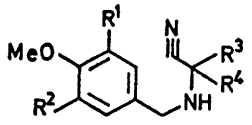
Rearrangement in the Synthesis of Isoquinolines from Benzylaminoacetonitriles

By D. N. HARCOURT* and N. TAYLOR
(*School of Pharmacy, University of Bath, Claverton Down, Bath* BA2 7AY)
and R. D. WAIGH
(*Department of Pharmaceutical Chemistry, University of Strathclyde, Glasgow* G1 1XW)

Summary The treatment of methoxybenzylaminoacetonitriles with concentrated sulphuric acid at 50° gave products arising from Hayashi-type rearrangement.

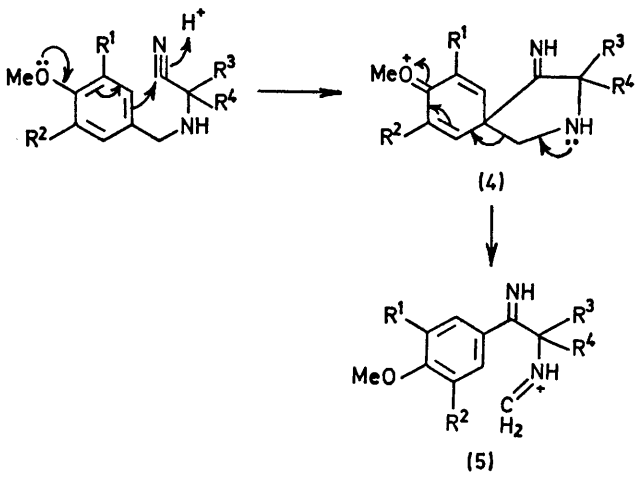
WE have reported[1] the formation of 1,2-dihydro-6,7-dimethoxyisoquinolin-4(3*H*)-ones by treatment of 3,4-dimethoxybenzylaminoacetonitriles with concentrated sul-

phuric acid at 50°. Work described here suggests that contrary to generally accepted mechanisms for the Pomeranz–Fritsch synthesis[2] and its modifications, cyclisation in this case occurs preferentially but not exclusively *via* a



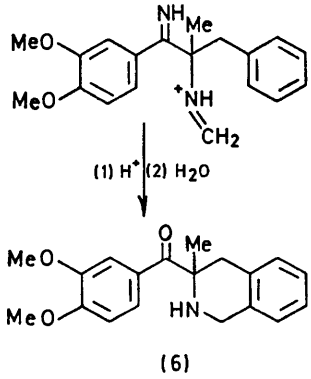
	R^1	R^2	R^3	R^4
(1)	H	OMe	Me	CH_2Ph
(2)	H	H	$-[CH_2]_5-$	
(3)	OMe	OMe	$-[CH_2]_5-$	

spiro-intermediate obtained from electrophilic attack *para* to the C-4 methoxy-substituent (Scheme 1).



SCHEME 1.

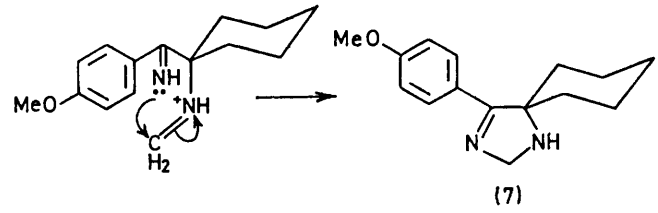
In the attempted preparation of a 3-benzylisoquinolinone from the aminonitrile (**1**), the sole product isolated was the isoquinoline (**6**), m.p. 138° (20% yield). We postulate a mechanism (Schemes 1 and 2) involving the spiro-intermediate (**4**), reminiscent of that suggested in the Hayashi rearrangement of *ortho*-benzoylbenzoic acids,[3] and subsequent formation of the iminium ion (**5**).



SCHEME 2.

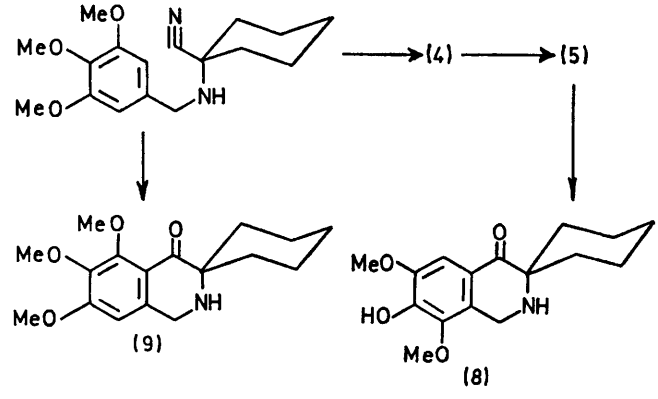
The fate of this intermediate is dependent upon the nature of the substituents R^3 and R^4 and the reactivity of the methoxy-substituted ring. The deactivating influence of the imino-group on the methoxy-ring favours Pictet–Spengler cyclisation to the benzyl substituent (**5**; $R^4 = CH_2Ph$) thus forming the 3,3-disubstituted-tetrahydroisoquinoline (Scheme 2).

The 4-methoxybenzylaminoacetonitrile (**2**) was converted into the spirocyclohexyl-3-imidazoline (**7**), m.p. 92° (80%) (Scheme 3). Here the low order of reactivity of the aromatic nucleus in the *ortho* positions and the absence of an alternative nucleophile allow only addition of the imine to the iminium ion with formation of the imidazoline ring.



SCHEME 3.

The hypothesis is supported by cyclisation of (**3**) (Scheme 4). Cyclisation *via* (**5**) to the spirocyclohexylisoquinolin-4(3*H*)-one (**8**), m.p. 149° occurred in 20—30% yield. The concomitant *O*-demethylation here observed is not in accord with the work of Grethe and his co-workers,[4] but may occur in the transition state (**4**), giving electronic stability and relieving steric strain. Such a central methyl group is comparatively easily lost under acidic conditions.[5] A small quantity (9%) of the "normal" spirocyclohexylisoquinolin-4(3*H*)-one (**9**), m.p. 128°, was also isolated. Thus "normal" cyclisation is not excluded.



SCHEME 4.

Preference for formation of the spiro-intermediate over electrophilic attack *para* to a C-3 methoxy-substituent is also evident in the cyclisation of 2-(2,3-dimethoxybenzylamino)-2-spirocyclohexylacetonitrile, where the only product isolated was 1,2-dihydro-5,6-dimethoxy-3-spirocyclohexylisoquinolin-4(3*H*)-one, m.p. 110°, in 9% yield.

Where the starting material possesses 3,4-dimethoxy-substitution and lacks alternative nucleophiles, as in the first examples we reported,[1] the product is the same whether produced by "normal" cyclisation or by rearrangement with cyclisation.

Structural assignments are based upon satisfactory elemental analysis, diagnostic i.r., n.m.r., and mass spectra

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