# Electro-oxidation of 1-phenethylisoquinolines

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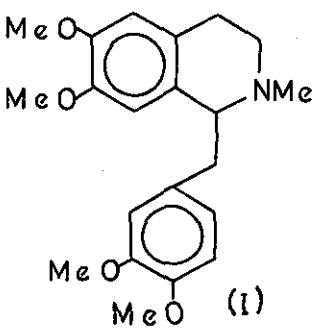
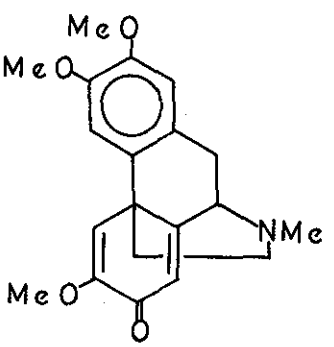
An examination of methoxylated derivatives of 1-phenethylisoquinoline has shown that the mode of electrochemical oxidation undergone by such compounds is different to that exhibited by analogous 1-benzyl-isoquinolines; in particular, intramolecular cyclisation through C-C bond formation is not observed.

The electrochemical oxidative cyclisation of 1,2,3,4-tetrahydro-1-benzyliso-quinolines has been extensively studied and with appropriate activation in the aromatic ring systems the products are morphinandienones; thus laudanosine (I) gives the O-methylflavinantine (II):

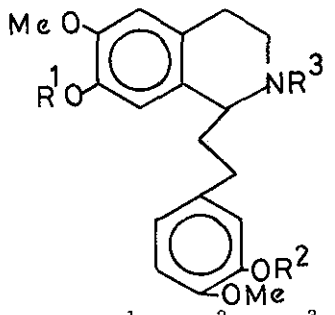



(I)

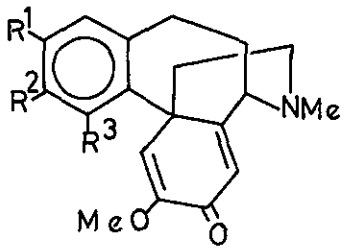



(II)

Several alkaloids are now known which are believed to arise naturally through the agency of 1-phenethylisoquinolines and derivatives of these have also been synthesised, along supposed biogenetic pathways, in the laboratory. Androcymbine (VII), for example, is a member of a novel group of homomorphinandienone alkaloids[2] and demethoxy-O-methyl-androcymbine (VIII) has been prepared in poor yield by phenolic oxidative coupling of the 1,2,3,4-tetrahydro-1-phenethylisoquinoline (III), followed by methylation of the product with diazomethane[3].



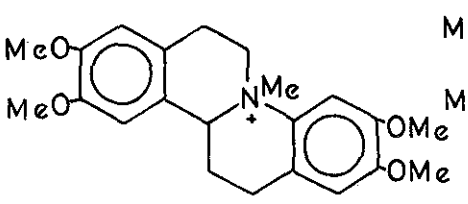
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (III) | H | H | Me |
| (IV) | Me | Me | Me |
| (V) | Me | Me | $COCH_3$ |
| (VI) | Me | Me | $COCF_3$ |



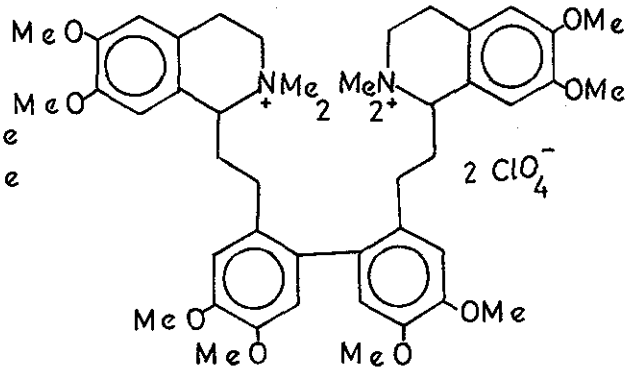
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (VII) | OMe | OH | OMe |
| (VIII) | OMe | OMe | H |

In view of these two sets of results we speculated that electrochemical oxidation of 1-(3',4'-dimethoxyphenylethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV) should lead to the same *androcymbine* derivative (VIII) directly but in higher yield.

The isoquinoline (IV) showed three anodic peaks (*Ep* + 0.62, +1.08 and +1.21 V vs S.C.E.) during cyclic voltammetry (in acetonitrile solution containing 10% sodium perchlorate), but a preparative electrolysis at a controlled anode potential of +1.2 V gave only the N-C coupled product (IX), isolated as the perchlorate salt, m.p. 172-173°C.



(IX)



(X)

It seems clear that the peaks at 1.08 and +1.21 V in the cyclic voltammogram of (IV) correspond to the removal of an electron from each of the two aryl units, whereas the low potential peak at +0.62 is due to the ionization of an electron from the nitrogen atom[4]. This is supported by the fact that the methoperchlorate of (IV) shows no peak at ~ +0.6 V. On the other hand the cyclic voltammogram of this compound exhibits, in addition to the expected redox couples at Ep 1.0 and Ep 1.4 V, a product peak at Ep +1.12 V.

A preparative electro-oxidation of the methoperchlorate salt also failed to yield an androcymbine-type structure; instead the product was the "dimer" (X), m.p. 172-173°C, the cyclic voltammogram of which has an anodic peak at Ep +1.12 V as predicted.

From these results we conclude that in order to effect the desired C-C intramolecular cyclisation the substrate for oxidation should not be an isoquinoline with a basic nitrogen atom, nor an isoquinolinium salt. A familiar solution to this type of problem is to protect the amine function by forming the corresponding N-acyl derivative[5], but so far attempts, in our hands, to oxidize (V) or (VI) have been unproductive despite the fact that recently Kupchan and his co-workers[6] have successfully cyclised (IV) to a homoaporphine derivative with vanadium oxyfluoride in trifluoroacetic acid solution.

Acknowledgments

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References

1. L.L.Miller, F.R.Stermitz and J.R.Falck, J.Amer.Chem.Soc., 93, 5941 (1971); ibid., 95, 2651 (1973); ibid., 96, 2981 (1974). T.Kametani, K.Shishido and T.Takano, J.Het.Chem., 12, 305 (1975).

2. J.Hrbek and F.Santavy, Coll.Czech.Chem.Comm., 27, 255 (1962); A.R.Battersby, R.B.Herbert, L.Pijewska and F.Santavy, Chem.Comm., 228 (1965).

3. T.Kametani, K.Fukumoto, M.Koizumi and A.Kozuka, J.Chem.Soc.(C), 1295 (1969).

4. L.L.Miller, F.R.Stermitz, J.Y.Becker and V.Rahachandran, J.Amer.Chem.Soc., 97, 2922 (1975).

5. See M.Sainsbury and J.Wyatt, J.Chem.Soc.Perkin 1, 661 (1976) and references cited therein.

6. S.M.Kupchan, O.P.Dhingra, C-Kyu Kim and V.Kameswaran, J.Org.Chem., 41, 4047 (1976).

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