Short Communications

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PARTIAL SYNTHESIS OF $\triangle_{15-20}$-ANHYDRO VINBLASTINE *

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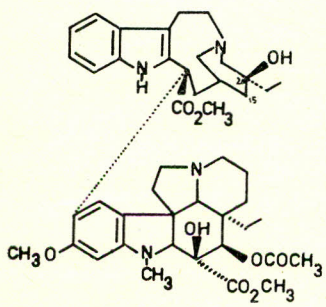
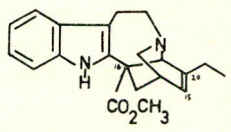
Vinblastine[1,2] (VLB)(I) is an oncolytic binary indole alkaloid and has been found to be active in a wide variety of neoplasms. It is particularly useful in the treatment of Hodgkins disease and choriocarcinoma.[3] However, its minute occurrence in *Vinca rosea* plants poses a serious problem to the pharmaceutical industry, and much attention has consequently focussed on its synthesis. We have previously described the first synthetic approaches to these binary alkaloidal systems[4–7] The synthesis of VLB itself has however eluded the efforts of many workers in the field so far.



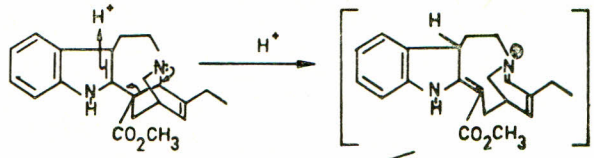
Vinblastine (VLB)
(I)

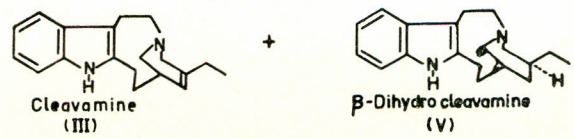


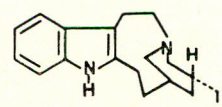
Catharanthine
(II)

Catharanthine(II)[7] is a major pentacyclic *Iboga* alkaloid in *Vinca rosea*. Examination of the structure of VLB shows that it consists of a tetracyclic indole moiety combined to a pentacyclic *Aspidosperma* alkaloid, vindoline. The nonoccurrence of such tetracyclic indole moieties in *Vinca rosea* led us to suggest previously that VLB and other similar binary indole alkaloids may be biosynthesized by the attack of vindoline on catharanthine-like pentacyclic compounds.[9] Such an attack at C-16 would be accompanied by the cleavage of C_{16}–C_{21} bond with the generation of the nine-membered ring found in the indole moiety of VLB.

In an attempt to verify this hypothesis, catharanthine was chosen as the starting point. It has been demonstrated that when catharanthine is refluxed in acid, it affords the tetracyclic cleavamine (III) α-and β-dihydro cleavamines, (IV) and (V), and decarbomethoxycatharanthine.[10,11]







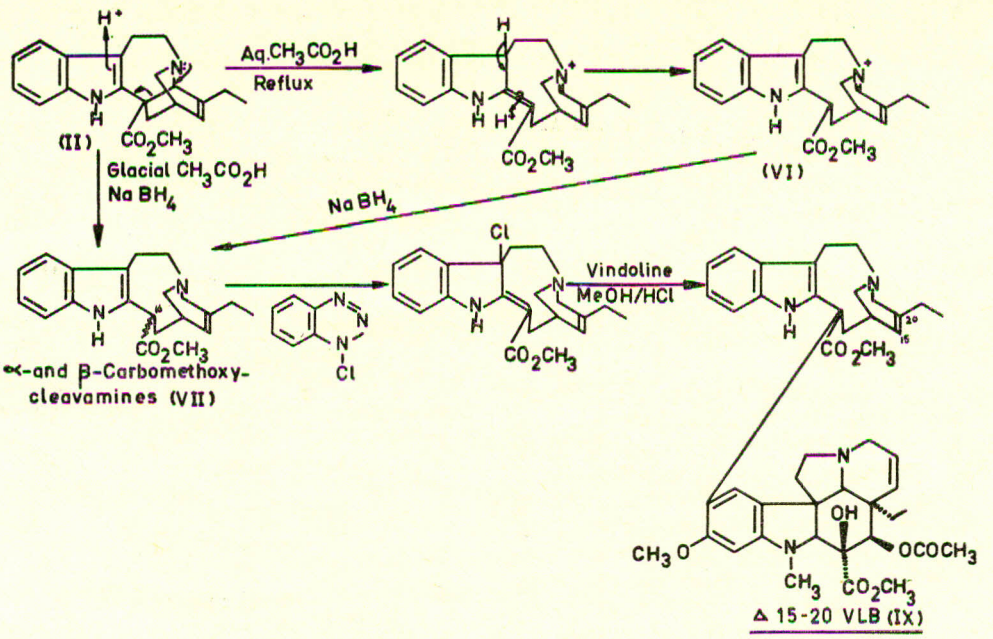
Both Neuss and Kutney have independently proposed mechanisms to account for the formation of the tetracyclic cleavamine molecules from catharanthine which involve the intermediacy of the ion (VI).[10,11] It seemed attractive therefore to attempt to reductively trap this ion with the object of obtaining 16-methoxycarbonyl cleavamine directly from catharanthine. It is evident that hydration or some other chemical manipulation of this molecule could then lead to 16-methoxycarbonyl velbanamine, the indole moiety of VLB.

When catharanthine was refluxed in aqueous acetic acid, a polar water soluble quaternary salt was obtained. Reduction of this with sodium borohydride afforded the two epimeric α-and β-carbomethoxycleavamines, m.p. 123°C (VII). The product possessed an indolic UV spectrum and showed an ester carbonyl in its IR spectrum. The mass spectrum showed the presence of the molecular ion at m/e=336 and a predictable cleavage fragmentation pattern. Better yields (over 80%) were obtainable when it was directly reduced in glacial acetic acid with portion wise addition of excess sodium borohydride.†

When 16-carbomethoxycleavamine (VII) was treated with t-butyl hypochlorite or *N*-chlorobenzotriazole,[12] it was completely transformed to the chloroindolenine (VIII). Treatment of the chloroindolenine in methanolic hydrogen chloride with vindoline afforded the binary substance,

* The numbering system used in this communication is that proposed by J. LeMen and W.I. Taylor, Experientia, **2.**, 508 (1965).

†After this work was complete, J.P. Kutney and his coworkers have reported a similar method of preparation of 16-carbomethoxy cleavamine: J.P. Kutney, W.J. Cretney, J.R. Hadfield, E.S. Hall and V.R. Nelson, J. Am. Chem. Soc., **9**, 1704 (1970).



$\Delta_{15'-20}$–anhydrovinblastine (IX), identified by its characteristic UV spectrum and mass spectrum.

This represents the closest synthetic approach to VLB so far. Methods of hydrating the double bond of 16-methoxycarbonyl cleavamine are currently under investigation and should lead to the synthesis of VLB itself.

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CONSTITUENTS OF LAVANDULA STOECHAS LINN.
Part III*.—Spectral Studies of Lavanol

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Lavanol was isolated from *Lavandula stoechas* linn. (local name Ustukhuddus). The crystalline product, gave an R_f value of 0.437 on TLC (silica gel, 250μ plate thickness) with 30% ethyl acetate in benzene as eluting solvent. Its formula has been now determined to be $C_{30}H_{48}O_3$ on the basis of mass molecular weight studies.

The high resolution IR spectrum of lavanol taken in KBr pellet gave peaks at 3610w, 3535mi, 3525m, 3505 mi, 3475 broadi, 2980si, 2950s, 2930s, 2875ms, 2860 msi, 1717s, 1697ms, 1654wi, 1625uwi, 1480wi, 1465mi, 1452m, 1387mi, 1385m, 1375m, 1358mw, 1347w, 1320w, 1310w, 1287mw, 1280 mw, 1272w, 1245mw, 1200 mw, 1180m, 1160mw, 1140mwi, 1120m, 1110mwi, 1100mw, 1090mw, 1080mwi, 1035m, 1027m, 998m, 972mw, 965mwi, 950mw, 940wi, 922vw, 912vw, 885vw, 866vw, 855vw, 829w, 819vw, 808w, 775wi, 762mw, 715vw, 732w, 715vw, 675,w 649m, 640mw, 605w,

*Parts I and II in this series were published as follows : Part I.—Spasmolytic Principle of *Lavandula stoechas* Linn. and its pharmacylogy, Pakistan J. Sci. Ind. Res., **7** (2), 111(1964). Part II.—Isolation of a new compound faom *Lavandula Stoechas* Linn, Pakistan J. Sci. Ind. Res., 10 (3), 164 (1967).

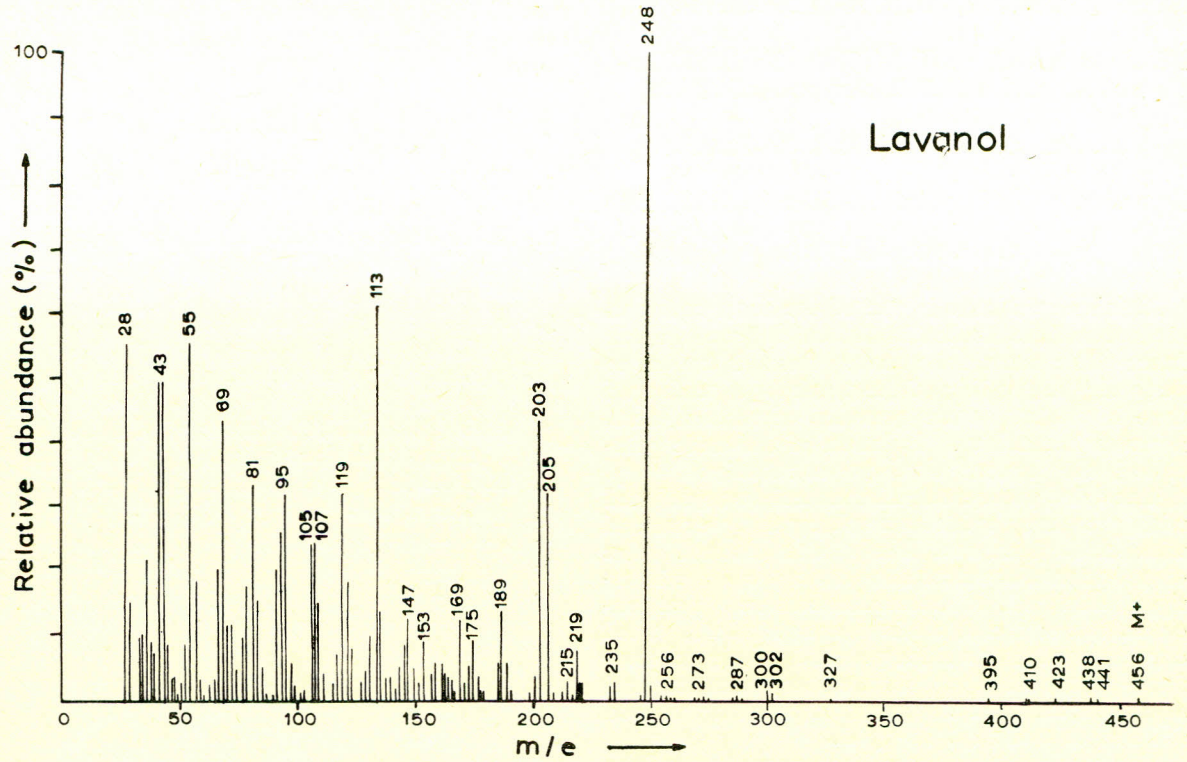

Fig. 1.—Mass spectra of lavanol.

563w, 535w, 510w cm^{-1} (s=strong, m=medium, w=weak, b=broad, v=very, i=inflexion). The hydroxyl peaks at 3610 (weak) and 1035m and 1027m cm^{-1} appear to be due to a 3 β-hydroxyl group in the molecule, which can be acetylated to give lavanol monoacetate. The ketone peak at 1717 and 1120m cm^{-1} is due to a six-membered ketone. The 1697 cm^{-1} peak of medium intensity is very likely due to a double bond in the molecule, as observed from its UV spectra which do not show any absorption maxima above 220 nm (a peak of moderate intensity appears at about 207nm). The 1697 cm^{-1} position is rather high for a double bond, but cannot be assigned to a conjugated ketone or a side-chain methyl ketone (no UV absorption maxima above 215 nm and no NMR peak near 8.0τ). The NMR peaks of lavanol taken in $CDCl_3$ solution appear at 9.42, 9.34, 9.22, 9.18, 9.10, 9.06, 9.0, 8.90, 8.85, 8.79, 8.72, 8.60, 8.52, 8.40, 8.32, 8.14, 8.10, 8.02, 7.84, 7.74, 7.43, 7.36, 6.88, 6.81, 6.30, 6.25 (doublet, 1H), 5.40, 5.28, 5.20, 5.08 (quartet, 1 or 2H), 4.78, 4.74, 4.70, 4.67 (quartet, 1H)τ.

The peak at 441 appears to be due to elimination of a methyl group. Elimination of a water molecule from the compound results in the peak at 438. The 423 and 410 peaks are indicated to be formed by elimination of water and methyl group and by elimination of water and carbon monoxide from the molecule, respectively.

Experimental

The high resolution IR spectrum was taken in KBr pellet, NMR was taken in $CDCl_3$ solution and the mass spectra was by probe injection method, and was carried out by the Physico-chemical Measurements Unit, Harwell, Didcot, U.K. The UV absorption spectra was taken in absolute ethanol.

Lavanol.—Lavanol has now been characterised as a $C_{30}H_{48}O_3$ compound (Found: C, 79.16; H, 10.14; O, 10.64%; mol wt (mass), 456. $C_{30}H_{48}O_3$ requires: C, 78.89; H, 10.59; O, 10.51%; mol wt, 456). On silica gel-G thin layer chromatography (250μ thickness) with 30% ethyl acetate in benzene, it gave an R_f value of 0.437, detected as a bright pink spot on 6N H_2SO_4 spray (after oven drying of plate) and subsequent heating over hot plate.

Lavanyl acetate reported previously is now assigned the formula $C_{32}H_{50}O_4$ (Found C, 77.33; H, 9.67, O, 13.14%; *O*-acetyl, 9.35%; mol wt (Rast), 474. $C_{32}H_{50}O_4$ requires: C, 17.06; H, 10.1; O, 12.83%, mol. wt., 498).

Acknowledgement.—The isolation work was carried out at PCSIR Laboratories, Karachi, with the help of Mr. Moquaddas Ali Khan.