

A SIMPLIFIED BERBINE SYNTHESIS

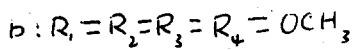
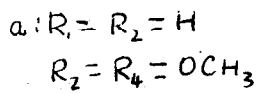
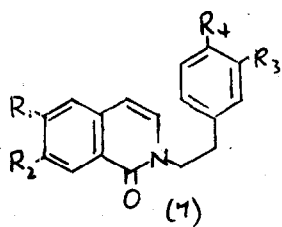
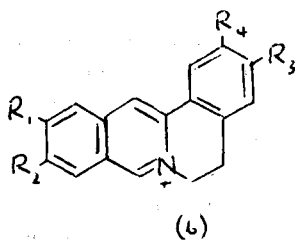
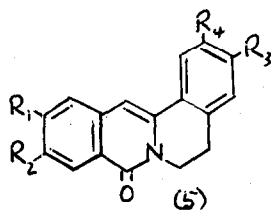
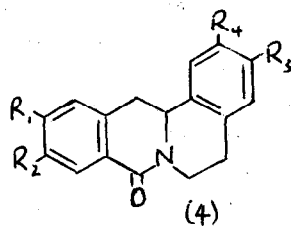
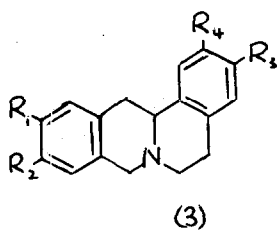
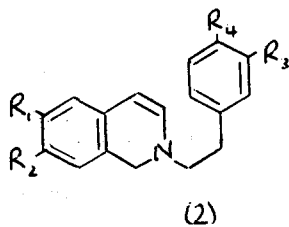
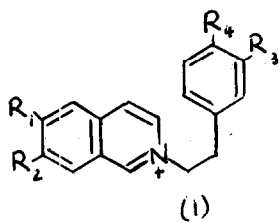
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Several methods have been described¹ for the synthesis of the berbine skeleton (3), but perhaps the most direct method involves^{2,3} the reduction, with lithium aluminium hydride, of the quaternary isoquinolinium salts of the type (1), followed by treatment of the intermediate 1,2-dihydroisoquinoline (2) with mineral acid. In this way 2,3-dimethoxyberbine (3a) has been obtained² in 18% yield, and norcoralydine (3b) in 40% yield.³

We have now found that treatment of the quaternary halide (1a) with aqueous alkali, followed by concentrated hydrochloric acid at room temperature for three to five days, gives (3a) in a 24% yield. The product was shown (superimposable infrared spectra and mixed melting point of the hydrochlorides) to be identical with the 2,3-dimethoxyberbine of Huffman and Miller². A second product (m.p. 142°) was isolated⁴ in 20% yield, and this was shown by a combination of spectral data and the following chemical evidence to be the lactam (4a). Thus, reduction of this compound with lithium aluminium hydride gave (3a), whereas dehydrogenation with palladium black yielded the isocarbostyryl derivative (5a), which was identical with the substance obtained by dehydrogenation of (3a) with iodine to (6a), followed by oxidation with potassium ferricyanide. Huffman and Miller² also describe (5a) which was obtained during the course of their unambiguous synthesis of 2,3-dimethoxyberbine (3a).

It is well known⁵ that quaternary isoquinolinium salts may undergo a mutual oxidation-reduction reaction in the presence of alkali to yield a mixture of a 1,2-dihydroisoquinoline and an isocarbostyryl. In the case of (1a), alkali treatment would be expected to yield (2a), and this would cyclise to (3a) in the presence of mineral acids. The



corresponding isocarbostyryl (7a) could not be detected in the reaction mixture, and we were able to show that authentic (7a), prepared by the oxidation of (1a) with potassium ferricyanide, was rapidly converted into (4a) by concentrated hydrochloric acid at room temperature.

This unexpected and novel type of reaction of an isocarbostyryl is being investigated further.

A 50% yield of (3a) was achieved from (1a) by treating the latter with alkali, then with hydrochloric acid as described above, and then treating the mixture of (3a) and (4a) formed directly with lithium aluminium hydride.

When the tetramethoxyisoquinolinium salt (1b) was treated with alkali and then with acids, norcoralydine (3b) was easily isolated in 33% yield. The isocarbostyryl (7b) was also formed, but none of (4b) could be detected in the reaction mixture. We have, so far, not been able to convert authentic (7b), prepared by the potassium ferricyanide oxidation of (1b), into (4b) by treatment with hydrochloric acid.

References

1. K. Pelz, Chem.Listy, 57, 1107 (1963).
2. J. W. Huffman and E. G. Miller, J.Org.Chem., 25, 90 (1960).
3. A. R. Battersby, D. J. Le Count, S. Garrett and R. I. Thrift, Tetrahedron, 14, 46 (1961).
4. Satisfactory analyses were obtained for all compounds reported in this communication.
5. R. C. Elderfield, Heterocyclic Compounds, 4, 361 (1952).