A STEREOSELECTIVE SYNTHESIS OF OXYGENATED CATHARANTHINE DERIVATIVES - POSSIBLE PRECURSORS FOR BISINDOLE ALKALOIDS[1]

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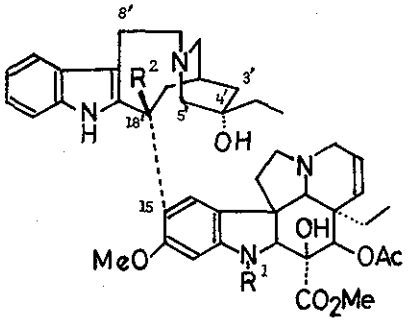
In order to synthesize the bisindole alkaloids (Ia,b) of vinblastine type, catharanthine(IIa) was converted to the lactones(IIIa,b,c) and the epoxy derivatives(IVa,b), which would be available as the precursors for the synthesis of the above natural alkaloids.

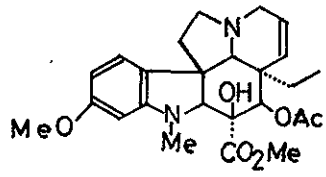
Vinblastine(Ia) and vincristine(Ib), bisindole alklaoids isolated from *Vinca rosea* Linn. (*Catharanthus roseus* G. Don), have been clinically used as two of the most important antitumor agents.[2] The successful dimerisation of catharanthine(IIa) N-oxide with vindoline(V) by the modified Polonovski reaction, has been developed by Potier,[3] who revealed that the main product possesses the same configuration at C_{18},-position as that of the natural alkaloid. This excellent method has been adopted by Kutney[4] and by Atta-ur-Rahman[5] for the syntheses of bisindole alkaloids of vinblastine type, whose works prompt-

ed us to report our recent results in this field.

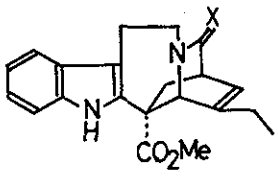
Our impending aim was directed to synthesize the oxygenated catharanthine derivatives of the favored stereochemistry, which could be available as the direct precursors for syntheses of the above alkaloids. The works in line with this principle have been independently developed by Kutney.[4]



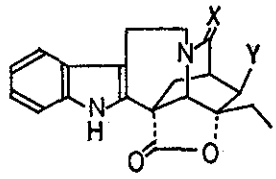
(Ia) R^1=Me, R^2=CO_2Me
(Ib) R^1=CHO, R^2=CO_2Me



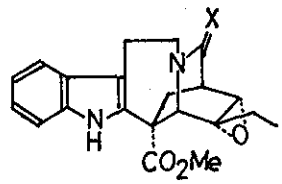
(V)



(IIa) X=H_2
(IIb) X=O



(IIIa) X=O, Y=I
(IIIb) X=O, Y=H
(IIIc) X=H_2, Y=H



(IVa) X=O
(IVb) X=H_2

The alkaloid, catharanthine(IIa), was regiospecifically oxidized with an excess of mercuric acetate in refluxing dioxane for 1 hr to afford the lactam[IIb, mp 230-232.5°, M^+ 350, IR(Nujol) ν 3250(NH), 1740(ester C=O) and 1660(lactam C=O) cm^{-1}; NMR($CDCl_3$) δ 1.10(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 3.70(3H, s, $OC\underline{H}_3$), 5.10 (1H, d, J=ca.2Hz, C(5)-H), 6.14(1H, b.d, J=7Hz, C(3)-H) and 8.16(1H, b.s, NH); 42% yield].[6] Hydrolysis of IIb by refluxing with aq. 20%KOH-MeOH for 1 hr to the corresponding carboxylic acid, followed by iodolactonization with KI_3-$NaHCO_3$, afforded the desired iodolactone[IIIa, mp 216-217°, M^+462, IR(Nujol) ν 3380(NH), 1785(lactone C=O) and 1695(lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.06(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 4.33(1H, s, C(5)-H), 4.54 (1H, d.d, J=4 & 2, C(3)-H) and 9.30(1H, b.s, NH); ca. 60% yield]. Reductive elimination of iodine was performed with tri-n-butyltin hydride[7] in refluxing tetrahydrofuran to give the lactam-lactone[IIIb, mp 197-199°, M^+336(100%), IR(Nujol) ν 3340(NH), 1770(lactone C=O) and 1690(lactam C=O); NMR($CDCl_3$) δ 1.04(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 4.20(1H, s, C(5)-H) and 9.43(1H, b.d, NH); 86% yield], which was further reduced with borane to the basic lactone[IIIc, mp 144-145°, M^+322, IR(Nujol) ν 3420(NH) and 1750 (C=O) cm^{-1}; NMR($CDCl_3$) δ 1.02(3H, t, J=7Hz, $CH_2\underline{CH}_3$) and 9.55 (1H, b.s, NH); 78% yield]. The lactone(IIIc) was hydrolyzed on standing with 5% KOH-MeOH at a room temperature for 1 hr to furnish the hydroxy-acid in a crude state, whose esterification was examined with diazomethane, but the attempt was not attainable, since relactonization readily occurred to give the initial

lactone(IIIc). Nevertheless, the lactone itself(IIIc) might be a suitable precursor for the synthesis of vinblastine(Ia) and vincristine(Ib). Therefore, the lactone was submitted to dimerization reaction with vindoline(V) according to the Potier's procedure,[3] which will be discussed in the forthcoming communication.

On the other hand, the epoxide[IVa, mp 278-280°(dec.), M^+ 366, IR(Nujol) ν3325(NH), 1738(ester C=O), 1670(lactam C=O); NMR($CDCl_3$) δ 1.00(3H, t, J=7Hz, $CH_2C\underline{H}_3$), 3.76(3H, s, $OC\underline{H}_3$), 4.78 (1H, s, C(5)-$\underline{H}$) and 8.12(1H, b.s, $N\underline{H}$); 97.5% yield] was readily obtained from the iodolactone(IIIa) on treatment with sodium methoxide in methanol at a room temperature for 2 hr. As a selective reduction of the amide carbonyl of IVa with borane was unsuccessful, IVa was treated with triethyloxonium fluoroborate($Et_3O^+BF_4^-$) and then reduced with sodium borohydride to afford the desired α-epoxide[IVb, colorless resin, M^+352, IR ($CHCl_3$) ν 3450(NH) and 1720(C=O); NMR($CDCl_3$) δ 0.96(3H, t, J=7Hz, $CH_2C\underline{H}_3$), 3.78(3H, s, $OC\underline{H}_3$) and 8.04(1H, s, $N\underline{H}$); ca. 10% yield] though in a low yield, which could be utilized as a precursor of 3',4'-epi-leurosine.[8] It must be an interesting dimer in a respect of the biological activities.

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Grant from the Mitsubishi Foundation, which are gratefully acknowledged.

REFERENCES AND NOTES

1 a) The paper was presented as a part of the lecture at the 10th International Symposium on the Chemistry of Natural Products held in Duniden, New Zealand, on August 26, 1976. b) The paper was read at the 20th Symposium on the Chemistry of Natural Products held in Sendai, on October 10, 1976.

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3 a) P. Potier, N. Langlois, Y. Langlois and F. Guéritte, J. Chem. Soc. Chem. Comm., 1975, 670. b) N. Langlois and P. Potier, Tetrahedron Letters, 1976, 1099. c) Y. Langlois, N. Langlois, P. Mangeney and P. Potier, ibid., 1976, 3945. d) N. Langlois, F. Guéritte, Y. Langlois and P. Potier, J. Amer. Chem. Soc., 1976, 98, 7017.

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The present direct oxidation of IIb with mercuric acetate should be compared with similar oxidations by other reagents (I_2 and CrO_3, etc),[6a,b,c] which were tried in this case at first. But the results were unsuccessful and complicated. Also see a similar reaction by Kutney et al.[4d]

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8 The stereochemistry of the oxirane bridge of leurosine was first suggested by Wenkert and Neuss et al. to be in 3'S,4'S configuration. [E. Wenkert, E. W. Hagaman, B. Lal, G. E. Gutowski, A. S. Ketner, J. C. Miller and N. Neuss, Helv. Chim. Acta, 1975, 58, 1560]. This was confirmed unambiguously by Potier[3c] and Kutney.[4c]

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