Conversion of *N*-2-Chloroallylanilines into 2-Methylindoles

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Summary *N*-2-Chloroallylanilines give moderate yields of 2-methylindoles when heated with polyphosphoric acid at 100°; possible mechanisms are discussed.

WE have found that the 2′-chloroallylamino-acid (I) when heated with polyphosphoric acid at 100° gives a poor yield of a yellow substance ($C_{14}H_{15}NO_2$) which we formulated tentatively as (II) or (III). Since the n.m.r. spectrum contains a low-field doublet (τ 2·05, J 10 Hz) which could be ascribed to an aryl proton *peri*- to a carbonyl group, we favour structure (II) for this product. To provide simpler analogies for such a transformation, we studied the effect of polyphosphoric acid on several 2′-chloroallylanilines.

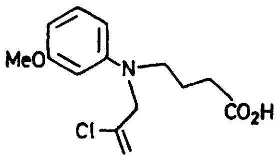
N-2-Chloroallylaniline and its *N*-methyl derivative both gave the corresponding 2-methylindoles in 50—60% yield when treated with polyphosphoric acid at 100°. *N*-2′-Chloroallyl-*m*-anisidine gave both 4-methoxy- (m.p. 98°)† and 6-methoxy-2-methylindole (m.p. 102°)[1] which were separated with difficulty by chromatography. In the case of *p*-anisidine, the yield of 5-methoxy-2-methylindole was low[2].

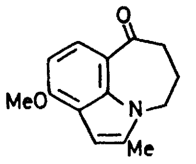
Three mechanisms at least can be considered. Firstly, a sigmatropic rearrangement[3] (IV), secondly, an electrophilic substitution[2] (*via* Va), and thirdly, an electrophilic substitution[4] (*via* Vb). Although the Fischer indole synthesis[5] is held to involve a sigmatropic rearrangement (of an ene-hydrazone), it is not so easy to invoke a similar explanation (IV) in the present case. Thus, while 4-nitrophenylhydrazones[6] do undergo the Fischer reaction, neither *N*-2′-chloroallyl-4-nitroaniline nor *N*-2′-chloroallyl-4-ethoxycarbonylaniline yielded the corresponding 2-methylindoles on heating with polyphosphoric acid. We had hoped to intercept possible sigmatropic rearrangement products (*e.g.* VI; R = NH or O) from the reaction of *N*-2′-chloroallyl-2,4,6-trimethylaniline, but the product was the aminoketone (VII) in good yield. This may have arisen *via* (VI; R = NH) followed by a Wagner–Meerwein shift (arrows), but could also be produced by an electrophilic substitution.

This new procedure is suitable for the production of polycyclic heterocyclic systems such as the indolopyridine (IX, 85%) from the amide (VIII). This contrasts with the failure of *N*-benzenesulphonamides to undergo cyclisation.[2] *N*-2 -Chloroallyl-2-aminopyridine gave the 3-methylindolopyridine (X),[7] thus ruling out a sigmatropic rearrangement.

We feel that an electrophilic cyclisation mechanism[2] [involving (Va)] is intrinsically more likely than the mechanism[4] [involving (Vb)] which requires the prior removal of chloride ion. While treatment of *N*-2′-chloroallyl-*N*-methylaniline with silver nitrate at 100° caused a reaction which produced many products, 1,2-dimethylindole was not one of them.

During the reaction of *N*-2′-chloroallyl-4-nitroaniline with polyphosphoric acid, a significant quantity of 4-nitroaniline was produced: this suggests that the initial reaction may proceed by attack of the electrophile on the nitrogen atom, leading to partial separation of a chloroallyl ion which would then attack the benzene ring where possible. This possibility, for which precedents[8] exist, has been discounted by the Russian workers[2] but the elegant study of ^{14}C effects carried out by George, Gill, and Hudson[4] does not exclude it, provided that the 'separated' aniline and chloroallyl ion remain bound in a solvent cage. It is not certain at present which mechanism(s) is operative.


(I)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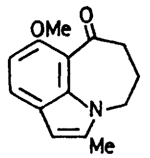
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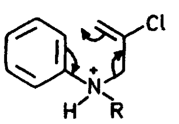
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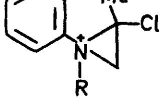
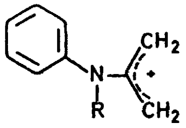
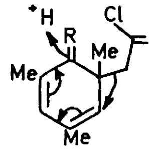
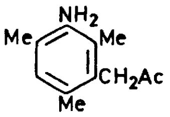

(Va)


(Vb)


(VI)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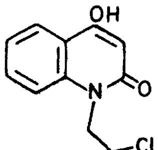
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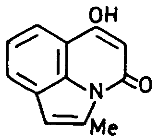
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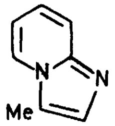
(X)

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† Satisfactory analytical data have been obtained for all new compounds.

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