STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. VIII[1]. THE COUPLING OF SEVERAL 3α,4α-SUBSTITUTED CATHARANTHINE DERIVATIVES WITH VINDOLINE.

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A detailed study involving the Polonovski-type coupling of vindoline with 4α-hydroxydihydrocatharanthinic acid lactone (1) and 3α,4α-epoxydihydrocatharanthine (9), two catharanthine derivatives prepared earlier in our laboratories, is described.

In Part IV of this series[2] we described a series of investigations which provided various novel oxygenated catharanthine derivatives. We indicated at that time that such intermediates could be important in the syntheses of various bisindole alkaloids and closely related analogues. Indeed, in a more recent study[1], we demonstrated the use of one of these compounds, namely 3β,4β-epoxydihydrocatharanthine in the synthesis of leurosine. This latter

study provided an unambiguous proof for the α-orientation of the oxirane function in that alkaloid. We would now like to discuss some of the more recent experiments which involve the utilization of two other oxygenated catharanthine derivatives, 4α-hydroxydihydrocatharanthinic acid lactone (1) and 3α,4α-epoxydihydrocatharanthine (9).

In accord with our previously established conditions[3,4], the lactone 1 was reacted with a one-mole equivalent of m-chloroperbenzoic acid in methylene chloride at low temperature (-25 to -30°C) and the resulting N-oxide intermediate coupled with vindoline in the presence of trifluoroacetic anhydride (-50°C). The resulting mixture, after treatment with sodium borohydride, provides upon chromatographic separation, three products which on the basis of extensive spectroscopic analyses[5] could be assigned the structures 2, 3 and 4.

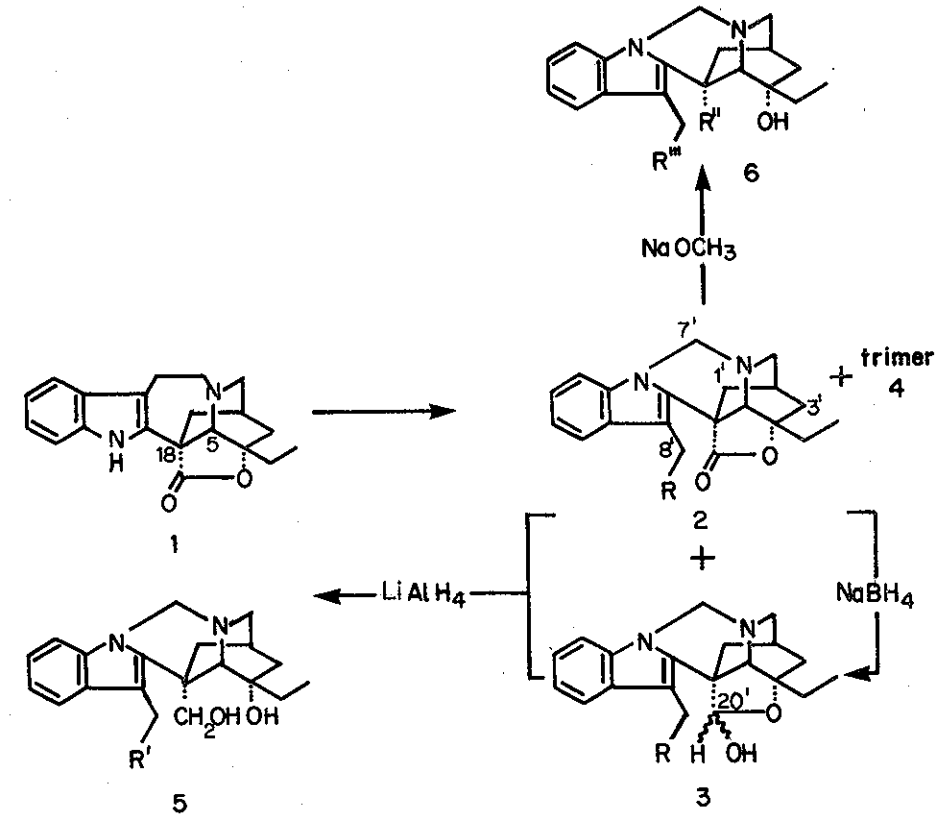
The major component (62% yield) was assigned the interesting bisindole structure 2 [IR: no NH, 1775, 1740 cm^{-1}; PMR: δ 6.6 (s, 1H, C_{14}-H, vindoline portion, see R), 6.09 (s, 1H, C_{17}-H, vindoline portion), 5.73 (m, 1H, C_7-H, vindoline portion), 5.38 (s, 1H, C_4-H), 5.13 (d, 1H, J = 10 Hz, C_6-H), 4.95 (AB quartet, 2H, J = 12 Hz, $C_{7'}$-CH_2), 4.43 (AB quartet, 2H, J = 16 Hz, $C_{8'}$-CH_2), 3.83 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 2.62 (s, 3H, NCH_3), 2.0 (s, 3H, $OCOCH_3$), 1.03 (t, 3H, J = 7 Hz, $C_{4'}$-$CH_2\underline{CH_3}$), 0.1 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 776 (M^+, $C_{45}H_{52}N_4O_8$), 717, 716, 702, 701, 700, 630, 629 617, 616, 615, 509, 508, 494, 323, 322, 321, 309, 308, 296, 282, 269, 267, 263, 236, 235, 234, 224, 209, 202, 200, 188, 139, 135 (base peak), 122, 121].

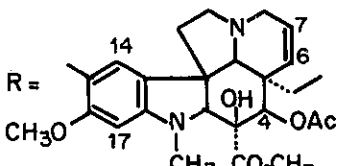
Another bisindole component (10% yield) was assigned the structure 3 [IR: no NH, 1740 cm^{-1}; PMR: δ 6.69 (s, 1H, C_{14}-H, vindoline portion, see R)

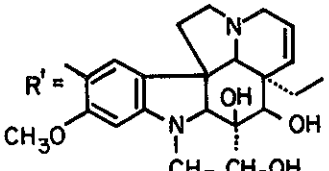
6.09 (s, 1H, C_{17}-H), 5.88 (m, 1H, C_7-H), 5.39 (s, 2H, C_4 and $C_{20'}$-H), 5.18 (d, 1H, J = 10 Hz, C_6-H), 4.97 (AB quartet, 2H, J = 12 Hz, $C_{7'}$-CH_2), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, $COOCH_3$), 2.65 (s, 3H, NCH_3), 2.03 (s, 3H, $OCOCH_3$), 1.01 (t, 3H, J = 7 Hz, $C_{4'}$-$CH_2\underline{CH_3}$), 0.25 (t, 3H, J = 7 Hz, C_5-$CH_2\underline{CH_3}$); MS: m/e 778 (M^+, $C_{45}H_{54}N_4O_8$), 776, 762, 719, 718, 702, 701, 700, 698, 660, 659, 658, 657, 644, 619, 618, 617, 512, 511, 510, 509, 497, 496, 495, 494, 481, 470, 469, 338, 324, 323, 322, 321, 310, 309, 308, 307, 283, 234, 222, 202, 200, 188, 174, 171, 154, 149, 136, 135 (base peak), 122, 121, 107].

It should be emphasized that at the outset two distinct spectral differences were noted in the spectra of components 2 and 3. One of these concerned the characteristic γ-lactone infrared absorption found in 2 which was absent in 3 while in the mass spectra, the molecular ion peak of 3 was two mass units higher than that of 2. The suspected lactone-lactol relationship shown was confirmed when 2 was reduced with sodium borohydride (methanol, $0^\circ C$) to provide 3. It was now clear that a portion of the major product 2 was being converted to 3 during the sodium borohydride treatment of the original coupling mixture.

A third component (6% yield) appears to be a trimer (4) corresponding to a structure derived from two vindoline units and one indole unit. The spectral data do not presently allow a complete structural assignment but a few salient features are noted. Thus in the ultraviolet spectrum of 4, the absorption bands due to the dihydroindole unit as observed in a normal bisindole system (for example 313 nm) are of significantly higher intensity while in the PMR spectrum, two sets of aromatic singlets (δ 6.82, 6.38, 6.08, 6.02), two N-CH_3 signals (δ 2.66, 2.64) and two methyl triplets (δ 0.28 and 0.0, J = 7 Hz) attributed to <u>two</u> vindoline units are noted in trimer 4.


NaOCH3
trimer
4
LiAlH4
NaBH4
1
2
3
5
6


R =
CH3O
OH
OAc
CH3
CO2CH3


R' =
CH3O
OH
OH
CH3
CH2OH

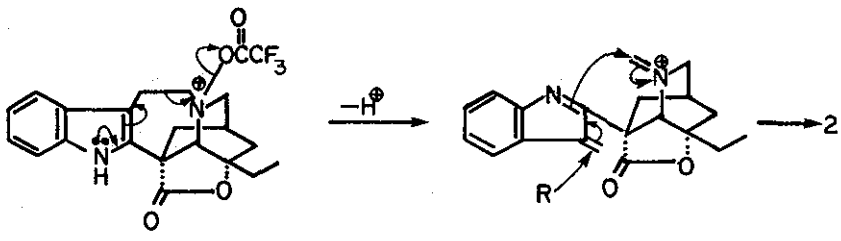
The two bisindole products 2 and 3 were clearly of further interest in this study so additional chemistry was performed to substantiate the assignments made. For this purpose the lactone 2 was reacted with sodium methoxide in methanol at room temperature, to provide the hydroxy ester 6 (R'' = $COOCH_3$; R''' = desacetylvindoline, where in R, OAc is replaced by OH) in 77% yield [IR: no γ-lactone absorption, 1720 cm^{-1}; PMR: δ 3.87, 3.84 (2s, 6H, OCH_3, C_3-$COOCH_3$), 3.54 (s, 3H, C_{18}'-$COOCH_3$), no acetyl; MS: m/e 766 (M^+, $C_{44}H_{54}N_4O_8$)]. It is of interest to note that catharanthine lactone (1) under these conditions is <u>not</u> converted to the corresponding hydroxyester thereby revealing a significant difference in reactivity when the rigid Iboga alkaloid system is intact. Also the lactol 3 is stable to these conditions, the only reaction being hydrolysis of the acetate group in 3.

Lithium aluminum hydride reduction of <u>either</u> 2 or 3 would be expected to provide the identical product and this was indeed the case. Thus when 2 or 3 were treated with $LiAlH_4$ in tetrahydrofuran at room temperature, the expected product 5 [IR: 3540, 3390 cm^{-1}, no carbonyl absorption); PMR: δ 3.86 (s, 3H, OCH_3), 2.98 (s, 3H, NCH_3), <u>no</u> acetyl or carbomethoxymethyl signals; MS: m/e 710 (M^+, $C_{42}H_{54}N_4O_6$)] was isolated in 94% yield from 2 and 60% yield from 3.

It is again of interest to note that catharanthine lactone 1 even under more severe reduction conditions (lithium aluminum hydride, refluxing THF) does <u>not</u> proceed to the corresponding diol normally expected but affords the intermediate lactol in 86% yield. This result again portrays a significant difference in reactivity between 1 and the corresponding lactone carbonyl group in the bisindole component 2.

It is important to emphasize at this point that all of our previous

investigations with various catharanthine derivatives[1,3,4] in the Polonovski-type coupling reactions have provided products resulting from fission of the C_5-C_{18} bond (see 1) in the catharanthine system. This is the <u>first</u> instance in our study in which an alternative fragmentation according to pathway, 7 → 8 → 2, has been observed. However this type of fragmentation has been described from the independent investigations of the French group[6].



7 8

In continuing our investigations in this area we have studied the coupling of the known[2] 3α,4α-epoxydihydrocatharanthine (9) with vindoline in the hope that these studies would provide the bisindole product isomeric at the oxirane function with that of leurosine obtained in earlier experiments involving the coupling of the 3β,4β-epoxydihydrocatharanthine derivative with vindoline[1]. However in spite of numerous experiments involving the coupling of 9 with vindoline under various conditions, the corresponding bisindole system which would result from the fragmentation of the C_5-C_{18} bond in 9 was never observed. Under optimum conditions, which involve coupling of vindoline with the N-oxide derivative of 9 (9 reacted with <u>m</u>-chloroperbenzoic acid, -20°C), at low temperature (-50°C) in the presence of trifluoroacetic anhydride, only one major bisindole product was isolated in 51% yield. The spectral data [IR: no

NH, 1740 cm^{-1}; PMR: δ 6.48 (s, 1H, C_{14}-H, vindoline portion), 6.12 (s, 1H, C_{17}-H, vindoline portion), 5.78 (m, C_7-H, vindoline portion), 5.39 (s, 1H, C_4-H), 5.02 (AB quartet, 2H, J = 11 Hz, $C_{7'}$-CH_2), 3.95 (s, 3H, OCH_3), 3.81 (s, 3H, $COOCH_3$), 3.62 (s, 3H, $COOCH_3$), 2.02 (s, 3H, $OCOCH_3$), 0.98 (t, 3H, J = 7 Hz, $C_{4'}$-$CH_2\underline{CH_3}$), 0.04 (t, 3H, J = 7 Hz, C_5-$CH_2\underline{CH_3}$); MS: m/e 806 (M^+, $C_{46}H_{54}N_4O_9$), 790, 737, 736, 731, 730, 718, 714, 684, 680, 658, 648, 647, 646, 645, 630, 629, 538, 351, 338, 282, 200, 188, 169, 149, 135 (base peak)] allowed the structural assignment 10 to this product. The other products isolated from this reaction are monomeric in nature and represent derivatives of catharanthine and vindoline.

9 10

In conclusion it is of interest to note that the fragmentation of the relevant bonds in the catharanthine system is clearly sensitive to the stereochemical orientation of oxygen functionality at C_3 and/or C_4. Thus in 1 and 9, where the substituents are in an α-orientation the process summarized by the sequence 7 → 8, appears essentially predominant, a marked contrast to that observed with the β-epoxy series[1] and the other C_3-C_4 non-oxygenated catharanthine derivatives[3,4]. Further studies are underway.

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