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STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. XIII[1].
A SYNTHESIS OF CATHARINE.

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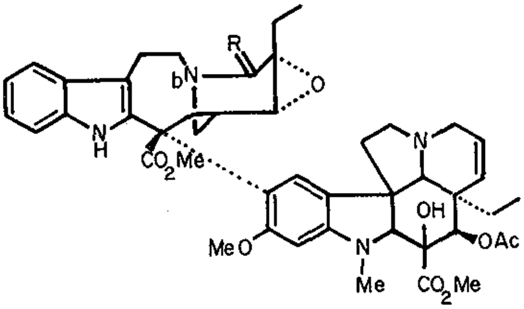
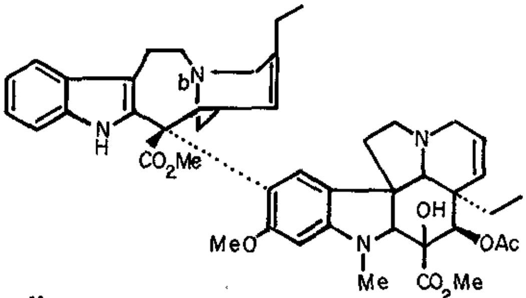
Oxidation of leurosine with t-butyl hydroperoxide provided the first synthesis of the alkaloid catharine. Some evidence for a radical promoted mechanism is given. A correction to an earlier structural assignment is made.

In an earlier report[2] the overoxidation product, formed in the preparation of leurosine I from 3',4'-dehydrovinblastine II, was assigned the lactam structure III. This assignment, based on spectroscopic data and plausible mechanistic grounds, has now been shown to be incorrect.

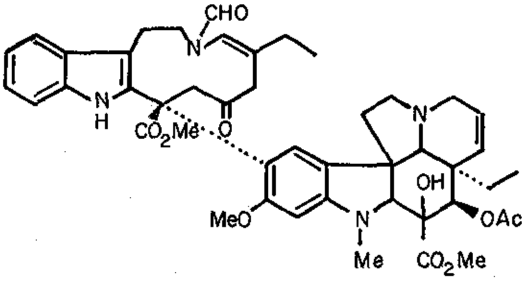
Some years ago, the Lilly group[3] isolated a series of bisindole alkaloids from Catharanthus roseus, but the structures of a number of these remained unknown until recently. Comparison of the spectral data of these natural bases[4] with that from various synthetic bisindole systems proved fruitful. In fact the product previously described as III was shown to be identical with the alkaloid catharine IV, the structure of which had been established by X-ray analysis[5].



I, $R=H_2$
III, $R=O$
V, $R=H_2, N_b$-oxide



II,
VI, N_b-oxide



IV

In the earlier work[2], IV was formed in low yield by the oxidation of either I or II with t-butyl hydroperoxide in a medium of tetrahydrofuran and aqueous trifluoroacetic acid. In view of the conditions employed, a radical and/or acid catalysed mechanism for the formation of IV seemed possible. However more recent investigations have shown that the absence of acid does not prevent the formation of catharine from either I or II (Table 1). On the other hand, reaction of I in the dark and in the presence of a radical inhibitor did not produce catharine but gave only the corresponding N_b-oxide V. Furthermore, neither pleurosine V, nor the corresponding N_b-oxide VI reacted under the original conditions. These preliminary results suggested leurosine, but not pleurosine, to be an intermediate in a radical type oxidation not involving acid catalysis.

TABLE 1

Substrate	Conditions	Products
II	THF/H_2O/TFA/t-BuOOH	I, IV
I	THF/H_2O/TFA/t-BuOOH	IV
VI	THF/H_2O/TFA/t-BuOOH	No Reaction
V	THF/H_2O/TFA/t-BuOOH	No Reaction
I	THF/H_2O/TFA/t-BuOOH/inhibitor†/dark	V
II	THF/H_2O/t-BuOOH	I, IV
I	THF/H_2O/t-BuOOH	IV
I	t-BuOOH/CH_2Cl_2	IV
II	t-BuOOH/CH_2Cl_2	Complex mixture, IV
I	t-BuOOH/CH_2Cl_2/inhibitor†/dark	No Reaction
I	CH_2Cl_2 only	No Reaction

† 3-t-Butyl-4-hydroxy-5-methylphenyl sulphide.

Leurosine was subsequently shown to be converted (48% yield) to IV by the action of t-butyl hydroperoxide in dichloromethane. The synthetic catharine had mp (acetone) 213-215° (lit.[5] 213-215°); mp (ethanol)[6] 162-166° (lit.[3] 171-175°), undepressed on admixture with an authentic sample; $[\alpha]_D$ -49° (c, 0.7, $CHCl_3$) (lit.[3] -51°). The ^{1}HNMR, UV, IR and mass spectra were exactly superimposable with those of authentic material.

The above-mentioned oxidations have provided a synthesis of catharine. However, in view of the facile oxidation of leurosine to IV, the classification of the latter as a natural product may deserve some reconsideration. The mechanism for the formation of catharine remains ambiguous.

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6. In our hands an authentic sample had mp 164-168°.

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