An Unusual Oppenauer Oxidation of (±) Ophiocarpine

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The Oppenauer oxidation of (±) ophiocarpine has been carried out to yield 3-(2′-vinyl-3′,4′-methylenedioxy) phenyl-4-hydroxyisoquinoline (**2**). Photolysis of this compound gave 3,4-dimethoxy-11,12-methylenedioxy-8,9-dihydro[1]benzoxepino(2,3-*c*) isoquinoline (**7**), whereas photolysis of the methyl ether of **2** produced *N*-norchelerythrine.

La réaction d'oxydation d'Oppenauer sur la (±) ophiocarpine conduit au 3-(2′-vinyl-3′,4′-méthylènedioxy) phényl-4-hydroxyisoquinoléine (**2**). La photolyse de ce composé conduit au 3,4-diméthoxy-11,12-méthylènedioxy-8,9-dihydro[1]benzoxepino(2,3-*c*) isoquinoléine (**7**), alors que la photolyse de l'éther méthylé de **2** conduit au *N*-norchelerythrine.

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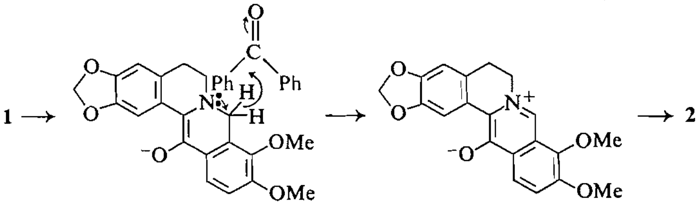
The modified (1) Oppenauer oxidation of a secondary alcohol function has been previously used with some success in the alkaloid field (2). We have applied this reaction to the oxidation of (±) ophiocarpine (**1**).

The benzylic secondary alcohol group in ophiocarpine might be expected to suffer oxidation under the conditions of the reaction and the resulting 13-ketotetrahydroberberine would almost certainly undergo further transformations in the presence of the strong base used. Such compounds have not been isolated, presumably because of their facile dehydrogenation to 13-hydroxyprotoberberinium salts. Hence our interest in this reaction.

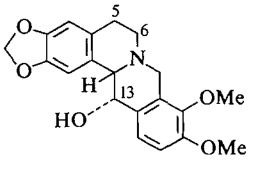
The oxidation carried out under Woodward's (1) conditions using dioxan as the solvent gave in *ca.* 60% yield 3-(2′-vinyl-3′,4′-methylenedioxy) phenyl-4-hydroxy-7,8-dimethoxyisoquinoline (**2**). The structure of **2** was evident from its p.m.r. spectrum which showed the characteristic pattern for the ABX system of the styrene unit with the coupling constants and chemical shifts of expected magnitude. The spectrum also contained a singlet integrating for one proton at δ 9.08 which could be assigned to the H-1 of the isoquinoline system (3). The resonances of the remaining protons were unexceptional. This structure was supported by the i.r. spectrum, ($\nu_{\text{—OH}}$ 3540 cm^{-1}) and by elemental analysis.

Several mechanisms may be written to rationalize the formation of this interesting product. By analogy with Woodward's original proposal (1) for the oxidation of the secondary alcohol group, it is possible to visualize a similar oxidation at the tertiary nitrogen atom which could be followed by a Hofmann elimination to yield **2** (Scheme 1).

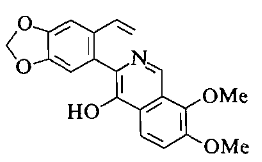
In order to test this hypothesis the reaction was repeated with (±) canadine (**3**) and with berberinium chloride (**4**). In both cases the



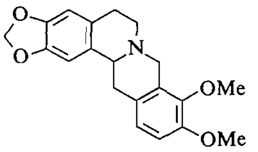
Scheme 1



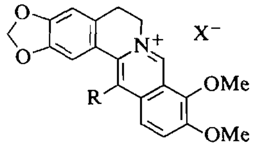
1



2



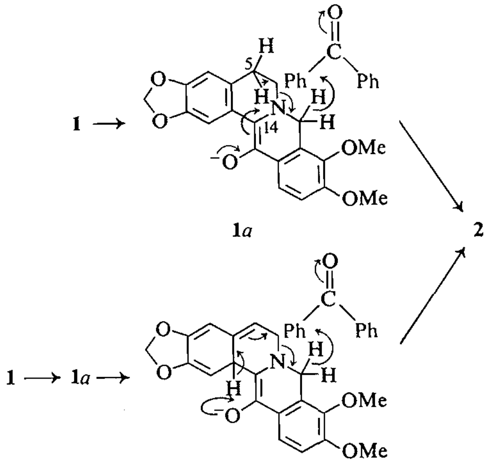
3



4 (R = H, X = Cl)
5 (R = OH, X = Cl)
6 (R = OMe, X = I)

starting material was recovered and no elimination products were obtained. The reaction was successful however, with 13-hydroxyberberinium chloride (**5**) and 13-methoxyberberinium iodide (**6**) (4). The product **2** was obtained in *ca.* 60% yield in the former case and *ca.* 20% yield in the latter.

It is therefore evident that the reaction does not take place via a simple Hofmann degradation and that the presence of an oxygen function at C-13 is indispensable for proton abstraction at C-5 and cleavage of the C_6—N bond. Two different mechanisms which recognize this fact are illustrated in Scheme 2. In the first instance proton transfer directly across ring B (in the boat conformation) from C-5 to -14 is postulated. Alternatively, the results may be rationalized by proposing a 1,3 proton transfer which is followed by a concerted rearrangement–elimination step. Minor variations of either mechanism could account for all the results stated above. There is however no easy way of deciding between them.



SCHEME 2

It has been recently shown (5) that *N*-methyl-1,2-dihydroisoquinolines similar to **2** are smoothly converted through an electrocyclic process to benzophenanthridine derivatives upon photolysis under suitable conditions. The photolysis of **2** was therefore attempted using a 3500 Å lamp and Pyrex filter under nitrogen in benzene solution.

This gave, *inter alia* the oxepine **7** readily recognized by the absence of the vinyl signals and presence of an A_2X_2 system consisting of two triplets centered at 4.8 and 2.83 δ (J_{AX} = 6.0 Hz). This structure was confirmed by the i.r. spectrum of **7** which was lacking in hydroxyl absorption. The oxepine **7** appears to be the first example of a new tetracyclic system.

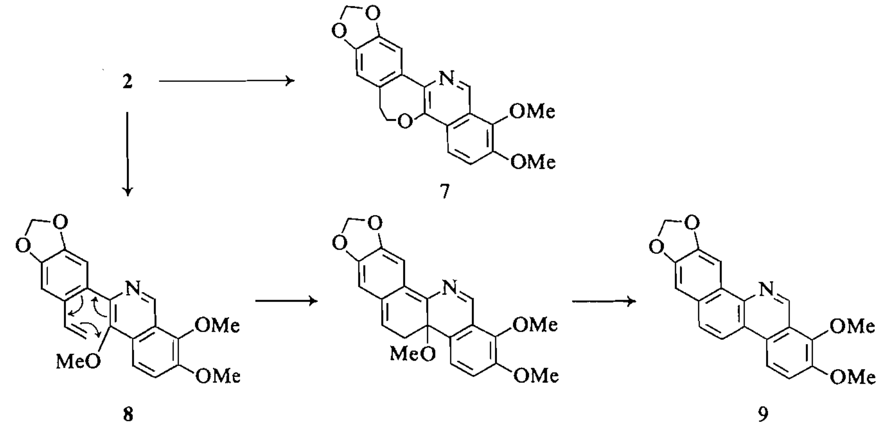
In order to block such a photo-addition reaction compound **2** was methylated with diazomethane to the *O*-methyl ether **8** which showed the presence of the extra methoxyl group at 3.62 δ in its p.m.r. spectrum, an upfield shift of $>$ 0.4 p.p.m. from the other two methoxyl groups at 4.06 and 4.14 δ. This shift is easily accounted for by the anisotropic effect of the benzene ring at position 3 of the isoquinoline system, in a non-coplanar conformation.

Photolysis of **8** under the same conditions as before led directly to *N*-norchelerythrine **9**. By analogy with the earlier work (5) the conversion may be regarded as an electrocyclic process followed by spontaneous elimination of methanol and concomitant aromatization (Scheme 3). The n.m.r. spectrum of **9** was fully compatible with its structure while the m.p. and the u.v. spectrum were identical with that of *N*-norchelerythrine already published (6).

This reaction therefore completes a three step conversion of a protoberberine to a fully aromatic benzophenanthridine. It may have some practical advantages over the earlier method (5) in that no dehydrogenation steps are required subsequent to the photolysis.

Experimental

Melting points were determined using a Fisher Meltemp unit and are uncorrected. The p.m.r. spectra were recorded using the frequency sweep mode of a Varian HA-100 spec-



SCHEME 3

trometer. Samples were dissolved in $CDCl_3$, unless otherwise specified, using added TMS as the internal locking signal. Chemical shifts were measured relative to TMS. A Beckman I.R. 10 spectrometer was used to record the i.r. spectra and a Coleman–Hitachi EPS-3T spectrophotometer was used for the u.v. spectra.

3-(2′-Vinyl-3′,4′-methylenedioxy)phenyl-4-hydroxy-7,8-dimethoxy Isoquinoline (2)

(*a*) Ophiocarpine (57 mg) in dry dioxan (3.5 ml) was refluxed under nitrogen with potassium *t*-butoxide (80 mg) and benzophenone (150 mg) for 20 h. The solvent was removed under reduced pressure and the residue extracted with 2% hydrochloric acid. The acid extract was washed with ether, basified with ammonia, extracted with chloroform, dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from methanol (33 mg) m.p. 191–192°.

The u.v. spectrum: λ_{max}^{EtOH} 235, 270(sh), 302, and 355 nm; log ε_{max} 4.56, 4.29, 4.12, and 3.61 respectively. The i.r. spectrum: $\nu_{max}^{CHCl_3}$ 3540 cm^{-1}. The n.m.r. spectrum (δ): 4.02 (3H, s) and 4.05 (3H, s), 6.00 (2H, s), 6.88 (1H, s), 7.17 (1H, s), 9.15 (1H, s), 5.11 (1H, d, d) 5.61 (1H, d, d) 6.44 (1H, q) ($J_{AB} = 18$ and $J_{AX} = 11$ Hz); 7.47 (1H, d) 7.95 (1H, d) ($J_{AB} = 9$ Hz).

Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.31; H, 5.14; N, 4.26.

(*b*) 13-Hydroxyberberinium chloride (**5**, 52 mg) in dry dioxan (10 ml) was refluxed under nitrogen with potassium *t*-butoxide (79 mg) and benzophenone (140 mg) for 42 h. The solvent was evaporated under reduced pressure and the residue extracted with 2% hydrochloric acid. The acid extract was washed with ether, basified with ammonia, extracted with chloroform, dried ($MgSO_4$), and evaporated. The residue was purified by t.l.c. (silica gel chloroform – 5% acetone) and crystallized from methanol (26 mg). It was identical in all its properties with **2**.

(*c*) 13-Methoxyberberinium iodide (**6**, 116 mg) in dry dioxan (12 ml) was refluxed under nitrogen with benzophenone (500 mg) and potassium *t*-butoxide (230 mg) for 36 h. The subsequent isolation and purification was carried out as before (17 mg.).

Reactions *b* and *c* were also successful without benzophenone. (±) Canadine (**3**) and berberinium chloride (**4**) were recovered unchanged after reactions by the above procedure.

Methylation of **2**

Compound **2** (372 mg) was dissolved in methylene chloride (30 ml) and treated with excess ethereal diazomethane at room temperature for 24 h. The solvents and excess diazomethane were allowed to evaporate and the residue purified by chromatography on a silica gel column in benzene–acetone (9:1). The product **8**, was a thick oily semisolid (310 mg) homogeneous on t.l.c. The n.m.r. spectrum; virtually identical with **2** but for an extra singlet (3H) at 3.62 δ.

3,4-Dimethoxy-11,12-methylenedioxy-8,9-dihydro[1]-benzoxepino[2,3-c] Isoquinoline (7)

Compound **2** (75 mg) was dissolved in dry benzene (100 ml) and irradiated in a Rayonet reactor at 3500 Å under nitrogen for 2 h. The solvent was evaporated and the residue purified by preparative t.l.c. (silica gel, benzene–acetone, 9:1) and crystallized from ethanol (25 mg) m.p. 145–147°. The u.v. spectrum: λ_{max}^{EtOH} 233, 264, 320, and 363 nm; log ε_{max} 4.59, 4.33, 4.34, and 3.82 respectively. The n.m.r. spectrum (δ): 2.83 (2H, t) and 4.80 (2H, t) ($J_{AX} = 6$ Hz), 4.01 (3H, s) 4.06 (3H, s), 5.98 (2H, s), 6.75 (1H, s), 7.47 (1H, s), 9.13 (1H, s), 7.45 (1H, d), and 7.95 (1H, d) ($J_{AB} = 9.0$ Hz).

Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.50; H, 5.06; N, 3.99.

N-Norchelerythrine (9)

Compound **8** (100 mg) in dry benzene (50 ml) was irradiated in a Rayonet reactor at 3500 Å under nitrogen for 4 h. The mixture was worked-up as before to yield the product which was crystallized from ethanol (52 mg), m.p. 215° (lit. 212–214°). The u.v. spectrum was identical with that already published (6). The n.m.r. spectrum (δ): 4.10 (3H, s), 4.17 (3H, s), 6.16 (2H, s), 7.24 (1H, s), 8.75 (1H, s), 9.78 (1H, s) 7.58 (1H, d), and 8.36 (2H, d) ($J_{AB} = 9.2$ Hz) and 7.86 (1H, d) ($J_{A'B'} = 9.0$ Hz).

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