Tetrahedron. Vol. 28, pp 4125 to 4130. Pergamon Press 1972. Printed in Great Britain

RHOEAGENINE AND RHOEADINE—III
THE HOFMANN DEGRADATION OF RHOEAGENINE METHIODIDE

M. D. ROZWADOWSKA
Institute of Organic Chemistry. Polish Academy of Sciences. Poznan. Poland

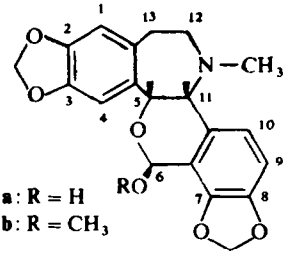
and

J. W. APSIMON
Department of Chemistry. Carleton University. Ottawa K1S 5B6. Canada

(*Received in the UK* 5 *April* 1972; *Accepted for publication* 18 *April* 1972)

Abstract The Hofmann degradation of rhoeagenine methiodide leads to several compounds resulting from the expected route or from base catalyzed reactions of the lactol grouping.

FOR several years we have been interested in the alkaloids of *Papaver Rhoeas*[1,2] particularly rhoeagenine **1a** and rhoeadine **1b**. The correct structure of rhoeadine was first proposed by Santavy[3] and the C-6 hydroxyl* orientation was assigned by Shamma.[5] Recently these results have been confirmed by an X-ray crystallographic study[6]† and by total synthesis.[7]



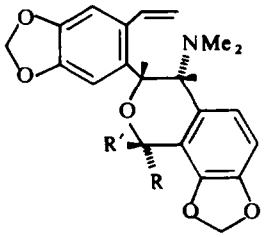
1a: R = H
b: R = CH_3

In this article we report some of our studies on the Hofmann degradation of the methiodide of rhoeagenine **1a**. From this reaction we obtained a mixture of several compounds, four of which we have been able to characterize. The low yields and lability of the other components of this reaction mixture make it unlikely that we will be able to examine all components, thus we report our definitive results.

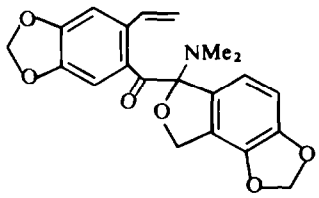
The main product (20·5%) of the reaction was desrhoeagenine,[8] **2a** whose NMR spectrum (Table 1) supported the structure shown. The mass spectrum of this compound parallels that reported by Santavy[3] for desrhoeadine (**2a** R′ = OMe, R = H)

* We use the numbering system proposed by A. Brossi *et al.* based on the basic rheadan skeleton.[4] This is indicated in formula 1.

† The absolute configuration of rhoeagenine methiodide is as indicated in this reference. Dr. C. S. Huber, unpublished work. cf. M. Shamma, J. L. Moniot, W. K. Chan and K. Nakanishi. *Tetrahedron Letters* 4207 (1971)

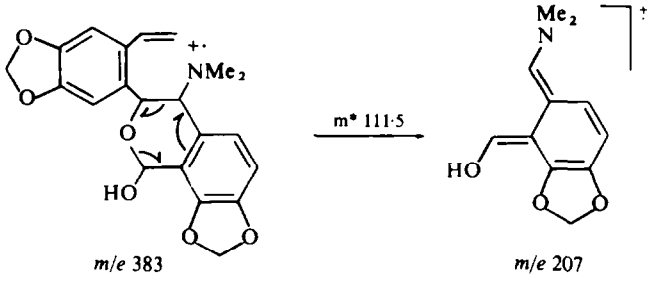


2a: R′ = OH:R = H
b: R′ = H:R = OH



3

in that the base peak* at *m/e* 206 (*m/e* 383–206 m* 111·5 calcd. 111·88) indicate a reverse Diels–Alder type process followed (scheme 1) by loss of $\cdot CH_3$(*m/e* 207 → 192, m* 178 calcd. 178·09) and then $\cdot NHCH_3$ (*m/e* 192–162, m* 137 calcd. 136·69). Treat-



m/e 383 *m/e* 207

SCHEME 1

ment of desrhoeagenine **2a** in methanol with a trace of HCl yielded desrhoeadine.[8]

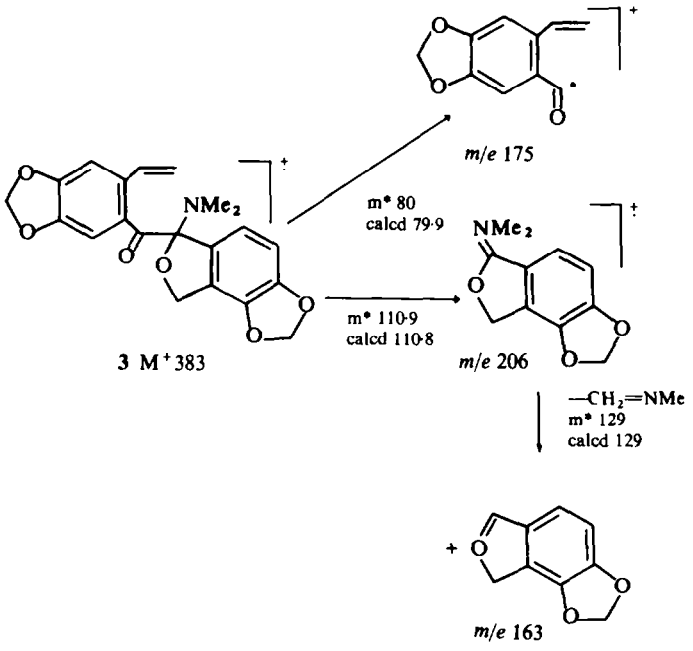
A second des-base was isolated in small amounts (1·3%) which we formulate as 6-epidesrhoeagenine **2b**. The mass spectrum of this compound differed only slightly in the relative intensities of some of the peaks to that of **2a**, and treatment of **2a** with base converts it into a mixture of materials of which **2b** is a major component. One possible source of this material is from 6-epirhoeagenine present as a contaminant in the starting material. Although we cannot rule out this possibility, all our physical data on rhoeagenine indicate that it is pure. The other source of **2b** is from the base-catalyzed opening-reclosing of the hemiacetal ring; this we favour.

The NMR spectrum of **2b** supported the formulation proposed from the coupling constants of C-5H and C-11H. In both **2a** and **2b** the coupling constants of C-5H and C-11H are about 2·5 Hz indicating a common stereochemistry about these sites (*cf* isorhoeadine Ref 3).

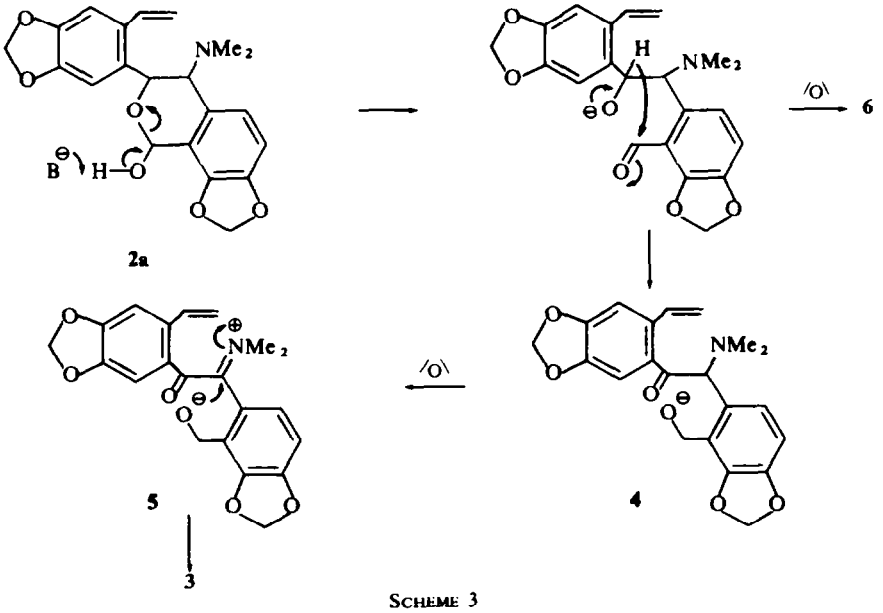
A third product (11·5%) is assigned structure **3** on the basis of its spectral properties and elemental analysis. Its NMR spectrum indicates the presence of the vinyl group and an extra AB system (quartet centered at 4·95 δ). The characteristic signals for the $C_5^{-}H$ and $C_{11}^{-}H$ of the parent alkaloid and derivatives are absent. The AB system is reminiscent of that observed in desmethoxyrhoeadine,[9] the smaller coupling constant in this case (12 Hz, *vs* 14·5–16 Hz in Ref 9) could possibly be a consequence

* The mass spectral fragmentations discussed herein are all supported by metastable peak data. These are indicated after the fragment in question.

of the smaller ring size incorporating the methylene group.[10,11] The mass spectrum of **3** displays two major peaks: the base peak at *m/e* 206 and another at *m/e* 163 (47%). These observations, together with a fragment at *m/e* 175 (4%) are consistent with the fragmentation of **3** as indicated in scheme 2.



SCHEME 2



SCHEME 3

TABLE 1. SOME NMR DATA[a] (IN δ BELOW TMS) OF THE DEGRADATION PRODUCTS OF RHOEAGENINE METHIODIDE

Compounds	$N(C\underline{H}_3)_2$	C_{11}-$\underline{H}$	C_5-$\underline{H}$	C_6-$\underline{H}$	$C_{12}C_{13}$ Vinyl Protons ABX Pattern[c]		C_1-$\underline{H}$	C_4-$\underline{H}$	C_9-$\underline{H}$ + C_{10}-$\underline{H}$	Notes
Des-rhoeagenine **2a**	2·09	3·67(d)[b] J = 3Hz	5·62(d)* J = 3Hz	6·34	$C\underline{H}_2$	5·20 5·52	7·24	6·96	6·80(ABq)	Assignment of C_1 + C_4 signals could be reversed.
					C$\underline{H}$	6·85				
14-epi-desrhoeagenine **2b**	2·32	3·17(d)* J = 3Hz	5·97(d)* J = 3Hz		$C\underline{H}_2$	5·25 5·52	7·24	6·84	6·54 (ABq)	
					C$\underline{H}$	6·96				
3	2·38		—	CH_2 4·95(q) J = 13Hz	$C\underline{H}_2$	5·02 5·40	7·26	6·97	6·78 6·8	Hydrochloride spectrum similar
					C$\underline{H}$	6·31				
6	2·62	4·58(d)* J = 10Hz	5·51(d)* J = 10Hz	—	$C\underline{H}_2$ca	5·15 5·30		6·88 6·90	6·60 (ABq)	$\underline{H}$ exchangeable: broad singlet centred at 3·9.
					C$\underline{H}$	7·25				

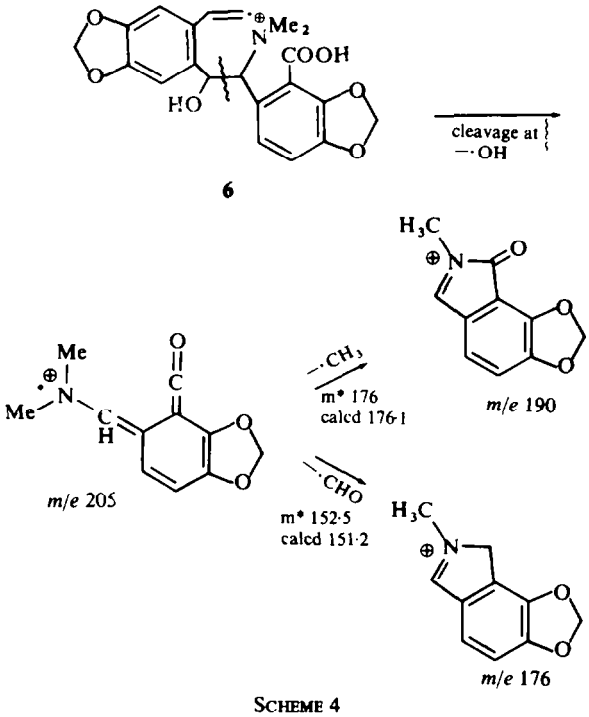
[a] Determined at 100 MHz on HA-100 or XL-100-12 spectrometers in $CDCl_3$ using THS as a standard. Methylene dioxy proton signals not reported.

[b] d = doublet; q = quartet; m = multiplet. * coupling between marked signals verified by decoupling.

[c] Centres of the main branches of ABX pattern are indicated.

Compound **3** would appear to arise *via* intermediate **5** (scheme 3) which in turn could arise from the oxidation of species **4** formed by an internal hydride ion transfer.[12] This process is supported by the observation (TLC 3 systems) that **3** is formed when **2a** is treated with base in the presence of air and that it is optically inactive (**5** has no asymmetric centres). The physical data obtained on the hydrochloride of **3** supports this structural proposal. Exclusion of air during the Hofmann degradation of rhoeagenine methiodide (argon atmosphere) resulted in an entirely different product distribution in which **3** could not be detected. Instead enhanced yields of **2a** and **2b** were obtained.

That the intermediates formed during this Hofmann degradation are sensitive to oxidation is exemplified further by the obtention of an amino acid for which we propose structure **6**, presumably formed by oxidation of the intermediate aldehyde obtained from opening of the lactol of **2a** (Scheme 3). Support for structure **6** comes from the NMR spectrum where amongst other signals (see Table I) the NMe_2 signal is shifted downfield to 2·6 δ indicating protonation of the nitrogen atom. The IR spectrum shows strong broad carboxylate absorption centered at about 1600 cm^{-1}. The mass spectrum of **6** shows intense peaks at *m/e* 205 (40%) 190 (25%) and at 176 (100%), probably arising as indicated in scheme 4.



SCHEME 4

EXPERIMENTAL

All m.ps were determined on a Kofler block and are not corrected. IR spectra were measured in KBr and chloroform, in 0·1 mm and 1 mm cells on a Unicam SP 200G, and in 1 cm cells on Pye-Unicam SP 700A spectrophotometers. NMR spectra were taken at 100 MHz on a Varian HA 100 or HX-100-12

and at 80 MHz on a Tesla BS 487A, using TMS and HMDSO as internal standards. See Table 1 for 100 MHz NMR data on the compounds described herein. Sample concentrations were approx. 10% w/v in $CDCl_3$ and DMSO. Mass spectra were determined on an AEI MS 12 spectrometer. Purity of all compounds described was checked by TLC on alumina plates (Woelm, neutral).

Rhoeagenine methiodide (**1a** *methiodide*). Rhoeagenine (1 g) was suspended in 20 ml of chloroform and 20 ml of MeI added. This mixture was refluxed for 4·5 hr. 1·3 g (90%) of crystalline ppt was obtained which was recrystallized two times from water, m.p. 230–235° dec. $[\alpha]_D^{20} = +169°$ (c = 1, MeOH); IR, ν cm^{-1} (KBr) 3260 (OH). (Found: I, 24·62%; Calc. for $C_{21}H_{22}O_6NI$: I, 24·85%).

Hofmann degradation of rhoeagenine methiodide. Rhoeagenine methiodide (5·18 g) was dissolved in 96% EtOH (55 ml) and 15% NaOH aq (55 ml) and the mixture was refluxed for 2·5 hr. The solvents were almost completely removed under reduced pressure when the remaining slurry was mixed with Hyflo-Super-Cel. This mixture was then dried and washed with MeOH, when removal of solvent left a glass 3·2 g. Chromatography on alumina (Woelm, neutral) yielded the compounds described below.

Compound **3**. Light petroleum–benzene (1:1) eluted an oil (0·43 g 11·5%) which partially crystallized on treatment with MeOH. Recrystallization from the same solvent gave needles m.p. 132–133° $[\alpha]_D^{20} = 0°$ (c = 1 $CHCl_3$); IR (KBr) ν_{max} 1690 cm^{-1} (c = 0). (Found: C, 66·36; H, 5·36; N, 3·59. Calc. for $C_{21}H_{19}O_6N$, C, 66·14; H, 4·98; N, 3·67%). M^+ 383 *m/e*, 206 (100%); 175 (4%); 163 (4%), hydrochloride m.p. 145–146°.

Compounds **2a** *and* **2b**. Chloroform eluted **2b** first which recrystallized from EtOAc–benzene (0·05 g, 1·3%) as needles, m.p. 216–7°C $[\alpha]_D^{20} = +13°$ (c = 0·2 in EtOH); IR ($CHCl_3$) ν_{max} 3200 (OH). (Found: C, 65·47; H, 5·54; N, 3·48. Calc. for $C_{21}H_{21}O_6N$, C, 65·79; H, 5·48; N, 3·65%): $M^+ - 18$ at *m/e* 365 (4%).

After crystallization of **2b**, des-rhoeagenine **2a** remained in the mother liquors and was crystallized from MeOH, $CHCl_3$, EtOAc or benzene m.p. 177–178°, $[\alpha]_D^{20} = -35°$ (c = 0·5 in EtOH); IR ($CHCl_3$) ν_{max} 3570 (OH). (Found: C, 65·74; H, 5·57; N, 3·70. Calc. for $C_{21}H_{21}O_6N$: C, 65·79; H, 5·48; N, 3·65%): M^+ not observed but $M^+ - 18$ at *m/e* 365 (3%).

Compound **6**. Elution with MeOH gave 0·34 g (9%) of **6** which was crystallized from MeOH, m.p. 180–182°, $[\alpha]_D^{20} = +139$ (c = 0·49); IR (KBr) ν_{max} 3400–3200 broad ($COO\underline{H}$ $Me_2\overset{+}{N}\underline{H}$, 1600 cm^{-1} ($COO^{\ominus}$). (Found: C, 62·99; H, 5·35. Calc. for $C_{21}H_{21}O_7N$: C, 63·16; H, 5·26%): Mass spectrum M^+—not observed but M-18 at *m/e* 381 (8%).

REFERENCES

[1] J. Suszko and M. D. Rozwadowska, *Bull. Acad. Polon. Sci., Ser. sci. chim.* **11**, 513 (1913)

[2] J. Suszko and M. D. Rozwadowska, *Ibid.* **12**, 767 (1964)

[3] F. Santavy, J. L. Kaul, L. Hruban, L. Dolejš, V. Hanuš, K. Bláha and A. D. Cross, *Coll. Czech. Chem. Comm.* **30**, 3479 (1965)

[4] W. Klotzer, S. Teitel, J. F. Blount and A. Brossi, *J. Am. Chem. Soc.* **93**, 4321 (1971)

[5] M. Shamma, J. A. Weiss, S. Pfeifer and H. Dohnert, *Chem. Commun.* 212 (1968)

[6] C. S. Huber, *Acta Crystallographica* **B26**, 373 (1970)

[7] H. Irie, S. Tani and H. Yamane, *Chem. Commun.*, to be published; W. Klotzer, S. Teitel and A. Brossi, *Helv. Chim. Acta* **54**, 2057 (1971)

[8] F. Santavy, M. Maturova, A. Nemeckova and M. Horak, *Coll. Czech. Chem. Comm.* **25**, 1901 (1960)

[9] J. Hrbek, Jr., F. Santavy and L. Dolejs, *Ibid.* **35**, 3712 (1970)

[10] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p 56–57. Holden-Day, San Francisco, London, Amsterdam (1964)

[11] T. A. Crabb and R. C. Cookson, *Tetrahedron Letters* 679 (1964); R. C. Cookson, T. A. Crabb, J. J. Frankel and J. Hadec, *Tetrahedron.* Supp. 7, 355 (1966)

[12] E. W. Warmhoff, *Molecular Rearrangements* Edited S. P. de Mayo Part 2. p 942. Interscience, New York (1964)