Preparation of Some *N*-Substituted 1,4-Dihydropyridines by Metal–Ammonia Reactions

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Summary Alkylpyridines react with Li–NH_3, followed by an alkylating agent, to give *N*-substituted 4,4′-bipyridyl derivatives; if ethanol is initially present the products are *N*-substituted dihydropyridines.

Quinolines react successively with Li–NH_3 and an electrophilic reagent to form *N*-substituted 1,4-dihydroquinolines.[1] By a similar procedure pyridines (**1**, R^1 = H,Me) give high yields of dimeric dihydropyridines (**2**, R^1 = H,Me). The substituent R^2 may be H, Me, Et, Pr^n, or CO_2Me, depending on the use of NH_4Cl, alkyl (Me, Et, or Pr^n) halide, or dimethyl carbonate respectively for quenching. The products are crystalline solids, and since the yields are high the method is preferable to previous syntheses.[2] The Table shows the results using 4-methylpyridine. The products showed interesting cleavages in the mass-spectrometer, to be discussed elsewhere, and are unstable to heat and to air.

Further reduction of (**2**, R^1 = Me, R_2 = CO_2Me) with Li–NH_3 gave monomeric products.

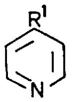
The course of reduction is changed by the initial presence of ethanol to give monomeric dihydropyridines, in accord with earlier work[3] in which their presence was deduced from hydrolysis experiments, but they were not isolated. The pyridine derivative (**1**, R^1 = H, Me) with ethanol (2 equiv.) in ammonia was treated first with Li (3 equiv.) and then the quenching agent to give (**3**, R^1 = H, Me) in 80—93% yield. The resulting liquids, which could be distilled with care, are lachrymators, apart from the NCO_2Me derivatives, which are also the most stable. This preparation of 1,4-dihydropyridines is superior to others in the literature.[4]

TABLE

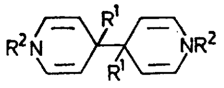
Reduction of 4-methylpyridine with Li–NH_3 and quenching

Product (**2**, R^1=Me)	Yield/%	m.p./°C	λ_{max}/nm (ethanol)	Formula by analysis
R^2 = H	92	66—67	223	$C_{12}H_{16}N_2$
R^2 = Me	93	82—83	236	$C_{14}H_{20}N_2$
R^2 = Pr	96	63—64	235	$C_{18}H_{28}N_2$
R^2 = CO_2Me	*ca.* 100	125—126	250 ($CHCl_3$)	$C_{16}H_{20}N_2O_4$

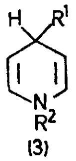
The structures all give satisfactory elemental analyses, and spectral data in accord with literature values,[5] [λ_{max} 220—230 and 260—280 nm (except when R^2 = CO_2Me, λ_{max} 234 nm only), ^1H n.m.r. (**2**, R^1, R^2 = Me) δ 1·07 (s, 2C-Me), 2·82 (s, 2N-Me), 4·29 (4H, β to N) and 5·78 (4H, α to N) (the last two in an AA′BB′ system); (**3**, R^1, R^2 = Me) 1·03 (d, C-Me), 2·75 (s, N-Me), 3·05 (m, 4-H), 4·28 (dd, 3-H, 5-H) and 5·63 (d, 2-H, 6-H).



(1)



(2)



(3)

The contrasting result with Li–NH_3, relative to quinolines, is probably due to the lesser possibility of delocalisation of charge in a dianion, resulting only in radical anion formation. Dimerisation of the radical anion occurs possibly in the form of ion pairs. Ethanol, being more acidic than ammonia, is capable of protonating the radical anion, allowing further electron-addition and monomeric reduction to proceed. The third equivalent of Li (excess over ethanol) maintains the nitrogen anion which is required as the precursor of (**3**).

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