ON THE REACTION OF DEACETYLVINDOLINE WITH THIONYL CHLORIDE

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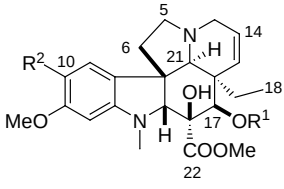
Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

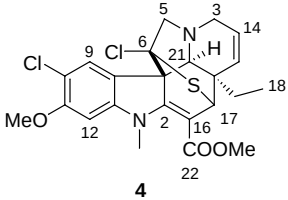
Reaction of deacetylvindoline (**2**) with excess thionyl chloride gave rise to hexacyclic 6,10-dichloro-6,17-epithio-11-methoxy-1-methyltabersonine (**4**) as a single product in 43.5% yield. The structure was deduced from ^{1}H and ^{13}C 1D and 2D NMR experiments as well as from mass spectra. A tentative mechanism of this complex transformation was also proposed.

Key words: Indole alkaloids; Deacetylvindoline; Chlorination; Cyclizations; Sulfur; NMR spectroscopy; Mass spectrometry; Reaction mechanism.

Vindoline (**1**) (the biogenetic numbering[1] is used throughout this paper), a highly oxygenated aspidospermine alkaloid, is one of the components of the vincaleukoblastine bisindole alkaloid group whose members have found broad applications in cancer chemotherapy. Consequently, serious attention was paid to the development of its chemistry, including total synthesis, with the aim of preparing suitable derivatives for bisindole synthesis[2,3]. In this regard, many interesting reactions have been revealed. For example, deacetylvindoline (**2**) on mesylation gave rise[4] to either 16-*O*- or 17-*O*-methanesulfonyl derivative depending on the base used (triethylamine and pyridine, respectively). Interestingly enough, diol **2**, on treatment with thionyl chloride in the presence of pyridine, afforded[4] **3**, the product of C-10 chlorination, in 71% yield. We report here on the results of the same reaction performed without any added base.



1, R^1= Ac, R^2= H
2, R^1= R^2= H
3, R^1=H, R^2= Cl



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EXPERIMENTAL

Melting points were determined on a Boetius microblock and are uncorrected. IR spectra (wavenumbers in cm^{-1}) were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer in chloroform. NMR spectra were measured on a Bruker 250-DPX spectrometer (250.13 MHz for ^1H, 62.89 MHz for ^{13}C) in chloroform at 30 °C; TMS was used as internal standard for ^1H spectra. Carbon signal multiplicity was determined by DEPT135. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. EI-Mass spectra were recorded on a Jeol D100 double focussing spectrometer and are shown as *m/z* (%). UV spectra were taken on a Specord Uvis (Zeiss) instrument in methanol solution (λ_{max} in nm (log ε)). Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

Deacetylvindoline (**2**)

A solution of vindoline (**1**; 0.500 g, 1.095 mmol) in concentrated hydrochloric acid (10 ml) was stirred at room temperature until the starting material completely disappeared on TLC (6.5 h). The solution was diluted with water (20 ml), benzene was added (50 ml) and the stirred mixture was brought to pH 9 with concentrated ammonia under cooling. The separated aqueous layer was extracted with benzene (20 ml). The combined extracts were washed with water (10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated to afford crystalline residue. Crystallization from benzene–hexane gave **2** as white crystals (0.437 g, 96.3%); m.p. 159–162 °C (ref.[5] 164–165 °C); $[\alpha]_D^{23}$ –33.5 (*c* 0.71, methanol) (ref.[6] $[\alpha]_D^{23}$ –26 (*c* 0.046, methanol)). ^1H NMR: 9.27 bs, 1 H (16-OH); 6.87 d, 1 H, *J*(9,10) = 8.2 (arom. H-9); 6.28 dd, 1 H, *J*(10,9) = 8.2, *J*(10,12) = 2.3 (arom. H-10); 6.06 d, 1 H, *J*(12,10) = 2.3 (arom. H-12); 5.87 ddd, 1 H, *J*(14,15) = 10.3, *J*(14,3β) = 4.8, *J*(14,3α) = 1.6 (H-14); 5.73 ddd, 1 H, *J*(15,14) = 10.3, *J*(15,3α) = 2.6, *J*(15,3β) = 1.4; 4.08 bd, 1 H, *J*(17,OH) = 6.6 (H-17); 3.84 s, 3 H ($COOCH_3$); 3.78 s, 3 H (C-11-OCH_3); 3.72 s, 1 H (H-2); 3.44 ddd, 1 H, *J*(3β,3α) = 15.8, *J*(3β,14) = 4.8, *J*(3β,15) = 1.4 (H-3β); 3.40 m, 1 H (H-5β); 2.84 ddd, 1 H, *J*(3α,3β) = 15.8, *J*(3α,15) = 2.6, *J*(3α,14) = 1.6 (H-3α); 2.72 s, 3 H (N-1-CH_3); 2.65 bs, 1 H (H-21); 2.53 m, 1 H (H-5α); 2.23 m, 2 H (H-6); 1.46 dq, 1 H, *J*(19,19′) = 13.8, *J*(19,18) = 7.4 (H-19); 1.01 dq, 1 H, *J*(19′,19) =13.8, *J*(19′,18) = 7.4 (H-19′); 0.67 t, 3 H, *J* = 7.4 (H-18). ^{13}C NMR: 173.28 (C-22); 161.13 (C-11); 153.72 (C-13); 130.73 (C-15); 125.11 (C-8); 123.63 (C-14); 122.77 (C-9); 104.29 (C-10); 95.79 (C-12); 83.06 (C-2); 80.75 (C-16); 73.90 (C-17); 67.99 (C-21); 55.30 (C-10-OCH_3); 52.90 (C-7); 52.20 ($COOCH_3$); 51.27 (C-5); 51.07 (C-3); 44.42 (C-6); 42.70 (C-20); 38.59 (N-CH_3); 32.47 (C-19); 7.67 (C-18).

6,10-Dichloro-6,17-epithio-11-methoxy-1-methyltabersonine (**4**)

Thionyl chloride (8.0 ml; twice distilled from bee's wax) was added to a solution of deacetylvindoline (**2**; 0.300 g, 0.724 mmol) in chloroform. The mixture was stirred at room temperature for 8.5 h and poured onto sufficient quantity of ice. Chloroform was added (35 ml) and the stirred mixture was made slowly alkaline with concentrated ammonia. The separated aqueous layer was extracted with chloroform (20 ml); the combined organic extracts were washed with water (2 × 10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated *in vacuo* leaving a foam (0.35 g), which was chromatographed on silica gel (0.063–0.200 mm; 5 g). Elution with benzene–chloroform (10 : 1–1.5) afforded, after evaporation a residue (0.186 g), which was crystallized from acetone. Compound **4** was obtained as off-white crystals (0.151 g, 43.5%) in two crops; m.p. 202–204.5 °C (dec.); $[\alpha]_D^{23}$ +352.8 (*c* 0.83, chloroform). For ^1H and ^{13}C NMR spectra see Table I. IR: 3 028, 3 019, 1 690, 1 634, 1 600, 1 499, 1 452, 1 438, 1 377, 1 237, 1 205, 1 190, 1 164, 1 142, 1 105, 1 073, 1 058, 1 045, 969. UV: 334 (3.83), 315 (3.81), 272 (3.56). MS: 483 (2, $[M + 1]^+$); 482 (5, M^+); 481 (6, $[M + 1]^+$); 480 (20, M^+); 479 (8, $[M + 1]^+$); 478 (28, M^+); 451 (3); 449 (4); 444 (7); 443 (7); 442 (15); 385 (13); 360 (6); 359 (16); 358 (17); 357 (44); 338 (10); 337 (38); 336 (22); 335 (100); 122 (8); 107 (4). For $C_{23}H_{24}Cl_2N_2O_3S$ (479.4) calculated: 57.62% C, 5.05% H, 14.79% Cl, 5.84% N, 6.69% S; found: 57.32% C, 5.07% H, 15.18% Cl, 5.68% N, 6.62% S.

RESULTS AND DISCUSSION

Vindoline (**1**) was deacetylated by treatment with concentrated hydrochloric acid at room temperature to give deacetylvindoline (**2**) in almost quantitative yield. The structure was proved by NMR spectroscopy; all hydrogen and carbon atoms were assigned on the basis of ^{13}C-DEPT135, ^1H-^1H-COSY and NOESY, and ^1H-^{13}C-HETCOR and HETCOR-LR experiments. The literature data (*e.g.*, ref.[6]) that in some instances differ from the present assignments should therefore be corrected. Deacetylvindoline (**2**) was treated with large excess of thionyl chloride in chloroform at room temperature and gave a crystalline substance, m.p. 202–204.5 °C (dec.), in moderate yield (43.5%) as the only isolable product. Mass spectrometry revealed molecular formula $C_{23}H_{24}Cl_2N_2O_3S$ (*m/z* 478–481, M^+ and $[M + 1]^+$), thus indicating incorporation of two chlorine and one sulfur atoms into the molecule. On the other hand, the compound contained two less oxygen atoms and its IR spectrum did not reveal the presence of any hydroxy group. UV spectrum was reminiscent of a β-anilinoacrylate chromophore, as judged also from high optical rotation $[\alpha]_D$ +352.8. Thus, the overall transformation must have been much more complex in nature.

^1H NMR spectrum showed, somewhat not surprisingly (*vide supra*), the presence of just two aromatic hydrogen atoms in a *para*-arrangement (singlets at δ 7.68 and 6.54), resulting from chlorination at C-10. Singlets (3 H each) at δ 3.68, 3.80 and 3.98 were easily assigned using

^{1}H-^{13}C-HETCOR and HETCOR-LR (J(C,H) = 10 Hz) experiments as *N*-methyl and two methoxy groups, the one with δ_C 51.4 being contained in an ester moiety (δ(C=O) 163.83). Of the remaining four hydrogens the one at δ 2.88 was identified as H-21. The COSY spectrum revealed its long-range coupling to both H-17 at δ 4.02 (J(17,21) = 1.2 Hz) and the more downfield shifted hydrogen H-5, whose α-orientation is supported by its contact in the NOESY spectrum with aromatic H-9 (Fig. 1). A quaternary carbon with a rather high chemical shift (77.44 ppm) was found in place of the original secondary carbon at C-6. The spatial arrangement of hydrogens at C-3 also follows from Fig. 1. The other hydrogen at C-5 is, according to the NOESY spectrum, spatially close to the upfield-shifted hydrogen at C-3, whereas H-3 hydrogen at δ 3.35 is in contact with H-21 and is therefore α-axial. All hydrogens and carbons were assigned on the basis of a combination of 1D and 2D ^{1}H and ^{13}C NMR experiments (COSY, NOESY, HETCOR and HETCOR-LR), and the structure of the compound was shown to be the hexacyclic 6,10-dichloro-6,17-epithio- 11-methoxy-1-methyltabersonine (**4**) (Table I).

The proposed fragmentation pattern in the mass spectrum of **4** is shown in Scheme 1. The ionized molecule, apart from the possible loss of ethyl group or hydrogen chloride (*m/z* 449 and 442 and the satellites), undergoes a retro [4+2] cycloaddition and gives ion-radical **5**. This ion in turn fragments through transfer of hydrogen by cyclic mechanism (McLafferty) and affords the most abundant fragment corresponding to thiopyrano-[4,3-*b*]indole **6** ($C_{16}H_{14}ClN_3OS$; *m/z* 335.0381, error +0.0001 mass units), accompanied by 3-ethylpyridine (*m/z* 107). Thiopyrane **5** can also fragment by an alternative mechanism (scission of the original C-5–C-6 bond) as evidenced by the presence in the spectrum of an ion at *m/z* 122, which corresponds to 1-methyl-3-ethylpyridinium.

Key to the proposed speculative mechanism of this complex transformation of deacetylvindoline (**2**) to the hexacyclic derivative **4** is the explanation of the sulfur bridge formation between C-17 and, at least formally, the unreactive C-6. Schmid *et al.*[7,8] have proposed a plausible mechanism for the transformation of hexacyclic aspidofractinine to heptacyclic kopsane alkaloids by β-elimination of N-4, acylation/alkylation and pyrrolidine ring reclosure. Such a process can be envisioned in this case also, in both inter- and intramolecular ways (Scheme 2). In the latter case, acylation at C-6 could proceed in chlorosulfite **7** and give rise finally to sulfinyl chloride **8**. Alternatively, β-anilinoacrylate **9** could undergo intermolecular acylation with thionyl chloride at C-6. Note that the acylation could also occur in **9** in the intramolecular way. The conversion of sulfinyl chloride **8** to α-chloro

TABLE I
^{1}H and ^{13}C NMR spectral data of **4**

Position	δ_H	δ_C	*J*(H,H)	HETCOR-LR[a]
2	–	152.51		
3α	3.35 ddd	46.52	18.0(3α,3β), 2.7(3α,15), 1.8(3α,14)	5,15
3β	3.14 ddd		18.0(3β,3α), 5.0(3β,14), 0.9(3β,15)	21
5α	4.09 bd	69.68	10.2(5α,5β), >0.0(5α,21)	5
5β	3.60 d		10.2(5β,5α)	5,6,7
6	–	77.44		
7	–	65.74		
8	–	123.00		
9	7.68 s	126.84		7,9,10,11,13
10	–	114.90		
11	–	156.22		
12	6.54 s	102.99		8,10,11,13
13	–	148.32		
14	6.14 ddd	128.55	10.4(14,15), 5.0(14,3β), 1.9(14,3α)	
15	5.69 ddd	131.93	10.4(15,14), 2.6(15,3α), 0.9(15,3β)	17
16	–	100.66		
17	4.02 d	47.39	1.2(17,21)	2,6,16,17,20 21,C=O
18	0.74 t	7.82	7.4(18,19)	18
19a	1.22 dq	32.43	13.8(19a,19b), 7.5(19a,18)	
19b	1.08 dq		13.8(19b,19a), 7.4(19b,18)	
20	–	43.02		
21	2.88 d	64.07	1.2(21,17)	5,6,7,19
1-Me	3.68 s	34.75		2,13
11-MeO	3.98 s	56.44		11,11-OCH_3
22-CO	–	163.83		
–OMe	3.80 s	51.40		C=O-OCH_3

[a] Experiment optimized for $J_{C,H}$ = 10 Hz.

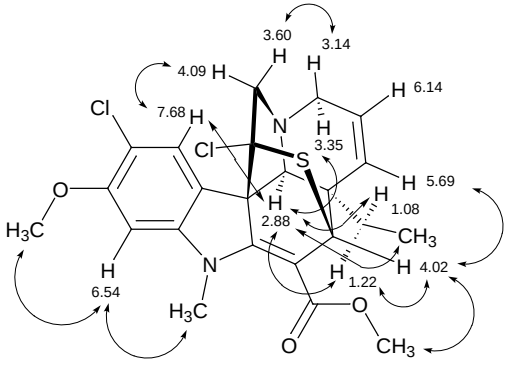
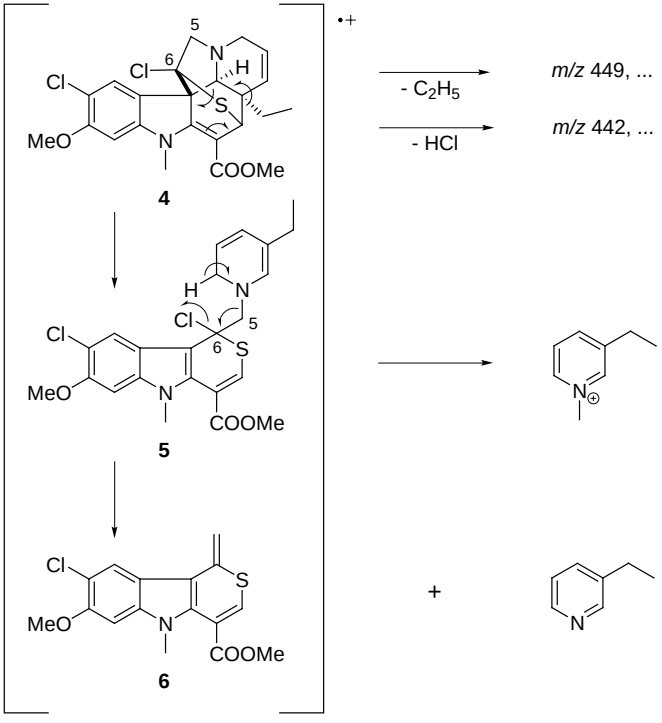
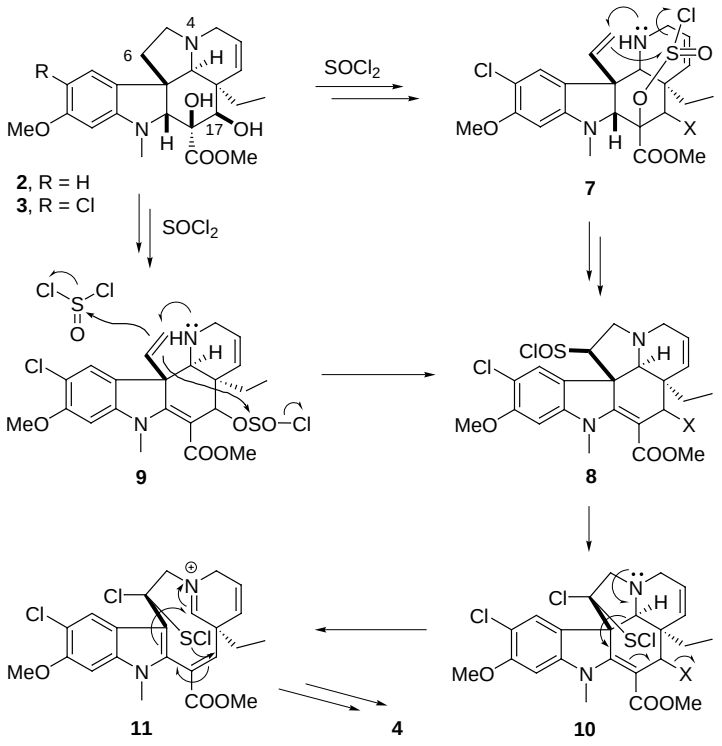


FIG. 1
Non-trivial contacts in the NOESY spectrum of **4**



SCHEME 1
Principal fragmentation pathway in the mass spectrum of **4**



SCHEME 2
Proposed mechanism of formation of **4**

sulfenyl chloride **10** could proceed with the intervention of a Pummerer-like process, and attack of chloride ion from the less sterically hindered side. Fragmentation in **10** with the intervention of N-4 then gives rise to the medium-ring intermediate **11**. Finally, addition of S-nucleophile onto the conjugated double bond could lead to the target hexacyclic derivative **4**.

In conclusion, structure of the reaction product of deacetylvindoline with excess thionyl chloride was determined and the speculative mechanism of its formation proposed.

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