The Mechanism of the Reaction of Aryl Nitrogen Mustards with Nucleophiles

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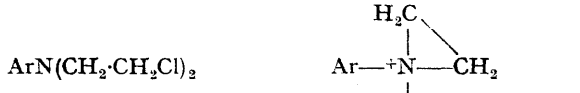
Summary Common opinion has been that the reactions of aryl nitrogen mustards with nucleophiles do not involve aziridinium ion intermediates: evidence is now reported which requires revision of this tenet.

NN-DI-2′-CHLOROETHYLANILINES (**1**), the so-called aryl nitrogen mustards, are generally cytotoxic and some have proved to be of clinical value in the chemotherapy of cancer.[1,2] The cytotoxicity of the mustards is apparently due to their ability to function as alkylating agents within the cell;[1,2] itself a consequence of the remarkably ready nucleophilic displacement of the side-chain halogen from these compounds.

In order to establish an index of the relative reactivity of the aryl nitrogen mustards towards this nucleophilic replacement, Ross[3] measured their "per cent hydrolysis" under standard conditions and noted that there was a striking increase in reactivity with increasing basicity of the aniline. However, in an early discussion of the mechanism of the hydrolysis reaction, Everett and Ross commented[4] that, in contrast to the behaviour of the alkyl nitrogen mustards, there was no evidence for the intermediacy of aziridinium ions, *e.g.* (**2**). This conclusion was based on the observations that hydrogen ion and chloride ion were liberated at the same rate; that the instantaneous thiosulphate titre (a measure of aziridinium ion concentration) was negligible; and that (**3**) and (**4**) underwent hydrolysis without rearrangement. It was realized and stated that this evidence did not exclude the transitory existence of aziridinium ions, but this qualification although subsequently re-stated[2] seems to have been largely ignored, and the reaction of aryl nitrogen mustards with nucleophiles is still commonly presented as proceeding by the process outlined in Scheme 1.

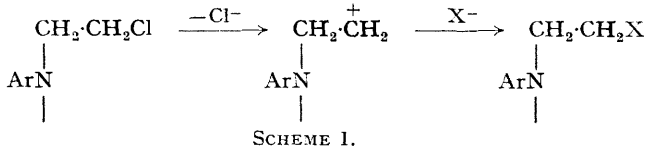


(**1**)

(**2**)

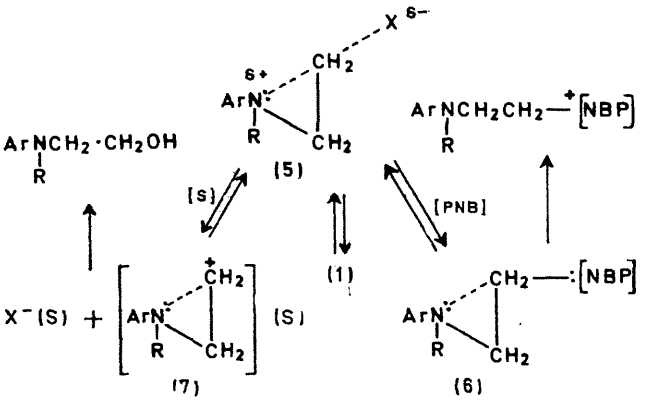
PhN(Et)CH_2·CHMe·Cl (**3**)

p-$ClC_6H_4N(CH_2$·CHMe·Cl$)_2$ (**4**)



SCHEME 1.

When Bardos *et al.*[5] examined the relative S_N1- and S_N2-type reactivities of the aryl mustards, as measured by "per cent hydrolysis" and alkylating activity [towards 4-(4′-nitrobenzyl)pyridine, PNB] respectively, they decided that: "the high-energy transition state of the hydrolytic reaction (**7**) is a solvated carbonium ion–nitrogen dipole (which has a conformation similar to an aziridine ring); collapse of this solvated ion-dipole gives the hydrolysis product. The transition state of the alkylation reaction is an 'S_N2-complex' (**6**) consisting of an unstable aziridinium ion in the state of a ring-opening attack by the nucleophilic reagent. Both reactions, however, would pass through the same reactive intermediate (**5**) which is comparable to the transition state for the formation of an aziridinium ion"; Scheme 2.



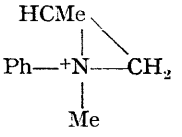
SCHEME 2

It has appeared to us, for some time, that the participation of the aniline nitrogen in the displacement reactions was most simply and reasonably interpreted as involving the formation of conventional aziridinium ions as reactive intermediates: a view also expressed recently by Price and his co-workers,[6] and by Williamson and Witten[7] who in addition presented an analysis of kinetic data to support this contention. The high reactivity of ions such as (**2**), compared to their alkyl analogues, seemed very reasonable, *i.e.* appreciable concentrations of aryl aziridinium ions were not to be expected; and we suspected that the non-rearrangement of (**3**) and (**4**) upon hydrolysis was due to preferential attack of nucleophile at the secondary centre in an intermediate aziridinium ion. Recent restatements[1,8] of the early mechanistic scheme induced us to undertake a re-investigation of the reaction of aryl nitrogen mustards with nucleophiles, with the results which we now describe.

Like Everett and Ross,[4] we were unable to obtain the side-chain isomer of (**4**); however we were able to obtain (**8**; X=OH),[9] the *N*-methyl analogue of (**3**) and its side-chain isomer (**9**; X=OH).[10] Chlorination (PCl_5–$CHCl_3$) of **8**; X=OH) gave the corresponding chloride (**8**; X=Cl), and this was also the major product from the similar chlorination

of (**9**; X=OH), together with smaller amounts of the unrearranged chloride (**9**; X=Cl). Acetolysis (NaOAc–AcOH) of the chloride mixture from (**9**; X=OH) gave even

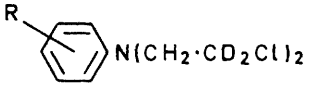
PhN(Me)CH_2·CHMe·X (**8**) PhN(Me)CHMe·CH_2X (**9**)



(**10**)

more predominantly (**8**; X=OAc). These isomerisations accord with our expectation that ion (**10**) would undergo attack by nucleophiles to yield (**8**) in preference to (**9**).

More pertinent and particularly compelling were the results of a study of three representative mustards labelled in the 2′-position with dueterium; (**11a**—**c**).†

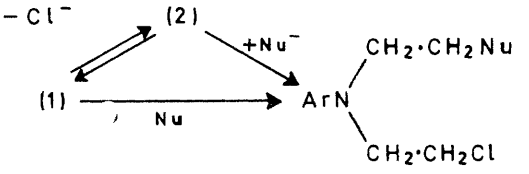


(**11a**; R = H) [H-1′:2′ 84:16]
(**11b**; R = 4-MeO) [H-1′:2′ 83:17]
[**11c**; R = 2,4-$(NO_2)_2$] [H-1′:2′ 84:16]

Thus, although (**11a**) underwent reaction with potassium *p*-thiocresolate in t-butyl alcohol to yield a dithioether with complete retention of the original label distribution, hydrolysis‡ or acetolysis gave respectively, the diol and diacetate in which the deuterium label was essentially equally distributed between the 1′- and 2′-positions.§

The more reactive (**11b**) gave dithioether with extensive label-scrambling (H-1′:-2′, 57:43), while acetolysis of (**11c**) although very slow gave the diacetate with complete scrambling.

Leaving aside the obvious and transparent details of intimate- and solvent-separated ion-pairs and transition-state geometries, we therefore suggest that nucleophilic displacement of the side-chain halogen from aryl nitrogen mustards may proceed by either of two competitive processes: one involving direct displacement, and the other proceeding by way of an aziridinium ion reactive intermediate; as shown in Scheme (3). The aziridinium ion pathway seems to be preferred, except in reactions involving very powerful nucleophiles.



SCHEME 3

These results and conclusions are compatible with those stemming from an examination of the reaction of nucleophiles with the dimethanesulphonates of 3-phenylthiopropane-1,2-diol and 2-phenylthiopropane-1,3-diol.[12]

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† Lithium aluminium deuteride reduction of *NN*-di-(methoxycarbonylmethyl)aniline[11] gave the diol corresponding to (**11a**), into which it was converted (PCl_5–$CHCl_3$), and purified by distillation. A similar sequence led from *p*-anisidine to (**11b**), although in this case the product has to be purified by chromatography as extensive label-scrambling occured on distillation. Nitration (AcOH–HNO_3) of (**11a**) gave (**11c**). The distribution of the label in the side-chain was determined by ^{1}H n.m.r. spectroscopy (of $CDCl_3$, or trifluoroacetic acid solutions).

‡ In order to drive the hydrolysis to completion it was necessary to remove chloride ion by continuous potentiometric titration with silver nitrate. Otherwise, as for example when a solution of (**11a**) in aqueous acetone containing suspended calcium carbonate was boiled for 48 h, the major product isolated was (**11a**) in which, as in minor hydroxyethyl products, the side-chain label was scrambled: results in accord with the relative nucleophilic properties of water and chloride ion.

§ The distribution of hydrogen in the diacetate showed a slight (*ca.* 52:48) preponderance of 2′-H. This presumably reflects a secondary deuterium isotope effect in the attack of acetate on a symmetrical intermediate.

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