Tetrahedron Vol 30, pp. 3013 to 3019. Pergamon Press 1974. Printed in Great Britain

REGIO- AND STEREOSPECIFIC MODELS FOR THE BIOSYNTHESIS OF THE INDOLE ALKALOIDS—III

THE ASPIDOSPERMA-IBOGA-SECODINE RELATIONSHIP

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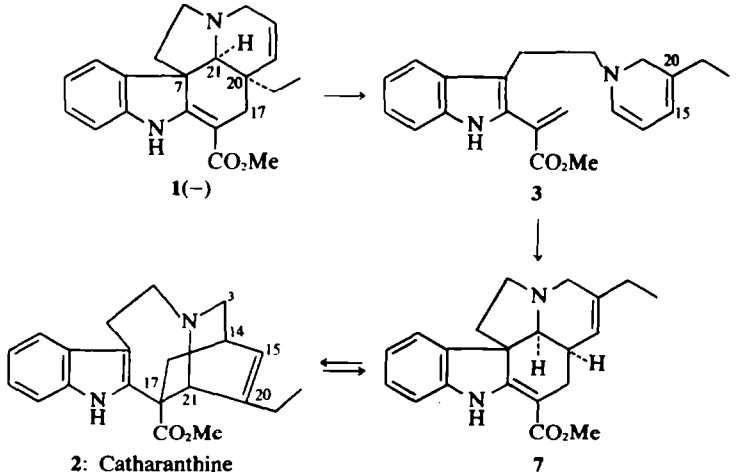
(*Received in the USA* 8 *March* 1974; *Received in the UK for publication* 18 *April* 1974)

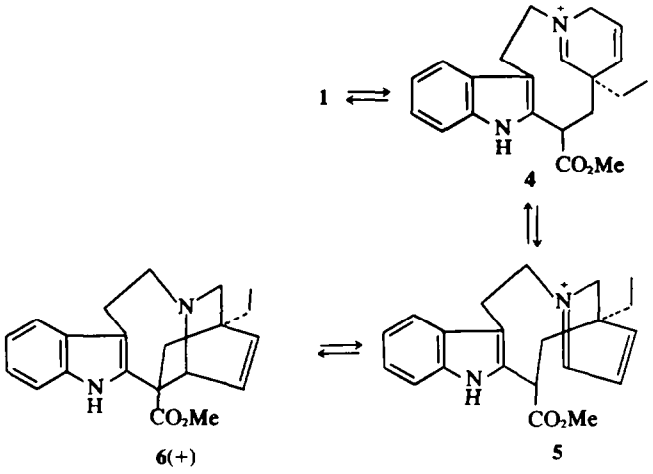
Abstract—*In vitro* transformation of the *Aspidosperma* alkaloid (−) tabersonine (**1**) to (±)-pseudocatharanthine (**7**) *via* (+) allocatharanthine (**6**) and dehydrosecodine A (**3**) is described as a model for the biochemical interconversion of *Aspidosperma* and *Iboga* alkaloids. Facile conversion of **1**, **2** and **7** in xylene solution to the carbazole (**9**) suggests the intermediacy of dehydrosecodines (as **8**) in these reactions. In methanol solution the racemic salt (**12**) is formed in 50% yield from catharanthine at 175°. Further pyrolysis of the salt yields the carbazole (**9**). Reduction of the salt (**12**) with $NaBH_4$ affords (±) dihydrosecodine (**16**) identical with the natural alkaloid from *Rhazya stricta*.

In 1968 we described the *in vivo*[1] and *in vitro*[2] transformations of the *Aspidosperma* alkaloid tabersonine (**1**) to the *Iboga* alkaloid catharanthine (**2**) and proposed an intermediate (**3**) in this reaction which has since been found in a variety of stabilised versions.[3] In 1969[4] Smith *et al* reported that, in their view, this reaction, which involves rupture of both the 7-21 and 17-20 bonds of **1**, proceeds only as far as cleavage of the 7-21 bond. The resultant immonium species (**4**) then rearranges to **5** and cyclises to allocatharanthine (**6**) an optically active isomer of catharanthine (**2**) and pseudocatharanthine (**7**), the latter two *Iboga* structures being interconvertible. We have emphasised in a previous paper[5] that both ionic and thermal requirements must be met in carrying out the full transformation which by passing through **3** affords the racemic products described earlier. In order to reconfirm and simplify the experiment, the ionic and thermal components have been separated as follows.

(−)-Tabersonine (**1**) was heated in acetic acid for 15 h (external bath temperature 140°). The resultant mixture was separated and (+) allocatharanthine[4] **6** (11%) isolated. A solution of **6** was applied to a silica gel TLC plate, the solvent removed, and the plate heated at 150° for 30 min. Elution and chromatography on $AgNO_3$-impregnated silica gel† plates afforded two major products. These were (±) pseudocatharanthine **7** (4%) identical with authentic material[7] and *optically pure* (−) tabersonine **1**

†This technique is particularly effective in separating pseudocatharanthine and tabersonine. For details see Table 1 in Part I of this series.[6a]

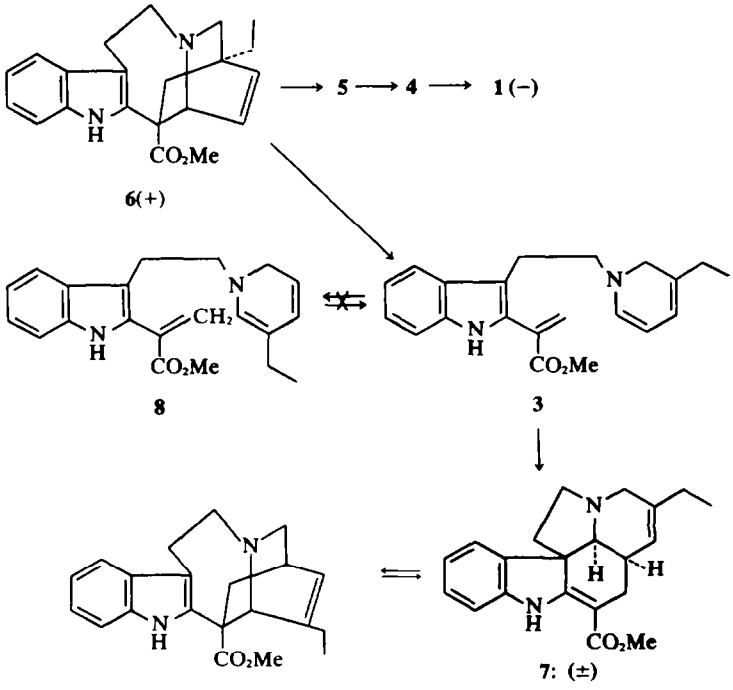


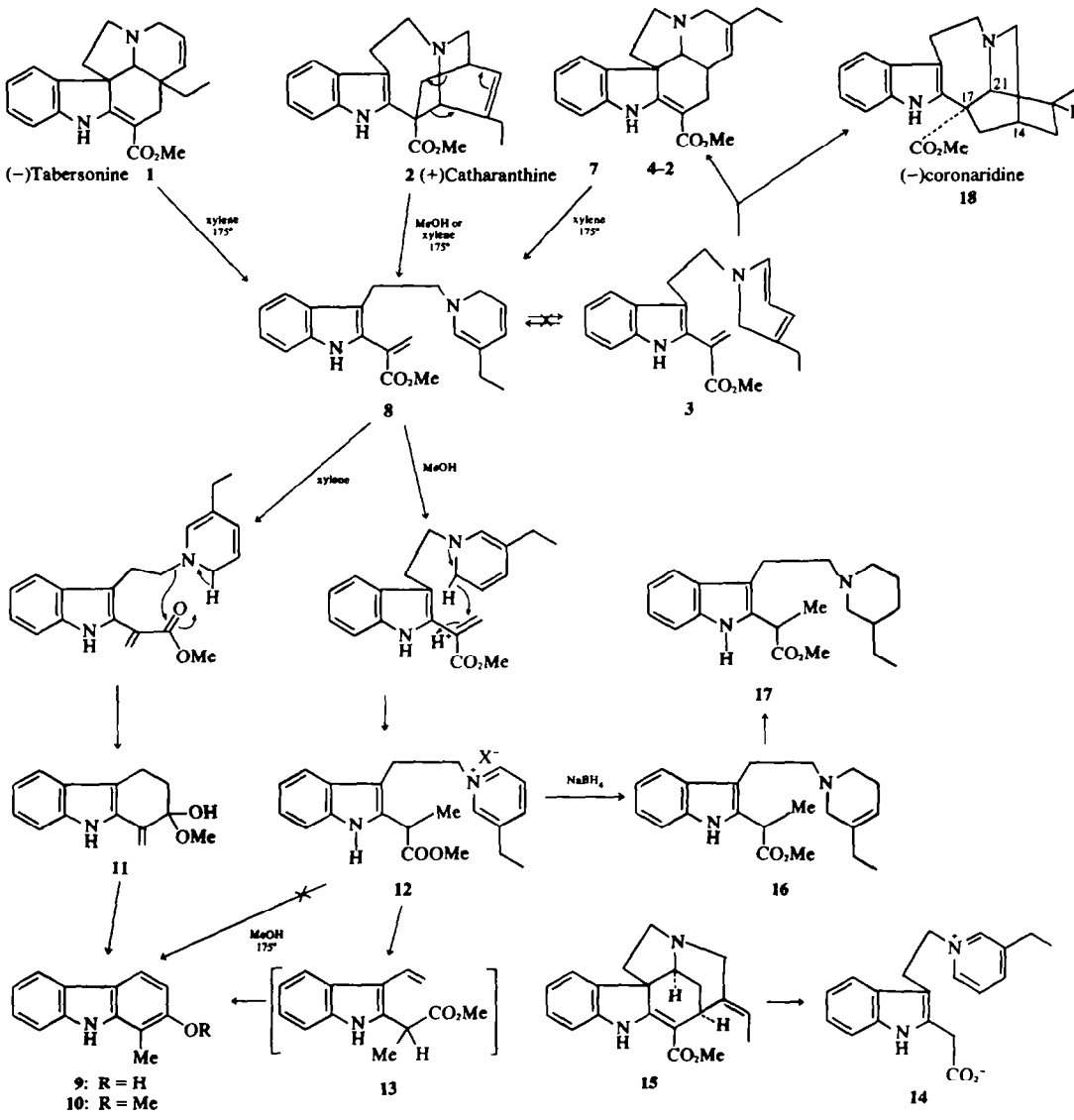


(4%). The absence of any racemisation of tabersonine indicates reversal of the formation of allocatharanthine without cleavage at $C_{17,20}$ *i.e.* by the pathway **6**→**5**→**4**→**1**. Thus not only is the *Aspidosperma* framework stable towards retro-Diels-Alder reaction but in confirmation of the complete specificity noted in the previous communication for the reaction of dehydro secodines A and B, *only the racemic product* (**7**) of cyclisation of dehydrosecodine A (**3**) is observed, there being no evidence for equilibration with the B isomer (**8**) which would have yielded (±) tabersonine.

In order to gain further evidence regarding the intermediacy of the secodine esters (**3** and **8**) we have also studied the thermal reactions of the key members of this series. When xylene solutions of the isomeric alkaloids (−)-tabersonine (**1**), (+)-catharanthine (**2**), and (±)-pseudocatharanthine (**7**) were maintained in sealed tubes for 1·5 h at the temperatures indicated (Scheme 1) in each case (but with a different energy requirement) the same products were isolated and characterized as 3-ethylpyridine and 1-methyl-2-hydroxycarbazole (**9**).

We suggest that the formation of these products





SCHEME 1.

takes place by way of a retro-Diels-Alder reaction to afford the fugitive ester (**8**) followed by an intramolecular rearrangement and hydrogen transfer from the dihydropyridine to the acrylic ester function yielding the hemiketal 11 with loss of 3-ethylpyridine as indicated. Elimination of methanol and further rearrangement then give the carbazole (**9**). In support of the latter process 1 - methyl - 2 - methoxycarbazole 10 could be detected and characterized as a minor product of the reaction.

More direct evidence for the formation of **8** was obtained by the capture in 50% yield of the racemic salt (**12**) when catharanthine was heated in methanol at 140° for 2 h. The structure followed from the NMR spectrum* which showed (D_2O) τ 1·7–3·3, 8H, m (Ar-H); 5·30 and 6·66, 4H, 2t ($-CH_2CH_2-$); 6·12, 1H, q, J = 7·5Hz ($CH(CH_3)CO_2CH_3$); 6·33, 3H, s (CO_2CH_3); 7·55, 2H, q, J = 7·5Hz (CH_2CH_3); 8·62, 3H, d, J = 7·5Hz ($CH(CH_3)CO_2CH_3$); 9·18, 3H, t, J = 7·5Hz (CH_2CH_3).

In contrast to the intramolecular formation of the carbazole from the dihydropyridineacrylic ester (**8**) in the aprotic solvent xylene, the availability of solvent protons in the latter case appears to divert the collapse of this intermediate in methanol *via* an ionic mechanism to the pyridinium salt (**12**). When

*s = Singlet; d = doublet; t = triplet; m = multiplet.

the reaction is carried out in CH_3OD solution, the NMR spectrum of the salt no longer shows a signal at τ 6·12 ($CD(CH_3)CO_2$-CH_3) and the doublet at τ 8·62 ($CH(CH_3)CO_2CH_3$) is replaced by a singlet (3H) in accord with the mechanism **8** → **12** as shown in Scheme 1. This salt is stable in methanol at 175° but on pyrolysis at this temperature affords the carbazole (**9**), presumably *via* elimination of ethylpyridine and cyclization of the resulting vinyl esters (**13**). The generation of **8** in methanol solution could also be rationalized by an ionic mechanism which recalls the formation of the betaine (**14**) from akuammicine (**15**).[8] Since the species **8** and **12** could be reached *in vivo* from stemmadenine, tabersonine (**1**) and catharanthine (**2**), it will be of interest to test these three alkaloids as biochemical precursors for secodines and secamines and also to consider the system **8**⇄**12** as a labile but isolable biosynthetic entity in the Aspido-*sperma* and *Iboga* metabolic grid.

Laboratory analogy for secodine formation from the salt (**12**) was obtained by reduction of **12** with sodium borohydride which gave (±) dihydrosecodine (**16**)[3a,b] as a crystalline racemic base (35% yield) identical in all spectroscopic properties with the amorphous natural alkaloid obtained from *Rhazya stricta*. Further (catalytic) reduction of **16** afforded tetrahydrosecodine (**17**) which co-occurs in *R. stricta*.[3a,b] This mode of formation of dihydrosecodine may be contrasted as a biosynthetic model with the extremely facile formation of (±)-tetrahydrosecodine (**17**)[6b] from stemmadenine acetate in 75% yield where it was suggested that rupture of the $C_{15\text{-}17}$ bond was facilitated by platinum-catalyzed isomerization of the 19, 20-double bond to the *endo* position thereby allowing collapse to the secodine system, as discussed in the previous paper of this series.

Finally we note that the earlier difficulties in rationalizing the lack of biochemical conversion of (+) catharanthine (**2**) to its 15,20-dihydro derivative, coronaridine (**18**) can now be understood since in *Catharanthus roseus* it has been found that these *Iboga* alkaloids bear antipodal absolute stereochemistry at C_{14}, C_{17} and C_{21}.[9] The co-occurrence of such antipodal species in the same plant may once again signify the onset of different synthetases acting on the same intermediate. Thus (−)-coronaridine is detectable at very early stages of germination of *C. roseus* whereas (+)-catharanthine is found only after prolonged germination and seedling growth.[1,10] The achiral ester dehydrosecodine A **3** (or its isomer B **8**) could serve as an intermediate which can undergo cyclization (Scheme 1) in either absolute stereochemical mode to furnish the series represented by (−) coronaridine (**18**) or (+)-catharanthine (**2**).

EXPERIMENTAL

For general directions see Part I of this series.

Thermolysis of allocatharanthine (**6**). A soln of allocatharanthine (40 mg) prepared as described in part II of this series (preceding paper) in 10% MeOH $CHCl_3$ (5 ml) was applied to a silica gel plate (F-254). After 30 min at 150° elution (MeOH) and chromatography on $AgNO_3$-silica afforded (±)-Ψ-catharanthine (1·6 mg) identical with authentic material (TLC, UV, MS, ORD). A second portion (1·6 mg) was shown to be (−)-tabersonine (TLC, UV, MS, ORD) identical with the natural alkaloid.

Catharanthine in tetralin at 190°. Catharanthine free base was generated from the hydrochloride salt by partitioning between $CHCl_3$ and 1N NaOH. The washed, dried $CHCl_3$ extract on evaporation yielded a white foam which was stable at − 20° but which discolored and decomposed on storage at 25°.

Catharanthine free base (275 mg) was dissolved in tetralin (75 ml, previously passed down a column of basic alumina) and heated at 190° under N_2 for 1 h. The cooled mixture was extracted well with MeOH-2N HCl (1 : 1) and this aqueous extract was washed with hexane, neutralized with 2N NaOH and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract yielded a gum (119 mg) with a strong characteristic odor of ethylpyridine. This material was subjected to chromatography on four 20 × 20 cm × 0·5 mm silica gel PF_{254} plates developed once in ether-hexane (1 : 1). The main band visible under UV light had separated from a minor band which had the same R_f as authentic 3-ethylpyridine. The main band was removed and eluted with $CHCl_3$-MeOH (9 : 1) and afforded a crystalline solid (84 mg). This material was recrystallized from acetone-chloroform to yield **9** as plates (29 mg); m.p. 221–225°; $[\alpha]_{300\text{-}600}$ 0·0° (MeOH): λ_{max} (EtOH) 216 (log ϵ 4·41), 238 (4·59), 252 (4·44 sh), 300 (4·13), 315 (3·87 sh), 328 nm (3·41 sh); NMR (60 MHz, CD_3COCD_3) τ 2·05, 1H, m, (H-5); 2·22, 1H, d, J = 8Hz (H-4); 2·40–3·00, 3H, m (H-6, -7 and -8); 3·15, 1H, d, J = 8Hz (H-3); 6·75, 1H, s, exchanges (OH); 7·53, 3H, s, (CH_3). Mass spectrum: base peak *m/e* 197; IR ν_{max} (KBr) 3440, 1460, 1225, 1075, 810, 770, 755, 735 cm^{-1}. (Found: C, 79·0; H, 5·5; N, 7·0. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·6; N, 7·1%).

Catharanthine in xylene at 140°. Catharanthine free base (13 mg) was heated under reflux under N_2 in xylene (4 ml). TLC examination of the solution after 1 hr showed only spots corresponding to 3-ethylpyridine and **9**.

Catharanthine in benzene at 80°. Catharanthine free base (50 mg) was dissolved in benzene (5 ml) and heated under reflux under N_2 for 24 hr. TLC examination showed the presence of **9** and unchanged catharanthine.

Catharanthine hydrochloride in xylene at 140°. Catharanthine hydrochloride (240 mg) in xylene (60 ml) was heated under reflux under N_2 for 4 hr. Catharanthine hydrochloride, which is insoluble *in xylene*, formed a yellow gum on the wall of the flask as the reaction proceeded. The cooled mixture was extracted with MeOH-2N HCl (1 : 1) and the aqueous phase then neutralized with 2N NaOH and extracted with $CHCl_3$. Evaporation of the dried extract yielded a gum (131 mg) which showed many spots on TLC in ether-hexane (1 : 1). The following authentic compounds were found to correspond in R_f and CAS color spray behavior to spots in this extract: Ψ-catharanthine (**7**), carbazole (**9**) 3-ethylpyridine, and catharanthine.

Catharanthine heated dry at 180°. Catharanthine free base (47 mg) was heated under N_2 with no solvent at 180° for 1 h. The resulting dark brown residue was dissolved in MeOH and subjected to chromatography on three 20 × 20 cm × 0·5 mm silica gel PF_{254} plates developed once in

ether-hexane (1:1). The two main bands under UV light had very similar CAS color spray behavior (blue grey → mauve overnight) and were removed separately and eluted with $CHCl_3$-MeOH (9:1). The more polar of the two bands yielded a crystalline solid (9 mg) which was identified by TLC, mass and UV spectroscopy as **9**.

The less polar band also yielded a crystalline solid (3 mg) which, from its mass spectrum (base peak 211 *m/e*) and UV spectrum [λ_{max} (EtOH) 237, 248 (sh), 298, 315 (sh), 329 nm (sh)] is formulated at **10**.

Tabersonine in xylene at 140°. Tabersonine free base (3·4 mg) was heated under reflux under N_2 in xylene (1 ml) for 1–½ hr. Mainly unchanged tabersonine could be detected by TLC after this time.

Ψ-Catharanthine in xylene at 140°. Ψ-Catharanthine (10 mg) was heated under reflux under N_2 in xylene (5 ml) for 24 h. Mainly unchanged Ψ-catharanthine could be detected by TLC after this time.

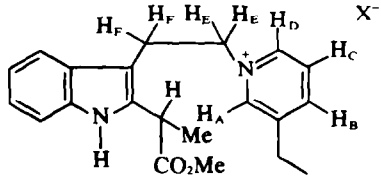
Tabersonine in xylene at 205°. Tabersonine (1·7 mg) in xylene (0·5 ml) was sealed under vacuum in a tube and heated at 205° for 1–½ hr. TLC examination of the products indicated unchanged tabersonine present as well as many other minor products. The mixture was subjected to chromatography on one 20 × 20 cm × 0·5 mm silica gel PF_{254} plate developed once in ether: hexane (1:1). The band corresponding in TLC properties with **9** was removed and eluted to give material (0·1 mg) which had an identical UV spectrum to that of **9** isolated from the previous experiment with catharanthine.

Ψ-Catharanthine in xylene at 175°. Ψ-Catharanthine (10 mg) in xylene (5 ml) was sealed in a tube under vacuum and heated at 175° for 7 h. TLC examination indicated unchanged Ψ-catharanthine and many products. It was possible to isolate by chromatography and identify **9** by UV spectroscopy.

Catharanthine in refluxing methanol. Catharanthine free base (50 mg) was dissolved in MeOH (7 ml) and heated under reflux under N_2 for 3 weeks. TLC examination indicated the major components to be **7** and catharanthine. The soln was evaporated to give a gum (43·6 mg) which was subjected to chromatography on two 20 × 20 cm × 0·5 mm silica gel PF_{254} plates developed twice in ether-hexane (1:3). The two main bands were removed and eluted separately to give (−)-Ψ-catharanthine (16 mg), λ_{max} (MeOH) 295 and 327 nm; ORD (EtOH) 345 (O-5500), 300 (+ 10,500), 275 (+ 3500), 250 (+ 8100). (The ORD is in the same sense as but only about 10% in magnitude of that of (−)-tabersonine), and catharanthine (22·5 mg). The catharanthine was dissolved in MeOH and treated with ethereal HCl soln whereupon the hydrochloride crystallized as needles, λ_{max} 283 and 292 nm; ORD (MeOH) 291 (O + 7000), 287 (+ 5200), 283 (+ 6000), 255 (− 7200). (The ORD curve was superimposable on that of authentic catharanthine hydrochloride).

Catharanthine in methanol at 150°. Catharanthine free base (800 mg) was dissolved in MeOH (80 ml) and the soln sealed under vacuum in tubes which were then heated at 150° for 2 h. The recombined MeOH soln was evaporated to dryness and partitioned between ether and water. Evaporation of the dried ether extract gave a foam (113 mg) while evaporation of the aqueous phase gave a yellow gum (353 mg).

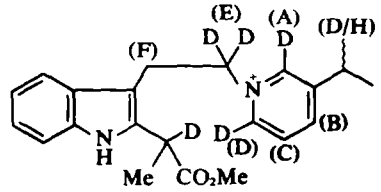
The water soluble fraction was subjected to chromatography on eleven 20 × 40 cm × 0·5 mm silica gel PF_{254} plates developed twice in $CHCl_3$-MeOH (17:3). The main band was removed and eluted with $CHCl_3$-MeOH (17:3) and yielded **12** as a yellow gum (241 mg). The gum appeared to be homogeneous by TLC but repeated attempts to crystallize the compound as a chloride, bromide, perchlorate, picrate or picrolonate salt failed. The compound had the following physical characteristics: λ_{max} (EtOH) 219, 269, 283 (sh), 291 nm; $[\alpha]_{500-600}$ 0·0° (EtOH); IR ν_{max} 1720 cm^{-1}; NMR (100 MHz, D_2O + 1% DSS) τ 1·65, 1H, d, $J_{D,C}$ = 6Hz (H_D); 1·88, 1H, d, $J_{B,C}$ = 8Hz (H_B); 2·16, 1H, s (H_A); 2·29, 1H, q, $J_{C,B}$ = 8Hz $J_{C,D}$ = 6Hz (H_C); 2·50–3·20, 4H, m (Ar-H); 5·24, 2H, t, $J_{E,F}$ = 5Hz (H_E, H_E); 6·03, 1H, q, J = 8Hz (-CHCH$_3$); 6·25, 3H, s (CO_2CH_3); 6·59, 2H, t, $J_{F,E}$ = 5Hz (H_F, H_F); 7·50, 2H, q, J = 8Hz (-CH_2CH$_3$); 3·52, 3H, d, J = 8Hz (-CHCH$_3$); 9·13, 3H, t, J = 8Hz (-CH_2CH$_3$).



The ether soluble fraction (see above), which appeared by TLC to be a complex mixture of products containing Ψ-catharanthine and **9**, was combined with a similar fraction from a repeat experiment to yield a total of 691 mg. This material was chromatographed on silica gel (30 g) and elution with ether-MeOH (9:1) gave Ψ-catharanthine (254 mg). Further elution with $CHCl_3$-MeOH (4:1) gave a residue (386 mg). The Ψ-catharanthine (254 mg) was recrystallized three times from MeOH to give prisms (98 mg) m.p. 110–114°, $[\alpha]_{320-440}$ (MeOH) 0·0°.

The residue (386 mg) was subjected to chromatography on ten 20 × 40 cm × 0·5 mm silica gel PF_{254} plates developed three times in ether-hexane (1:3). The band corresponding in TLC properties with **1** was removed and eluted with $CHCl_3$-MeOH (9:1) to yield material (50 mg) which was shown to be **9** by UV and mp.

Catharanthine in d_1-methanol at 150°. Catharanthine free base (100 mg) was dissolved in d,-methanol (10 ml), sealed under vacuum and heated at 150° for 2 h. The soln was evaporated and the residue partitioned as before into an aqueous extract (71 mg) and an ether extract (28 mg). The signals in the NMR spectrum of the aqueous extract (deuterated salt, see **i** below) had changed in the following manner: τ 1·65, exchanged; 1·88, 1H, d, $J_{B,C}$ = 8Hz (H_B); 2·16, exchanged; 2·29, 1H, d, $J_{C,B}$ = 8Hz (H_C); 2·80–3·20, 4H, m (Ar-H); 5·24, exchanged; 6·03, exchanged; 6·25, 3H, s (CO_2CH_3); 6·59, 2H, s (H_FH_F); 7·50, partially exchanged, ~1H, q, J = 8Hz (-CH_2CH$_3$); 8·52, 3H, s (-CDCH$_3$); 9·13, 3H, m (-CH_2CH$_3$).



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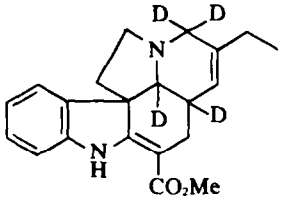
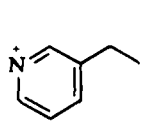
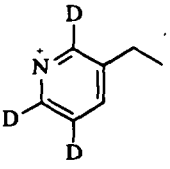
The ether extract was subjected to chromatography on two 20 × 20 cm × 0·5 mm silica gel PF_{254} plates developed twice in ether-hexane (1:3). The band corresponding to Ψ-catharanthine was eluted to afford a gum (2·4 mg). Mass spectroscopic examination of this material and au-

thentic ψ-catharanthine showed that four deuterium atoms had been incorporated (considerable *m/e* 340 peak in the labeled material; molecular ion peak for authentic compound: *m/e* 336). The shift of the *m/e* 107 peak to 110 and of the *m/e* 122 peak to 126 indicates that the four deuteria are located as shown:

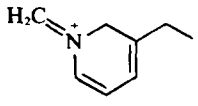




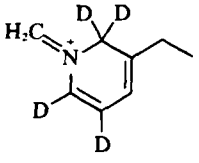
m/e 107



m/e 110



m/e 122



m/e 126

Salt (**12**) *in methanol at* 150°. The salt **12** (10 mg) was dissolved in MeOH (4 ml), sealed under vacuum and heated at 150° for 2 h. TLC examination of the resultant solution showed only unchanged salt present and none of the ether soluble products from the catharanthine-MeOH experiment detectable. Hence the salt is stable under the conditions of its generation and is not the precursor of the ether soluble products.

Salt heated dry at 175°. The salt **12** (10 mg) was heated in a sealed tube with no solvent at 175° for 30 min. The residue was subjected to chromatography on one 20 × 20 cm × 0·5 mm silica gel PF_{254} plate developed once in ether-hexane (1 : 1). The one major band observed in this system was removed, eluted and shown to be **9** by comparison with an authentic sample.

Catharanthine and salt (**12**) *heated dry at* 150°. Samples of catharanthine free base and the salt (**12**) were sealed separately in tubes with no solvent and heated at 150° for 2 h. TLC examination of the products indicated considerable conversion of catharanthine to **9** has occurred under these conditions but that the salt is essentially unchanged, only a trace amount of the carbazole being detectable. This indicates that carbazole formation from catharanthine probably does not occur by way of **12** as an intermediate.

Tabersonine in methanol at 145°. Tabersonine free base (10 mg) was dissolved in MeOH, sealed under vacuum and heated at 145° for 2 h. TLC examination of the products could detect no **12** but indicated a good yield of **9**. (The carbazole (1·2 mg) was isolated by chromatography and shown to be identical to 1 - methyl - 2 - hydroxycarbazole). These observations contrast with the behavior of catharanthine and may reflect the relative ease with which the respective retro-Diels-Alder products can undergo the internal hydrogen transfer and become pyridinium rather than eliminate 3-ethylpyridine and give the carbazole.

Dihydrosecodine (**16**). The salt **12** (250 mg) was dissolved in MeOH (10 ml) and cooled in ice while an excess of $NaBH_4$ was added to the stirred soln. The mixture was then partitioned between water-$CHCl_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to yield a gum (215 mg).

This material was subjected to chromatography on six 20 × 40 cm × 0·5 mm silica gel GF_{254} plates developed once in $CHCl_3$-MeOH (19 : 1). The main band was removed and eluted with $CHCl_3$-MeOH (9 : 1) to yield a pale yellow gum (154 mg) which crystallized on standing. Two recrystallizations from ether gave **16** (74 mg) as needles, m.p. 122–124°, $[\alpha]_{300-600\,nm}$ 0·0° (MeOH); λ_{max} (MeOH) 225 (ε 31200), 277 (8080 sh), 284 (8850), 292 nm (7820); IR ν_{max} (KBr 1730, 1430, 1180, 1160, 850, 745 cm^{-1}. Mass spectrum: *m/e* 340 (7%), 124 (100%), no other peak greater than 5%; NMR (100 MHz, $CDCl_3$) τ 1·48, 1H, broad s (NH); 2·40–3·10, 4H, m(Ar-H); 4·55, 1H, septet, $J_{B,C}$ = 6Hz, $J_{B,A_1} = J_{B,K_1} = J_{B,K_2}$ = 3Hz (H_B); 5·93, 1H, q, J = 7·5Hz (-CHCH$_3$); 6·32, 3H, s (CO_2CH_3); 7·01, 4H, m (H_{A_1}, H_{A_2}, H_{F_1}, H_{F_2}); 7·38, 4H, m (H_{K_1}, H_{K_2}, H_{D_1}, H_{D_2}); 7·80, 2H, m (H_C, H_C); 8·02, 2H, q, J = 8Hz (-CH_2CH$_3$); 8·46, 3H, d, J = 7·5Hz (-CH-CH_3); 8·98, 3H, t, J = 8Hz (CH_2CH_3). (Found: C, 74·1; H, 8·4; N, 8·1. $C_{21}H_{28}O_2N_2$ requires: C, 74·1; H, 8·3; N, 8·2%). Comparison of this sample (TLC in three solvent systems; NMR, mass spectrum, IR, UV) with the amorphous naturally occurring 16,17-dihydrosecodine $[\alpha]_D^{22°}$ EtOH + 11° showed complete identity (except for optical activity). We thank Drs. G. F. Smith and G. A. Cordell (Manchester University) for making the TLC comparison and exchanging data.

Tetrahydrosecodine. Dihydrosecodine (48 mg) was dissolved in EtOAc (10 ml) and hydrogenated at 1 atm. and room temp over 10% Pd/C for 3 h. The soln was filtered through celite and the filtrate was evaporated under reduced pressure to give tetrahydrosecodine (48 mg) identical with the sample prepared by catalytic reduction of stemmadenine acetate (see previous paper[6b] for spectroscopic properties).

Acknowledgement—This work was supported by a grant from the National Institutes of Health (CA 11095-01-04).

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