[CONTRIBUTION NO. 764 FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Reduction of Schiff Bases with Sodium Borohydride

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A new method has been developed for the selective reduction of the Schiff base linkage occurring in compounds of the *N*-benzylidenaniline type. This method involves the use of sodium borohydride under a variety of conditions with the yields of secondary amines generally ranging from 91–99%. Reducible groups such as the nitro and chloro groups are not affected during the course of the reduction. The Schiff base, *N*-benzylidene-*p*-aminophenol failed to yield any detectable amount of its corresponding secondary amine under the conditions employed probably due to a tautomerization involving a quinoid-type structure.

In connection with some other work on di-secondary amines, it was found desirable to prepare secondary amines from their corresponding Schiff bases, some of which contained groups which are usually reducible. The need for nitro substituted secondary amines eliminated the possible use of catalytic hydrogenation of the corresponding Schiff base. All other methods of reduction thus far reported in the literature were eliminated as possibilities on the basis of this need. Since sodium borohydride is such a highly selective reducing agent and normally will not attack the nitro group, attention was focused on its potential use for the reduction of Schiff bases.

The Schiff bases which were studied were the nitro, chloro, methoxy, and hydroxy derivatives of the parent compound, *N*-benzylidenaniline. Their preparation generally involved reacting equimolar amounts of the aldehyde and amine using standard procedures.

The general reaction by which this series of Schiff bases was reduced is given by the following equation in which Ar and Ar′ may be a phenyl group or a nitro-, chloro-, methoxy-, or hydroxyphenyl group. Table I contains a list of secondary amines

$$\mathrm{Ar{-}CH{=}N{-}Ar'} \xrightarrow{\mathrm{NaBH_4}} \mathrm{Ar{-}CH_2{-}NH{-}Ar'}$$

which were prepared by this method. In Table II are listed the benzoyl derivatives of these secondary amines.

The yields of secondary amines obtained by this method were quite high, generally being in the range of 91–99%. The slightly low yields of the nitro-containing compounds (VII) and (IX) were due to the ready decomposition which these two compounds underwent. In both of these cases, a 6–7% yield of a high-melting decomposition product was obtained in addition to the expected secondary amine.

It was found that the reduction conditions were not very critical. All of the reactions were accompanied by a color change which served to indicate that a reduction was taking place. In general, one of the two techniques was used to effect a reduction. Technique A involved the addition of a solution of sodium borohydride to a refluxing solution of the Schiff base. A reverse order of addition did not prove to be very satisfactory. The concentrations of the solutions were not very critical. A simpler technique, B, involved the portionwise addition of solid sodium borohydride to a solution of the Schiff base. In this case it was generally more desirable to have the Schiff base solution at a temperature below the refluxing point of the solvent in order to moderate the vigorous reaction.

Absolute methanol proved to be a convenient medium for the reaction in spite of the increased rate of decomposition of sodium borohydride in this solvent. Ethanol was found to be superior to methanol in that the rate of decomposition of sodium borohydride in ethanol was considerably reduced. However, the rate of dissolution of the hydride in ethanol was also reduced as well as the rate of reduction. It was also found that it was not necessary for the Schiff base to be completely soluble in the solvent in order for a reduction to be effected. On the other hand, it was necessary for the sodium borohydride to be soluble in the solvent, otherwise no reduction took place. In this connection no reductions were effected in anhydrous chloroform in which the hydride was insoluble.

The secondary amines were liberated from the reaction solution by the addition of sodium hydroxide plus water or by water alone. Since (VII) and (IX) were quite susceptible to decomposition by base, these two compounds were liberated as solids by the use of water alone. In fact, some of (IX) was obtained directly from the reaction solution without the addition of water or base.

When (XVI) and (XVII) were treated with sodium borohydride under the usual conditions, no detectable amounts of the corresponding secondary amines were obtained. It is believed that the abnormal behavior of (XVI) and (XVII) may be explained on the basis of tautomerization. The location of the hydroxyl group in the ortho or para position of the aniline portion of the Schiff base molecule might result in the formation of a quinoid-type structure by means of a tautomeric shift as follows:

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TABLE I

SECONDARY AMINES

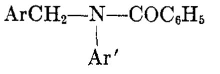
$Ar—CH_2—NH—Ar'$

Ar	Ar'		M.P., °C. (Corr.)	Yield, %	Analyses		
						Calcd.	Found
Phenyl	Phenyl	I	37–38 [a]	97.4			
p-Chlorophenyl	*p*-Chlorophenyl	II	70.5–71[b]	92.8	Cl	28.12	27.85
o-Chlorophenyl	*p*-Chlorophenyl	III	47–47.5	93.5	Cl	28.12	27.85
p-Chlorophenyl	*m*-Chlorophenyl	IV	—	95.0[c]			
Phenyl	*p*-Chlorophenyl	V	48.5–49[d]	91.2	Cl	16.26	16.34
Phenyl	*o*-Chlorophenyl	VI	39.5–40[b,d]	93.3			
p-Nitrophenyl	*p*-Nitrophenyl	VII	185–185.5[e]	83.3	N	15.49	15.49
m-Nitrophenyl	*m*-Nitrophenyl	VIII	138.5–139	98.2	N	15.49	15.60
p-Nitrophenyl	Phenyl	IX	67–68[f,g]	87.2			
m-Nitrophenyl	Phenyl	X	84–84.5[h]				
Phenyl	*p*-Nitrophenyl	XI	146.5–147[i]	90.0			
Phenyl	*m*-Nitrophenyl	XII	106–106.5[j]	94.1			
p-Methoxyphenyl	Phenyl	XIII	46.5–47[b]	93.2	C	78.84	78.43
					H	7.10	7.03
Phenyl	*p*-Methoxyphenyl	XIV	50–50.5[b]	91.0			
m-Hydroxyphenyl	Phenyl	XV	103.5–104[k]	96.0	C	79.16	78.92
					H	5.62	5.59

[a] M. Hasselblatt [*Z. anorg. Chem.*, **119,** 347 (1921)] reported m.p. 36.5–36.8°. [b] A. Roe and J. Montgomery, *J. Am. Chem. Soc.*, **75,** 911 (1953). [c] Secondary amine was high-boiling oil. Yield based on benzamide derivative. See Table II. [d] D. Peacock, *J. Chem. Soc.*, **125,** 1979 (1924). [e] C. Paal and C. Benker, *Ber.*, **32,** 1256 (1899). [f] J. Strakosch, *Ber.*, **6,** 1062 (1873). [g] C. Paal and Sprenger, *Ber.*, **30,** 69 (1897). [h] Purgotti and Monti, *Gazz. Chim. Ital.*, **30,** 256. [i] F. Kehrmann and M. Tichvinsky, *Ann.*, **290,** 293 (1896). [j] R. Meldola and F. W. Streatfield, *J. Chem. Soc.*, **51,** 114 (1887). [k] E. Bamberger and J. Müller, *Ann.*, **313,** 112 (1900). Analysis of corresponding Schiff base m.p. 101–102°: Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.92; H, 5.59.

TABLE II

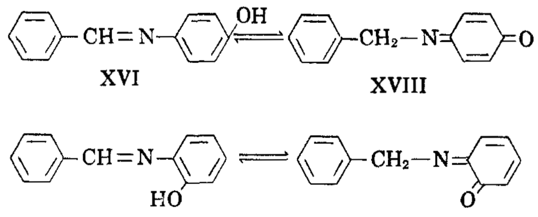
BENZOYL DERIVATIVES OF SUBSTITUTED *N*-PHENYLBENZYLAMINES



$$ArCH_2—\underset{\displaystyle Ar'}{\underset{|}{N}}—COC_6H_5$$

Secondary Amine	Benzamide M.P., °C. (Corr.)	Analysis %	
		Calcd.	Found
I	107–107.5[a]		
II	111	Cl, 19.91	Cl, 20.06
III	162.5–163	Cl, 19.91	Cl, 20.16
IV	98–98.5	Cl, 19.91	Cl, 19.95
V	137–137.5[b]	Cl, 10.98	Cl, 10.98
VI	110.5–111[b]		
VIII	121–121.5	C, 63.66	C, 64.27
		H, 4.01	H, 4.22
IX	118–118.5	C, 72.28	C, 72.92
		H, 4.85	H, 4.94
X	100–100.5	C, 72.28	C, 72.88
		H, 4.85	H, 4.82
XII	120–120.5	C, 72.28	C, 73.05
		H, 4.85	H, 4.83
XIII	71–71.5	C, 79.47	C, 80.18
		H, 6.03	H, 5.83
XIV	61.5–62	C, 79.47	C, 80.13
		H, 6.03	H, 6.13
XV	99.5–100	C, 79.59[c]	C, 79.20
		H, 5.20	H, 5.19

[a] R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., p. 88, John Wiley and Sons, Inc., New York, 1948. [b] See ref. *e* of Table I. [c] Analysis for dibenzoylated secondary amine.



XVI

XVIII

XVII

On the basis of this postulation, the quinoid-type structure necessarily would be favored under the basic conditions of this reduction method in order to account for the lack of a reduction. If such a tautomeric shift occurs, it would be necessary, in order for a reaction to take place, for the sodium borohydride to attack a nitrogen to carbon double bond in which the carbon atom would be involved in a quinoid ring system. However, no instance has been reported in which such a ring system has been reduced with sodium borohydride. Furthermore, such a tautomerization would involve a shift from a ring system of relatively lesser resonance to the highly resonating quinoid-type ring system. This increase in resonance might be expected to show up as a bathochromic shift in the ultraviolet spectrum of (XVI) and (XVIII). It was found that the spectrum of an alcoholic solution of (XVI) exhibited a peak at 335 mμ. When alcoholic potassium hydroxide was added to the sample solution it became pale yellow and the peak shifted to 390 mμ and possessed about the same relative intensity. Furthermore, when the basic solution was acidified with alcoholic acetic acid, the spectrum obtained was identical with that of the initial alcoholic solution of (XVI). Although there is the possibility of phenoxide ion formation, the very large bathochromic shift of 55 mμ along with development of color, in base, and the lack of chemical reactivity tend to favor the existence of a quinoid structure and to indicate an existing tautomerization.

Conversely, when the hydroxyl group is located in a meta position on the aniline portion of the Schiff base, or in any position on the benzaldehyde portion of the molecule, there is no opportunity for such a quinoid structure to exist. A methoxyl group, in the ortho or para position of the aniline portion of the Schiff base would likewise prevent the formation of a quinoid structure. Hence reduction would be expected in such cases. This latter condition has been substantiated, though not rigorously, by the successful reduction of *N*-(*m*-hydroxybenzyliden)-aniline (XV) and *N*-benzylidene-*p*-anisidine (XVI).

EXPERIMENTAL

Reduction technique A. A 5–10% solution of the Schiff base, dissolved in absolute methanol, was placed in a 3-necked flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser. A 2–10% solution of sodium borohydride, double the molar amount of Schiff base, was dissolved in absolute methanol. When the dropwise addition of the sodium borohydride was complete, the reaction solution was refluxed an additional 15 min. and then cooled. To this solution was added an equal volume of cold tap water whereby a precipitate of the secondary amine formed. In some earlier experiments, the secondary amine was liberated by the addition of a molar amount of sodium hydroxide which was twice that of the sodium borohydride used. In these cases, the sodium hydroxide was added as a 6*N* solution; this being followed by the addition of cold tap water which was equal in volume to that of the total solution. The precipitate of secondary amine was then collected by suction filtration, washed with water, and dried. In many cases the product was of sufficient purity that no recrystallization was necessary.

Reduction technique B. A 5–10% solution of the Schiff base, dissolved in absolute methanol, was placed in a 3-necked flask fitted with two glass stoppers and a reflux condenser. This solution was warmed or left at room temperature. To this was added an equimolar amount of solid sodium borohydride. The portion-wise addition was made through one of the necks of the flask. If the reduction reaction became too vigorous, the flask was momentarily placed in cold water. When the initial reaction had subsided, the contents of the flask were refluxed for 15 min. and then cooled. The secondary amine was liberated by means of water or sodium hydroxide plus water as in technique A. The precipitate of secondary amine thus formed was collected, washed with water, and dried. In many cases no recrystallization was necessary.

Preparation of benzoyl derivatives. The benzoyl derivatives were prepared from benzoyl chloride by the usual method and recrystallized from 95% ethanol.

Ultraviolet absorption analysis. N-Benzylidene-*p*-aminophenol of concentration 5.0 mg./l. was placed in a silica cell and the ultraviolet absorption curve obtained. A Beckman DK double beam instrument with matched cells was used. The reference cell was filled with 95% ethanol, the solvent from which the spectrum was obtained. After securing this absorption curve, two drops of a 1% solution potassium hydroxide solution in 95% ethanol was added to each cell. The color of the sample solution turned pale yellow. After obtaining this spectrum, 4 drops of a 2% acetic acid solution in 95% ethanol was added to each cell and a reading again taken.

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Arylation of Aromatic Compounds by the Meerwein Reaction. Evidence for Aryl Radicals from Orientation Studies[1]

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Benzene, nitrobenzene, and chlorobenzene have been arylated under homogeneous Meerwein reaction conditions. Isomer distributions have been determined and have been found to correspond to radical orientation. This information supports the conclusion that the Meerwein reaction involves aryl radicals.

Although the mechanism of the Meerwein reaction has been the subject of several recent investigations[2–4] the question of free aryl radical intermediates remains unanswered. This omission is primarily a result of the inapplicability of standard tests for free radicals in such complex systems. A new approach to this problem was provided by the observation that benzene was arylated under Meerwein reaction conditions.[2] Consequently, nitrobenzene and chlorobenzene have been arylated in the

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(2) A part of the present paper has appeared in preliminary form: S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Org. Chem.*, **21**, 380 (1956).

(3) J. K. Kochi, *J. Am. Chem. Soc.*, **78**, 1228 (1956).

(4) O. Vogl and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **78**, 3799 (1956).