

ALKALOIDS

Part I. The Oxidation of Papaverine to Papaveraldine (Xanthaline) by Selenium Dioxide

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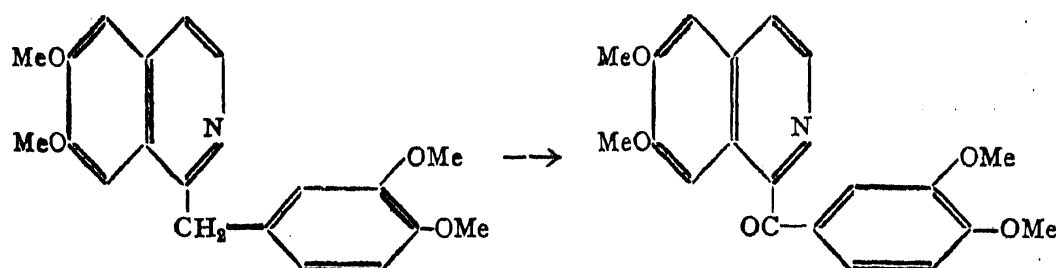
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ONE of the most successful methods for elucidating the constitution of alkaloids is the examination of the behaviour of the alkaloids towards oxidising agents. Very often the initial products of the oxidation are further attacked by the oxidising agent resulting in degradation products of comparatively small molecular weight and often much oxalic acid. It is mainly for this reason that it has frequently been found difficult to isolate the initial product of the oxidation and that, in its place, a variety of degradation products derived from one or the other half of its molecule are the only substances that can be discovered. This leads to difficulties in rigidly fixing the constitution of the substance.

In the course of some investigations it became evident that the oxidative methods commonly employed are not helpful in deciding alternative possibilities of ring structure. It was found that selenium dioxide oxidation was useful in getting workable quantities of the primary oxidation products, but interpretation of the results became difficult due to the lack of specific knowledge concerning the action of selenium dioxide on condensed polynuclear heterocyclic structures. In order to gain insight in this direction it was decided to examine the behaviour of selenium dioxide towards alkaloids of known constitution.

Riley¹ gives an excellent review of the use of selenium dioxide as an oxidising agent and a perusal of the literature shows that the outstanding feature is the highly specific nature of the oxidising action of selenium dioxide. Although selenium dioxide is undoubtedly a relatively vigorous oxidising agent, its action stops at specific stages even though the compound produced is unstable towards oxidising agents and highly reactive, as in the case of mesoxalic ester,² ketohydroxysuccinic ester,³ pyridine and quinoline aldehydes⁴, etc. Hence the hope is entertained that selenium dioxide oxidation would prove a very useful tool in alkaloid chemistry.

When papaverine, in acetic acid solution, is oxidised with selenium dioxide it is converted into papaveraldine (xanthaline).



This result is in conformity with the observation that an aryl group can activate the adjacent methylene group and render it susceptible to attack by selenium dioxide⁵. The quantitative yield of papaveraldine and the absence of other degradation products is specially noteworthy.

Papaveraldine, first isolated by Smith⁶ from opium in which it occurs only in minute quantities, was examined by Dobson and Perkin⁷ and proved to be identical with the product⁸ obtained by the oxidation of papaverine, dissolved in sufficient dilute sulphuric acid to form the acid salt, with cold 2% potassium permanganate solution. The identity of the selenium dioxide oxidation product was established by a comparison of the melting points of the alkaloid, its methiodide and picrate.

Experimental

To papaverine (10 g.) dissolved in acetic acid (100 c.c.) was added pure selenium dioxide (4 g.) and the mixture heated on the water-bath for 1½ hrs. and then refluxed for the same period. After oxidation the acetic acid solution was filtered and the filtrate evaporated to dryness on the water-bath. The residue was ground up with 100 c.c. of 50% hydrochloric acid when the product went into solution and after a short time the hydrochloride separated out. 400 c.c. of water was added and the mixture heated on the water-bath. The solution was filtered from a small quantity of insoluble impurity and allowed to cool when the hydrochloride (m.p. 200°) separated out. This was decomposed with ammonia and the free base crystallised from methylethyl ketone yielding plate-like crystals melting at 209–211° (Literature⁷–210°). The methosulphate was converted into methiodide and crystallised from dilute methyl alcohol in orange yellow crystals melting at 133–135° (Literature^{7,9}–132 and 135°). The picrate crystallised in fine yellow needles melting at 208–209° (Literature⁹–208–209°). The platinum chloride analysed for the formula $(C_{20}H_{19}O_5N.HCl)_2 PtCl_4.H_2O$.

Summary

The selenium dioxide oxidation of papaverine yields papaveraldine.

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