THE MODIFIED POLONOVSKI REACTION OF CATHARANTHINE LACTONE N-OXIDE FOR COUPLING WITH VINDOLINE[1]

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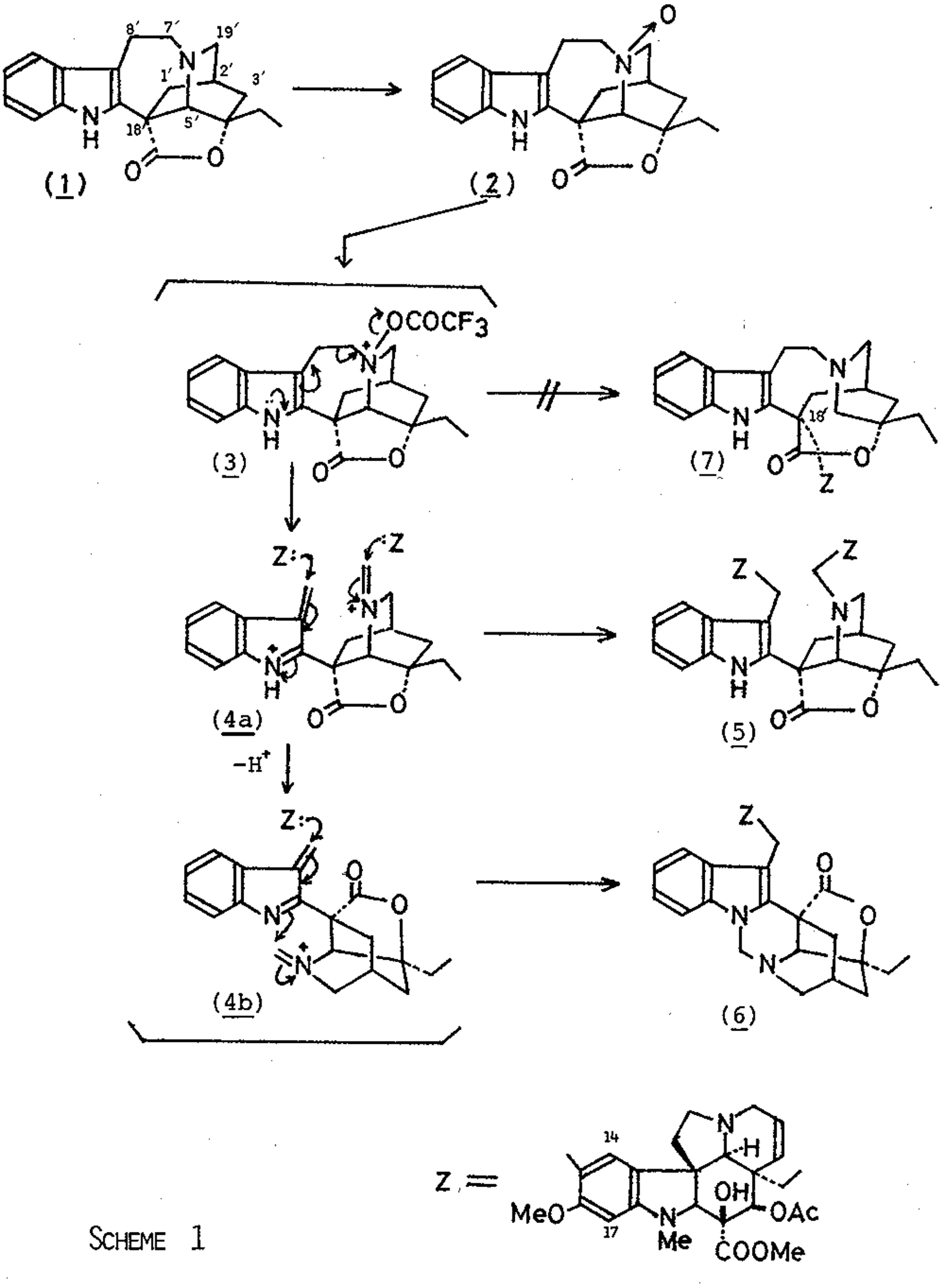
For synthesis of bisindole alkaloids of vinblastine type, catharanthine lactone N-oxide(2) was submitted to the modified Polonovski reaction for coupling with vindoline according to Potier's method. The products were proved to be 5 as a main product, 6 and the other one of an uncertain structure as by-products.

It was reported in the previous communication that catharanthine was converted through iodolactonization as a key step to catharanthine lactone(1), which was assumed to be available as a synthetic precursor for the synthesis of vinblastine.[2] Since the lactone(1) was found to be hardly converted to the corresponding hydroxy-ester, catharanthine lactone N-oxide(2) was submitted to the modified Polonovski reaction for coupling with vindoline by Potier's method[3] in anticipation of obtaining the desired dimeric product(7).[4] The results of this reaction are described in this communication that revealed the


8′
7′
19′
1′
2′
3′
18′
5′
N
NH
O
(1)
(2)
OCOCF3
(3)
(7)
Z
Z:
(4a)
−H+
(5)
(4b)
(6)
Z =
14
17
MeO
N
Me
OH
OAc
COOMe
H

SCHEME 1

products to be 5, 6 and the other one of an uncertain structure.

The procedure of the reaction was in principle same as Potier's description.[3d] Namely, to a solution of catharanthine lactone(1) in methylene chloride was added m-chloroperbenzoic acid(1.2mol.eq.) at room temperature and the whole solution was stirred for 3 hr, cooled to -15°, to which were added vindoline(1 mol.eq.) and the excess of trifluoroacetic anhydride. The resulting mixture was stirred at -10~-15° for 4 hr, to which ethanol and sodium borohydride were added, and the solution was stirred at room temperature for further 1 hr to give a crude product. The preparative thin layer chromatography on alumina furnished three products. Although the ratio of the products were sensitively variable under reaction conditions exercised, the first compound was usually obtained as a main product in 19-33% yields, whose structure was assigned the formula(5) by the physicochemical properties[amorphous solid, MS(m/e): M^+ ca. 1230 by the field desorption method.[5] (Calcd. for $C_{70}H_{84}N_6O_{14}$: 1232). IR($CHCl_3$) ν3460, 1740, 1615, 1500, 1460 1430 and 1370 cm^{-1}. UV(EtOH)λ_{max}213, ca. 225(sh), 257, 288, 295 and 305 nm, λ_{min}243 and 280 nm (suggestive of an additive absorption of indole and indoline). NMR($CDCl_3$) δ0.05, 0.29 and 0.74(each one, 3H, t, J=7Hz, $CH_2C\underline{H}_3$), 2.04(3Hx2, s, $OCOC\underline{H}_3$), 2.66 and 2.68(each one, 3H, N-$C\underline{H}_3$), 3.74, 3.76 and 3.80(3Hx4, s, $CO_2C\underline{H}_3$ and arom.-$OC\underline{H}_3$), 5.11(1Hx2, d, J=10, C(6)-$\underline{H}$), 5.30 (1Hx2, s, C(4)-H), 5.71(1Hx2, m, C(7)-$\underline{H}$), 6.01 and 6.08(each one, 1H, s, C(17)-H), 6.37 and 6.82(each one, 1H, s, C(14)-H), 6.74 ∼ 7.30(4H, m, arom.-H in indole part), 8.61(1H, s, NH) and 9.6(1Hx2, broad, OH). These nmr data are indicative of the presence of one indole and two vindolines.].

The second compound was obtained in a yield of 15% at best by column chromatography on alumina of a crude product eluted with ethyl acetate and hexane(2:1), which was better than the preparative thin layer chromatography for isolation of this product. The structure of this product should be represented by the formula(6) due to the following data [amorphous solid, MS(m/e): M^+ 776 (Calcd. for $C_{45}H_{52}N_4O_8$, MW=776)[5], IR($CHCl_3$) ν 1775, 1740, 1615, 1500, 1455, 1430 and 1370 cm^{-1} (an NH absorption is lacking). UV(EtOH) λ_{max} 213, 225(sh), 255, 288, 295 and ca. 308(sh) (suggestive of an additive absorption of indole and indoline). NMR($CDCl_3$) δ0.14(3H, t, J=7Hz, CH_2CH_3 in vindoline part), 1.06(3H, t, J=7Hz, CH_2CH_3 in the lactone part), 2.04(3H, s, $OCOCH_3$), 2.66(3H, s, N-CH_3), 3.75 and 3.85(3Hx2, s, OCH_3 and CO_2CH_3), 4.88 and 5.03(each one 1H, d, J=12Hz, N-CH_2-N), 5.14(1H, d, J=10Hz, C(6)-H), 5.38(1H, s, C(4)-H), 5.74(1H, dd, J=10 and 4 Hz, C(7)-H), 6.08 and 6.57(1Hx2, s, C(17)-H and C(14)-H), ca. 6.9∼7.4(4H, m, arom.-H in indole part), ca. 9.5 (1H, broad, OH)].

The third one was obtained in 24% yield at best on the above column chromatography, but the structure has remained to be decided as a future problem, although the product was proved to be dimeric (M^+776), but not to be the objective compound(7, MW=778).

The spectral data of this product are in the following: [MS(m/e): M^+ 776 (Calcd. for $C_{45}H_{52}N_4O_8$, MW=776),[5] IR($CHCl_3$) ν 3450, 1740, 1615, 1500, 1460, 1435 and 1375 cm^{-1}. UV(EtOH) λ_{max}213, 223(sh), 253, 287, 294 and ca. 308(sh). λ_{min}245, 278 and 290. The uv spectrum is suggestive of an additive absorption due to one indole and one indoline. NMR($CDCl_3$) δ 0.04 and 0.70(3H x 2, t, J=7Hz, $CH_2C\underline{H}_3$), 2.03(3H, s, $OCOC\underline{H}_3$), 2.48(3H, s, ?), 2.67(3H, s, N-$C\underline{H}_3$), 3.77 and 3.91(3H x 2, s, $OC\underline{H}_3$ and $CO_2C\underline{H}_3$), 5.10(1H, d, J=10Hz, C(6)-$\underline{H}$), 5.34(1H, s, C(4)-$\underline{H}$), 5.70 (1H, dd, J=10 and 4 Hz, C(7)-$\underline{H}$), 6.12(1H, s, C(17)-$\underline{H}$), 6.37 (1H, s, C(14)-$\underline{H}$), 6.86～7.36(4H, m, arom.-H in indole part), 8.82(1H, s, N$\underline{H}$) and ca.9.7(1H, bs, O$\underline{H}$). These nmr data are indicative of the presence of one indole and one vindoline parts in the molecule.].

The plausible mechanism for generation of these products is shown in the Scheme 1, which is similar to the proposal made by Potier,[3d] although the trimer($\underline{5}$) was first isolated in the present work.

Thus, the present work clearly indicates that the lactone bridge in $\underline{1}$ obstructed the approach of vindoline as a nucleophile toward C(18') position. Therefore, the other approaches are being investigated.

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REFERENCES AND NOTES

1 The compound(1) is called "catharanthine lactone" as a trivial name.

2 Y. Honma and Y. Ban, Heterocycles, 1977,

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.

4 J. P. Kutney et al.[4a~d] and Atta-ur-Rahman et al.[4e] made contributions to extension of this modified Polonovski reaction for the syntheses of bisindole alkaloids, such as leurosine[4b,c] and vinblastine.[4e] a) J. P. Kutney, A. H. Ratcliffe, A. M. Treasurywala and S. Wunderly, Heterocycles, 1975, 3, 639. b) J. P. Kutney, J. Balsevich, G.H. Bokelman, N. Hibino, I. Itoh and A. H. Ratcliffe, ibid., 1976, 4, 997. c) J. P. Kutney and B. R. Worth, ibid., 1976, 4, 1777. d) J. P. Kutney, G. H. Bokelman, M. Ichikawa, E. Jahngen, A. V. Joshua, P.-H. Liao and B. R. Worth, ibid., 1976, 4, 1267. e) Atta-ur-Rahman, A. Basha and M. Ghazala, Tetrahedron Letters, 1976, 2351.

5 The measurements of mass spectra of the coupling products were very difficult as they were thermally labile. The M$^+$ peak of the compound (5) was observed only by field desorption technique done by T. Aoyama, JEOL Company, and the other spectra were carefully taken on electron impact through kind offices of Professor K. Yamakawa, Science University of Tokyo, and Dr. T. Oishi, The Institute of the Physical and Chemical Research. We sincerely thank all of them for the measurements.

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