Synthesis of 3-Arylisoquinolines by Thermolysis of 3-Aryl-1,2-dihydroisoquinolin-4(3*H*)-one Salts

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Summary 3-Aryl-1,2-dihydroisoquinolin-4(3*H*)-one salts give mixtures of 3-arylisoquinolines and 3-aryl-4-hydroxyisoquinolines after heating in dimethylformamide and extraction.

MASS spectra of salts (hydrochlorides or hydrogen sulphates) of 3-aryl-1,2-dihydroisoquinolin-4(3*H*)-ones (**1**) show two main peaks, $M - 2H$ and $M - H_2O$. The former corresponds to loss of 2H from the 1,2-bond with enolisation to give the aromatic 4-hydroxyisoquinoline (**2**) and the latter suggests loss of oxygen attached to the 4-position and two hydrogens to give the 4-unsubstituted aromatic isoquinoline (**3**). The first process is expected, but the loss of doubly-bonded oxygen is difficult to explain by the usual fragmentation pathways, since it involves a dual reduction–oxidation occurring simultaneously at different parts of the heterocycle. We therefore envisaged a thermal process, and repeated it by heating the salts in evacuated tubes. This was successful with very small samples, but with synthetically useful quantities gums were produced from which only small amounts of product could be isolated. We resorted to the use of a high-boiling inert solvent

[dimethylformamide (DMF)], and obtained a satisfactory synthetic procedure, which replaces the three steps previously necessary to effect the conversion.[1] Yields of (**2**) and (**3**), after work-up and isolation by preparative thin-layer or column chromatography in four cases, are given in the Table.

TABLE

R	Anion	Yield (%) (3)	Yield (%) (2)
Ph	HSO_4^-	56	14
		64[a]	12[a]
3,4-Dichlorophenyl	HSO_4^-	43	29
4-Pyridyl	Cl^-	23[b]	44
3,4-Dimethoxyphenyl	Cl^-	25	38
		52[a]	21[a]
2-Pyridyl		see text	
H	Cl^-	see text	

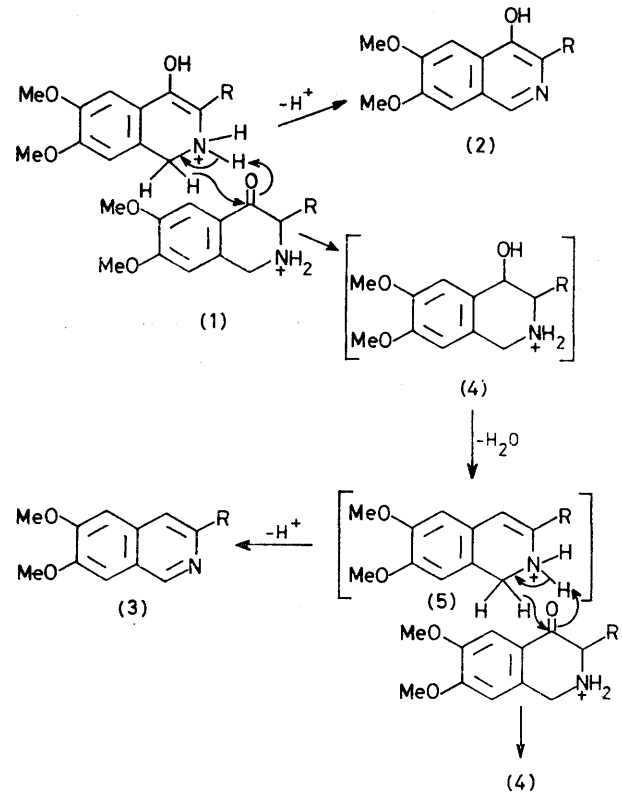
[a] Under nitrogen. [b] Also some *O*-demethylated isoquinoline (9%).

Since the 4-hydroxyisoquinoline (**2**) is an expected product of air oxidation we repeated two of the reactions under nitrogen and, as expected, the yield of (**3**) was increased (see Table).

While this thermolysis is reminiscent of the synthesis of naphthalenes from 3,4-dihydronaphthalen-1(2*H*)-ones[2,3] and of phenols from cyclohexane-1,4-diones,[4] the reaction conditions are different. Naphthalene production is strongly hindered by a substituent adjacent to the carbonyl,[3] which also suggests a different mechanism. Since the 4-hydroxyisoquinoline (**2**) is produced under nitrogen and in high vacuum, we suggest an intermolecular mechanism (Scheme), where the hydroxytetrahydroisoquinoline (**4**) is re-generated. Dehydration of (**4**) would give the powerfully reducing[5] 1,2-dihydroisoquinoline (**5**). Thus every time the chain was initiated, a molecule of (**2**) would be produced, but thereafter consumption of (**1**) would produce only (**3**).

Alternative intramolecular and bimolecular (head-to-tail) mechanisms fail to account for the production of (**2**). However, it must be recognised that oxidation to the 4-hydroxyisoquinoline is very easy. In the case where R = 2-pyridyl, we have been unable to isolate the isoquinolinone from the previous synthetic step, the product oxidising rapidly to (**2**; R = 2-pyridyl).

Mass spectra of the free bases of these 3-arylisoquinolinones also exhibit peaks corresponding to $M - 2H$ and $M - H_2O$, but these no longer represent the major fragments. The main peaks correspond instead to a *retro*-Diels–Alder homolysis in which the nitrogen atom is lost together with C-3 and the 3-substituent as a benzylidene imine. Where the 3-substituent is lacking as in (**1**; R = H), this mode of decomposition leads to loss of methylene imine even when the hydrochloride is used, and there is no sign of aromatisation to isoquinoline (**3**). The hydrochloride (**1**; R = H) also gave an intractable product when heated in DMF, as did the free base when fused with NaOH–KOH.[2] The major function of the 3-aryl substituent in the thermolysis is probably to assist enolisation (Scheme).



SCHEME

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