Rearrangement on Borohydride Reduction of a Nitrophenoxy-ester

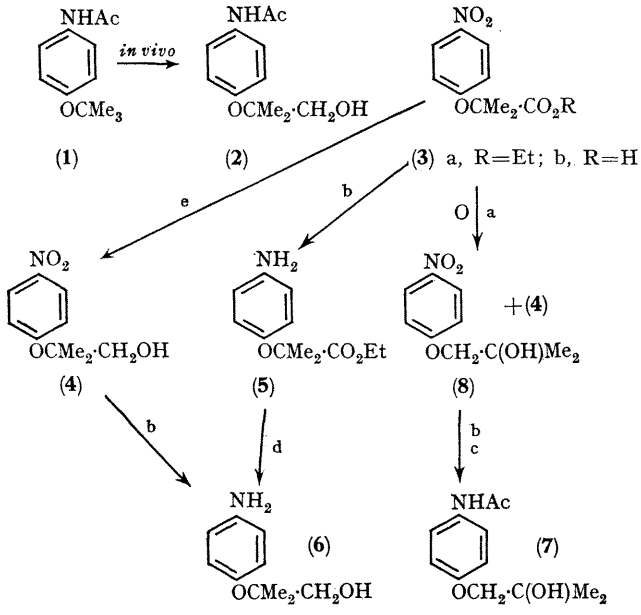
By MORTON HARFENIST* and EDNA THOM

[*The Wellcome Research Laboratories, Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, New York* 10707]

Summary Reduction of ethyl 2-methyl-2-(4-nitrophenoxy)-propionate (**3a**) with lithium borohydride in diglyme led to rearrangement to give the nitrophenoxy-alcohol (**8**); the unrearranged nitrophenoxy-alcohol (**4**) was produced by diborane reduction of the acid (**3b**).

WE wished to synthesize the alcohol (**2**), which was postulated[1] to be the polar, non-phenolic metabolite isolated from its glucuronide after feeding the acetamidophenoxybutane (**1**)[2] to dogs. If confirmed, this would represent an unusual *in vivo* hydroxylation at an unactivated carbon.

The nitrophenoxy ester (**3a**) was made. Its elemental analysis and ^{1}H n.m.r. and i.r. spectra were in accord with the assigned structure. Heating (**3a**) with lithium borohydride in diglyme[3] gave what was later shown by t.l.c. to be a pair of nitro-alcohols. The mixture had the correct elemental analysis for (**4**). By reduction of the nitro-group, followed by acetylation of the resulting anilino-alcohol an acetanilide (**7**) was produced which had the ^{1}H n.m.r. spectrum expected for metabolite (**2**), but which was isomeric with (**2**).



Reagents: a, $LiBH_4$; b, Fe + ethanolic HCl or Adams' PtO_2 + H_2; c, Ac_2O in ethanol; d, $LiAlH_4$ in ether; e, BH_3.

Compound (**7**) was shown to correspond to the major product of the borohydride reduction, which must be (**8**) both in view of mass spectral evidence (peaks attributed to $[O_2NC_6H_4OMe]^+$ and $[Me_2COH]^+$) and because (**7**) is isomeric with (**2**) and has an n.m.r. spectrum similar to that of (**2**) prepared by the two routes given below, which are unlikely to give rearrangement, one of which goes by way of the un-rearranged nitro-alcohol (**4**).

Since it seemed obvious that whichever of the two likely mechanisms of rearrangement was operating required activation by an electron-withdrawing (here a *p*-nitro) group, the alternative preparation of (**2**) by prior reduction of nitro-ester (**3a**) to the amino-ester (**5**) was carried out, followed by reduction of the ester group with lithium aluminium hydride and acetylation of the (**6**) so produced.

Compound (**2**) was obtained in this way in excellent yield, despite the two active hydrogens present in (**5**). With (**8**), (**2**), and (**7**) available for comparison, it was possible to study the reduction of the acid (**3b**) [available by saponification of (**3a**)] with boron hydride as a route to un-rearranged nitro-alcohol (**4**). Borane should reduce a carboxylic acid group without affecting a nitro-group[4] but should be a far weaker base than the borohydrides and so not promote a rearrangement presumed to require conversion of (**3**) into a strongly nucleophilic species. In accord with these expectations, the acid (**3b**) gave a single nitro-alcohol (t.l.c. and g.l.c.) shown to differ from (**8**) on t.l.c., and to be reducible to amino-alcohol (**6**), which was converted into (**2**). Thus, this nitro-alcohol must have the structure (**4**).

Two mechanistic pathways can be considered for formation of (**8**) from (**3a**). The one we regard as more likely involves formation of some unrearranged reduced species, *e.g.* the anion of the nitro-alcohol (**4**), although some intermediate stage of reduction may rearrange faster. A Smiles[5] rearrangement involving attack of the nucleophilic

terminal oxygen on the *aromatic* carbon *para* to the nitro-group (five-membered ring in the transition state) would then lead to production of rearranged alcohol (**8**).

The alternative path would involve attack of the nucleophilic terminal oxygen on the aliphatic ethereal carbon, to give an epoxide (three-membered ring in the transition state) and *p*-nitrophenolate anion, with the latter attacking the epoxide at the less-hindered carbon to give (**8**).

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