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PERIVINE*

Marvin Gorman and Janice Sweeny

Lilly Research Laboratories, Eli Lilly and Company

Indianapolis, Indiana

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Perivine[1] (I), $C_{20}H_{22}N_2O_3$,** represents a major alkaloid of the "B" fraction[2] obtained from the leaves of Vinca rosea Linn (Catharanthus roseus G. Don). An examination of the ultraviolet spectrum (FIG. I) of this base indicated that it was a member of the group of 2-acyl indole alkaloids,[3] which have recently been shown to form "dimeric" alkaloids such as voacamine[4]. In this communication we wish to show that perivine is the N_b-demethyl derivative of vobasine[5] (II) and to describe its conversion into normacusine-B,[6] a naturally occurring pentacyclic indole alkaloid.

Reduction of perivine (KBH_4-methanol) yielded the corresponding alcohol, perivinol (III), $C_{20}H_{24}O_3N_2$, m.p. 183°C, $[\alpha]_D$ + 30.2° ($CHCl_3$) characterized by an ultraviolet spectrum typical of a 2,3-disubstituted indole. The n.m.r. spectrum of perivine, run in several solvents, was poorly resolved due

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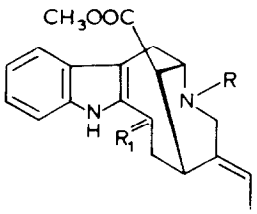
**Consistent microanalytical data or unambiguous mass spectral molecular weights have been obtained for all compounds whose empirical formulae are given.

to intermolecular association; however, that of perivinol was well defined. Examination of this spectrum indicated that perivinol was closely related to vobasinol.[5] The presence of a carbomethoxyl function magnetically shielded by the indole ring was indicated by the three proton singlet at 2.45 δ which disappeared after $LiAlH_4$ reduction. An ethylidene group with methyl doublet at 1.78 δ, and a vinyl proton quartet at 5.48δ was evident in both compounds. The major differences in the spectra of these substances were due to the presence of an N-methyl signal (2.54 δ) in vobasinol which was absent in perivinol. Treatment of perivine with acetic anhydride and pyridine led to the formation of a neutral compound which possessed a new band in the infrared at 6.05 μ, suggesting further that perivine possessed a secondary basic nitrogen. When perivine was caused to react with excess methyl iodide followed by treatment of the resulting quaternary salt with mild alkali (most conveniently by slurrying with IRA401 (OH^-) resin in methanol-water) a methine was obtained identical to the one found from vobasine under similar conditions.[5]

Final proof of the relationship between the two alkaloids was afforded by the direct reductive methylation of perivine (1:1 formalin-dioxane in the presence of hydrogen and 10% Pd/C as catalyst) which yielded vobasine.*

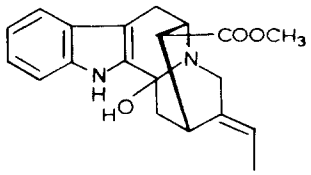
*Reduction of the ethylidene double bond in perivine with Raney Ni at 80°/1300 p.s.i. in EtOH afforded a single dihydro-isomer that could be methylated to yield the alkaloid dregamine, a dihydrovobasine.



I. R = H, R_1 = O

II. R = CH_3, R_1 = O

III. R = H, R_1 < H / OH



IV.

It was shown previously[5] that the carbomethoxyl function of vobasine could be epimerized by alkali to yield a new base epivobasine in which the n.m.r. signal due to the ester methyl no longer showed the enhanced shielding mentioned above. The ultraviolet spectrum (FIG. II) of the new compound was essentially unaltered by this epimerization. When this reaction was carried out on perivine (3 hours, room temp., sodium methoxide-methanol), the resulting substance, epiperivine (IV), $C_{20}H_{22}N_2O_3$, m.p. 143-145°C $[\alpha]_D$ + 39.4 ($CHCl_3$), showed the corresponding shift of the methyl signal in the n.m.r. (to 3.88 δ). An examination of the ultraviolet spectrum (FIG. I) revealed, however, that the 2-acyl indole chromophore absorption had practically disappeared, and the resulting compound appeared to be a 2,3-disubstituted indole. When epiperivine was acetylated as above, a neutral N-acetyl derivative was obtained with a typical 2-acyl indole spectrum. Reduction of epiperivine with KBH_4-methanol afforded epiperivinol, $C_{20}H_{24}O_3N_2$, $[\alpha]_D$ - 36.2 ($CHCl_3$), hydrochloride, m.p. 215-217°C. Therefore, epiperivine exists primarily in the

carbinol-amine form. The above conclusion is supported by pK_a' values obtained (Table I) for the natural and epi- compounds.

TABLE I: pK_a' in 66% DMF

Perivine	7.7	Vobasine	6.95
Epiperivine	6.5	Epivobasine	7.05

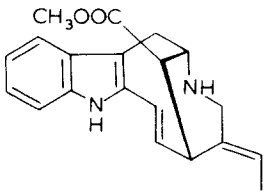
A careful comparison of the ultraviolet spectra of perivine and vobasine (FIG. I and II) indicates that in the former there is a shoulder at 227 mμ, most likely due to a small amount of carbinolamine form in perivine.

This evidence of a transannular interaction in perivine, but not in vobasine, suggested that it might be possible to cyclize the corresponding alcohols to pentacyclic substances even though attempts at this had failed[5] with vobasine derivatives. When perivinol was refluxed in glacial acetic acid under nitrogen,* two new substances were obtained which could be separated by chromatography over alumina. The minor component (V) showed an ultraviolet spectrum similar to those of uleine[7] and tabernoschizine.[7] This is undoubtedly the α-vinyl indole formed by elimination of water from perivinol. The n.m.r. spectrum showed two new vinyl protons (6.48 δ, 5.78 δ) of the proper multiplicity for such a structure (V).

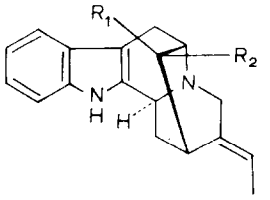
The major product (yield 40%), $C_{20}H_{22}O_2N_2$, m.p. 225-227°C, $[\alpha]_D$ + 2.9° ($CHCl_3$) was clearly the transannular cyclization product (VI). The ester methyl group still showed enhanced shielding (3 proton singlet 3.05 δ), but to a lesser extent than in the tetracyclic compounds. When this pentacyclic

*This reaction failed with mineral acids under a variety of conditions.

ester was treated under the conditions which epimerized perivine, the resulting product (methyl ester signal 3.78 δ) was found to be identical with dehydroxymethyl akuammidine (VII)[8] by comparison with a sample from akuammidine.* Reduction of this substance with $LiAlH_4$ yielded normacusine-B (VIII).[8]



V.



VI. R_1 = $COOCH_3$, R_2 = H

VII. R_1 = H, R_2 = $COOCH_3$

VIII. R_1 = H, R_2 = CH_2OH

The structures of normacusine-B and akuammidine are known from x-ray[9] studies, and thus those of perivine and other compounds described herein are as shown.

It has been found that reaction of vobasinol with the activated aromatic ring of voacangine in the presence of acid yields the alkaloid voacamine.[4] Because of the resemblance of voacamine to the dimeric Vinca alkaloids,[10] it was of interest to carry out a similar reaction between perivinol and vindoline.[10] Equimolar quantities of these substances reacted (methanolic hydrogenchloride, reflux) to yield a new

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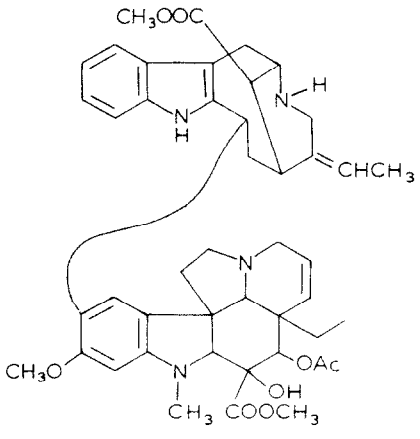
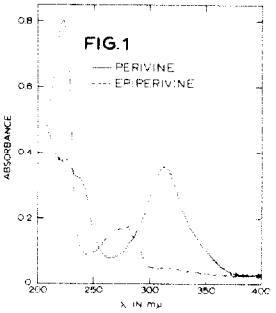
*We wish to thank Prof. Le Men, Ecole Nationale, Reims, France, for the comparison sample. When the identical reaction was carried out on epiperivinol, the analogous two substances were obtained. The pentacyclic derivative was found to be, as expected, dehydroxymethyl akuammidine.

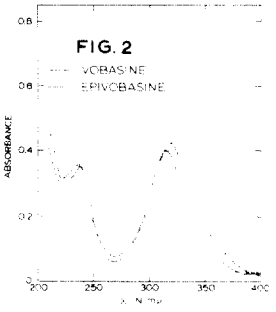
substance, perivindoline. Perivindoline could be purified through gradient pH separation[11] and the crystalline sulfate prepared, m.p. >300°C. A comparison of titration molecular weights, ultraviolet spectra and infrared spectra of the new dimeric substance with those of the starting materials and other dimeric alkaloids[11] indicated that perivindoline had structure IX. The n.m.r. spectrum was also in full agreement with this formulation.

Perivindoline was found to be inactive against the P-1534 leukemia, a test very sensitive to the biological properties of vinblastine and vincristine.[11] It is of interest to note that to date no perivinol type dimeric alkaloids have been found to occur in Vinca rosea Linn., although vindoline and perivine are major alkaloids[11] of this plant.



IX





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