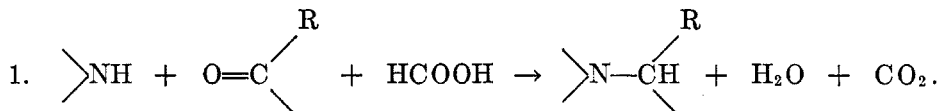


A STUDY OF THE WALLACH REACTION FOR ALKYLATION
OF AMINES BY ACTION OF ALDEHYDES OR KETONES
AND FORMIC ACID¹

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This manipulatively simple alkylation procedure requires heating together a primary or secondary amine, an aldehyde or ketone, and formic acid at a temperature at which carbon dioxide is evolved. The over-all reaction appears to be:



The method is sometimes credited to Leuckart (1), who alkylated ammonia by heating carbonyl compounds with ammonium formate. Ott (2) and Ingersoll, Brown, Kim, Beauchamp, and Jennings (3) found that formamide may replace ammonium formate. Wallach (4) showed that in the presence of formic acid, alkylation of an amine by a carbonyl compound proceeds at lower temperatures, and that the method so modified is capable of considerable extension (5). The role of formic acid in the alkylation has not been wholly clear following Plöchl's observation (6) that formalin and ammonium sulfate (in the absence of added formic acid) yield methylamines and carbon dioxide, a procedure studied by Werner (7), by Brochet and Cambier (8), and by Emde and Hornemann (9, 10), and now familiar (using ammonium chloride) for the preparation of the hydrochlorides of methylamine and trimethylamine (11); it was extended to methylation of amines by Eschweiler (12).³ Emde and Hornemann (10) reported that in this reaction one molecule of formaldehyde is oxidized for each molecule of formaldehyde reduced to N-linked methyl, and Knudsen (13) demonstrated the presence of formic acid in the reaction mixture of the Plöchl procedure. Werner (7) attributed the reduction jointly to formaldehyde and formic acid; this inference is consistent with the observation (18) that in reactions involving amine, formaldehyde and formic acid the amounts of carbon dioxide produced are less than is required by equation 1. Aldehydes other than formaldehyde, and all ketones, are ineligible to perform reduction with disengagement of carbon dioxide. The possibility that benzaldehyde might serve as reducing agent (without liberation of carbon dioxide), but so slowly that its action would be overlooked in the

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³ To facilitate discussion the several procedures for alkylation of amines are designated as follows: (1) Plöchl-Eschweiler method: methylation of ammonia or amine by formaldehyde alone; (2) Leuckart method: alkylation involving aldehyde or ketone and ammonium formate or a formamide; (3) Wallach method: alkylation of amine by aldehyde or ketone and formic acid.

presence of formic acid, was excluded by the negative result of an experiment in which piperidine hydrochloride and benzaldehyde were heated together; no N-benzylpiperidine could be detected after a thirty-hour heating period. The similarities among the Plöchl-Eschweiler, the Leuckart, and the Wallach procedures will appear more clearly below, and justify a suspicion of identity with respect to underlying steps.

There are reported here the results of experimental studies of (a) the stoichiometry of the Wallach reaction, (b) the influences of time and temperature, (c) the incidence and effect of formylation, (d) the influence of water, (e) the influence of the amount of formic acid, and (f) the possible role of alkylidene-bis-amines or alkylolamines as intermediates. For the experimental study two alkylations were selected: (A) benzylation of piperidine by benzaldehyde and formic acid, and (B) formation of N-cyclohexylpiperidine from cyclohexanone, piperidine, and formic acid. These represent alkylations of secondary amine by aldehyde and by ketone and are relatively simple, involving only one stage of alkylation and permitting ready separation of the alkylated amines. To learn the fates of initial and intermediate reactants by analysis of aliquots of the reaction mixture at intervals there was elaborated for the system piperidine-benzaldehyde-formic acid an analytical procedure for the estimation of all products and reactants, excepting N-formylpiperidine. No satisfactory method was found for the estimation of the latter in the presence of other components of the mixture. Alkylations were effected in the apparatus represented by Figure 3.

(a) *The stoichiometry of the Wallach reaction.* The results of some experiments conducted quantitatively appear in Table I. They indicate that alkylation is representable by equation 1. In the preparation of N-benzylpiperidine yields increased with time, but throughout each experiment the molar ratios of formic acid, benzaldehyde, and piperidine consumed to carbon dioxide and benzylpiperidine formed remained close to unity. In the preparation of N-cyclohexylpiperidine this product and carbon dioxide were formed in equivalent amounts, corroborating earlier findings (19). The ratio of alkylated product and carbon dioxide was determined in many of the experimental trials referred to later, and in all cases it approximated unity. It is concluded that in these reactions the reduction is performed exclusively by the formic acid.

(b) *Influence of time and temperature.* The evolution of carbon dioxide usually begins near some threshold temperature, is in some cases very rapid for a time and may slacken rather abruptly, and in all Wallach reactions observed (including a number not reported here) it continued thereafter at decreasing rates for long periods (to sixty hours) and was actually never brought to a definite termination. This behavior doubtless is responsible for the extended heating periods recommended for such alkylations. The first experiment conducted quantitatively revealed for the system benzaldehyde-piperidine-formic acid an initial reaction rate unexpectedly high. In fifteen minutes (the shortest interval permitted by the manipulations involved) the reaction was 60% complete; this increased to 70% during the next fifteen minutes, after which the rate decreased markedly, with an additional yield of only 8% in four and one-half hours.

Results for the system cyclohexanone–piperidine–formic acid are qualitatively similar. The essential data are plotted as curves I and II in Figure 1, which includes also the very dissimilar time–yield curve for the reaction of N-formylpiperidine (instead of piperidine) with benzaldehyde and formic acid, discussed in section (c). The effect of temperature, discernible in some of the results in Tables II and IV but apparently never very pronounced, was not examined systematically. Some Wallach reactions, *e.g.*, the methylation of methylaniline (19) start at room temperature or on slight warming. Threshold temperatures

TABLE I
STOICHIOMETRY OF THE WALLACH REACTION

	REACTION PERIOD, HOURS			
	0.5	1.0	3.0	5.0
A. N-Benzylpiperidine^a				
Reactants, moles				
Formic acid	0.98	0.97	0.95	0.93
Benzaldehyde.....	1.00	1.00	0.95	1.00
			0.98	
Piperidine.....	0.96	0.97	1.00	0.91
			0.94	
Products, moles				
Carbon dioxide.....	1.00 ^b	1.00	1.00	1.00
			1.00	
N-Benzylpiperidine.....	0.99	0.97	0.98	0.96
			0.94	
Yield ^c of N-Benzylpiperidine, %.....	69.7	71.5	74.7	78.4
			75.1	
B. N-Cyclohexylpiperidine^a				
Products, moles				
Carbon dioxide.....	1.00 ^b	1.00	1.00	1.00
N-Cyclohexylpiperidine.....	0.96	0.98	0.98	0.94
Yield ^c of N-Cyclohexylpiperidine,%.....	17.4	27.6	29.2	31.8

^a Piperidine, carbonyl compound, and 88% formic in ratio 1:1:2.5. Reaction temperature, 114–118°.

^b To obtain readily comparable ratios the quantity of carbon dioxide is arbitrarily set at 1.00.

^c Yields based on piperidine.

for the reactions under consideration were about 60° (benzylpiperidine) and 90° (cyclohexylpiperidine), but for the former there is some evidence that incipient action may occur near room temperature. There may be an optimum temperature for each reaction, as was observed by Crossley and Moore (20) for some Leuckart reactions. In practice it seems satisfactory to heat to refluxing temperatures, which in the cases reported here ranged from about 105° to 130°.

(c) *Formylation as a factor in the Wallach reaction.* Wallach (4) reported that formylation decreased the rate of alkylation by the Leuckart procedure and, to minimize formylation by decreasing reaction temperature, he used an excess of formic acid or formic with acetic acid, a procedure which, in view of the ease of

formylation of amines, seems not well designed to exclude formylation. Experiments to test the effects of primary formylation of the amine to be alkylated by the Wallach procedure were performed using N-formylpiperidine, benzaldehyde, and formic acid in proportions such as to duplicate conditions in the usual

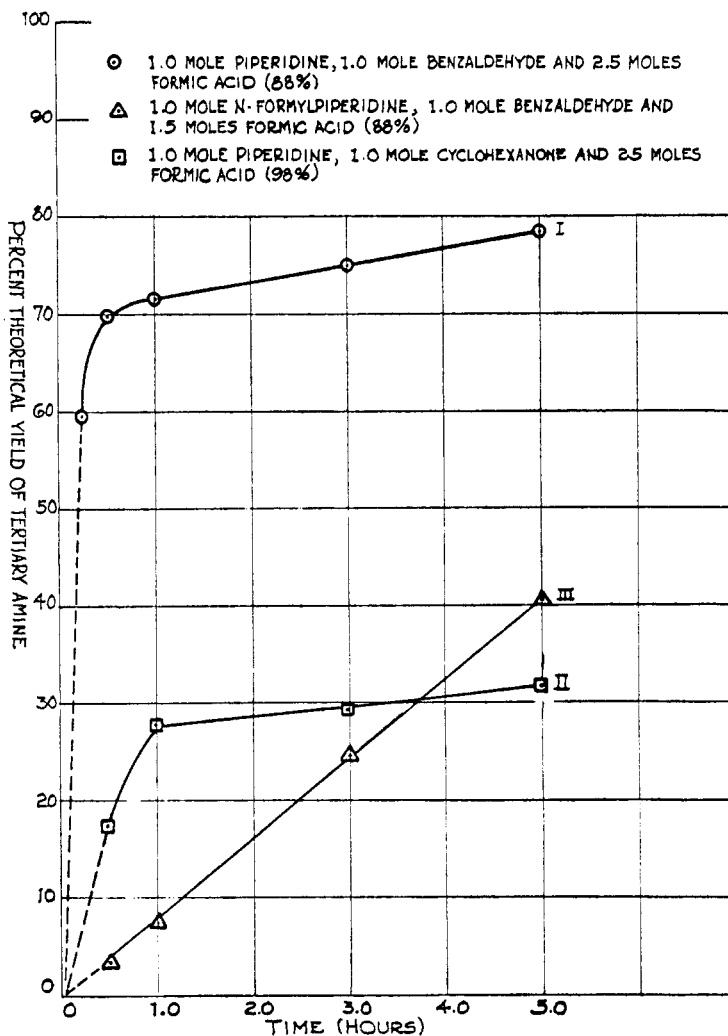


FIGURE 1. TIME-YIELD CURVES FOR WALLACH ALKYLATIONS

Wallach procedure if initial formylation of amine is complete. The results (curve III, Figure 1) are decisive in showing (a) that alkylation does occur when preformed formylpiperidine is used and (b) that the rate of alkylation is greatly depressed, the initial rapid phase being absent. Similar results were obtained in experiments with N-formylpiperidine, cyclohexanone, and formic acid.⁴ It

⁴ It was observed earlier (25) that both N-formylpiperidine and N-acetylpyperidine yielded N-methylpiperidine when heated with formalin and formic acid, but that reactions

seems clear that the substituted formamide is not involved in the normal sequence of reactions, and that formylation is an obstructive reaction. To decrease preliminary formylation in all subsequent experiments formic acid was added to the other reactants at ice-bath temperature, and the mixtures were warmed immediately and rapidly to reaction temperatures. The extent to which formylation occurs during the Wallach reaction must be related to the rapidity and extent of reaction during the initial phase, and it can be inferred only roughly from the time-yield curves in Figure 1. The initial rapid reaction appears to involve only amine, carbonyl compound, and formic acid. During the secondary and much slower alkylation the decrease in rate may be attributed jointly to decreasing concentrations of reactants and to presence of formylamine.

(d) *The effect of water.* Under usual conditions both the Leuckart and the Wallach reactions proceed in the presence of part or all of the water produced together with any initially present.⁵ In the Wallach reaction it seems that the water introduced with the formic acid, or in formalin used for methylations, together with the accumulated water of reaction, has affected yields insufficiently to arouse curiosity as to its possible effects. If the first step in the alkylation sequence is the condensation of amine with carbonyl compound it appears certain that water in presence of acid will interfere, especially in reactions with ketones.

In experiments to test the influence of water the molar proportion of formic acid was kept constant but the concentrations of the acid were varied from 99% to 70%, with water as diluent. The results, in Table II, show clearly the unfavorable influence of water in substantial amounts, and that the effect is greater with ketone than aldehyde. To test the possible advantage of practically anhydrous conditions experiments were performed with anhydrous calcium sulfate⁶ present in amount sufficient to combine with the water present in the 99% formic acid and that formed in the reaction. The results in Table II show that, associated with approximately anhydrous conditions, there is a small but consistently positive effect, which is somewhat greater in the presence of cobalt salt ("indicating Drierite").⁷ Chemical removal of water was attempted by operation in presence of N-formylpiperidine (26), but the resulting small increase (5%) in the yield of N-cyclohexylpiperidine cannot be attributed solely to dehydration by formylpiperidine since this process liberates piperidine and formic acid which

were slow (yielding respectively 54% in 47 hours and 45% in 44 hours) as compared with those with piperidine, formalin, and formic acid (74% in 36 hours). Horning and Schock (30) made preparative use of this alternative for methylation of amine obtained as formyl derivative. In the present study N-acetylpiperidine, benzaldehyde, and formic acid yielded only 7.9% of N-benzylpiperidine in 3 hours.

⁵ In the Leuckart procedure water is sometimes removed progressively by distillation, but probably never so promptly or completely as to keep the reaction mixture anhydrous.

⁶ Calcium sulfate is considered preferable to other common drying agents because it does not decompose formic acid and retains one-half molecule of water below 163°.

⁷ This favorable influence, like that of anhydrous magnesium chloride in the experiments of Webers and Bruce (24) using benzophenone, may be exerted upon the initial condensation of carbonyl compound and amine; Reddelien (34) reported a similar effect due to anhydrous zinc chloride in condensations of amines with ketones.

are reactants. In the aggregate these results indicate that water exerts a retarding effect upon the Wallach reaction. A more decisive test under the anhydrous conditions secured by using instead of piperidine and benzaldehyde the preformed product of their condensation, benzylidene-*bis*-piperidine, is discussed in section (f).

(e) *The effect of amount of formic acid.* The operation of formic acid as a reducing agent in the Wallach (and perhaps also the Leuckart) reaction involves its aldehydic function. If the acid properties of formic acid have a negligible or a favorable effect a large excess of acid should intensify reduction and promote alkylation. If its acid character leads to reactions which obstruct essential earlier steps in the alkylation sequence it is to be expected that for each reaction there can be found an optimum quantity of formic acid and clear indications that

TABLE II
INFLUENCE OF WATER ON THE WALLACH REACTION^a

CARBONYL COMPOUND	FORMIC ACID CONC., %	REACTION TEMPERATURE, °C.	N-ALKYL-PIPERIDINE 3-HR. YIELD, %
Benzaldehyde	99	123-125	85.6
	98	122-124	84.5
	98	104-106 ^b	75.0
	88	115-117	76.0
	88	104-105 ^b	61.7
	70	105-106	53.4
In presence of CaSO ₄ (Drierite)	99	123-125	88.2
CaSO ₄ (Indicating Drierite)	99	123-125	93.5
Cyclohexanone	99	114-116	29.2
	88	111	15.2
	70	107	7.7

^a Piperidine, carbonyl compound and formic acid in ratio 1:1:2.5. Water introduced in diluted acid.

^b Reaction at temperature of mixture containing 70% formic acid, to eliminate temperature effect.

excessive acid is detrimental. In experiments to test these points alkylations of piperidine by benzaldehyde and by cyclohexanone were effected with quantities of formic acid (98%) which ranged from 1 to 5 equivalents. The results, in Table III, reveal that the large amounts of formic acid hitherto specified, *viz.*, 4 to 5 equivalents by Wallach (4) or 2.5 equivalents by Clarke, Gillespie, and Weisshausz (18), are harmful and wasteful; the highest yields are obtained with only one equivalent of formic acid.⁸ This means that formic acid is an effective reducing agent even in the low concentrations present late in the reaction, and permits the inference that if formic acid functions as an acid it may be as an acid catalyst; this view is considered in section (g).

⁸ Yields with one equivalent of formic acid are probably affected by a negative error owing to the fact that stratification of the reaction mixture occurred (in absence of excess formic acid which keeps the mixture homogeneous), thus decreasing the yield obtainable in 3 hours.

In alkylation with only one equivalent of formic acid the reaction mixture becomes basic, for the total of the basic compounds remains constant while the acid is progressively destroyed. To test whether or not alkylation will occur in continuously basic environment an experiment was performed using two equivalents of piperidine and one each of benzaldehyde and formic acid. The yield of 72% in three hours showed that these conditions are not optimal but that a predominantly acidic environment is not essential. The unfavorable influence of a large excess of formic acid may be attributed jointly to repression of the dissociation of amine formate, to obstruction of condensation of amine and carbonyl compound, and to formylation of amine.

(f) *Interaction of benzylidene-bis-piperidine and formic acid.* The effects of water, and of excess formic acid, are believed to be adverse because these agents interfere with primary condensation of amine and carbonyl compound, which condensation liberates water and must be progressively impeded by its accumulation. Exclusion of the condensation step by use of the preformed condensation

TABLE III
INFLUENCE OF AMOUNT OF FORMIC ACID

CARBONYL COMPOUND	FORMIC ACID 98%, EQUIV.	REACTION TEMPERA- TURE, °C.	N-ALKYL- PIPERIDINE 3- HR. YIELD, %
Benzaldehyde	1.0	114-116	83.2
	2.5	122-126	81.6
	5.0	122-125	69.4
Cyclohexanone	1.0	110-112	61.7
	2.5	114-116	29.2
	5.0	120-122	12.8

product should therefore improve the conditions for alkylation. Clarke, *et al.* (18), found that methylene-*bis*-amines and formic acid produced methylated amines in good yields, though these results led to no important conclusions. This matter has now been examined, for the preparation of N-benzylpiperidine, by heating preformed benzylidene-*bis*-piperidine⁹ with formic acid. The results of these experiments were impressively different from those under other conditions. Reaction started spontaneously at or below room temperature, and without application of heat was 75-80% complete when gas evolution subsided. Upon heating the mixture as usual for the remainder of a three-hour period the yield of benzylpiperidine was 100%. It thus appears that by use of the preformed condensation product the optimum conditions for this alkylation are attained.

⁹ Benzylidene-*bis*-piperidine appears to be the only known condensation product of benzaldehyde and piperidine. Laun (27) was unable to obtain the aminocarbinal, and in the present study attempts to make and isolate it were unsuccessful. If present in the Wallach reaction it would probably be converted thermally (28) to benzylidene-*bis*-piperidine. No similar condensation products of piperidine and cyclohexanone are known; Mannich and Davidsen (29) obtained only the secondary product N-(1-cyclohexenyl)piperidine.

In these experiments the formic acid was present in appreciable excess; since benzylidene-*bis*-piperidine represents two equivalents of amine the usual amount of formic acid was doubled. It is noteworthy that so considerable an excess of acid above that required for reduction (sufficient markedly to decrease yields when the starting compounds are piperidine and benzaldehyde) has no adverse effect upon conversion of benzylidene-*bis*-piperidine to benzylpiperidine. The inference is clear that excess formic acid impedes the primary condensation but not the subsequent reduction of the condensation product. If this condensation product is an essential intermediate, initial conditions in the usual Wallach reaction should be such as to encourage its formation, *viz.*, 2 equivalents of amine to one of carbonyl compound and no undue excess of acid. To ascertain the effects of such conditions experiments were performed in which carbonyl compound, piperidine, and formic acid were present in the ratio 1:2:2.5. Inter-

TABLE IV
COMPARISON OF WALLACH ALKYLATIONS UNDER VARIOUS CONDITIONS

REACTANTS	MOLAR RATIO	N-BENZYLPIPERIDINE		N-CYCLOHEXYL-PIPERIDINE	
		3-hr. yield, %	Reaction Temp., °C.	3-hr. yield, %	Reaction Temp., °C.
Benzaldehyde, Piperidine, 98% Formic Acid	1:1:2.5 ^a	81.6	114-117	29.2	114-116
	1:2:1 ^b	72.1	104-114		
	1:1:1	83.2	114-116	61.7	110-112
	1:2:2.5 ^c	97.9	112	80.8	114-116
Benzylidene- <i>bis</i> -piperidine, 98% Formic Acid	1:2.5 ^d	100	135		

^a These are the customary proportions (18).

^b Experiment in basic environment.

^c Proportions favorable for formation of alkyldene-*bis*-piperidine.

^d Based on piperidine represented; 5 equivalents based on benzylidene-*bis*-piperidine.

action of benzaldehyde, piperidine, and formic acid started feebly at room temperature and on heating as usual was initially vigorous; the yield of benzylpiperidine after three hours was 97.9%. A similar experiment with cyclohexanone, piperidine, and formic acid produced a yield of 80.8%, that by the usual procedure being 29%. In these experiments piperidine was present as formate, and the excess formic acid served at first to keep the mixture homogeneous, but was consumed as reaction progressed, so that after the alkylation reached 50% the bases were present in excess.

The experiments with preformed condensation product, and those using conditions favorable to its formation *in situ* thus produced the highest yields of alkylated amine yet reported; the next best yields resulted when carbonyl compound, amine, and formic acid were used in equivalent amounts. Table IV permits comparison of the results using several reaction conditions.

(g) *The course of the Wallach reaction.* Results presented above are believed to be significant with respect to the course of the Wallach alkylation and, in

conjunction with some earlier results with analogous systems, permit extension of the view that a common basis exists for a number of reactions of amines and carbonyl compounds in presence of acid and for certain hydrogenation-dehydrogenation reactions involving amines and aldehydes or ammono-aldehydes. It was shown in section (c) that formylamine (formamide) is not a normal intermediate in the Wallach reaction, but that formylation may not be avoidable, so that part (or much) of the alkylated product may be derived from the formylamine; to this extent the reaction may be considered to be a Leuckart reaction with added formic acid (3, 20). For this reason the Wallach reaction cannot be discussed apart from the Leuckart reaction.

The course originally suggested for the Leuckart reaction (using ammonium or amine formate) by Wallach (4) involves primary thermal dissociation of ammonium formate into ammonia and formic acid, followed by additive union of ammonia and carbonyl compound to yield an α -aminocarbinal, and reduction of this by formic acid, analogous to the reduction of triphenylcarbinal to triphenylmethane by formic acid (31). Emde (9) represented the reduction step to occur by thermal decarboxylation of the ester produced by interaction of the α -aminocarbinal and formic acid. Alexander and Wildman (21) considered such esters to be improbable intermediates, apparently judging them to be of the "homo-polar" type (*e.g.*, methyl or benzyl formate) found by Bowden, Clark, and Harris (32) to require temperatures from 200° to 400° for decomposition, rather than of the "polar" type [*e.g.*, triarylmethyl and related formates (33a)] which decompose at much lower temperatures.

The demonstration that formamides can be used in the Leuckart reaction (2, 3) led to speculation as to the manner of their involvement. The relatively high temperatures (150–200°) used would suffice to convert ammonium or amine formates to formamides, but a conclusion that the alkylation proceeds via the formamide cannot well be reconciled with Alexander and Wildman's finding (21) that ammonium formate reacts under conditions so mild that formamide fails to react, which result appears to confirm the claim of Crossley and Moore (20) that formamide is not an essential reactant. The contrary view has not been abandoned (22, 23, 24); it assumes initial addition of formamide to carbonyl

compound to form an intermediate aminohydrin $\text{RC}(\text{OH})\text{NCHO}$ reducible to RCHNCHO (formyl derivative of alkylated amine). This view finds partial support in the observation of Nabenhauer (17) that N,N-dialkylformamides, which are incapable of such condensation, do not yield tertiary amines by the Leuckart procedure. They do so, however, in the presence of formic acid, and this result is consistent with the favorable effect of formic acid added to the usual Leuckart reactants (3, 20). Webers and Bruce (24), in seeking an explanation for the apparent catalytic effect of ammonium salt (and of anhydrous magnesium chloride⁷) upon the Leuckart reaction, assumed formation of the same intermediate by the addition of a proton (from ammonium salt) to the carbonyl compound and addition of the resulting carbenium-oxonium ion to formamide;

it should not be overlooked that ammonium salt may serve also as a source of ammonia which may be a reactant.

These views as to the course of the Leuckart reaction have led to no generally accepted conclusion. Speculations which involve formamide as an essential reactant cannot apply to the Wallach reactions reported here, since formylpiperidine is incapable of additive union with carbonyl compounds. Development of the view that the Leuckart and the Wallach reactions involve a single essential mechanism leads to a reaction course in which the earlier ideas of Wallach and of Emde are recognizable. The primary reactants are assumed to be ammonia (amine), carbonyl compound, and formic acid. In Leuckart reactions in which formamide is used the availability of ammonia and of formic acid may be attributed to thermal dissociation of formamide into ammonia and carbon monoxide,¹⁰ and to condensation of ammonia with the carbonyl compound with liberation of water, which hydrolyzes formamide to yield the essential reactants, ammonia and formic acid. The condensation product is hydrogenated by the latter compound. In this way the needed reactants may be available throughout the reaction. The presence of much water, at the high temperatures used, would interfere as was shown experimentally by Crossley and Moore (20), probably by impeding condensation of amine and carbonyl compound. Complete absence of water, or its continued removal by a dehydrating agent, would decrease the yield of alkylated amine, as was observed by Alexander and Wildman (21), because in this case the only source of ammonia is the thermal dissociation of formamide, which results in loss of potential formic acid (as carbon monoxide) needed for reduction.¹¹ In practice the initiation of Leuckart reactions of formamides may include also the hydrolytic effect of water incidentally present. As thus represented the Leuckart and the Wallach reactions are identical throughout the actual alkylation sequence. The Wallach reaction uses as starting materials the essential reactants, which in the Leuckart procedure are obtainable, in preliminary steps, from ammonium or amine formate or from a formamide.

A suggested course of the Wallach reaction, presented in the accompanying diagram (Figure 2), is based jointly upon evidence reported above and upon analogies with systems studied earlier. The principal steps are the condensation of amine and carbonyl compound to yield intermediates such as hydroxyalkylamines, alkylidene-*bis*-amines or (from primary amines) alkylidene-imines or Schiff bases; reduction of the condensation product to alkylamine by formic acid by two alternative paths, one represented as a sequence initiated by formation of a salt of the condensation product and terminated by transfer of

¹⁰ Formamide dissociates readily on heating (23, 24). Some thermal dissociation of *N*-formylpiperidine may be inferred from the results of experiments with this as a starting compound [section (c)], for the amounts of formic acid consumed exceeded by 20-30% the amounts of carbon dioxide formed, contrasting with the deviations of 2-7% from the 1:1 ratio observed in experiments with piperidine, benzaldehyde, and formic acid (Table I).

¹¹ It is possible that formamide, functioning as aquo-ammono-formic acid, *i.e.*, as an aldehyde, may effect hydrogenation [*cf.* (40)]. This also would lead to decreased yields of alkylated amine.

hydrogen from the aldehydic grouping of the formate ion, and the other a unidirectional hydrogenation-dehydrogenation of Cannizzaro type involving formic acid (as carbonic aldehyde) and an ammono-aldehyde or ammono-ketone.

Interaction of primary and/or secondary amines with carbonyl compounds is believed to be initially additive, yielding hydroxyalkylamines (III; reaction A), readily and often spontaneously convertible to alkylidene-*bis*-amines (IV; reaction B) (28, 35, 36) or to Schiff bases (VIII; reaction J). Alkylidene-*bis*-amines (IV) from aldehyde and primary or secondary amines are familiar (28, 37); generally either IV or VIII can be obtained from primary amines (reaction J) by suitable adjustment of conditions (37, 38). Compounds of types III, IV, and VIII, though susceptible to acid hydrolysis, may form in the presence of water and acid¹² (36), and seem qualified to serve as transient intermediates in the Wallach alkylation if it involves their irreversible removal as represented. No such compound from cyclohexanone and piperidine is known, hence this intermediate can only be assumed, but benzylidene-*bis*-piperidine, the only known condensation product of benzaldehyde and piperidine, was indicated to be a plausible intermediate by its quantitative conversion to benzylpiperidine by formic acid.

No direct evidence is available, or is expected, to establish the presence of the carbenium-ammonium salt IX obtained from VI, VII, or VIII respectively by loss of water (reaction E₁), or of amine (reaction E₂), or by addition of acid (reaction E₃). Analogous hypotheses have been invoked to explain certain acid-catalyzed dehydrations and deaminations; assumption of the intermediate operation of carbenium ion IX has proved helpful in elucidation of several acid-induced reactions (39, 40), and of problems of mechanism presented by other reactions studied in this laboratory (41).

The results in Table I indicate that a quantitative transfer of hydrogen from formic acid to the group $\text{C}_6\text{H}_{10}\text{N} \cdot \overset{\text{H}}{\underset{|}{\text{C}}} \cdot \text{C}_6\text{H}_5$ occurs; in Figure 2 this is represented

(reaction F) to involve the two ions of the salt IX. The hydrogen must be transferred as hydride ion, as in certain organic redox reactions (33b, 42), and the reduction resembles in a formal sense a unidirectional crossed Cannizzaro reaction (40). It is interesting to observe that compound IX is actually, in highly polar form, the ester intermediate proposed by Emde (9), who assumed it to be formed by action of formic acid on the hydroxyalkylamine (III). In Figure 2 the formation of IX is represented to involve condensation products III, IV, or VIII and in such manner as to endow compound IX inevitably with the high polarity found by Bowden, Clark, and Harris (32) to be requisite to decarboxylation and transfer of hydrogen at temperatures within or near the range effective for Wallach reactions. It cannot be stated whether the primary change is decarboxylation or transfer of hydrogen; the latter was admitted by McLaughlin and Wagner (40) to account for a similar reaction which involved no decarboxylation and which the presence of acid occurred at a much lower temperature.

¹² Benzylidene-*bis*-piperidine was observed to dissolve in cold concentrated formic acid without detectable decomposition to benzaldehyde and piperidine.

Paths G and H are suggested because of the possibility that reductions of III, IV, or VIII [the last two shown to be functionally aldehydic (44)] may be reactions of unidirectional Cannizzaro type, with formic acid functioning as an aldehyde which invariably serves as a hydrogen-donor. When the carbonyl compound represented is a ketone, the direction of the hydrogen-transfer is further fixed by the fact that compounds III, IV, or VIII can then serve only as hydrogen-acceptors. The Plöchl-Eschweiler reaction has been assumed to include two operations of Cannizzaro type (7, 43). Direct reductions of Schiff bases (VIII) by formic acid were reported to fail, yielding at most tarry products without gas evolution (18, 21), but by use of triethylammonium formate instead of formic acid Alexander and Wildman (21) obtained a high yield of benzylaniline from benzylidene aniline. These results are now explicable, for it seems clear that formic acid functioned as an acid but that in triethylammonium formate, which lacks acid character, the combined formic acid was able to function as an aldehyde.

Practical considerations. The findings reported above may be applied to the selection of favorable conditions for the Wallach reaction, which is a preparative procedure of some utility. The suggestions ventured here apply to monoalkylation and will require alteration when dialkylation is intended; further they are based on results of the two cases studied and may require modification as applied to other groups of reactants.¹³

For general purposes a mixture of equivalent amounts of amine and carbonyl compound may be treated, at low temperature, with one equivalent or slightly more of formic acid of high concentration (at least 88%; probably best 99–100%), and the mixture brought promptly to reaction temperature, which is maintained for about three hours if reaction is initially vigorous or longer if it is not. The use of larger amounts of formic acid, or of acid of lower concentration, may decrease the yield of alkylated product; in any case the water present should be minimal. If the amine and carbonyl compound yield an isolable compound of type III, IV, or VIII it may be advantageous to treat this preformed compound with formic acid or with the formate of a tertiary base such as triethylamine. Increased yields may result also by use of amine, carbonyl compound, and formic acid in the ratio 2:1:2.5. In this procedure, and in the preceding one if alkylidene-*bis*-amine is used, at least one-half of the original amine is finally present. If this interferes with isolation of the alkylated product (as in the preparation of *N*-methylpiperidine, which is not easily separable from piperidine) the procedure may be without advantage. For rapid reaction the extent of formylation should be minimal; this is not wholly controllable, but is favored by suggestions given above. It is possible, however, to alkylate formylamines and also acetylamines by extended heating with carbonyl compound and formic acid. Alkylation by the Wallach procedure tends to be exhaustive and is most useful for preparation of tertiary amines. The Leuckart procedure permits preparation of primary amines (from ammonium formate or formamide) or of secondary amines (from *N*-substituted formamides) (14, 15, 16), but preparation of tertiary amines from

¹³ Reports as to the utility of these suggestions are invited.

N,N-disubstituted formamides requires the presence of formic acid (17). The two procedures are therefore usefully complementary. The findings reported above for the Wallach reaction, considered in their applicability to the Leuckart reaction, make it appear that the conditions of the latter are actually unfavorable for rapid and extensive alkylation.

EXPERIMENTAL

Primary reactants (Eastman, Paragon, Baker and Adamson) were purified as follows. *Piperidine* was dried over sodium hydroxide and distilled; the 105–106°¹⁴ fraction was used. *Benzaldehyde*, preserved with hydroquinone, was distilled under nitrogen and the 176–177° fraction was collected under nitrogen and stored in well-stoppered bottles; freshly distilled material was used for each series of experiments. *Cyclohexanone* was dried over magnesium sulfate and distilled; the 155° fraction was used. *Formic acid* of nominal 90% and 98–100% concentrations was used generally without purification, but was assayed by the mercurous chloride method outlined later and was found to contain respectively 88% and

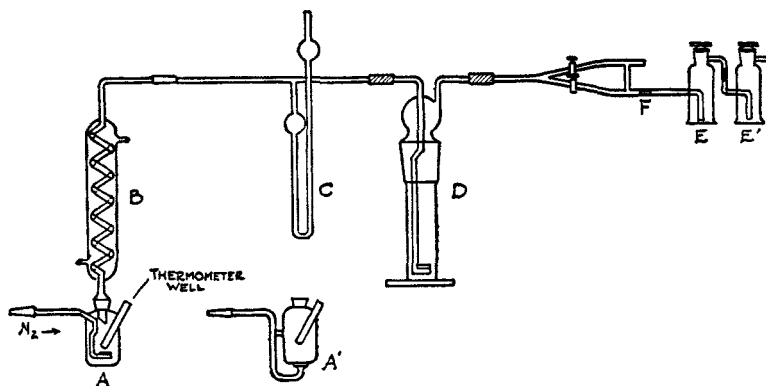


FIGURE 3

97.5–98.5% formic acid by weight. To obtain a more concentrated acid the 98% material was treated for several days with anhydrous copper sulfate¹⁵ and was distilled in an all-glass apparatus with exclusion of atmospheric moisture. The 100.5–101° fraction was submitted to concentration by partial freezing (four repetitions) with separation of the solid phase at about 5°. The resulting acid assayed 99.5%. *N-Formylpiperidine*, b.p. 218–220°, was made by the method of Auwers (47), and *N-acetyl piperidine*, b.p. 226°, by the method of Hofmann (48). *Benzylidene-bis-piperidine* was made from benzaldehyde (21.2 g.; 0.2 mole) and piperidine (34.0 g.; 0.4 mole), which reacted spontaneously, the mixture solidifying; to complete the reaction the mass was warmed below 50° for 15 minutes and was then crystallized twice from 95% ethanol. The pure product (33.6 g.; 65%) melted at 80–81° (corr.), the value given by Laun (27). *Piperidine hydrochloride* was prepared by passing hydrogen chloride into a solution of piperidine in absolute ethanol. The washed and air-dried salt melted at 244° (corr.); Vorländer and Wallis (49) reported 245°.

Apparatus (Figure 3). The reaction vessel A, capacity about 50 ml., is provided with a gas inlet tube with sintered-glass diffusion disc and a thermometer well. Reaction vessel A' is used when reaction mixtures include solid dehydrating agents in order to assure

¹⁴ Melting points and boiling points are "observed" values unless otherwise specified.

¹⁵ Copper sulfate is probably incapable of yielding anhydrous formic acid, but more rigorous treatment, such as elaborate fractionation or use of boric anhydride (45) was judged inadvisable in view of the reported instability of very concentrated formic acid (46).

effective agitation by the gas stream. The flask is joined to a wide-bore reflux condenser B, and this to a tube with a branch to a mercury manometer C (to this point all connections are glass) and connected to a gas-washing bottle D the inlet tube of which ends in a sintered-glass gas diffuser. Absorber D contains concentrated sulfuric acid and serves as a trap to remove traces of formic acid from the gas stream. The manometer indicates internal pressure before the acid trap and serves as a safety valve in case excessive pressure develops during rapid reactions. Two absorption bottles E and E' (Stetser-Norton type), containing Ascarite, are connected in series to F, which provides a relief outlet as shown. During the entire course of each experiment, except the period of active evolution of carbon dioxide, there is passed a stream of nitrogen; this is used instead of air to exclude the possibility that carbon monoxide (from the reaction or from formic acid decomposed in the acid trap D) might be oxidized to carbon dioxide and absorbed by the Ascarite. The effectiveness of these precautions was tested by refluxing 90% formic acid in the apparatus, with the highest manageable flow rate of nitrogen; after 3 hours the gain in weight of receivers E and E' was less than 1 mg.

PROCEDURE FOR ANALYSIS OF REACTION MIXTURES FOR FORMIC ACID, BENZALDEHYDE,
PIPERIDINE, AND N-BENZYLPIPERIDINE

Formic acid is estimated in a separate portion, following a preliminary acid hydrolysis to obtain any formic acid bound as N-formylpiperidine (for determination of which in these mixtures no satisfactory method could be devised), by an adaptation of the method of Franzen and Egger (50). A sample containing about 0.1 g. of formic acid is heated under reflux for an hour with 25 ml. of 10% hydrochloric acid. The solution is made slightly alkaline with sodium hydroxide and is then evaporated to dryness on a steam-bath, to remove amines and benzaldehyde. The solution of the residue in water is made slightly acid with hydrochloric acid and is treated with 30 ml. of mercuric chloride reagent (HgCl_2 100 g., NaCl 150 g. per liter). Water is added to a volume of about 300 ml., and then 10% sodium hydroxide solution to faint permanent turbidity, followed by 30 ml. of saturated sodium acetate solution. The volume is increased to 400 ml., and the mixture is kept in a steam-bath for 6 hours, and is then cooled to room temperature. The mercurous chloride is collected in a weighed glass filter crucible, washed sparingly with water and then with 95% ethanol, dried to constant weight at 105° and weighed.

Benzaldehyde is estimated in a separate portion of the reaction mixture, using the method of Houghton (51). The aliquot taken, containing about 0.25 g. of benzaldehyde, is treated with 5 ml. of 95% ethanol followed by 50 ml. of water, and to the clear solution is added, with stirring, a solution of 0.30 g. of 2,4-dinitrophenylhydrazine in 50 ml. of 2 N sulfuric acid. After 30 minutes on a steam-bath the mixture is cooled and the precipitate is collected in a weighed glass filter crucible, washed with 2 N sulfuric acid to remove precipitant, then with water to remove acid, and is dried at 110° and weighed. This method is satisfactory only if the benzaldehyde is nearly equivalent to the reagent used, as the low solubility of dinitrophenylhydrazine causes it to separate if present in considerable excess.

Piperidine and *N-Benzylpiperidine* are estimated in a portion of the reaction mixture containing about 0.5 g. of the amines, using a procedure based upon the solubility of piperidine and the virtual insolubility of benzylpiperidine in water and upon the fact that piperidine is so effectively salted out from aqueous solution by sodium hydroxide as to be rapidly and completely extractable in ether. In order to estimate piperidine present as formylpiperidine as well as free piperidine the aliquot is first refluxed with hydrochloric acid as outlined above. Benzaldehyde is then removed by steam-distillation. In the residual liquid, chilled in ice, is dissolved sodium hydroxide sufficient to produce a concentration of 20%. The mixed amines are extracted into ether; three extractions usually suffice. The ether solution is extracted with numerous small portions of 10% aqueous sodium chloride solution until the piperidine is all present in the aqueous extract, in which it is titrated with 0.1 N acid, using Methyl Orange as an indicator; it is easy in this way to make certain of the extraction of all the piperidine. The ether solution containing the benzylpiperidine,

in a side-arm flask, is heated just sufficiently to evaporate the ether; more vigorous heating may cause loss of benzylpiperidine from the wet liquid. The residue in the flask is dissolved in 95% ethanol and the benzylpiperidine is titrated with 0.1 *N* acid to an end-point with Methyl Orange.

The procedures described were first tested individually and were then applied to a simulated reaction mixture, with the following results.

	TAKEN	FOUND
Formic acid	38.8%	38.2 ± 0.3%
Benzaldehyde	27.4%	26.5 ± 0.2%
Piperidine	20.3%	19.5 ± 0.0%
<i>N</i> -Benzylpiperidine	10.2%	11.4 ± 0.1%

The errors, negative for the first three compounds (but not exceeding -5%), and positive for benzylpiperidine, are believed to represent small actual changes in the composition of the mixture due to incipient reaction prior to analysis, as suggested also by the evolution of some bubbles of gas. The error of about +10% for benzylpiperidine is without serious effect for it was found that the amount of this product is accurately indicated by the amount of carbon dioxide produced.

N-Cyclohexylpiperidine is isolated and estimated by the following procedure devised by Borkowski (19). A weighed aliquot of the reaction mixture is refluxed with hydrochloric acid as outlined above to hydrolyze formylpiperidine, and the solution is made just alkaline and is extracted with ether to remove cyclohexylpiperidine (and some piperidine). The ether extract is dried over potassium carbonate and transferred to a small separatory funnel (with necessary rinsings with ether), from which it is admitted dropwise into a dried and weighed semimicro distillation outfit (consisting of a 25-ml. distillation flask with a small condenser sealed to the side-arm) which is warmed on a steam-bath, permitting removal of ether and accumulation of the amines in the flask. When the ether has been transferred, the separatory funnel is replaced by a thermometer, and the flask is heated with a small flame until piperidine (b.p. 106°) has distilled and the vapors reach a temperature of about 215-220°. A weighed receiver is now attached, and a few drops of distillate are collected to verify the boiling point of the residue; cyclohexylpiperidine boils at 230°. The entire apparatus, including the receiver is cooled and weighed, and the increase is recorded as *N*-cyclohexylpiperidine. Tests showed this procedure to be capable of results accurate to within 2%.

GENERAL PROCEDURE FOR THE STUDY OF WALLACH ALKYLATIONS

The reactants, previously chilled in an ice-bath, are mixed as specified below for individual experiments, and a portion (usually about 20 g.) of the mixture is weighed into reaction vessel A (the total weight also is recorded); the remainder is reserved for analysis. The apparatus is assembled, with temporary omission of absorbers E and E', and is flooded with nitrogen for 15-20 minutes. The weighed absorbers are attached, the time is noted, and the reaction mixture is warmed by raising a preheated oil-bath (Fisher Bath Wax) so as to immerse the flask A. The bath is heated by a "micro" burner with sensitive gas control, the process being adjusted so that the time required to induce vigorous reaction or refluxing is 5-6 minutes and is reproducible. The reactions under consideration are both exothermic, and initially and briefly they may reach temperatures a few degrees above the temperature of steady refluxing. Zero time for the reaction is taken as the moment the mixture reaches the highest observed temperature, which is usually coincident with onset of refluxing. During the period of active evolution of carbon dioxide little or no nitrogen is passed, but as the reaction subsides and steadies the stream of nitrogen is increased to a moderately rapid rate and is continued for the duration of the reaction period. A drift of several degrees in reaction temperature may occur as the composition of the mixture changes with the progress of the reaction. At the end of the heating period the oil-bath is withdrawn, the reaction flask is wiped, and it is immersed in an ice-bath. The time when the cooling bath is substituted for the heating bath is taken as the end of the reaction period. Since the cooling

period represents an overlap with respect to the succeeding reaction period, it is timed by observation of the temperature so as to permit uniformity of operation through successive stages of an extended experiment. The stream of nitrogen is continued for 30 minutes to assure transfer of carbon dioxide completely to receivers E and E', which are then weighed. The reaction vessel A and its contents are weighed to ascertain any loss of volatile material other than carbon dioxide (total loss minus carbon dioxide determined). Portions of the cool reaction mixture are analyzed for products and/or reactants as outlined earlier. If reaction is to be continued through a further interval, the reaction flask and receivers are reattached to the train and the described procedure is repeated. For each set of conditions the alkylated products were identified: *N*-benzylpiperidine as *picrate*, m.p. 178° (52) and *N*-cyclohexylpiperidine as *methiodide*, m.p. 248–249° (29).

Individual experiments. The capacities of the apparatus and the nature of the manipulations made it convenient to operate generally on a 0.1 molar basis. To avoid frequent repetitions below it is entered here that 0.1 molar weights of the compounds named are as follows: benzaldehyde, 10.61 g.; cyclohexanone, 9.81 g.; piperidine, 8.51 g. For formic acid the 0.25 molar amounts most frequently used are: 88%, 13.05 g.; 98%, 11.75 g.; 99%, 11.50 g. Other quantities of reactants are indicated fully as usual.

Piperidine hydrochloride and benzaldehyde. In this experiment, under the conditions of the Plöchl-Eschweiler reaction, a solution of 6.08 g. (0.05 mole) of piperidine hydrochloride and 26.60 g. (0.25 mole) of benzaldehyde in 25 ml. of 95% alcohol was heated on a steam-bath for 30 hours. No benzylpiperidine was isolated by the procedure outlined above.

Determination of stoichiometric relationships. Sections (a) and (b). In two series of experiments the reactants were 0.1 mole of benzaldehyde or cyclohexanone, 0.1 mole of piperidine, and 0.25 mole of 88% or 98% formic acid, all previously chilled, and mixed in the order named. Upon mixing benzaldehyde and piperidine some solid benzyldene-*bis*-piperidine separated; it dissolved upon addition of formic acid. The reaction with benzaldehyde was run at 114–117°, and that with cyclohexanone at 114–118°. Data for intervals of 0.5, 1.0, 3.0, and 5.0 hours are presented in Table I. The yield of *benzylpiperidine* in 15 minutes was 59.5%. Time-yield data are represented by curves I and II in Figure 1.

Influence of acylation of amine. Section (c). For the preparation of benzylpiperidine the reactants were *N*-formylpiperidine (11.31 g.; 0.1 mole), benzaldehyde (0.1 mole), and 98% formic acid (7.83 g.; 0.15 mole). Reactions at 125–128° gave yields of 2.8% in 0.5 hour, 6.5% in 1.0 hour, 26.5% in 3.0 hours, and 43.1% in 5.0 hours. These results are represented by curve III in Figure 1. By the use of acetyl piperidine (12.71 g.; 0.1 mole), benzaldehyde (0.1 mole) and 88% formic acid (0.25 mole), reaction at 125° for 3.0 hours produced 7.9% of benzylpiperidine.

For the preparation of cyclohexylpiperidine the reactants were cyclohexanone (0.1 mole), formylpiperidine (11.31 g.; 0.1 mole) and 98% formic acid (7.05 g.; 0.15 mole). The yield in three hours at 136–138° was 14.4%.

Influence of water. Section (d). In each of four experiments piperidine (0.1 mole) was treated with 0.25 mole of formic acid of, respectively, 70%, 88%, 98% or 99% concentration, followed by 0.1 mole of benzaldehyde. Stratification occurred in the reaction with 70% acid. Reaction temperatures and 3-hour yields appear in Table II. Two similar experiments, using 99% formic acid and 12 g. of finely ground Drierite in one, and 12 g. of Indicating Drierite in the other, were performed in reaction vessel A' (Figure 3). Reaction temperatures and 3-hour yields are given in Table II. In each of three experiments piperidine (0.1 mole) was treated with 0.25 mole of formic acid of, respectively, 70%, 88% or 98% concentration, followed by 0.1 mole of cyclohexanone. Data for these experiments appear in Table II. In an experiment to test the utility of *N*-formylpiperidine as a dehydrating agent piperidine (0.1 mole) was treated with 0.1 mole of 98% formic acid (4.70 g.), followed by 11.32 g. (0.1 mole) of *N*-formylpiperidine and then 0.1 mole of cyclohexanone. Reaction at 114° for 3.0 hours produced 66.7% of cyclohexylpiperidine.

Influence of the amount of formic acid. Section (e). In each of three experiments 0.1 mole of piperidine was treated with 98% formic acid in one of these amounts: 0.1 mole (4.70

g.), 0.25 mole (11.75 g.), 0.5 mole (23.50 g.). Benzaldehyde (0.1 mole) was added and the experiments were run at the temperatures, and with the results, given in Tables III and IV. In a second series of three experiments cyclohexanone (0.1 mole) was used instead of benzaldehyde.

Effect of excess piperidine. Section (e). Piperidine (17.02 g.; 0.2 mole) was treated with 98% formic acid (0.1 mole), followed by benzaldehyde (0.1 mole). Reaction at 104–114° for 3 hours produced 72.1% of benzylpiperidine.

Effect of excess piperidine formate. Section (f). Piperidine (17.02 g.; 0.2 mole) was treated with 98% formic acid (0.25 mole), followed by benzaldehyde (0.1 mole), and the reaction was run at 112°. In a similar experiment cyclohexanone (0.1 mole) was used instead of benzaldehyde; reaction temperature was 114–116°. The 3-hour yields appear in Table IV.

Benzylidene-bis-piperidine and formic acid. Section (f). Benzylidene-bis-piperidine (12.92 g.; 0.050 mole) was added slowly to 0.25 mole of chilled 98% formic acid. Solution occurred with slight gas evolution. When the mixture was removed from the ice-bath and allowed to come to room temperature gas evolution became vigorous and the reaction developed sensible heat. Active evolution of carbon dioxide continued without applied heat for about 20 minutes and then subsided. Analysis of an aliquot of the mixture at this stage showed that over 75% of benzylpiperidine was present; the reaction was continued at a temperature of 135° for 3 hours. The yield of benzylpiperidine was quantitative.

SUMMARY

Results of a semiquantitative study of the formation of N-benzylpiperidine and N-cyclohexylpiperidine by the Wallach alkylation reaction and by experimental modifications thereof lead to the following conclusions.

1. The reactants (amine, carbonyl compound, and formic acid) and the products (carbon dioxide and alkylated amine) are involved in equivalent amounts.¹⁶

2. Formylation of amine retards but does not prevent alkylation. The reactions studied are characterized by a rapid initial phase which is absent when formylpiperidine is used instead of piperidine. It is inferred that formylamine is not involved in the normal alkylation sequence.

3. The initial reaction appears to be the condensation of amine and carbonyl compound, for alkylation is promoted by conditions which favor condensation and is impeded by conditions which hinder it. Treatment of benzylidene-bis-piperidine, the preformed condensation product of benzaldehyde and piperidine, with formic acid led to rapid alkylation and a quantitative yield of benzylpiperidine.

4. Formic acid functions chiefly as an aldehyde and appears to be the sole operative reducing agent in the reaction.¹⁶ The acid character of formic acid is helpful to the extent that acid catalysis is involved, and perhaps as a solvent, but is otherwise obstructive.

5. The course of the Wallach alkylation is represented to involve hydrogenation of the condensation product of amine and carbonyl compound by formic acid, either through an intermediate carbenium-ammonium formate [essentially identical with the ester intermediate previously suggested (9)] or by a hydrogen-

¹⁶ This is not true of methylations by formaldehyde and formic acid, in which reduction is affected jointly by both compounds.

ation-dehydrogenation reaction of the Cannizzaro type. It is believed that the Wallach and Leuckart reactions involve the same essential steps.

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