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A New Approach to the Preparation of 1,6- and 1,7-Naphthyridines

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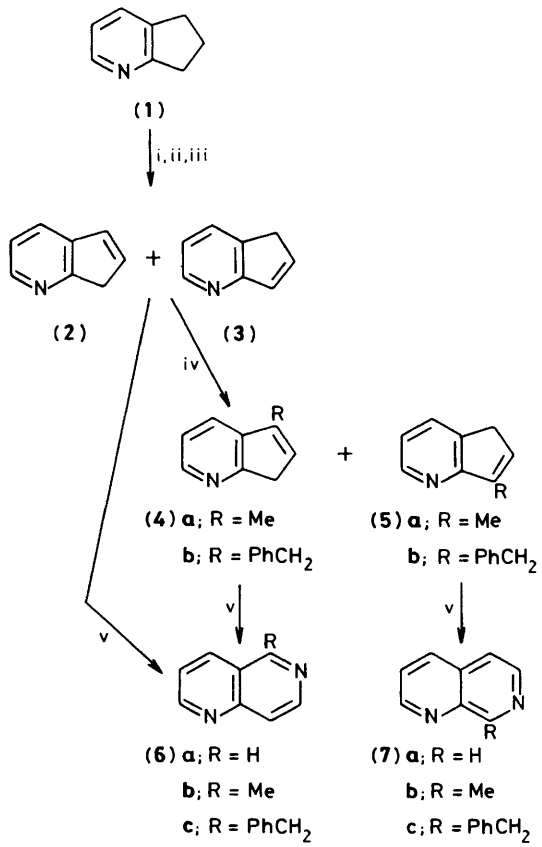
Substituted 1,6- and 1,7-naphthyridines can be prepared by a simple route from readily available pyrindane; this method is more flexible and produces higher yields than previous routes.

1,6- and 1,7-Naphthyridines have been prepared by various methods;[1] however, most of the procedures involve many steps,[2,3] produce low yields, and require amino-, nitro-, cyano-, or carboxyamido-pyridine derivatives as starting materials.[1] Often the required substituted pyridines are not readily available. Cyanopyridine derivatives have been used extensively for formation of naphthyridines;[4] however, 8-alkyl-1,7-naphthyridines cannot be prepared by this method. Recent reports[5,6] of conversion of indene into isoquinoline prompted us to investigate a new route for preparation of naphthyridines, especially 1,6- and 1,7-naphthyridines starting from pyrindane (**1**)‡ (Scheme 1).

The commercially available pyrindane is easily converted[7] into a mixture of 7*H*-1- (**2**) and 5*H*-1-pyrindine (**3**). Pyrindane, when treated with acetic acid and hydrogen peroxide, gave a 94% yield of pyrindane *N*-oxide; the *N*-oxide with acetic anhydride yielded 7-acetoxy-6,7-dihydro-5*H*-1-pyrindine (77%). This ester on treatment with concentrated sulphuric acid gave a mixture (74% yield) of 7*H*-1- (**2**) and 5*H*-1-pyrindine (**3**). Ozonolysis and treatment of this mixture with ammonium hydroxide[5] gave 1,6- (**6a**) and 1,7-naphthyridine (**7a**) in a ratio of 1:2 (Table 1). The pyrindine or naphthyridine isomers can be separated on a medium pressure silica gel column (2.5 × 75 cm) using 2:1 hexane–diethyl ether as the eluant. Ozonolyses were performed with a Welsbach T34 ozonator. Typically, a solution of 10—20 mmol of the pyrindine in 50 ml of methanol was cooled to −78 °C and ozonized until a blue or bluish-green colour indicated that ozone was in excess. The reaction mixture was purged with nitrogen, and 2 g of sodium hydrogen carbonate were added followed by dimethyl sulphide (0.2 ml/mmol of pyrindine). The mixture was kept at room temperature for 6 h. Ammonium hydroxide (20 ml) was added and the mixture was left at room temperature for 6 h. The mixture was then poured into 100 ml of water and extracted with methylene dichloride. Chromatography of the methylene dichloride extracts on neutral alumina (ether–hexane) yielded the pure naphthyridines.

Treatment of a mixture of (**2**) and (**3**) with n-butyl-lithium and methyl iodide[8] gave isomeric 5-methyl-7*H*-1- (**4a**) (39%) and 7-methyl-5*H*-1-pyrindines (**5a**) (37%). If methyl iodide was replaced by benzyl bromide, 5-benzyl-7*H*-1- (**4b**)(14%)



Scheme 1. *Reagents:* i, $MeCO_2H$, 30% H_2O_2, 75 °C, 12 h; ii, Ac_2O, 100 °C, 3.5 h; iii, H_2SO_4, 125 °C, 2 h; iv, Bu^nLi, MeI, or $PhCH_2Br$; v, O_3, Me_2S, $NaHCO_3$, NH_4OH.

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‡ Available from the 1982 Aldrich catalogue under the name 2,3-cyclopenteno pyridine.

Table 1. One-flask synthesis of naphthyridines from pyrindines.

Naphthyridine[a]	% Yield[b]	Combined yield
1,6- (**6a**)	24	72
1,7- (**7a**)	48	
5-Me-1,6- (**6b**)	40	90
8-Me-1,7- (**7b**)	50	
5-$PhCH_2$-1,6- (**6c**)	20	45
8-$PhCH_2$-1,7- (**7c**)	25	

[a] All new compounds gave satisfactory elemental analyses. [b] Isolated yield after alumina chromatography based on pyrindine used.

and 7-benzyl-5*H*-1-pyrindine (**5b**) (56%) were obtained. General procedure for preparing alkylated pyrindines: to a solution containing 32 ml of a 1.6 M n-butyl-lithium solution in hexane and 4 ml of tetramethylethylenediamine in 100 ml of hexane at O °C were added 3.0 g of the pyrindine and 10 ml of hexane. The solution was stirred at 0 °C for 1 h and then 30 mmol of the alkyl halide in 10 ml of hexane was added at 0 °C. The solution was stirred for 8 h at room temperature and quenched with a saturated ammonium chloride solution. The hexane layer produced an oil which was chromatographed on neutral alumina (ether-hexane) to yield the substituted pyrindines. Mixtures of alkylated pyrindine isomers were converted into the corresponding alkylated napthyridines (**6b,c**) and (**7b,c**) as described for (**6a**) and (**7a**). Ozonolysis of the alkylated pyrindines went to completion, as verified by t.l.c. Treatment with ammonium hydroxide produced the desired naphthyridines (Table 1).

The above method offers several advantages over existing synthetic routes to 1,6- and 1,7-naphthyridines: (1) starting materials are readily available and inexpensive; (2) alkylation of 5*H*-1- and 7*H*-1-pyrindine leads to two separable isomers resulting in various substituted naphthyridines; and (3) this one-pot procedure is simpler and gives higher yields than previously reported routes to substituted 1,6- and 1,7-naphthyridines.

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