A New Synthesis of 4-Oxo-1,2,3,4-tetrahydroisoquinolines

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DURING some synthetic work on 3-arylisoquinolines, we prepared certain 4-oxo-1,2,3,4-tetrahydroisoquinolines. None of the reported routes[1,2] possessed the flexibility that we sought, with the exception of the unsuccessful attempt[3] to cyclise α-amino-nitriles of the type (I), which are formed in good yield by a modified Strecker synthesis,[4] and potentially afford ready variation in substitution at the C-3 position of the isoquinoline. In view of the recorded[2] instability of simple 4-oxo-isoquinolines, we considered this route warranted investigation, and found the mild conditions for the cyclisation of a number of nitriles (I; R^1 = OMe). The nitrile (2 g.) was dissolved in concentrated sulphuric acid (10 ml.) and heated at 50° for 4 hr., or left overnight at room temperature. Dilution followed by basification with 5N sodium hydroxide gave the product (II) in good yield and a high state of purity.

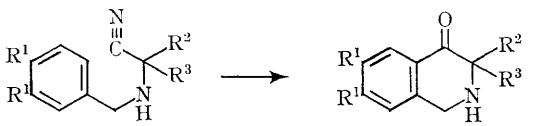
4-Oxo-1,2,3,4-tetrahydroisoquinolines (II; R^1 = OMe)

R^2	R^3	% yield	m.p.† (°C)
Ph	H	53	138
Ph	Me	83	150
Me	Me	60	135
$CH_2{\cdot}[CH_2]_3{\cdot}CH_2$		80	147

† Determined for analytical sample on a Kofler hot-stage.

Structural assignment of the isoquinolines is based upon elemental analysis and diagnostic i.r. and n.m.r. spectra.

Some difficulty was encountered in the isolation of the free base (II; R^1 = OMe, R^2 = Ph, R^3 = H) and best yields were obtained by isolation as the hydrochloride. We are further preparing the 3-mono- and 3-un-substituted 4-oxo-1,2,3,4-tetrahydroisoquinolines in view of the low yields recently reported[5] for the cyclisation of *N*-benzylglycine esters in the 6,7-dimethoxy-series.



(I) (II)

Attempted cyclisation of amino-nitriles (I; R^1 = H) has so far resulted in failure; with the conditions described here, conversion to the corresponding amide occurs.

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