at by titrating either *in vacuo* or in the presence of an excess of free bromine from the very beginning of the test. Three methods of analysis are described in detail, and criteria are presented for a normal course of bromination.

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[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

The Knoevenagel Reaction and the Synthesis of Unsaturated Nitro Compounds

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It has long been known that organic bases may be used to condense aldehydes with substances containing an active methylene group, yet the role played by the amines is still obscure. The explanation offered by Knoevenagel and others of the intermediate formation of a Schiff base does not account for the activity of tertiary amines as Hann and Lapworth[1] have pointed out. These investigators proposed a hypothesis in which the base is assumed to function by lowering the concentration of hydrogen ions, through the formation of small amounts of an ammonium derivative, thereby facilitating dissociation of the tautomeric substance. The ammonium salt or the dissociated enol reacts with the aldehyde forming a β-hydroxy derivative that is unstable, spontaneously changing into an unsaturated compound through the loss of water. They showed experimentally with acetoacetic ester that tertiary amines are effective, but were unable to isolate the intermediate derivatives. The nitro series offers a more promising field in a study of the mechanism of this reaction, for the corresponding derivatives are more stable. Phenylnitroalcohol, $C_6H_5CHOHCH_2NO_2$(1), for example, has been isolated.[2] Accordingly, the action of various amines on nitromethane has been investigated despite the fact that Knoevenagel and Walter[3] obtained unsaturated compounds and recorded that primary amines only were effective.

It has now been found in accordance with Haworth's views that nitromethane and benzaldehyde condense under the influence of diethyl and triethylamines, forming I. A similar reaction takes place with the primary aliphatic amines and the production of nitrostyrene (II) is due to secondary effects. When an amine is added to the above mixture it reacts with water, normally present to some extent, forming an ammonium base. The base tends to react with the acidic enol, thus promoting dissociation of the latter and therefore its addition to the aldehyde.

$$\text{Amine} + H_2O \rightleftharpoons \text{Amine } H^+ + OH^-$$

$$\text{Amine } H^+ + OH^- + CH_2NOO^- + H^+ \leftrightarrows CH_2NOO \text{ amine } H + H_2O$$

Accordingly, it is not surprising that the reaction may be strongly repressed by avoiding the presence of water. No further changes result with a tertiary amine.

The effect of a primary amine is apparently entirely different. A Schiff base is formed even with small amounts of the organic base while the final product is II. This suggests the formation of an addition product of nitromethane with the Schiff base, followed by decomposition into II and the amine. But such an addition product containing an aliphatic amine has never been isolated. Moreover, the assumption is unnecessary as I decomposes in the presence of primary aliphatic amines into nitrostyrene and water. The real function of the Schiff base is to furnish through hydrolysis a small amount of free base which then reacts like triethylamine in causing the formation of I. The latter substance then decomposes into II. The reaction takes place much more slowly than with a tertiary amine and the mixture will stand the application of heat, precisely the effects one would predict from the smaller concentration of available amine.

Secondary amines react less rapidly and less completely with aldehydes and therefore are more destructive. They are the least suitable of the amines for the synthesis of unsaturated nitro compounds.

o-Chloro and *m*-nitrobenzaldehydes react much more readily than benzaldehyde with nitromethane, provided triethylamine is present. The reaction, on the contrary, is sluggish with a primary amine. The acidic character of the molecule is increased in these substituted benzalde-

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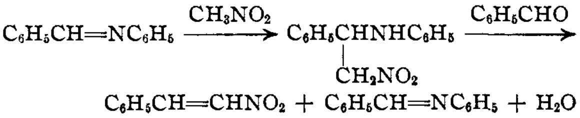
[1] Hann and Lapworth, *J. Chem. Soc.*, **85**, 46 (1904).

[2] Holleman, *Rec. trav. chim.*, **23**, 299 (1904).

[3] Knoevenagel and Walter, *Ber.*, **37**, 4503 (1904).

hydes, promoting thereby the activity of the amine. But the Schiff base, formed with the primary amine, is accordingly more stable and therefore less readily hydrolyzed than usual. A smaller concentration of amine is available so that the total effect is to slow down the speed of the reaction. The non-reactivity of triethylamine with nitromethane and vanillin is due to the formation of a salt with the phenolic group of the aldehyde.

Aromatic amines, aniline for example, are also effective in promoting nitrostyrene formation. Since aniline is without action on phenylnitroalcohol, the role of the base must be different from that of an aliphatic amine. It seems necessary to assume the active participation of benzalaniline in the following cycle of changes.



$$C_6H_5CH{=}NC_6H_5 \xrightarrow{CH_3NO_2} \underset{\displaystyle CH_2NO_2}{C_6H_5\overset{}{C}HNHC_6H_5} \xrightarrow{C_6H_5CHO} C_6H_5CH{=}CHNO_2 + C_6H_5CH{=}NC_6H_5 + H_2O$$

Addition products of this type have been synthesized (from nitrostyrene)[4] and decompose in the manner indicated.

Other facts support this interpretation. While in general the activity of amines seems to parallel their activity as bases, there are some exceptions. *p*-Toluidine is many times as effective as *o*-toluidine, while *β*-naphthylamine is far more powerful than *α*-naphthylamine. These results are all out of proportion to the differences in basicity of the substances and may be supposed to measure the speed of the addition of nitromethane to the Schiff base, a reaction susceptible to steric hindrance. These same amines also are inactive toward nitrostyrene.[4]

Experimental

Benzaldehyde, nitromethane and *n*-amylamine, regardless of the order of mixing, produced benzalamylamine and water. The reaction on standing rapidly became uncontrollable unless cooled, boiling violently for some minutes due to the formation of gases containing carbon dioxide. Cooling simply delayed the action, as eventually a black tar was obtained. Amines were found useful only in small concentrations. Heat may be used then to speed up the reaction. No advantages resulted from working with excessively small amounts. A maximum yield of 66% of II was obtained using 1% of amylamine and heating to 100° for sixty hours while 64% was obtained after heating for only forty minutes with 5% of the amine. Longer heating rapidly cut down the yield. The following table summarizes results obtained with various amines. The benzaldehyde–nitromethane mixture (one-tenth gram mole of each) was sealed in a large test-tube with the amine and heated in boiling water until no further separation of water took place or marked decomposition was observed. The products after neutralization with dilute acid were steam distilled.

TABLE I

EFFECT OF 5% MOLAR CONCENTRATION OF BASES[a]

Base	Hours	Yield, %	Base	Hours	Yield, %
Conc. ammonia sol.	2	14	*o*-Toluidine	8	4
Hydrobenzamid	5	14	*m*-Toluidine	8	38
n-Butylamine	2/3	54	*p*-Toluidine	8	41
Ethanolamine	5/6	54	*p*-Toluidine	12	61
Allylamine	1 1/2	57	*p*-Chloroaniline	8	23
Benzylamine	3	61	*p*-Anisidine	8	57
Piperidine	1/5	14	*p*-Aminodimethylaniline	4	54
Pyridine[b]	2	trace	*α*-Naphthylamine	8	<1
Aniline	8	32	*β*-Naphthylamine	8	24

[a] With aromatic amines 10% molar equivalents used.

[b] Similar results obtained using the molar equivalent of pyridine.

Action of Benzalbutylamine.—Two mixtures of nitromethane and benzaldehyde were prepared, containing anhydrous freshly distilled material; 5% of the molar equivalent of benzalbutylamine was then run into each solution, one of which was stoppered in a desiccator, while the other was exposed to the air. The first solution stood for approximately sixty hours before the formation of water was noticed. The mixture exposed to air became cloudy in two to three hours. A good yield of nitrostyrene was obtained in each case. Similar results were obtained with benzalamylamine.

Secondary Amines.—Pure diethylamine was prepared through the nitroso derivative. A vigorous destructive reaction took place with nitromethane–benzaldehyde mixtures unless the base was used in small amounts. Even then heat must be avoided to obtain a respectable yield. Using 5% molar equivalent of diethylamine the mixture became decidedly warm in ten to fifteen minutes. Traces of water were formed. The viscid dark red liquid after standing for an hour slowly expelled bubbles of gas. A maximum yield of 38% was obtained. Equally poor results were obtained with dibenzylamine, dibutylamine and diethanolamine.

Tertiary Amines.—Although slower in starting, triethylamine had the same destructive action as the other bases on nitromethane–benzaldehyde mixtures unless used in small amounts. No water was liberated and the amount of heat evolved was more moderate than with diethylamine. A clear but viscid red liquid was obtained with 5% of the molar equivalent of triethylamine after standing for fifteen hours in a cool place. This product was identified as phenylnitroalcohol. It was steam distilled, first adding a small excess of acid; yield 52%. The action of the amine, which could be hindered by working with dry reagents, must be quite rapid, as a similar mixture after two hours at 30–35° produced 45% of pure nitrostyrene. A 53% yield was obtained with triethanolamine.

Experiments with Phenylnitroalcohol.—This substance, prepared by the method of Holleman, decomposed quan-

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(4) Worrall, THIS JOURNAL, **49**, 1598 (1927).

titatively into nitrostyrene on steam distillation with a trace of acid. All three classes of amines quickly brought about its destructive decomposition unless used in small quantities. On mixing a few drops of *n*-amylamine with 3 g. of nitro alcohol, the liquid clouded up in a few minutes from water separation and the odor of benzalamylamine became apparent. The pasty mass after eight hours was worked up, yielding 2 g. of nitrostyrene contaminated with polymerized nitrostyrene. Similar experiments with diethylamine and triethylamine produced black liquids. No separation of nitrostyrene or its insoluble polymer took place. Five grams of nitro alcohol remained unchanged after standing for three weeks even on the application of heat with the equivalent amount of *p*-toluidine. was observed under similar conditions on heating the addition product with aniline. Amylamine, on the contrary, converted it into benzalamylamine, aniline and nitromethane. Considerable tar also resulted from secondary reactions. Attempts to prepare anilinophenylnitroethane from the three components were fruitless. Benzalaniline resulted under all conditions.

The following table contains results obtained with substituted aldehydes. The solutions containing primary amines were heated in a water-bath; those with tertiary amines were kept at room temperature. The product of the reaction in each case was acidified and steam distilled The desired substance when non-volatile was recrystallized from alcohol after removal of volatile impurities by steam.

Aldehyde	Base	Hours	Yield, %	Remarks
o-Chlorobenzaldehyde	$C_5H_{11}NH_2$	$^2/_3$	3–4	No water formation observed
o-Chlorobenzaldehyde	$(C_2H_5)_2NH$	1	50	Cooled after mixing
o-Chlorobenzaldehyde	$(C_2H_5)_3N$	2	70	Temp. rose to 50°
m-Nitrobenzaldehyde	$C_5H_{11}NH_2$	$^2/_3$	9	Product non-volatile
m-Nitrobenzaldehyde	$(C_2H_5)_3N$	2	47	Excess nitromethane used as solvent. Temp. rose rapidly so cooled at 50°
m-Nitrobenzaldehyde	$(C_2H_5)_3N$	$^1/_4$	40	$^1/_{40}$ molar equiv. used. Temp. rose 34° in five minutes
p-Bromobenzaldehyde	$C_5H_{11}NH_2$	$^2/_3$	67	
p-Bromobenzaldehyde	$(C_2H_5)_3N$	2	50	
Anisaldehyde	$C_5H_{11}NH_2$	$^1/_3$	62	Heated only twenty minutes as water formation rapid
Anisaldehyde	$(C_2H_5)_3N$	2	39	Product almost non-volatile
Piperonal	$C_5H_{11}NH_2$	$^2/_3$	96	Rapid, form H_2O. Solid (at 100°) product in thirty minutes
Piperonal	$(C_2H_5)_3N$	2	8	Non-volatile. Resin formation (5 g.) cut down yield.
Benzaldehyde	$C_5H_{11}NH_2$	$^2/_3$	25	Monobromonitromethane
Benzaldehyde	$(C_2H_5)_3N$	24	5	Substituted for nitromethane
Vanillin	$C_5H_{11}NH_2$	$^1/_{20}$	80	Heating stopped at five minutes as contents turned solid and vigorous reaction. Non-volatile
Vanillin	$(C_2H_5)_3N$	20	0	Products after steam distn. completely sol. in hot water

Experiments with Nitrostyrene.—Both primary and secondary amines in molar equivalents rapidly and violently decomposed nitrostyrene. Using solvents and low temperatures simply delayed but did not prevent this procedure. Triethylamine, however, had absolutely no effect and it was possible to recrystallize nitrostyrene from this base. It is true that on long standing the mixture turned black and otherwise gave evidences of decomposition.

Anilinophenylnitroethane was prepared; 5 g. of this substance mixed with an equivalent amount of benzaldehyde was heated on a water-bath for two hours. Nitrostyrene, benzalaniline and water were formed. No effect

Summary

It has been shown that aromatic as well as aliphatic primary amines are effective in the condensation of aromatic aldehydes with nitromethane to form unsaturated nitro compounds.

It has also been found that with tertiary aliphatic amines only nitro alcohols are formed.

The role of the base in these reactions has been discussed.

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