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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXXI[1]
UNUSUAL POLONOVSKI REACTION OF SOME VINCA ALKALOIDS

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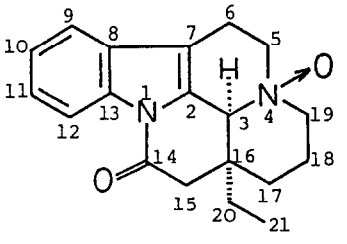
Abstract: *In the course of the Polonovski reaction of some indole alkaloids a new type of dimerization has been found.*

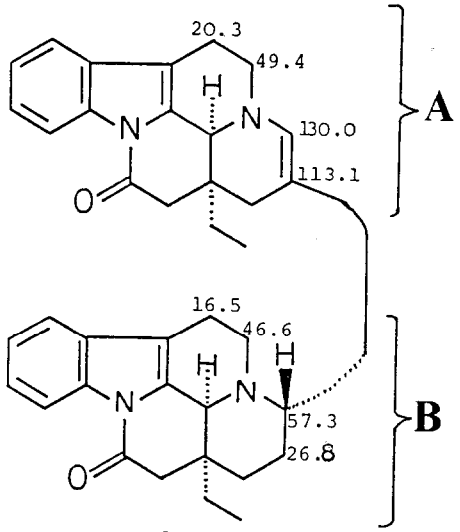
The Polonovski reaction and its modification by P. Potier are widely used in alkaloid chemistry[2]. Starting from systems containing β-carboline moiety the reaction usually leads to the corresponding imminium salts. E.g. on converting eburnamonine into its N-oxide and on treatment of the latter with trifluoroacetic anhydride the corresponding imminium salt was obtained, which on reduction gave rise to trans-eburnamonine[3].

In view of these results we were surprised to find an entirely different behaviour of vincamone N-oxide[3] (1). When 1 (40 mmol) was treated with acetic anhydride (0.53 mol; 50 ml) at room temperature for 24 h crystals of the dimeric indole derivative 2[4] precipitated in 52 % yield.



1

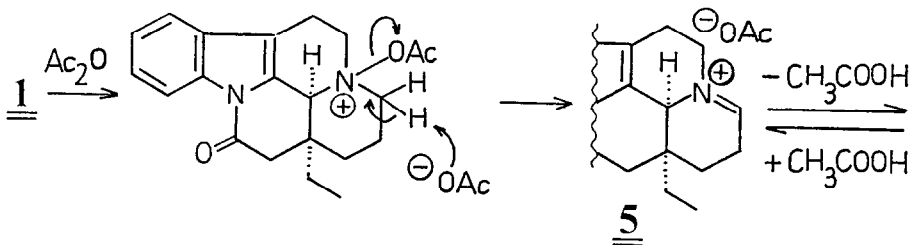
Some of the ^{13}C-NMR shifts are indicated at the corresponding carbon atoms.

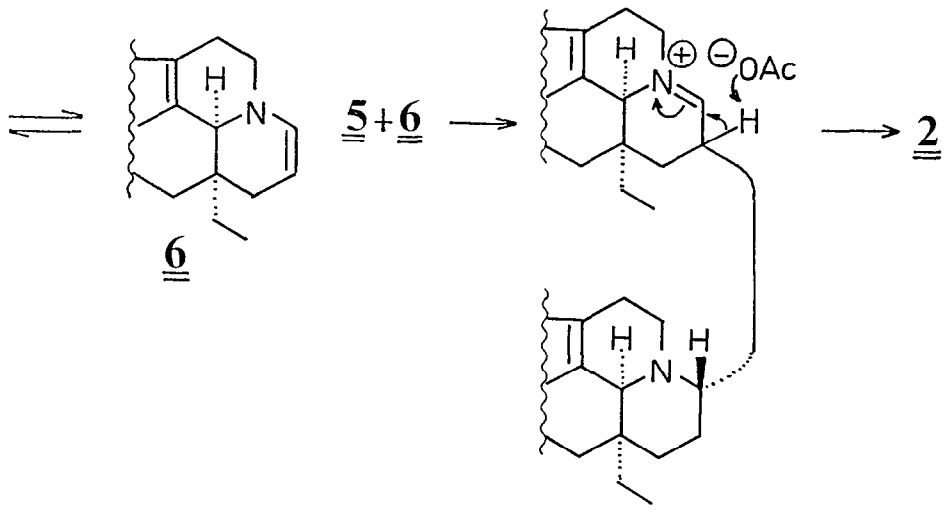


2

Results were similar when the N-oxides of the alkaloid vincamine[5] and of apovincaminic acid ethyl ester[5] were reacted with acetic anhydride. The obtained dimers (**3**[6] from vincamine N-oxide[7] and **4**[8] from apovincaminic acid ethyl ester N-oxide[9]) have structures similar to **2**, thus the reaction seems to be rather general.

A possible reaction sequence leading to the dimers may be the following. The electrophilic imminium salt **5** and the nucleophilic enamine **6** both present in equilibrium in solution react with each other yielding the end product after deprotonation.





In order to substantiate the supposed mechanism the separately prepared enamine 6[10] was treated with acetic acid. The reaction indeed provided dimer 2, as expected.

Using the modified conditions of the Polonovski reaction (i.e. trifluoroacetic anhydride in CH_2Cl_2) 1 gave 2 only in a very low yield in addition to other products.

Investigations concerning the scope and limitation of the above reaction sequence are in progress.

A detailed discussion of the NMR data will be published later.

Acknowledgement: The authors wish to thank J. Tamás and M. Mák for mass spectra.

References and Notes

1. For part XXX see SZABÓ, L.; MÁRVÁNYOS, E.; KALAUS, Gy.; TÓTH, G.; SZÁNTAY, Cs. Jr.; SZÁNTAY, Cs.; Heterocycles in press.
2. VOLZ, H.: Kontakte (Darmstadt), 1984 (3), 14
3. Belg. 873.373 (Omnium Chimique S. A.) / C. A. 1979 (91) 175 596e
Note that eburnamonine and vincamone are enantiomers.
4. mp 304-306 °C; $[\alpha]_D^{25}$=-345.4° (c=0.2;$CHCl_3$); MS m/e (%): 584 (M^+, 53), 556 (6), 555 (7), 527 (1.3), 526 (2.5), 360 (1), 331 (100), 330 (18), 318 (5), 301 (10), 292 (34; M/2), 263.5 (5), 238 (6), 224 (28), 196 (3), 181 (4), 180 (4), 168 (8), 167 (8); UV (EtOH + HCl): λ_{max} [nm], (lgε): 202 (4.69), 240 (4.60), 265 (4.24), 300 (3.97); IR (KBr): 1700, 1610, 1670 [cm^{-1}];

^{1}H-NMR (The NMR spectra have been recorded on a Jeol FX-100 instrument in $CDCl_3$) δ: 0.87 (3H, t, $-CH_2-C\underline{H}_3$), 0.98 (3H, t, $-CH_2-C\underline{H}_3$), 3.80 (1H, s, C3-H), 4.10 (1H, s, C3-H), 5.80 (1H, s, C19-H ; in part A), 7.10-7.50 (6H, m, C9-H, C10-H, C11-H), 8.35 (2H, m, C12-H) 1.10-3.70 (23H, m, skeletal + + $-C\underline{H}_2-CH_3$).

5. Structures see e.g.: SZABÓ, L.; KALAUS, Gy.; SZÁNTAY, Cs.: Archiv der Pharmazie 1983 (316) 629
6. mp 246-249 °C; $[\alpha]_D^{25}$=-141,1° (c=0.2; $CHCl_3$); MS m/e (%): 704 (M^+,88), 686 (3.3), 675 (5.6), 645 (14), 644 (23), 585 (9.3), 584 (18), 391 (100), 352 (50; M/2), 343 (18), 331 (65), 292 (16), 284 (21), 266 (36), 224 (40), 208 (25), 170 (17), 169 (14), 168 (20), 167 (17); UV (EtOH + HCl): λ_{max} [nm], (lg ε): 203 (4.52), 224 (4.82), 276 (4.19) ; IR (KBr): [cm^{-1}] 1720, 1650 (enamine); ^{1}H-NMR δ: 0.83 (3H, t, $-CH_2-C\underline{H}_3$), 0.96 (3H, t, $-CH_2-C\underline{H}_3$), 3.75 (3H, s, $-COOC\underline{H}_3$), 3.84 (3H, s, $-COOC\underline{H}_3$), 4.04 (1H, s, C3-H), 4.80 (1H, s, C3-H), 3.40 (1H, s, O$\underline{H}$), 4.54 (1H, s, O$\underline{H}$), 5.80 (1H, s, C19-H; in part A), 7.00-7.75 (6H, m, C10-H, C11-H, C12-H), 7.47 (2H, m, C9-H), 1.10-3.70 (23H, m, skeletal + $C\underline{H}_2-CH_3$).
7. Fr. Demande 2.162.282 (Synthelabo S. A.) / C. A. 1974 (80) 19 575 g
8. mp 220-221 °C ; $[\alpha]_D^{25}$=-209.6° (c=0.2; $CHCl_3$); MS m/e (%): 696.365 (M^+, 43), 667 (5), 651 (2), 638 (1), 623 (2), 594 (0.5), 526 (0.5), 429 (1.4), 416 (3), 387.2080 (81), 374 (8), 357 (6), 348 (26; M/2), 308 (3), 294 (6), 281 (24), 280 (100), 252 (24); UV (EtOH + HCl): λ_{max} [nm], (lgε): 204 (4.66), 226 (4.73), 271 (4.31), 316 (4.04) ; IR (KBr): 1730, 1680, 1640 [cm^{-1}]; ^{1}H-NMR δ : 0.95 (3H, t, $-CH_2-C\underline{H}_3$), 1.08 (3H, t, $-CH_2-C\underline{H}_3$), 1.35 (3H, t, $-COOCH_2C\underline{H}_3$), 1.40 (3H, t, $-COOCH_2C\underline{H}_3$), 4.40 (2H, q, $-COOC\underline{H}_2CH_3$), 4.38 (2H, q, $-COOC\underline{H}_2CH_3$), 3.94 (1H, s, C3-H), 4.30 (1H, s, C3-H), 5.82 (1H, d, J=1.7 Hz, C19-H; in part A), 6.10 (1H, s, C15-H), 6.36 (1H, s, C15-H), 7.00-7.30 (6H, m, C10-H, C11-H, C12-H), 7.45 (2H, m, C9-H), 1.20-3.80 (19H, m, skeletal + $C\underline{H}_2-CH_3$).
9. SZABÓ, L.; SZÁNTAY, Cs.; et al.: unpublished results
10. BENCELMANS, R.; HERLEM, D.; HUSSON, H.-P.; KHUONG-HUU, F; LE GOFF, M.-T.: Tetrahedron Letters 1976 435

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