, CH_2CH_3), 1·55 (d, 3H, CH_3–CH–CO_2Me), 3·64 (s, 3H, –$COOCH_3$), 4·1 (q, 1H, CH_3–CH–CO_2Me), 7·0 ~ 7·5 (4H, m, ArH), 8·4 (s, 1H, >NH), identical with an authentic sample.[16]

Precondylocarpine acetate (**30**). A procedure similar to that reported by Schmid[11] was followed. Compound **25** (80 mg) and Pt (from 340 mg of PtO_2) in 10 ml of EtOAc was stirred under 1 atom of O_2 for 8 hr. After removal of the catalyst by filtration and evaporation of solvent, the crude mixture was purified *via* preparative TLC (silica gel, to give **30** (19 mg, 33%); λ_{max}^{MeOH} 221, 273, 282 (sh), 291 (sh) nm; *m/e* 394 (M^+), 335 ($M^+ - O\overset{O}{\overset{\|}{C}}CH_3$), 321, 278; NMR δ ($CDCl_3$), 1·55 (d, 3H, C=CHC$\underline{H}_3$), 3·60 (s, 3H, $CO_2C\underline{H}_3$), 5·2 (q, 1H, =C$\underline{H}$–CH_3), 6·8–7·2 (m, 4H, ArH).

Dihydropreakuammicine acetate (**15**). Dihydrostemmadenine acetate (9·8 mg) and Pt (from 90 mg of PtO_2) in EtOAc (10 ml) was stirred under 1 atom O_2 for 1 hr. Filtration and evaporation of the solvent gave a mixture which was purified *via* TLC (silica gel, 10% MeOH in $CHCl_3$) to give preakuammicine acetate (2·5 mg; 25% yield), λ_{max}^{ether} 228, 260, 288 (sh), 294 (sh) nm; *m/e* 396 (M^+), 337 ($M^+ - O-\overset{O}{\overset{\|}{C}}CH_3$), 336, 323.

Reaction of precondylocarpine acetate with sodium methoxide. Precondylocarpine acetate (2 mg) in 5 ml MeOH was added to NaOMe (5 mg). The resulting soln was heated at 60 ~ 70° for 5 min. After normal alkaloidal workup, the crude mixture was purified *via* TCL (silica gel, 20% MeOH–$CHCl_3$) and the zone corresponding to condylocarpine eluted. The product was shown to be condylocarpine by comparison of the spectroscopic properties (mass, UV, ORD spectra) and coincident TLC behavior.

Reaction of dihydropreakuammicine acetate with methanol. A soln of dihydropreakuammicine acetate (2 mg) in abs MeOH (2 ml) was stirred under N_2 for 4 hr. The mixture was then separated on TLC (silica gel, Ether–light petroleum (1:1)) to give *d*-methoxydihydro-Ψ-catharanthine* and the *l*-diastereomer in a 9:1 ratio. Both had λ_{max}^{MeOH} 226, 298, 328 nm; *m/e* 368 (M^+) 337 ($M^+ - OCH_3$), 154 (base peak). *d*-methoxydihydro-Ψ-catharanthine showed $[\Phi]_{345nm}$ + 25000 and the *l*-isomer had $[\Phi]_{354nm}$ − 28000.

Thermolysis of dihydropreakuammicine acetate in ethanol. Dihydroakuammicine acetate, obtained from the oxidation of dihydrostemmadenine (9 mg), was dissolved in abs EtOH (5 ml) and heated at 80° under N_2 for 15 min. After purification on TLC (silica gel, ether–light petroleum (1:1)), the mixture gave *d*-ethoxydihydro-Ψ-catharanthine and the *l*-diastereomer in 10:1 ratio (total yield from dihydrostemmadenine 3·5%). Both had λ_{max}^{MeOH} 228, 300, 328 nm; *m/e* 382 (M^+), 337 ($M^+ - OCH_2CH_3$) 336 ($M^+ - CH_3CH_2OH$), 168 (base peak). *d*-ethoxydihydro-Ψ-catharanthine had $[\Phi]_{345nm}$ + 26000, while the *l*-isomer had $[\Phi]_{345}$ − 28000.

Thermolysis of dihydropreakuammicine acetate in ethyl acetate. A soln of dihydropreakuammicine acetate (1·2 mg) in EtOAc (1 ml) was heated in an evacuated sealed tube at 100° for 4 hr. Purification on TLC (silica gel, ether–light petroleum (1:1)) gave 1-methyl-2-hydroxycarbazole which was identified spectroscopically (UV, mass), and by TLC comparison with an authentic sample.[16]

Thermolysis of dihydropreakuammicine acetate on silica gel. Dihydropreakuammicine acetate (2 mg) in 10% MeOH-$CHCl_3$ (4 ml) was spotted on a silica gel plate (F-254) and heated in the oven at 150° for 20 min. Purification (silica gel, ether–light petroleum (1:1)) gave Ψ-catharanthine in yields ranging from 2–5% with different runs (the yield was estimated by the UV absorption using E_{328nm} $1·5 \times 10^4$ $cm^{-1}M^{-1}$). Identification of the product was made by spectroscopic means (mass spectra, UV) and TLC [silica gel, ether–light petroleum (1:1); 5% $AgNO_3$ on silica gel, ether–light petroleum (1:2)] comparison with the authentic compound. In addition, it showed $[\Phi]_{300-600nm}$ 0°.

Thermolysis of dihydrostemmadenine acetate on silica gel.† Dihydrostemmadenine acetate (23 mg) in $CHCl_3$ (5 ml) was spotted on a silica gel plate (5 × 5 cm, 0·25 mm thickness) and heated at 150° for 45 min in air. Using previous purification and identification procedures,[4] Ψ-catharanthine was obtained in 1% yield, $[\Phi]_{250-600}$ 0°. In addition, dihydro-Ψ-catharanthine was isolated in 0·5% yield.

Thermolysis of dihydroprecondylocarpine acetate on silica gel. Precondylocarpine acetate (6 mg) in EtOAc (5 ml) was hydrogenated on 10% Pd-C (12 mg) at room temp for 15 min. Without further purification, the mixture, which showed the presence of tetrahydrosecodine, was heated at 150° for 25 min. Racemic tabersonine (0·2% yield) and racemic vincadifformine (0·2% yield) were isolated by TLC as described previously.[4]

Thermolysis of stemmadenine acetate hydrochloride on silica gel. Stemmadenine acetate hydrochloride (9·5 mg), which was prepared by passing HCl gas through a soln of stemmadenine acetate and crystallizing the *salt* from benzene was dissolved in methylene chloride and spotted on a TLC plate (2 × 5 cm, 0·25 mm). After heating in the oven at 150° for 25 min, the mixture was purified to give racemic vincadifformine in 0·13% yield.

Acknowledgement—We thank S.R.C., The Nuffield Foundation and N.I.H. for supporting this work.

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*The symbol Ψ- is used to denote *pseudo* throughout the experimental section for the sake of brevity e.g. d-methoxydihydropseudocatharanthine becomes d-*methoxydihydro-Ψ-catharanthine*.

†We thank Dr. M. Uskokovic (Hoffmann-LaRoche, Nutley, N. J.) for carrying out independent confirmation of this experiment using analytical TLC[4] for identification purposes.

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