Alkylation of Phenacylpyridine with β-Dimethylaminoethyl Chloride and Sodamide (Mixture B).—To a cooled suspension of sodamide (from 6.3 g. of sodium) in 200 cc. of toluene was added 49.2 g. (0.25 mole) of phenacylpyridine in 250 cc. of toluene. A vigorous evolution of ammonia ensued and the suspension was heated and stirred on the steam-bath for three hours. A solution of 30 g. (0.28 mole) of β-dimethylaminoethyl chloride in 25 cc. of toluene was added dropwise and the mixture heated and stirred for two hours. An additional 15 g. of the halide was added and the reaction was continued for sixteen hours. Water was added and the reaction mixture was processed in the usual manner; yield 56.7 g. (84.5%), b. p. 145–180° (3 mm.), $n^{24}\mathrm{D}$ 1.5908, yellow, viscous oil. The latter was redistilled and obtained as a yellow, viscous oil, yield 52.4 g. (78%), b. p. 155–164° (0.5 mm.), $n^{27}\mathrm{D}$ 1.5920. *Anal.* Calcd. for $C_{17}H_{20}ON_2$: N, 10.45. Found: N, 10.81.

Phenylacylpyridine Oxime.—When one gram of mixture B, one gram of hydroxylamine hydrochloride, five cc. of pyridine and five cc. of absolute alcohol were refluxed for several hours, there was obtained a white solid which melted at 119–120° after a recrystallization from alcohol–water. *Anal.* Calcd. for $C_{13}H_{12}ON_2$: C, 73.55; H, 5.70; N, 13.21. Found: C, 74.20; H, 5.85; N, 13.37. A mixed melting point of this oxime with an authentic sample of phenacylpyridine oxime, m. p. 119.5–120° (lit.[10] m. p. 120) showed no depression.

Catalytic Reduction of Mixture B—α-Stilbazole.—A solution of 13.4 g. (0.05 mole) of mixture B in 150 cc. of methanol was reduced with hydrogen and Raney nickel catalyst at room temperature and atmospheric pressure. The theoretical amount of hydrogen was absorbed rapidly. The catalyst was removed by filtration, the filtrate and washings concentrated *in vacuo* and the residual yellow oil distilled; yield 7.5 g., b. p. 145–152° (0.5 mm.). The oil which partly solidified was dissolved in petroleum ether, cooled and filtered. The white solid was recrystallized from alcohol–water and melted at 90.5–91.5°. A mixed melting point with an authentic sample of α-stilbazole (91–92°) showed no depression.

Decomposition of Mixture B with Sulfuric Acid.—A solution of 43.6 g. of mixture B in 150 cc. of 25% sulfuric acid was heated for one hour on a steam-bath, poured on ice and made basic with ammonia. Both a solid and an oil separated, which were extracted with ether, dried, the ether evaporated and the oily residue distilled. There was obtained 21.2 g. (65%) of a yellow oil boiling at 134–140° (0.3–0.5 mm.) which crystallized upon standing, m. p. 48–50°. Recrystallization from alcohol–water raised the melting point to 55–56° and a mixed melting point with an authentic sample of phenacylpyridine, m. p. 55–56° (lit.[10] m. p. 59°), was not depressed. The second fraction, yield 8.3 g., b. p. 140–149° (0.3 mm.), did not crystallize. Upon redistillation, the fraction boiling at 157–162° (0.1 mm.), $n^{26}\mathrm{D}$ 1.5750, was analyzed and the ultraviolet absorption spectrum was determined. The analysis indicated that this sample was contaminated with phenylacylpyridine. *Anal.* Calcd. for $C_{17}H_{20}ON_2$: C, 76.06; H, 7.51; N, 10.45. Found: C, 77.74; H, 7.18; N, 9.87.

Acknowledgment.—The authors wish to express their appreciation to Mr. Edwin Conner for the microanalyses, the ultraviolet absorption spectra data and curves.

Summary

In contrast to Eisleb's observation that the alkylation of desoxybenzoin with diethylaminoethyl chloride and sodamide in toluene results in the formation of γ-phenyl-γ-benzoyl-N,N-diethylpropylamine exclusively, we have found that this reaction yields a mixture of the amino ketone and enol ether, the former resulting from C-alkylation and the latter by O-alkylation. Similarly, C- and O-alkylation result when desoxybenzoin is alkylated with dimethylaminoethyl chloride and sodamide or sodium methoxide. Phenacylpyridine reacts similarly but gives higher yields of the O-alkylated product. Only small yields of the C-alkylated amino ketone could be isolated from this experiment. The absorption spectra data support the chemical evidence.

BLOOMFIELD, NEW JERSEY RECEIVED DECEMBER 15, 1949

[CONTRIBUTION FROM THE RÖHM & HAAS CO.]

The Behavior of Aliphatic Aldehydes in the Leuckart–Wallach Reaction

BY PETER L. DEBENNEVILLE AND JANE H. MACARTNEY

The reductive alkylation of amines by aldehydes and ketones in the presence of formic acid has been variously called the Leuckart and Wallach reactions. While this reaction has been very extensively investigated[1] very little work has been done with aliphatic aldehydes other than formaldehyde. Wallach[2] carried out a few reactions with valeraldehyde, and obtained the expected products. There is no case reported of the reaction involving an aliphatic aldehyde and a purely aliphatic mono-secondary amine.

We have been studying this reaction as a possible preparative procedure for wholly aliphatic tertiary amines and have obtained some rather interesting results. The Leuckart–Wallach reaction with aliphatic aldehydes and secondary amines is initiated at a generally lower temperature than in the case of ketones and aromatic aldehydes, and gives generally good yields of product. And while we do not propose to offer a mechanism in this report, we have found an additional possible intermediate for this reaction in the form of the enamines, $(R\overset{|}{C}{=}CHNR_2)$, a class of compounds which was reported by Mannich and Davidsen in 1936.[3]

It has been pointed out by Moore[1] that secondary amines are more limited as to possible intermediates than ammonia and primary amines since they cannot eliminate water with the formation of a $>C{=}N-$ structure. Staples and Wagner[4]

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(1) Moore, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 301–330.

(2) Wallach, *Ann.*, **343**, 54 (1905).

(3) Mannich and Davidsen, *Ber.*, **69B**, 2106 (1936).

(4) Staples and Wagner, *J. Org. Chem.*, **14**, 559 (1949).

TABLE I

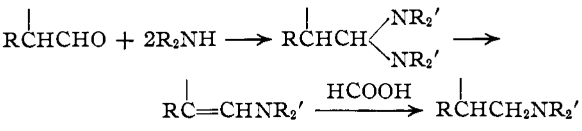
PREPARATION AND REDUCTION OF ENAMINES

RCHO R =	Amine	Yield of enamines %	B. p., °C. (uncor.)	Mm.	Nitrogen, % Calcd.	Found	Yield of saturated amine %	B. p., °C. (uncor.)	Mm.	Nitrogen, % Calcd.	Found
n-C_3H_7	Morpholine	95	105–110	20	9.92	10.1	54	94–99	25	9.78	9.70
i-C_3H_7	Morpholine	29	89–93	20	9.92	10.0	73	80–85	20	9.78	9.83
n-C_6H_{13}	Morpholine	76	91–94	2	7.65	7.59	32	90–95	2	7.57	7.33
n-C_6H_{13}	Piperidine	60	111–112	3	7.74	7.60	84	78–82	1	7.65	7.47
C_7H_{15}[a]	Morpholine	41	95–115	1	7.12	7.17	60	81	0.7	7.04	7.16
C_8H_{17}[b]	$(CH_3)_2NH$	42	46–50	1	8.29	8.20	80[c]	46	1.5	8.19	8.04
C_8H_{17}[b]	$(i\text{-}C_3H_7)_2NH$	23	79–81	2	6.17	5.83	62	98–100	4	6.17	5.97
C_8H_{17}[b]	Morpholine	79	107–110	3	6.58	6.63	85	81–83	2	6.58	6.58
C_8H_{17}[b]	$(HOC_2H_4)_2NH$	52[d]	105–110	0.7	6.12	6.16	84	147–150	1.3	6.06	6.11
C_8H_{17}[b]	$CH_3NHC_9H_{19}$	70	117–121	1	4.98	4.69	57	124–133	1.5	4.94	4.73

[a] 2-Ethylhexaldehyde. [b] 3,5,5-Trimethylhexaldehyde. [c] Yield using 87% HCOOH was 92%. [d] Excess ethanolamine was removed by a cold water wash before distillation.

have shown that in addition to the addition product $RCH(OH)NR_2$, the diimines $[RCH(NR_2)_2]$, not only are a possible intermediate but that they are more active in the Leuckart–Wallach reaction than the aldehyde and amine taken separately. A great deal of this activity is probably due to the elimination of water as a by-product of the reaction. They have found the concentration of formic acid to have considerable effect on this reaction, for example.

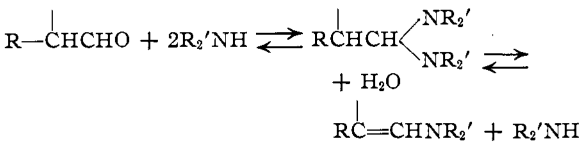
When an aldehyde bears a hydrogen atom on the alpha carbon atom, this hydrogen atom can become involved through the mechanism of enamine formation, and we believe this explains the very mild conditions under which these particular reactions occur



$$\mathrm{R\overset{|}{C}HCHO} + 2\mathrm{R_2NH} \longrightarrow \mathrm{R\overset{|}{C}HCH}\begin{matrix}\nearrow \mathrm{NR_2'} \\ \searrow \mathrm{NR_2'}\end{matrix} \longrightarrow$$

$$\mathrm{R\overset{|}{C}{=}CHNR_2'} \xrightarrow{\mathrm{HCOOH}} \mathrm{R\overset{|}{C}HCH_2NR_2'}$$

In fact, if desired, the reaction can be carried out stepwise in just this manner, all steps occurring at relatively low temperatures. In a direct alkylation procedure the first two reactions can be considered in equilibrium



$$\mathrm{R{-}\overset{|}{C}HCHO} + 2\mathrm{R_2'NH} \rightleftarrows \mathrm{R\overset{|}{C}HCH}\begin{matrix}\nearrow \mathrm{NR_2'} \\ \searrow \mathrm{NR_2'}\end{matrix} \rightleftarrows$$

$$+ \mathrm{H_2O} \qquad \mathrm{R\overset{|}{C}{=}CHNR_2'} + \mathrm{R_2'NH}$$

Preparation and Reduction of Enamines.—A number of enamines have been successfully prepared using essentially the conditions of Mannich and Davidsen,[3] within the limitations proposed by these authors. With a few exceptions yields were excellent. All of these enamines have been reduced by the dropwise addition of formic acid at temperatures from 50–95° to give good yields of the tertiary amines. In most cases reaction initiated at a low temperature; the reduction of isobutenyl morpholine took place vigorously at room temperature. Some variation was necessary in the case of enamines derived from n-butyraldehyde and n-heptaldehyde. It seemed advantageous in these cases to maintain strongly acid conditions, so the direction of addition was reversed, and an excess of formic acid used. Otherwise, one mole of formic acid was quite adequate for the reduction.[4] The concentration of formic acid appeared to have little effect; both 87 and 98% formic acid were successfully used. If two moles of formic acid were used, direct distillation of the reaction mixture gave not only the desired product, but also a constant-boiling fraction which analyzed correctly for a 2:1 addition product of formic acid and tertiary amine. Data on these reactions are given in Table I and in the experimental part.

Direct Leuckart–Wallach Alkylations.—A somewhat wider range of study was included in these alkylations in order to correlate enamine formation with direct alkylation. In general the reactions occurred at temperatures in the same range as enamine reductions, and gave corresponding yields. Propionaldehyde was not effective in the reaction; it is our belief that side-reactions occur here to reduce the yield. Methylaniline did not give good yields; Mannich and Davidsen[3] have reported that methylaniline gave only very poor yields of enamine. Cyclohexanone and acetophenone were also included in this study, since Mannich and Davidsen[3] reported enamine formation from the former under special conditions. Acetophenone gave no enamine in their study. Setting 100° as the maximum temperature at which enamine formation would be a factor in the reaction, results show that the reaction of cyclohexanone with piperidine and formic acid will take place to give a low yield of cyclohexylpiperidine, but that the corresponding reaction with acetophenone does not occur to a measurable extent. The data thus correlate fairly well with the concept that the α-hydrogen atom of the aldehyde (or ketone) may be involved in Leuckart–Wallach reactions of this type. Table II gives the results of this study in detail.

TABLE II

LEUCKART–WALLACH ALKYLATIONS

RCHO R =	Amine	Yield, %	B. p., °C. (uncor.)	Mm.	Nitrogen, % Calcd.	Found
C_2H_5	Morpholine	5	72–82	35	10.9	10.2
n-C_3H_7	$(CH_3)_2NH$	60	94–96	760	Picrate, m. p. 95–96°[a]	
n-C_3H_7	Morpholine	34	95–98	22	9.78	9.26
i-C_3H_7	$(CH_3)_2NH$	59	70–76	760	Picrate, m. p. 125–126°[b]	
i-C_3H_7	Morpholine	57	80–84	15	9.78	9.55
n-C_6H_{13}	Morpholine	46	76–87	1	7.57	7.36
C_7H_{15}[c]	$(CH_3)_2NH$	60	88–90	20	8.93	9.15
C_8H_{17}[d]	$(CH_3)_2NH$	84	52–55	3	8.19	8.04
C_8H_{17}[d]	$(i$-$C_3H_7)_2NH$	47	85–88	2	6.17	5.88
C_8H_{17}[d]	$CH_3NHC_9H_{19}$	54	115–121	1.5	4.94	4.67
C_8H_{17}[d]	$CH_3NHC_6H_5$	17	117–140	1.7	6.02	6.05
Cyclohexanone	Piperidine	25	113–115	18	8.24	8.32
Acetophenone	Piperidine	0	.....	...	...	...

[a] Clarke [*J. Chem. Soc.*, **103**, 1696 (1913)] reported m. p. 96°. [b] Hanhart and Ingold [*ibid.*, 1017 (1927)] reported m. p. 124°. [c] 2-Ethylhexaldehyde. [d] 3,5,5,-Trimethylhexaldehyde.

Experimental Part

Raw materials were good commercial grades obtained from the usual sources, and were used without purification. 3,5,5-Trimethylhexaldehyde is the product of the oxo reaction on diisobutylene and is available from several sources. Methylnonylamine was prepared from this aldehyde by reductive alkylation with methylamine. Dimethylamine (gas) is a commercial product of the Rohm & Haas Co.

Preparation of Enamines.—Our method followed closely the method of Mannich and Davidson,[3] using either anhydrous potassium carbonate or lime as catalyst and temperatures of 5–50°. Conversion of the intermediate diimine to the enamine was accomplished by simple distillation.

Reduction of Enamines.—The following general method was used: to one mole of the enamine was added dropwise at the indicated temperatures from 1 to 1.1 moles of 98% formic acid with stirring. Carbon dioxide was immediately evolved. In most cases after addition the mixture was heated for one to two hours at 50–70°, occasionally 90°. The mixture was poured into dilute hydrochloric acid to decompose any unreacted enamine, and extracted with ether to remove aldehyde. The aqueous solution was then made basic with sodium hydroxide, extracted with ether, the ether extract dried and distilled to yield the tertiary amine.

For the preparation of *n*-butylmorpholine and *n*-heptylpiperidine, one mole of the enamine was added dropwise with stirring to two moles of formic acid at 60–70° over a one-hour period. Reaction and isolation were carried out as above.

In one experiment, formic acid (48 g., 1.1 moles) was added dropwise to 3,5,5-trimethylhexyldimethylamine (84.4 g., 0.5 mole) at 50°. The resulting product was distilled *in vacuo* to yield 37 g. (44%) of the saturated amine, b. p. 80–90° (10 mm.) and 52 g. (40%) of a fraction which distilled at 90–108° (10 mm.). Redistillation of the latter fraction gave 37 g., b. p. 104° (8 mm.) which analyzed correctly for $C_9H_{19}N(CH_3)_2 \cdot 2HCOOH$: Calcd.: C, 59.3; H, 11.0; N, 5.32. Found: C, 59.0; H, 11.0; N, 5.28.

Direct Leuckart–Wallach Alkylations.—For these reactions the amine formate was usually first prepared by the addition of the appropriate amount of amine, as gas or liquid, to formic acid in 1:1 mole ratio. The temperature was then raised to about 60° and the aldehyde added dropwise over a one hour period. The mixture was then generally heated on the steam-bath until carbon dioxide evolution ceased (about one hour) and worked up as described above. For *n*-butyraldehyde and propionaldehyde, the formic acid–amine ratio used was 2:1.

Acknowledgments.—Analyses were carried out under the direction of Dr. E. L. Stanley. Mr. E. Smialkowski performed a number of the experiments described.

Summary

A study of the Leuckart–Wallach reaction using aliphatic aldehydes and secondary amines indicates that these reactions are initiated and completed at a generally lower temperature and under milder conditions than in other known instances of this reaction. One possible explanation for this is the possible involvement of the hydrogen on the alpha carbon atom of the aldehyde through an enamine intermediate.

A number of enamines have been prepared and reduced in good yield with formic acid.

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