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AN IMPROVED ROUTE TO ISOQUINOLINES; SYNTHESIS OF THE ALKALOIDS ESCHOLAMINE AND TAKATONINE.

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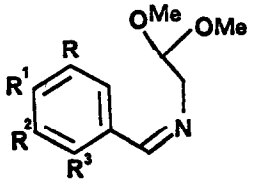
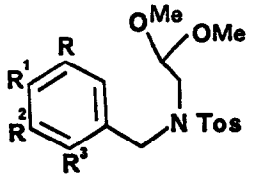
The difficulties in the synthesis of certain isoquinolines by the traditional Pomeranz-Fritsch reaction are well known[1,2,3] although the Bobbitt[4,5] modification has made possible the preparation of tetrahydroisoquinolines in good yields. More recently we have shown[6] that the N-tosyl derivative (2,R=R^1=H,R^2=OMe,R^3=O.CH_2Ph) may be cyclised by hydrochloric acid in dioxan to the N-tosyldihydroisoquinoline (4,R =OCH_2Ph) which leads to the corresponding isoquinoline on treatment with potassium t-butoxide. We now report a new modification which affords isoquinolines directly in high yield using the acid conditions alone. Thus the Schiff's bases (1a,b,c,d, and e)

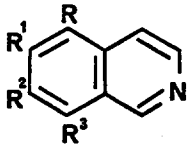


(1)



(2)

	R	R^1	R^2	R^3
a)	H	H	OMe	H
b)	OMe	OMe	OMe	H
c)	H	O—CH_2—O		H
d)	H	H	OMe	OMe
e)	H	OMe	OMe	H



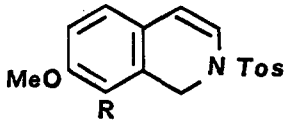
(3)

after hydrogenation and tosylation gave the corresponding tosylates (2) which on heating under reflux with 6N-hydrochloric acid [3.7 ml per 1 g. of (2)] in dioxan (24 ml) in the dark under an atmosphere of nitrogen for 5 hr. gave the isoquinolines (3) in the yields shown in the Table.

Table

Isoquinoline	Yield (%)	m.p.	Lit. m.p.
3a	70	48-48.5°	49° [7]
3b	90	picrate 180-182°	179° [8]
3c	85	122-123°	124° [7]
3d	88	picrate 197-198°	200-201° [10]
3e	90	90-91°	89-91° [11]

That cyclisation of the acetal (2a) precedes elimination of toluenesulphinic acid was shown by the isolation of N-tosyl-7-methoxy-1,2-dihydroisoquinoline (4,R =H) m.p. 112-113°; the latter was formed rapidly as a discrete intermediate which was then transformed more slowly into the isoquinoline (3a).



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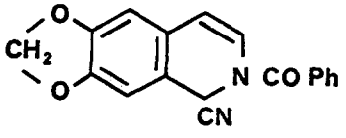
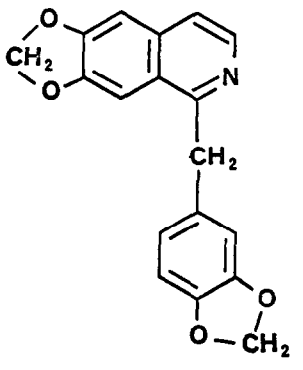


(5)

As examples of the application of this reaction in alkaloid synthesis, the isoquinoline (3c) was converted[6] to the Reissert compound (5) m.p. 134-135°, and then treated with 3,4-methylenedioxybenzylchloride. The product was decomposed with alkali to give escholamine free base, (6), m.p. 163-164° [60.5% yield from (3c)] ; methiodide m.p.266-267° (Lit.[9] 265-266°). Similarly, the isoquinoline (3b) was converted into takatonine[12] free base (7) methiodide m.p. 181-182°, Lit[12] 181-182°) in 75% yield.



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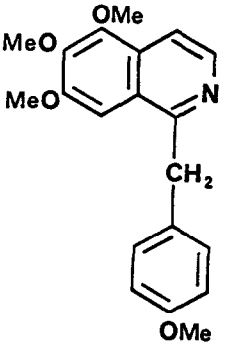

(7)

All the compounds were fully characterized by spectroscopic methods and all the crystallised compounds gave acceptable elemental analyses.

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