SYNTHETIC APPROACHES TO CATHARANTHINE, ISOXAZOLIDINE AS A POTENTIAL INTERMEDIATE.

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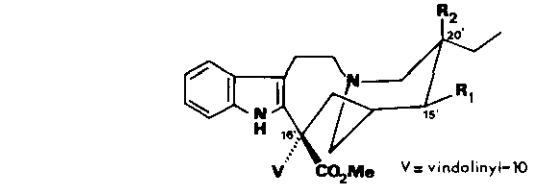
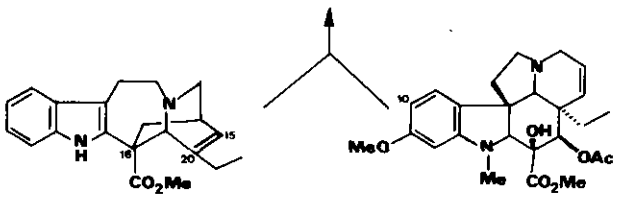
The preparation of catharanthine 3 from isoxazolidine 5 shows that this latter compound could be a good target in total synthesis.

Anhydrovinblastine 1, a key intermediate in the partial synthesis[1] and in the biosynthesis[2] of antitumour alkaloids of the vinblastine 2 group, is prepared by the coupling of catharanthine 3 and vindoline 4[1a]. This fact enhances the interest of several total syntheses of alkaloids 3 and 4[3,4].



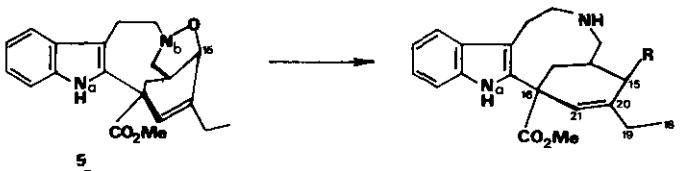
1 $R_1, R_2 = \Delta$
2 $R_1 = H$, $R_2 = OH$



3 4

The isoxazolidine 5 could be a potential intermediate in a total synthesis of catharanthine 3 based upon a nitrone cycloaddition reaction[5]. To evaluate this new approach we first examined the possibility of preparing catharanthine 3 with the isoxazolidine 5 as starting material[6].

Hydrogenolysis of isoxazolidine 5 (H_2, Pd/C 10%[6]) led quantitatively the amino alcohol 6.



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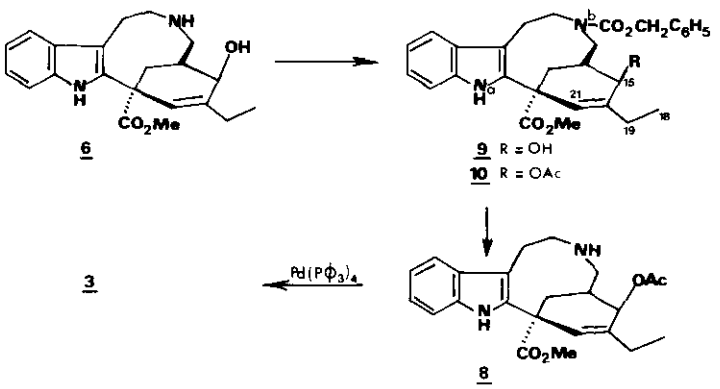
6 R = OH
7 R = Cl
8 R = OAc

Several attempts to prepare catharanthine 3 by a direct cyclisation of the amino alcohol 6 in acidic medium were unsuccessful leading only to rearranged products.

Alternatively the allylic chloride 7 (prepared with thionyl chloride and pyridine) is too unstable to be used as an intermediate. Our efforts were therefore directed towards the preparation of the corresponding amino acetate 8.

The secondary amino group of 6 was protected by formation of a benzyloxycarbonyl derivative 9 [i.r. ν CO : 1720 and 1670 cm^{-1} ; u.v. (EtOH) λ_{max} 224, 286, 294 nm ; m.s. : 488 ($M^{+\cdot}$), 429, 385, 353 ($M-CO_2CH_2C_6H_5$), 335, 305, 266, 234, 215, 171, 144, 143, 130, 91 (100%) ; p.m.r. : δ/TMS ($CDCl_3$) : 8.38 (N_a-H), 7.24 ($C_6\underline{H}_5$-CH_2 + arom.), 6.04 (C_{21}-H), 5.08 ($\underline{CH}_2$ C_6H_5), 4.55 (C_{15}-H), 3.69 (3H, s, CO_2CH_3), 1.15 (3H, t, J = 7 Hz, C_{18}-H)]. The corresponding acetate 10 [m.s. : 530 ($M^{+\cdot}$), 488, 471, 470, 427, 411, 395, 335, 305, 266, 234, 215, 177, 171, 144, 143, 130, 91 (100%) ; p.m.r. δ($CDCl_3$) : 8.30 (N_a-H), 7.3-6.9, 9H arom.), 6.20 (1H, C_{21}-H), 5.70 (1H, C_{15}-H), 5.16 and 5.05 (CH_2-OCO-Nb), 3.66 (3H, s, CO_2CH_3), 2.10 and 1.75 (3H, 2s, $OCOCH_3$), 1.00 (3H, t, J = 7 Hz, C_{18}-H)] was deprotected (H_2, Pd/C 10%) to afford the desired amino acetate 8, isolated in quantitative yield from the isoxazolidine 5 [i.r. : 3380, 2925, 1720 cm^{-1} ; u.v. : 226, 287, 295 nm ; m.s. : 396 ($M^{+\cdot}$), 337 (100%), 336, 267, 248, 171, 144, 135, 130, 122 ; p.m.r. 400 MHz[7] δ($CDCl_3$) : 8.19 (1H, s, N_a-H), 7.44 and 7.29 (2H, 2d, J = 8 Hz, C_9-H and C_{12}-H), 7.17 and 7.08 (2H, 2dd, J = 8 Hz, C_{10}-H and C_{11}-H), 6.27 (1H, s, C_{21}-H), 5.66 (1H, d, $J_{14,15}$ = 7 Hz, C_{15}-H), 3.68 (3H, s, CO_2CH_3), 2.06 (3H, s, $OCOCH_3$), 1.06 (3H, t, J = 7 Hz, C_{18}-H)].



The cyclisation of the amino acetate 8 in the presence of Pd (PPh_3)$_4$ as catalyst[8] led to catharanthine 3 (yield not optimized 40%).

The results from these preliminary investigations show that the isoxazolidine 5 could be a good target in the total synthesis of catharanthine 3.

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References :

1. (a) P. Potier, N. Langlois, Y. Langlois and F. Guéritte, J. Chem. Soc. Chem. Commun., 1975, 670. (b) N. Langlois, F. Guéritte, Y. Langlois and P. Potier, J. Am. Chem. Soc., 1976, 98, 7017. (c) N. Langlois and P. Potier, Tetrahedron Letters, 1976, 1099. (d) Y. Langlois, N. Langlois, P. Mangeney and P. Potier, Tetrahedron Letters, 1976, 3945. (e) P. Mangeney, R.Z. Andriamialisoa, N. Langlois, Y. Langlois and P. Potier, J. Am. Chem. Soc., 1979, 101, 2243. (f) J.P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A.H. Ratcliffe, A.M. Treasurywala and S. Wunderly, Helv. Chim. Acta, 1976, 59, 2858.

2. (a) S.B. Hassan and C.R. Hutchinson, Tetrahedron Letters, 1978, 1681. (b) A.I. Scott, F. Guéritte and S.L. Lee, J. Am. Chem. Soc., 1978, 100, 6253. (c) R.L. Baxter, C.A. Dorschel, S.L. Lee and A.I. Scott, J. Chem. Soc. Chem. Commun., 1979, 257. (d) K.L. Stuart, J.P. Kutney, T. Honda, B.R. Worth, Heterocycles, 1978, 9, 1391. (e) ibid., 1978, 9, 1419.

3. (a) G. Büchi, P. Kulsa, K. Ogasawara and R. Rosati, J. Am. Chem. Soc., 1970, 92, 999. (b) J.P. Kutney and F. Bylsma, Helv. Chim. Acta, 1975, 58, 1672. (c) R.J. Sundberg and J.D. Bloom, Tetrahedron Letters, 1978, 5157. (d) B.M. Trost and J.P. Genêt, J. Am. Chem. Soc., 1976, 98, 8516. (e) B.M. Trost, S.A. Godleski and J.L. Belletire, J. Org. Chem., 1979, 44, 2052. (f) A.U. Rahman, J.A. Beisler and J. Harley-Mason, Tetrahedron, 1980, 36, 1063.

4. (a) M. Ando, G. Büchi and T. Ohnuma, J. Am. Chem. Soc., 1975, 97, 6880. (b) J.P. Kutney, U. Bunzli-Trepp, K.K. Chan, J.P. de Souza, Y. Fujise, T. Honda, J. Katsube, F.K. Klein, A. Leutwiler, S. Morehead, M. Rohr and B.R. Worth, J. Am. Chem. Soc., 1978, 100, 4220. (c) Y. Ban, Y. Sekine and T. Oishi, Tetrahedron Letters, 1978, 151. (d) S. Takano, K. Shishido, M. Sato, K. Yuta

and K. Ogasawara, J. Chem. Soc. Chem. Commun., 1978, 943. (e) M.E. Kuehne J.A. Huebner and T.H. Matsko, J. Org. Chem., 1979, 44, 2477.

5.(a) G.B. Mullen, Ph.D., 1978, State University of New York at Buffalo. (b) J.J. Tufariello, Accounts of Chemical Research, 1979, 12, 396. (c) W. Oppolzer, S. Siles, R.L. Snowden, B.H. Bakker, Tetrahedron Letters, 1979, 4391. (d) J.J. Tufariello and G.E. Lee, J. Am. Chem. Soc., 1980, 102, 373.

6. Y. Langlois, F. Guéritte, R.Z. Andriamialisoa, N. Langlois, P. Potier, A. Chiaroni and C. Riche, Tetrahedron, 1976, 32, 945.

7. S.K. Kan and coll., to be published.

8.B.M. Trost, Tetrahedron, 1977, 33, 2615.

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