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THE PREPARATION OF SECONDARY AMINES THROUGH THE WALLACH REACTION[1]

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Staple and Wagner (1) in a recent paper have discussed the mechanism of the Wallach reaction and have determined the optimum conditions for its application. Their work deals largely, however, with the conversion of secondary into tertiary amines. It seemed of interest to examine the reaction as a means of preparing secondary amines.

Except for the cumbersome debenzylation procedures, no general method is presently available for the unambiguous preparation of secondary amines (since the elegant Decker method is seldom applicable except for methyl secondary amines). While the utility of a new method would be greatest in cases where the separation of primary, secondary, and tertiary amines is difficult, it is obvious that the exploration should be made through cases permitting ready separation of the basic products.

The chief possibility for an unambiguous synthesis of secondary amines lay in the reduction of preformed Schiff bases and it was apparent *a priori* that this reduction should be at its best in the substantial absence of water. Amide formation, found by Staple and Wagner to diminish their yields, would be welcome in this case since the Schiff bases cannot be acylated and acylation of the secondary amines would prevent further undesirable reactions.

The generality of the reaction was investigated by the reduction of Schiff bases derived from veratric aldehyde and from cyclohexanone. Secondary amines were obtained from nearly all the reactions studied but, in general, the yields were not such as to encourage the belief that homogeneous products would be obtained when separation would be difficult. The products of these reductions are shown in Table I. The yields shown are minimal and better conditions—especially the use of smaller amounts of formic acid—would doubtless improve them. At the same time certain losses appear unavoidable. The use of absolute formic acid does not appear practical, hence the Schiff base suffers some hydrolysis. It is probable that the chief advantage in using minimal quantities of formic acid stems from this fact—less water being introduced along with

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[1] A large part of the work reported here is taken from a thesis submitted by Otto Kauder in partial fulfillment of the requirements for the M.S. degree in chemistry at the Polytechnic Institute of Brooklyn, June 1949. A recent paper by Staple and Wagner (1) classifies reductive alkylations of amines by carbonyl compounds in which formic acid is the reducing agent under the name of the Wallach reaction. Under this classification the Clarke-Eschweiler reaction appears as a special case when the carbonyl compound is formaldehyde. The term Leuckart reaction is used to denote the more drastic procedures in which formamides or formates of ammonia or amines are used without the presence of appreciable quantities of free acids.

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the formic acid. Another advantage of the use of minimal quantities of formic acid appears when the product is a benzylamine. Clarke, Gillespie, and Weisshaus (2) found that when dibenzylamine was converted to dibenzylmethylamine about 10% of the material appeared as benzyldimethylamine. This might be due either to reductive debenzylation or to the cleavage of a benzylammonium ion (3), probably the latter. When dibenzylamine was methylated with formalin and 1.5 equivalents of formic acid, pure dibenzylmethylamine hydrochloride was isolated in 95% yield and less than 5% of a more volatile base was present. Similarly, when benzhydrylamines are methylated by the usual Clarke procedure extensive cleavage results but this can be minimized by use of smaller amounts of formic acid.

TABLE I

REDUCTION PRODUCTS

COMPOUND	METHOD OF PREPARATION[a]	YIELD, %	FORM ANALYZED	M.P., °C.	ANALYSES			
					C		H	
					Calc'd	Found	Calc'd	Found
N-Cyclohexyl-*n*-butylamine	A (B)	37[b]						
N-Cyclohexylbenzylamine	A (B, C)	27[b]						
N-Veratryl-*n*-butylamine	A (B)							
N-Veratrylethanolamine	A (B)		Hydrochloride	115.5–116	53.3	53.8	7.3	7.6
N-Veratryl-*p*-toluidine	A (B, C)	35[b]	Hydrochloride	198–199	65.5	65.7	6.9	6.9
N-Cyclohexyl-*p*-toludine[f]	C	29[b]						
N-Cyclohexyl-*p*-chloroaniline	C	63[b]	Hydrochloride	205–207	58.5	58.8	7.0	6.8
N-2-(Cyclohexylamino)pyridine	C	44[c,d]						
N-2-(Veratrylamino)-pyridine	C	78[c,e]	Free base	102–103	68.8	69.1	6.6	6.3

[a] The letters in parentheses indicate that reduction by that method was successful but that the yield was inferior. [b] Yields calculated on the basis of hydrochloride recrystallized from isopropanol-ether mixtures, without isolation of base. [c] Yields calculated on the basis of recrystallized base. [d] Crystallized from aqueous isopropanol. [e] Needles from ligroin. [f] Ref. 5.

The effect of different conditions in the reduction of N-cyclohexylidene-*n*-butylamine is shown in Table II. The use of sodium formate in acetic acid (Method C) was suggested by the work of Alexander and Wildman (4). It is successful in the reduction of mixtures of cyclohexanone with *p*-chloroaniline and 2-aminopyridine and of veratric aldehyde with 2-aminopyridine which failed by Method B. The results of Runs V–VII (Table II) show that Method C is not superior to Methods A and B where all are effective. Probably the advantage of Method C lies in the diminished acidity of the medium, and is apparent only when the starting amine is very feebly basic or has little tendency to add to the carbonyl compound.[3]

While the Wallach reaction does not appear to afford an exemplary preparation of secondary amines it is of some utility when alkyl halides are unreactive (cyclohexyl halides) or react in undesired fashion (anisyl halides). For example, N-hydroxyethylpiperazine has been converted to its N′-anisyl derivative in 44% yield, which is a better result than would be probable with anisyl chloride. Similar results have been obtained in reactions employing cyclohexanone together with piperazine and morpholine.

TABLE II

COMPARISON OF REDUCTION PROCEDURES FOR THE PREPARATION OF N-CYCLOHEXYL-*n*-BUTYLAMINE

RUN[c]	REDUCING MIXTURE	TIME OF REDUCTION, HOURS	TEMPERATURE OF REDUCTION, °C.	YIELD OF AMINE	
				grams	%
I	0.5 mole of 98% HCOOH	4	90	9.4	61
II	0.5 mole of 98% HCOOH[a] + 2.5 g. of acetic anhydride	4	90	8.0	52
III	0.5 mole of 90% HCOOH	4	90	5.9	39
IV[b]	0.5 mole of 98% HCOOH	4	90	6.5	42
V	0.3 mole of HCOONa + 80 cc. of acetic acid	17	115–120	8.2	54
VI	0.5 mole of HCOONa + 80 cc. of acetic acid	17	115–120	7.5	49
VII	0.4 mole of HCOONa + 80 cc. of acetic acid	4	115–120	6.5	42
VIII	0.11 mole of 98% HCOOH	4	90	12	71

[a] This mixture was allowed to stand overnight before it was added to the Schiff base.
[b] In this case 0.1 mole each of cyclohexanone and *n*-butylamine were used.
[c] Note that 0.1 mole of N-cyclohexylidene-*n*-butylamine was used in each run.

EXPERIMENTAL[4]

The results of the various reductions are summarized in Table I.

PREPARATION OF THE SCHIFF BASES

N-Cyclohexylidenebenzylamine. One-tenth mole quantities of cyclohexanone and benzylamine were mixed in 150 cc. of benzene. There was immediate warming and separation of

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[3] The alkylolamine resulting from the primary addition is a weaker base than its precursor. Where the latter has little tendency to add to a carbonyl compound—as would probably be the case with a semi-amidine such as 2-aminopyridine—increased acidity will tend to prevent the addition and hence the over-all Wallach reaction. When the starting amine, like *p*-chloroaniline, is itself an extremely weak base, it may be that the alkylolamine will be significantly less cationic in formic acid than its precursor, with consequent effect on the equilibrium of addition.

[4] Melting points are uncorrected.

water. The solution was refluxed with removal of water (Dean-Stark water trap) until no more water was being removed (4 hours), and the benzene was evaporated *in vacuo*. The residual orange-colored oil was distilled *in vacuo*, yielding 11.8 g. (63%) of a viscous light yellow oil, b.p.$_{.1}$ 125–128°; n_D^{25} 1.5452. This substance gave no reaction with 2,4-dinitrophenylhydrazine in isopropanol and acetic acid, but yielded cyclohexanone dinitrophenylhydrazone on the addition of a little concentrated hydrochloric acid. The mother liquors when basified gave the known phenylbenzylthiourea with phenyl isothiocyanate.

Similar reactions of cyclohexanone and veratric aldehyde with the appropriate bases afforded the following substances.

N-Cyclohexylidene-n-butylamine, colorless oil, b.p.$_{.2}$ 64–65°; n_D^{25} 1.4669, 77% yield.

N-Veratrylidene-n-butylamine, yellow oil, b.p.$_{.2}$ 135–137°, 69% yield.

N-Veratrylidenebenzylamine (6), yellow oil, b.p.$_{.2}$ 204–209°, 72% yield.

N-Veratrylidene-p-toluidine, yellowish needles from *n*-propanol, m.p. 91–93°, 31% yield.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7.
Found: C, 75.4; H, 6.4.

Similar treatment of cyclohexanone and ethanolamine afforded a liquid, b.p.$_{.2}$ 59–61°, to which Cope and Hancock (7) have assigned the structure of spiro[cyclohexane-1,2'-oxazolidine]. Veratric aldehyde and ethanolamine, however, gave in 46% yield a substance crystallizing from ethyl acetate in colorless plates, m.p. 105.5–106.5°, which is apparently N-veratrylideneethanolamine.

Anal. Calc'd for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2.
Found: C, 63.2; H, 7.2.

The ultraviolet absorption spectrum showed absorption bands with peaks at 3030 and 2700 Å, thus resembling the spectrum of a carbonyl compound.

Neither veratric aldehyde nor cyclohexanone gave evidence of Schiff base formation with 2-aminopyridine.

REDUCTION PROCEDURES

Method A. Reduction of the Schiff bases. The Schiff bases were mixed with 5 equivalents of 98% formic acid. Some heat developed during the mixing and evolution of gas commenced at about 80°. The solutions were heated under reflux for four hours (oil-bath at 100–110°). An excess of concentrated hydrochloric acid was then added and the solutions were evaporated *in vacuo* on the steam-bath. N-Cyclohexyl-*n*-butylamine (8), N-veratryl-*p*-toluidine, and N-cyclohexylbenzylamine [further identified as the phenylurea (9)] were isolated directly as their hydrochlorides by crystallization from isopropanol-ether mixtures.

N-Veratryl-*n*-butylamine and N-veratrylethanolamine could not be purified directly by crystallization. The residues from the evaporation were basified and primary amines were removed *in vacuo* and by washing with water. N-veratrylethanolamine was then isolated as its picrate (m.p. 155–156°; mixture melting point with ethanolamine picrate, 123–129°) which was converted to the hydrochloride. N-Veratryl-*n*-butylamine was isolated as the hydrochloride and compared with an authentic specimen (10).

Similar treatment of N-veratrylidenebenzylamine and of spiro[cyclohexane-1,2'-oxazolidine] led only to hydrolysis; no carbon dioxide was evolved.

Method B. Direct reductive alkylation. Equivalent quantities of a carbonyl compound and an amine were added to 98% formic acid (5 moles). Thereafter the procedure was identical with that described under Method A. Yields were similar but tended to be not quite so good.

Method C. Reductive alkylation with sodium formate in acetic acid. One-tenth mole portions of carbonyl compound and base were added to 0.3 mole of sodium formate in 80 cc. of glacial acetic acid. The solution was heated under reflux in an oil bath (135–140°) for 18 hours and poured into 200 cc. of water. From such an aqueous solution N-(2-cyclohexyl)-aminopyridine (11) and N-(2-veratryl)aminopyridine crystallized as bases. The other secondary amines prepared by this procedure were isolated as hydrochlorides.

Comparison of reductive procedures. N-Cyclohexyl-*n*-butylamine was prepared in a series of parallel experiments using 0.1 mole of N-cyclohexylidene-*n*-butylamine or, in Run IV, 0.1 mole each of cyclohexanone and *n*-butylamine. The results are shown in Table II. In each case, after the time indicated, an excess of hydrochloric acid was added, the solution was evaporated *in vacuo*, and the residue was heated one hour on the steam-bath with 50 cc. of 6 *N* hydrochloric acid. The solution was then cooled, neutral material was removed by extraction with ether, and the aqueous layer was basified. The basic products were extracted with ether, dried over potassium carbonate, and distilled *in vacuo*. Distillation residues were extremely small but considerable amounts of neutral material were observed.

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SUMMARY

The Wallach reaction has been examined as a method for the preparation of secondary amines. For this purpose it is not generally superior although occasionally serviceable.

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