Reaction of Sodium Borohydride with Heteroaromatic Nitro Compounds

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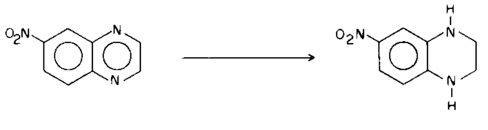
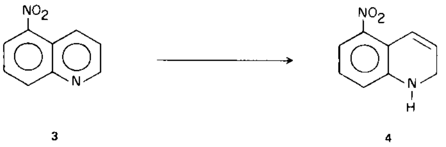
Although a variety of methods are available for the reduction of carbocyclic aromatic nitro compounds, their application to the corresponding heterocyclic systems poses some problems. Chief among these is the susceptibility of the ring system to reduction and the different methods vary in their ability to bring about this side reaction. Of the many types of reducing agents commonly available, metal hydrides are employed less frequently for this purpose because of their generally low degree of reactivity towards the nitro group (2). In particular, the reaction of aromatic nitro compounds with sodium borohydride has been studied only briefly to date. Shine and Mallory (3) as well as Otani *et al.*, (4) reported the formation of azoxy-, azo- and hydrazobenzenes from nitrobenzenes which carried substituents characterized by positive sigma values. In the case of dinitrobenzenes or nitropyridines, reduction of the ring appears to be the predominant reaction with ethanolic borohydride (5,6).

In connection with another synthetic program, amines such as 6-aminoquinoxaline and 6-aminoquinoline were needed and reduction of the corresponding nitro compounds was examined. When 6-nitroquinoxaline (**1**) in methanol was treated with sodium borohydride a dark red solution resulted which on extraction and chromatography gave a bright orange red crystalline compound. Analytical and spectral data indicated that the product was 6-nitro 1,2,3,4 tetrahydroquinoxaline (**2**). It was described earlier by Ramage *et al.*, (7) who prepared it by the cyclization of *N*-2′-chloroethyl 2-amino-4-nitroaniline.



A survey of literature showed that no simple quinoxalines have been reduced in this manner. Haddadin *et al.*, reported the reduction of the di *N*-oxide of 2,3-dimethylquinoxaline by borohydride to the corresponding tetrahydro derivative (8). Reduction of quaternized quinoxaline and pyrazine derivatives has been reported (9). Since quinoxaline itself is unaffected by borohydride in methanol, presence of electron withdrawing groups appears to be necessary to provide the necessary activation of the C=N bonds for the nucleophilic attack by the hydride.

When 5-nitroquinoline (**3**) was analogously treated with borohydride in methanol, a complex mixture of unstable products resulted. However, when the reaction was performed in acetic acid at 5°, the product consisted mainly of one component which on recovery and purification proved to be the hitherto unknown 1,2-dihydro-5-nitroquinoline (**4**). This represented considerable improvement over the same reaction in methanol, ethanol or ethylacetate/methanol. (Although acetic acid is not commonly used as solvent for borohydride reductions, there appears to be some precedent for its use such as in the case of reduction of steroidal enamines (10) reported by Marshall and Johnson).

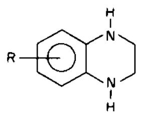


As has been the case with the quinoxalines, application of the borohydride reaction to quinoline derivatives appears to have been limited to quaternary salts so far (9). For instance, Severin and coworkers (11) reported the reduction of 1-methyl-3-nitroquinolinium iodide to 1-methyl-1,2 dihydro-3-nitroquinoline.

When the acetic acid-borohydride procedure was applied to the 6-nitroquinoxaline, the reaction proceeded much more smoothly and the product could be crystallized directly without the aid of chromatography. Using this technique a series of quinoxaline and quinoline derivatives were reduced and the results are given in Tables I and II. The nmr spectral data for the four isomeric nitro 1,2 dihydroquinolines is given in Table III.

In contrast to the nitroquinolines which yielded the 1,2-dihydro derivatives,5-nitroisoquinoline (**5**) underwent further reduction to form the 1,2,3,4-tetrahydro derivative (**6**). This is, perhaps to be expected since the reaction may be visualized to proceed through the following steps: reduction of the 1,2 double bond, protonation of the resultant enamine at C-4 and addition of hydride to the imminium cation to form (**6**).

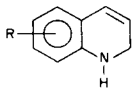
TABLE I



R	M.p., °C	Yield %	Recryst. from	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1 6-NO$_2$	114-115	76	(a)	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.86	5.26	23.75
2 5-NO$_2$	127-128	87	(b)	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.36	4.87	23.74
3 6-CN HCl salt	236-237	75	(c)	$C_9H_{10}N_3Cl$	55.25	5.15	21.47	55.07	4.87	21.53
4 6-COOC$_2$H$_5$ HCl salt	193-194	43	(d)	$C_{11}H_{15}N_2O_2Cl$	54.43	6.23	11.53	54.40	6.53	11.51
5 6-CF$_3$	123-124	52	(e)	$C_9H_9N_2F_3$	53.46	4.48	13.84	53.50	4.42	13.81

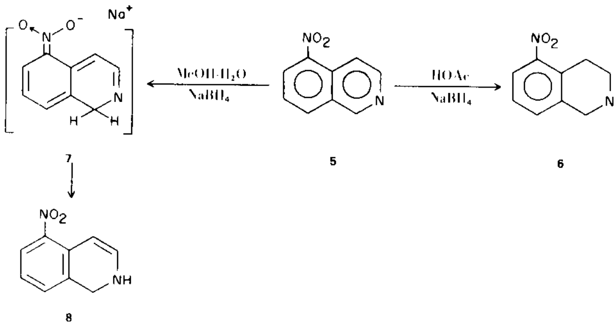
(a) Toluene; (b) Benzene/cyclohexane; (c) *n*-Butanol/acetonitrile; (d) Water; (e) Cyclohexane.

TABLE II



R	M.p., °C	Yield %	Recryst. from	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1 5-NO$_2$	90-91	77	(a)	$C_9H_8N_2O_2$	61.36	4.58	15.89	61.41	4.62	16.11
2 6-NO$_2$	154-155	90	(b)	$C_9H_8N_2O_2$	61.36	4.58	15.89	61.16	4.38	15.98
3 7-NO$_2$	88-89	67	(c)	$C_9H_8N_2O_2$	61.36	4.58	15.89	61.40	4.51	15.92
4 8-NO$_2$	93-94	71	(d)	$C_9H_8N_2O_2$	61.36	4.58	15.89	61.51	4.31	16.15

(a) Carbon tetrachloride; (b) Acetic acid; (c) Cyclohexane; (d) Carbon tetrachloride-hexane.



When **5** was treated with sodium borohydride in aqueous methanol a yellow solution resulted which on acidification gave a yellow crystalline solid. Analytical and spectral evidence showed that it was the 1,2-dihydro derivative (**8**). The compound behaves as an acid, presumably because of its conversion to a species such as **7**.

The use of borohydride/acetic acid method appears to have general applicability for the selective reduction of the quinoline, isoquinoline and quinoxaline systems which contain other reducible functions such as a nitro group.

EXPERIMENTAL

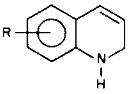
Melting points were determined on a Fisher Johns apparatus and were uncorrected. Nmr spectra were obtained using a Varian A60A spectrometer.

General Procedures for the Borohydride Reaction.

To an ice-cold solution of the nitro compound in acetic acid (300 mg. in 10 ml.) was added small portions of sodium borohydride until tlc examination of the reaction mixture showed the absence of starting material. The solution was then diluted with water (75 ml.) and extracted twice with chloroform. The organic layer was washed once with water, dried over sodium

TABLE III

Nmr Data for 1,2-Dihydroquinolines (a)



R	Solvent	Proton	Chemical Shift	J (H_2)	
5-NO_2	$CDCl_3$	1	3.61 (bs)	J_{23} = 4	J_{24} = 1.5
		2	4.23 (dd)		
		3	5.85 (dt)	J_{32} = 4	J_{34} = 10
		4	6.97 (m)		
		6	6.97 (m)		
		7	6.97 (m)		
		8	6.53 (dd)	J_{87} = 7	J_{86} = 2
6-NO_2	TFA	1	4.00 (bs)		
		2	4.44 (dd)	J_{23} = 4	J_{24} = 1.5
		3	6.41 (dt)	J_{32} = 4	J_{34} = 10
		4	7.00 (bd)	J_{43} = 10	
		5	8.29 (bs)		
		7	8.36 (dd)	J_{78} = 9	
		8	7.81 (bd)	J_{87} = 9	
7-NO_2	$CDCl_3$	1	3.80 (bs)		
		2	4.32 (dd)	J_{23} = 4	J_{24} = 1.5
		3	5.76 (dt)	J_{32} = 4	J_{34} = 10
		4	6.30 (bd)	J_{43} = 10	
		5	6.81 (d)	J = 8	
		6	7.36 (dd)	J_{65} = 8	J_{68} = 2
		8	7.10 (bd)	J_{86} = 2	
8-NO_2	$CDCl_3$	1	4.10 (bs)		
		2	4.59 (dd)	J_{23} = 4	J_{24} = 1.5
		3	5.65 (m)		
		4	6.90 (bd)	J_{43} = 7	
		5	6.35 (m)		
		6	6.35 (m)		
		7	7.83 (dd)	J_{76} = 8	J_{75} = 2

(a) Chemical shifts (S) are relative to TMS (S = 0.00). Signals are designated as follows: bs, broad singlet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; bd, broad doublet; d, doublet.

sulfate and concentrated to dryness. The residue was either crystallized directly or converted to the hydrochloride by dissolving in acetone and adding dropwise a solution of 1 ml. of concentrated hydrochloric acid in 10 ml. of acetone.

5-Nitro-1,2,3,4-tetrahydroisoquinoline (**6**).

A solution of **5** (100 mg., 0.57 mmole) in acetic acid (10 ml.) was treated with sodium borohydride as above. The reaction mixture was then diluted with water (50 ml.) and washed once with chloroform, then made basic with potassium carbonate and extracted twice with chloroform. The organic layer was dried over sodium sulfate and evaporated. The residue was crystallized from cyclohexane to give a solid (m.p. 56-58°) which was converted to the hydrochloride salt. Crystallization from methanol-acetone (1:4) gave 80 mg. of the hydrochloride; yield, 65%; m.p. 259-260°.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot HCl$: C, 50.35; H, 5.16; N, 13.04; Cl, 16.52. Found: C, 50.57; H, 5.05; N, 13.28; Cl,

5-Nitro-1,2-dihydroisoquinoline (**8**).

To 200 mg. (1.14 mmoles) of **5** in 25% methanol in water (30 ml.) was added a three-fold excess of sodium borohydride. When the solution became yellow (about 20 minutes) it was cooled and acidified slowly with dilute hydrochloric acid. The orange crystalline mass was collected and washed with water and acetone and air dried, yield, 150 mg. (74%); m.p. 140-144°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.51; H, 4.45; N, 15.82.

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