A Novel Reduction of Carbonyl to Methylene by the Action of Sodium Borohydride

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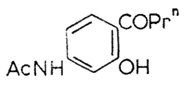
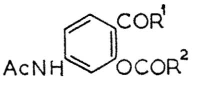
Summary *o*-Alkylphenols are produced by sodium borohydride reduction of esters of *o*-hydroxy-aromatic ketones.

SODIUM BOROHYDRIDE is a widely used reagent for the reduction of ketones to secondary alcohols.[1] Recently[2] this reagent has been used to reduce toluene-*p*-sulphonylhydrazones of aldehydes and ketones to the corresponding hydrocarbons. I report here that while sodium borohydride reduces *o*-hydroxy-aromatic ketones to the expected secondary alcohols, esters of such ketones give good yields of the corresponding *o*-alkylphenols.

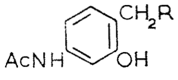
Thus, reduction of the hydroxy-ketone (I) with an excess of sodium borohydride in aqueous ethanol gave the alcohol (IVa) (m.p. 131—132°, decomp.) which was also the sole product of hydrogenation over palladium on charcoal in isopropyl alcohol containing a trace of triethylamine, while treatment of the ester (IIa) under the same conditions gave 4-n-butyl-3-hydroxyacetanilide (IIIa) (m.p. 144—146°, lit.[3] 142—143°) in 90% yield. (IIIa) could be obtained from (I) by a Clemmensen reduction[4] using amalgamated zinc in aqueous acetic acid.

A plausible mechanism for this novel reduction is initial reduction of the carbonyl group in (IIa) to give the acetoxy-alcohol (IVc) followed by migration of the acetyl group under the influence of base to give the more stable secondary acetate (IVb) via an intermediate such as (V). Again, under the basic conditions of the reaction (IVb) can behave as the partially charge-separated species (VI), the electrophilic benzylic carbon atom being susceptible to attack by borohydride with expulsion of acetate ion to give the fully reduced product (IIIa). Alternatively the reaction may have some S_N1 character, in which case it could proceed *via* a substituted quinone methide.

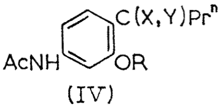

(I)


(II)

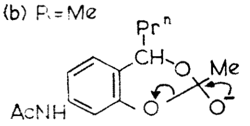
(a) $R^1 = Pr^n$; $R^2 = Me$
(b) $R^1 = R^2 = Me$
(c) $R^1 = R^2 = Pr^n$
(d) $R^1 = Pr^n$; $R^2 = Ph$

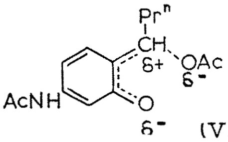

(III)

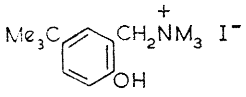
(a) $R = Pr^n$
(b) $R = Me$

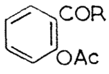

(IV)

(a) X,Y=H,OH; R=H
(b) X,Y=H,OAc; R=H
(c) X,Y=H,OH; R=Ac


(V)


(VI)


(VII)


(VIII)

(a) R = Me
(b) $R = Pr^n$

A similar acyl group migration has been demonstrated in compounds related to saligenin,[5] and the second reduction is analogous to the reduction by lithium aluminium hydride of the quaternary ammonium compound (VII) to 2-methyl-4-t-butylphenol.[6]

When (IIa) was hydrogenated over palladium on charcoal in isopropyl alcohol, the product, obtained after the uptake of 1 mole of hydrogen, was not the expected acetoxy-compound (IVc) but the isomeric phenol (IVb) [m.p. 131—133° decomp., i.r. max (Nujol) 3250 (NH), 3040 (OH), 1700 (ester CO) 1650 cm.$^{-1}$ (amide CO); n.m.r. in $(CD_3)_2SO$: τ 4·00, (triplet CHOAc, J 6 c./sec.) 7·98 (singlet, 6H, NAc, OAc)]. Reduction of (IVb) with sodium borohydride in ethanol then gave the phenol (IIIa), thus supporting the mechanism suggested.

Preliminary experiments suggest that this is a general reaction. Compound (IIb) gave (IIIb) (m.p. 174—177°), identical with the product of amination of 4-ethylresorcinol[7] followed by acetylation; the butyrate (IIc) and the benzoate (IId) behaved similarly to the acetate (IIa), and the acetate esters of *o*-hydroxyacetophenone (VIIIa) and *o*-hydroxybutyrophenone (VIIIb) were reduced to *o*-ethylphenol (3,5-dinitrobenzoate m.p. 103—106°, lit.[8] 107—108°) and *o*-n-butylphenol (characterised as the phenoxyacetic acid m.p. 103—105°, lit.[9] 104—105°), respectively.

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