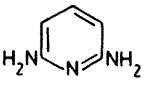
A Convenient Synthesis of 2,3,5,6-Tetrahalogenopyridines and of 3,5-Bis(alkylthio)pyridines from 2,6-Diaminopyridine

By TED K. CHEN and WILLIAM T. FLOWERS*

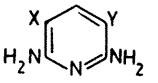
(*Department of Chemistry, University of Manchester Institute of Science and Technology, Manchester* M60 1QD)

Summary Controlled chlorination of 2,6-diaminopyridine (**1**) affords 2,6-diamino-3,5-dichloropyridine (**2a**) which is then bis(diazotised) to give 2,3,5,6-tetrachloropyridine (**3a**); similarly prepared are other 2,3,5,6-tetra(chloro/bromo) pyridines and 2,6-dichloro-3,5-bis(thiocyanato)-pyridine (**3h**), from which 3,5-bis(alkylthio)pyridines are easily obtained.

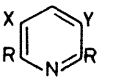
2-AMINOPYRIDINE may readily be converted into 2-amino-3,5-dihalogenopyridines by using halogen (chlorine or bromine) in ethanol,[1] or aqueous acid,[2] or by adding hydrogen peroxide to the amine in the hydrohalic acid;[3] diazotisation of the aminohalogenopyridines affords the 2,3,5-trihalogenopyridines.[4] Reaction of excess of chlorine with 2,6-diaminopyridine (**1**) in strong acid solution provides a route to pentachloropyridine;[5] we now describe how controlled chlorination or bromination of the diamine (**1**) affords a facile laboratory synthesis of 2,3,5,6-tetrahalogenopyridines (**3**), thus making available 2,3,5,6-tetrachloropyridine (**3a**), a compound of much current interest, at present prepared, in admixture with other isomers, by the reduction of pentachloropyridine.[6]



(1)



(2)



(3)

a; X = Y = Cl
b; X = Y = Br
c; X = H, Y = Cl
d; X = H, Y = Br
e; X = Cl, Y = Br
f; X = Y = SCN

a; X = Y = R = Cl
b; X = Y = Cl, R = Br
c; X = Cl, Y = R = Br
d; X = Y = R = Br
e; X = Y = Br, R = Cl
f; X = Br, Y = R = Cl
g; X = H, Y = R = Cl
h; X = Y = SCN, R = Cl
i; X = Y = SMe, R = Cl
j; X = Y = SMe, R = H

In situ formation of halogen in 2 molecular proportions by the addition of hydrogen peroxide to an HCl or HBr solution of the diamine (**1**) gives the previously unreported 2,6-diamino-3,5-dihalogenopyridines (**2a**) (m.p. 203—205 °C) and (**2b**) (m.p. 218—221 °C), respectively in > 60% yield; using half the amount of peroxide gives the 2,6-diamino-3-halogenopyridines (**2c**) and (**2d**),[7] either of which may then be similarly converted into 2,6-diamino-3-bromo-5-chloropyridine (**2e**) (m.p. 214—216 °C) in *ca.* 50% overall yield.

Although the bis(diazotisation) of the diamine (**1**) to give 2,6-difluoropyridine has been achieved,[8] simultaneous introduction of chlorine or bromine into the 2- and 6-positions has not. However, use of $NaNO_2$–HCl and $NaNO_2$–HBr,Br_2 on compounds (**2a**), (**2b**), and (**2e**) gives good yields of the tetrahalogenopyridines (**3a**—**f**), the compounds (**3c**) (m.p. 91—92 °C), (**3e**) (m.p. 86 °C), and (**3f**) (m.p. 80—81 °C) being previously unreported, and the others, (**3a**),[9] (**3b**),[10] and (**3d**)[11] available only by less convenient routes. The overall yields of (**3a**) and (**3d**) are increased to 45 and 65%, respectively, by using a one-pot procedure and not isolating the intermediate dihalogenodiamines (**2a**) and (**2b**).

Small quantities of trihalogenopyridin-2-ones are formed during the bis(diazotisation), but are easily removed by aqueous base; mass spectrometry indicates that halogen exchange at the 3- and 5-positions occurs to a small extent during diazotisation in HBr–Br_2 solution, but single recrystallisation (aq. EtOH) results in compounds of > 99% purity (m.s., elemental analysis, ^{13}C n.m.r.).

For successful diazotisation, it would appear that halogen needs to be present at both the 3- and 5-positions, since no identifiable products were obtained when the diamine (**1**) was treated under the above conditions, and the monochlorodiamine (**2c**) afforded 2,3,6-trichloropyridine in only 13% yield.

The 3,5-bis(thiocyanation) of the diamine (**1**) has already been achieved.[12] We have now shown that the 3,5-bis(thiocyanate) (**2f**) may be successfully bis(diazotised) in

HCl solution to afford 2,6-dichloro-3,5-bis(thiocyanato)-pyridine (**3h**). Treatment of (**3h**) with tributylphosphine in methanol[13] gives the corresponding dichlorobis(methylthio)pyridine (**3i**), $LiAlH_4$ treatment of which affords 3,5-bis(methylthio)pyridine (**3j**)[14] in near-quantitative overall yield.

We thank the Hulme Hall Trust Foundation for financial support

(*Received*, 28*th July* 1980, *Com.* 822)

[1] A Chichibabin and A Egorov, *J Russ Phys-Chem Soc*, 1928, **60**, 683
[2] T J Kress, L L Moore, and S M Costantino, *J Org Chem*, 1976, **41**, 93, K Schofield, 'Hetero-aromatic Nitrogen Compounds,' Butterworths, London, 1967, p 168
[3] F Friedrich and R Pohloudek Fabini, *Pharmazie*, 1964, **19**, 677
[4] S A Majid, Ph D thesis, UMIST, 1967
[5] W T Flowers, R N Haszeldine, and S A Majid, *Tetrahedron Lett*, 1967, 2503
[6] P Sutter and C D Weis, *J Heterocycl Chem*, 1980, **17**, 493
[7] M M Boudakin, U S Pat 3,849,429/1974 (*Chem Abstr*, 1974, **80**, 146,026m)
[8] M M Boudakin, U S Pat 3,798,228/1974 (*Chem Abstr*, 1975, **82**, 125,287y)
[9] H J Den Hertog and J de Bruyn, *Rec Trav Chim Pay-Bas*, 1951, **70**, 182, I F Mikhailova and V A Barkhash, *Zhur Obshchei Khim*, 1967, **37**, 2792
[10] F Mutterer and C D Weis, *Helv Chim Acta*, 1976, **59**, 229
[11] H J Den Hertog, *Rec Trav Chim Pays-Bas*, 1946, **65**, 129
[12] A Maggiolo, *J Am Chem Soc*, 1951, **73**, 5815, J A Baker and S A Hill, *J Chem Soc*, 1962, 3464
[13] W T Flowers, G Holt, F Omogbai, and C P Poulos, *J Chem Soc*, *Perkin Trans* 1, 1976, 2394
[14] K Krowicki, *Pol J Chem*, 1979, **53**, 503 (*Chem Abstr*, 1979, **91**, 74,433u)