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REACTIONS OF n-BUTYL-LITHIUM WITH 2,3,5,6-TETRACHLORO-4-MERCAPTO- AND 2,3,5,6-TETRACHLORO-4-METHYLMERCAPTO-PYRIDINE

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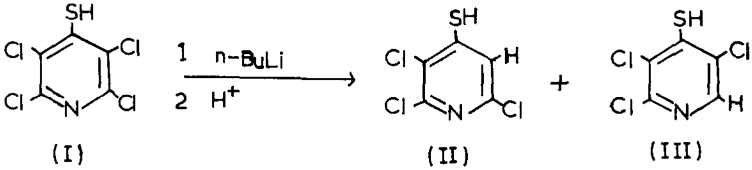
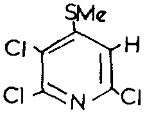
In connection with other work it became necessary for us to prepare 2,3,6-trichloro-4-mercaptopyridine (II). A sulphur atom in organosulphur compounds, such as thiophens (1) and benzo[b]thiophens (2), is known to be capable of complexing with n-butyl-lithium, and it seemed, therefore, that reaction of n-butyl-lithium with 2,3,5,6-tetrachloro-4-mercaptopyridine (I) would be a possible route to II as shown (eqn. 1):



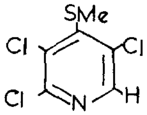
(1.1)

An ethereal solution of 2,3,5,6-tetrachloro-4-mercaptopyridine (I), prepared in almost quantitative yield by reacting pentachloropyridine with potassium hydrogen sulphide (3), was treated with two equivalents of n-butyl-lithium to give, after hydrolysis, a product (70% yield) which was shown by n.m.r. spectroscopy to be a mixture of 2,3,6-trichloro- (II) (70%) and 2,3,5-trichloro-4-mercaptopyridine (III) (30%). The fact that both II and III are formed is rationally accounted for by assuming that competitive co-ordination of the n-butyl-lithium occurs with both the sulphur atom of the side-chain (probably $-\overset{(-)}{S}\overset{(+)}{Li}$) and with the ring nitrogen atom prior to the halogen-metal exchange reaction. It was not possible to separate the mixture by chromatographic methods, but compound (II), m.p. 103-103.5° [chemical shifts (CCl_4) of τ 2.83 (β-H) (singlet) and τ 5.7 (SH) (broad singlet) (exchangeable proton)]* was obtained pure by fractional recrystallization of the mixture from hexane (4). We were not able to obtain compound (III) analytically pure, though an impure sample contaminated with II had m.p. 63-64° [Lit. (3b), m.p. 67°] [chemical shifts (CCl_4) of τ1.75 (α-H) (singlet) and τ5.2 (SH) (broad singlet) (exchangeable proton)]. It was obtained by fractional recrystallization of the residue from methanol and gave a mass spectrum consistent with the postulated structure (III).

The above result was confirmed by carrying out the reaction of the mercaptopyridine (I) with n-butyl-lithium, followed by isolation of the mixture of II and III and its treatment with dimethyl sulphate under alkaline conditions. This gave an almost quantitative yield of a mixture of 2,3,6-trichloro-4-methylmercaptopyridine (IV) (75%) and 2,3,5-trichloro-4-methylmercaptopyridine (V) (25%). A chromatographic separation of the components on silica gel, using carbon tetrachloride to elute the products, gave IV, m.p. 129-130° [chemical shifts ($CDCl_3$) of τ 3.12 (β-H) (singlet) and τ 7.49 (CH_3) (singlet)] and V, m.p. 45-47° [Lit. (3b), m.p. 41.2°] [chemical shifts (CCl_4) of τ 1.75 (α-H) (singlet) and τ 7.40 (CH_3) (singlet)] (4).



(IV)

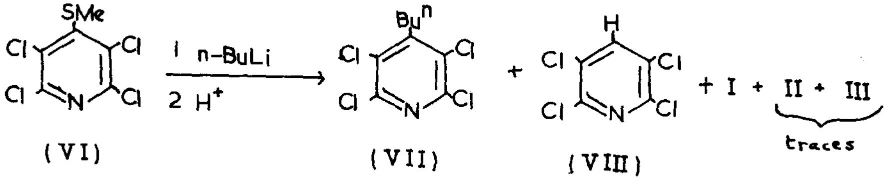


(V)

A similar reaction between 2,3,5,6-tetrachloro-4-methylmercaptopyridine (VI), prepared in almost quantitative yield by treating an alkaline solution of 2,3,5,6-tetrachloro-4-mercaptopyridine (I) with dimethyl sulphate, and n-butyl-lithium gave, after hydrolysis, 4-n-butyl-

* Compounds were also identified by elemental analysis, infrared and mass spectroscopy.

2,3,5,6-tetrachloropyridine (VII) as the major product (eqn. 2):

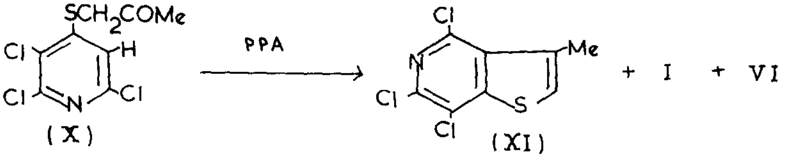


(2)

In addition, significant amounts of I and 2,3,5,6-tetrachloropyridine (VIII) and traces of II, III and two unidentified compounds were also formed. That VIII arises by hydrolysis of 2,3,5,6-tetrachloro-4-pyridyl-lithium was established by hydrolysis of the reaction mixture with deuterium oxide, which gave an almost equivalent amount of 2,3,5,6-tetrachloro-4-deuteropyridine. A recent report (5) is of interest in that the oxygen analogue of (VI), namely 2,3,5,6-tetrachloro-4-methoxypyridine, also suffers replacement of the ether group on reaction with n-butyl-lithium to give, after hydrolysis, 4-n-butyl-2,3,5,6-tetrachloropyridine (VII).

It is noteworthy that Cook and Wakefield (5) have recently shown that other 4-substituted tetrachloropyridines (*e.g.* 2,3,5,6-tetrachloro-4-piperidinopyridine) will undergo halogen-metal exchange with n-butyl-lithium in the 3-position. It seems likely that metallation in this position is favoured by co-ordination of the n-butyl-lithium with the substituent.

2,3,6-Trichloro-4-mercaptopyridine (II) is potentially useful as a starting material for the synthesis of polychloroheterocyclic systems: for example, an aqueous solution of the sodium salt of II reacts with chloroacetone to give (2,3,6-trichloropyridyl-4-thio)acetone (X) (90% yield),



(3)

m.p. 136-138°, ν_{max} 1715cm^{-1} (C=O) [chemical shifts ($CDCl_3$) of τ 3.0 (β-H) (singlet) τ 6.13 (CH_2) (singlet), and τ 7.65 (CH_3) (singlet)] which, on treatment with polyphosphoric acid at 170°, gave 4,6,7-trichloro-3-methylthieno-[3,2-*c*]pyridine (XI)(10% yield), m.p. 190-192° [chemical shifts (CS_2) of

τ 2.83 (2-H) (quartet) and τ 7.33 (CH_3) (doublet)], together with considerable amounts of I (the major product) and VI (eqn. 3).

We are continuing to investigate the synthetic uses of polychloromercaptopyridines as starting materials for other polychloroheterocyclic systems containing sulphur and other heteroatoms.

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3. a. C. D. S. Tomlin, J. W. Slater, D. Hartley and C. J. Clayton, *British 1,059,990* (1967): I.C.I. Ltd., *Neth.Appl. 6,516,409* (1966); *Chem.Abstr.*, **65**, 18564 (1966).
   b. H. Johnston, *U.S. 3,364,223* (1968); *Chem.Abstr.*, **69**, 27254 (1968).
4. Compounds II and IV are claimed in a recent Patent (3b). The methods given for their preparation starting from 2,3,4,6-tetrachloropyridine are less convenient than those reported here starting from pentachloropyridine, since the latter is commercially available, and the structures of the patented products were not proved. The m.p.'s for II (80°) and IV (113°) given in the Patent are significantly different from ours.
5. J. D. Cook and B. J. Wakefield, *J.Chem.Soc., C, Org.*, 9/074, in the press.