Isolation and Reactions of 7a-Hydroperoxy-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizine

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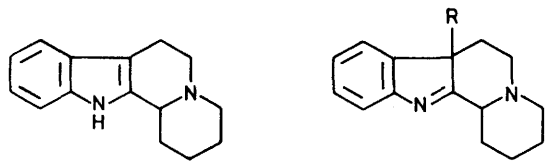
Dye-sensitized photo-oxygenation of the octahydroindoloquinolizine (**1**) provided the title compound (**2**) which was converted into the corresponding spiro-oxindole *N*-oxide (**3**), the hydroxyindolenine (**4**), into (**5**), which is the *N*-5-oxide of (**4**), the oxo-amide (**6**), the quinolone (**7**), and the 1,4-oxazine derivative (**8**) under various conditions, whereas the 2-acylindole (**11**) was obtained from the chloride (**10**).

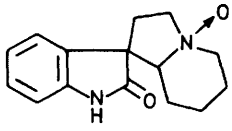
In continuation of our work[1] on the oxidation of indoles, we have investigated the oxygenation of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) as a simple model of indole alkaloids. In this communication we report the isolation of the 7a-hydroperoxyindolenine derivative (**2**) for the first time which may be a model for an intermediate in the biosynthesis of camptothecin.[2]

A methanolic solution of the indoloquinolizine (**1**) was irradiated with a 500 W halogen lamp for 1 h with ice-cooling in the presence of rose bengal under a continuous stream of oxygen gas. The solvent was concentrated *in vacuo* at below 15 °C (4 h) and the precipitated hydroperoxide (**2**) (61%) was collected. Prolonged evaporation (7.5 h) decreased the yield of (**2**) (**44**%) and the spiro-oxindole *N*-oxide (**3**) (stereochemistry



(1)

(2); R = O_2H
(4); R = OH



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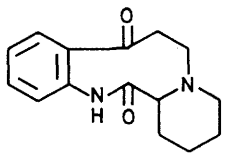
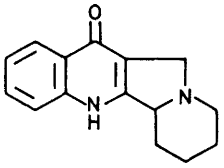
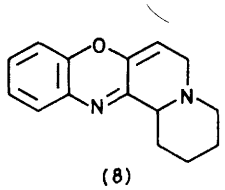


(6)



(7)



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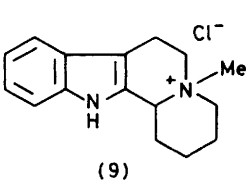
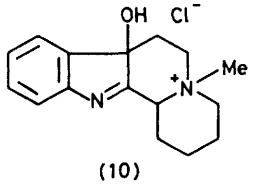
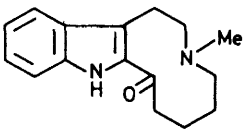


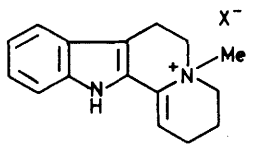
(9)



(10)



(11)



(12) a; X = AcO
b; X = I

undetermined)† was formed in 10% yield. On the other hand, direct reduction of the above reaction mixture with Me_2S gave (**4**) in 89% yield. The structural assignment of the products are based on spectral data‡ and a positive peroxide test. The structure (**2**) was further substantiated by its ready reduction to the hydroxide (**4**).‡

When (**2**) was refluxed in EtOH for 1 h, the oxo-amide (**6**)† was obtained as a pale yellow amorphous solid, while refluxing (**2**) under similar conditions for 8 h gave the quinolone (**7**) in 99% yield. The compound (**6**) was not stable and converted into (**7**) during isolation and purification by alumina or silica gel chromatography. Treatment of (**2**) with 10% NaOH–EtOH (pH 8) also provided (**7**) quantitatively.‡[3]

On the other hand, treatment of (**2**) with Ac_2O in methylene chloride, AcOH, or without solvent led to a complex mixture. When (**2**) was treated with $(CF_3CO)_2O$ at room temperature for 45 min the 1,4-benzoxazine derivative (**8**)† was produced in 29% yield, showing that (**2**) underwent a Baeyer–Villiger type rearrangement[1b,c,4] followed by deprotonation to give (**8**), whereas (**3**) (30%), (**4**) (9%), the *N*-5-oxide of (**4**) [(**5**), 11%],† and (**7**) (8%) were formed when the oxygenation reaction mixture was kept for 90 h at below 10 °C. On treatment with hydrochloric acid, the hydroxyindolenine derivative (**4**) readily gave the $\Delta^{5,12b}$-indoloquinolizidinium salt.[5,6]

The similar oxygenation of an aqueous solution of the chloride (**9**) in the presence of methylene blue (0.1 mol. equiv.) for 3 h was followed by reduction with Me_2S.§ The aqueous solution was washed with methylene chloride to remove the dye and lyophilized. The resulting residue was subjected to an ion exchange column (Amberlite CG-400). After elution with 1 M AcOH adjusted to pH 8 with 10% NaOH the product was extracted with methylene chloride. Evaporation of the solvent gave the 2-acylindole (**11**) (16%), m.p. 134—139 °C, instead of the corresponding hydroxyindolenine (**10**).¶ The structure of the 2-acylindole (**11**) was identified by direct comparison with an authentic specimen.[7] Further elution with 1—3 M AcOH provided (**12a**) which was converted into its iodide, (**12b**), m.p. 185—189 °C (26%).[6]

These results provide one possible mechanism for the formation of 2-acylindole alkaloids from the corresponding indole alkaloids *via* a hydroperoxide of type (**2**) as well as a model for an intermediate in the biosynthesis of camptothecin.

We thank the Ministry of Education, Science, and Culture (Grant-in-Aid for scientific research) for financial support.

Received, 22nd March 1982; Com. 323

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† Satisfactory spectral data were obtained.

‡ Compound (**2**): m.p. 133.5—134 °C (decomp.); u.v. λ_{max} (EtOH) 220, 225sh, and 265 nm (ϵ 3800); i.r. ν_{max} (KBr) 3080 (OOH), 1625, and 1610 cm^{-1}; *m/z* (%) 258 M^+ (7), 242 M^+-O (72), and 225 M^+-OOH (100); the n.m.r. spectrum of (**2**) was not obtained owing to its insolubility in $CDCl_3$, Me_2SO, and CD_3OD. Compound (**4**): m.p. 181—182 °C; λ_{max} (EtOH) nm (ϵ) 219 (21 000), 225sh (15 200), and 263(4080). Compound (**7**): m.p. 276—278 °C (decomp.); λ_{max} (EtOH) nm (ϵ) 213 (28 200), 236 (30 900), 314 (12 600), and 327 (14 100); *m/z* (%) 240 M^+ (100); ^1H n.m.r. $\delta(CF_3CO_2H)$ 1.80—2.80 (6H, m, CH_2), 3.60—4.00 (2H, m, CH_2N), 5.00—5.50 (2H, m, CH_2N), 5.60 (1H, m, CHN), and 8.64 (1H, d, *J* 8 Hz, aromatic H). All new compounds given with melting point gave satisfactory elemental analyses.

§ The u.v. spectrum of the reaction mixture was similar to that of the hydroxyindolenine (**4**).

¶ We found that it is difficult to reproduce the results obtained by previous experiments.[7] In the previous report, 2-acylindole was probably derived from the reduced product formed during work-up.