A SUMMARY OF THE REACTIONS OF ALDEHYDES WITH AMINES

MURRAY M. SPRUNG

Research Laboratory, General Electric Company, Schenectady, New York

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I. INTRODUCTION

Most reactions of aldehydes involve the carbonyl oxygen and are, in the first instance, addition reactions. Primary and secondary amines are especially suited to the study of the addition reactions of aldehydes, since they contain one or two easily detachable ("active") hydrogen atoms.

The first references to the reactions of aldehydes and amines appeared nearly a century ago, and a voluminous literature has grown up in this field. The present paper will attempt to summarize and systematize the literature from about 1880 to the present date (approximately June, 1939).

The general features of the problem may be stated in very simple terms. In most cases the first recognizable step is addition of the amine to the carbonyl group of the aldehyde, in the sense of the first phase of the aldol condensation.

$$RCHO + R'NH_2 \rightarrow RCHOHNHR'$$

In the majority of cases, the α-hydroxy amine which results is not capable of isolation; it reacts further, in one of several ways. It may, for example, lose water, to give an imine (Schiff base); this corresponds to the "crotonaldehyde stage" of the aldol condensation.[1]

$$RCHOHNHR' \rightarrow RCH{=}NR' + H_2O$$

Alternately, the hydroxy amine may react further with one or the other of the reagents or with itself; or the Schiff base may be involved in the various subsequent reactions which are encountered, and which often lead to the formation of complex reaction products.

The attempt will be made to indicate as many as possible of the types of "follow" reactions which occur. Since the nature of the aldehyde and of the amine is the determining factor, even more frequently than the experimental conditions, it has been found convenient to subdivide the material under discussion so as to accord with a classification of the reactants into "aliphatic–aliphatic," "aliphatic–aromatic," and "aromatic–aromatic" categories. This order is indicated in the table of contents.

Since tertiary amines bear no "active" hydrogen, they seldom enter into reaction with aldehydes, unless the amino nitrogen is attached directly to an aromatic nucleus. Tertiary amines will therefore not be considered in the present review.

II. REACTION OF ALIPHATIC ALDEHYDES WITH AMMONIA AND WITH ALIPHATIC AMINES

A. Formaldehyde and ammonia

The reaction between ammonia and formaldehyde, curiously enough, occupies an almost unique position in the present discussion. When

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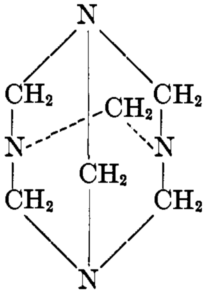
[1] We shall refer to this type of imine in the discussion which is to follow as a Schiff base, although this term has often been restricted to the imines formed from aromatic aldehydes and amines. We shall not use the term "azomethine", which has frequently been used to designate the essential C=N linkage involved here.

ammonia and formaldehyde are mixed in aqueous solution, hexamethylenetetramine is formed (as was first observed seventy-eight years ago by Butlerow (11)), according to the following equation:

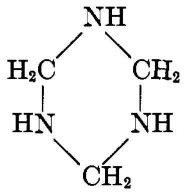
$$6H_2O + 4NH_3 \rightarrow (CH_2)_6N_4 + 6H_2O$$

Hexamethylenetetramine is a well-defined, crystalline solid, the crystal structure of which is known in detail (27, 159). All six carbon atoms are stereochemically equivalent, as are the four nitrogen atoms. The lines joining carbon atoms and nitrogen atoms in the molecular model form a regular octahedron and a regular tetrahedron, respectively. This structure possesses a very high degree of symmetry. The generally-accepted structure of hexamethylenetetramine,

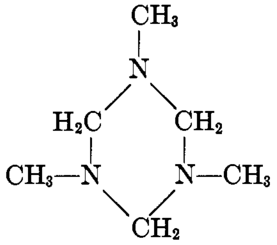


follows from the crystallographic data, from its molecular weight, and from the reactions involved in its synthesis and degradation (19, 34, 120). The construction of a model easily convinces one that this structure involves four sterically equivalent, six-membered, virtually strainless rings, and that the molecule is completely symmetrical. An alternate formula for hexamethylenetetramine, however, has frequently been proposed, and is still presented in some texts, as follows: $N(CH_2N{=}CH_2)_3$. The latter formula is said to explain more readily the easy regeneration of formaldehyde and ammonia from hexamethylenetetramine, as well as the fact that the compound acts as a monoacid base, thereby indicating that one nitrogen atom may be different from the other three.

Despite the fact that this stable end product is the only one isolated in the reaction between ammonia and formaldehyde, there is considerable evidence that a number of simpler intermediate substances are formed, and that aqueous solutions of hexamethylenetetramine break down through a succession of stages involving these same intermediates. Thus it is possible that mono-, di-, and tri-methylolamines, NH_2CH_2OH, $NH(CH_2OH)_2$, and $N(CH_2OH)_3$, are all formed, by a series of successive addition reactions. As a matter of fact, the sulfite esters of these substances have been prepared by the interaction of formaldehyde and ammonia in the presence of sodium bisulfite (17, 103). Another postulated intermediate in the reaction is methylenediamine, $NH_2CH_2NH_2$, the nitrogen analog of methylene glycol. Salts of this substance have been obtained by treating methylene bisformamide, $HCONHCH_2NHCHO$, with strong acids (68). The formation of the six-membered ring compound, trimethylenetriamine,



has also been postulated (34), by analogy with the known formation of trimethyltrimethylenetriamine,



from methylamine and formaldehyde, and the formation of trioxymethylene by polymerization of formaldehyde. It is likely that trimethylenetriamine is formed, but that the presence of the three active hydrogen atoms in this substance enables the condensation with formaldehyde and ammonia to continue until the completely saturated and completely symmetrical structure represented by hexamethylenetetramine ultimately results.

In the presence of acids, the reaction between ammonia and formaldehyde takes an entirely different course. When formaldehyde is heated with ammonium sulfate or ammonium chloride, the products are mono-, di-, and tri-methylamines, formic acid, and carbon dioxide (98, 153). This reaction apparently involves simultaneous oxidation and reduction of the formaldehyde. It is more likely, however, that methylolamines are first formed, and are then reduced by excess formaldehyde to methylamines, e.g.:

$$CH_2O + NH_3 \xrightarrow{\text{addition}} HOCH_2NH_2 \xrightarrow[\text{reduction}]{CH_2O} CH_3NH_2 \xrightarrow[\text{addition}]{CH_2O}$$

$$CH_3NHCH_2OH \xrightarrow[\text{reduction}]{CH_2O} CH_3NHCH_3, \text{ etc.}$$

$$(\text{Oxidation of } CH_2O \rightarrow HCOOH,\ CO_2,\ \text{and } H_2O)$$

B. Aliphatic aldehydes and ammonia

When aliphatic aldehydes of low molecular weight are treated in ether solution with gaseous ammonia, or when their aqueous or alcoholic solutions are treated with strong ammonia, crystalline solids are obtained which correspond in composition to simple addition compounds. These are the "aldehyde ammonias." They are relatively unstable substances, for on standing in moist air, or on treatment with dilute acids, they readily revert into their constituents.

$$RCHO + NH_3 \rightleftharpoons RCHOHNH_2$$

Furthermore, on standing over concentrated sulfuric acid or on heating in a vacuum they lose water and give imines, usually as trimers.

$$RCHOHNH_2 \rightarrow H_2O + RCH{=}NH \rightarrow (R\underset{|}{C}H\text{—}NH\text{—})_3$$

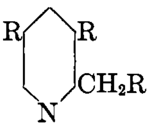
On long standing the aldehyde ammonias are changed to amorphous materials, presumably by dehydration and polymerization.

The aldehyde ammonias themselves do not in general correspond to the simple monomeric formula pictured above. Thus, acetaldehyde ammonia has a molecular weight in solution which corresponds to something between a dimeric and trimeric structure (2, 20). In the vapor phase it is partially dissociated into monomeric ethylidenimine, $CH_3CH{=}NH$. At 260°C. and 30 mm. the dissociation is complete (117). If the vapors are then suddenly cooled, the liquid ethylidenimine monomer may be obtained, but this is slowly converted to the trimer on standing. The latter has been shown to have the usual six-membered ring structure (23).

The aldehyde ammonia derived from chloral is monomeric in acetic acid, dimeric in benzene, and dimeric or higher in ethylene dibromide (21). The cyclic trimer has been reported to exist in two isomeric modifications, one melting at 105–6°C. and the other at 150–5°C. (3).

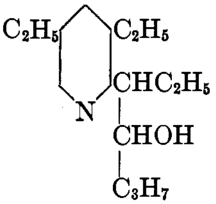
1. The Tschitschibabin reaction

An interesting and important reaction was discovered in 1905 by Tschitschibabin. It consists in passing the vapors of an aliphatic aldehyde and ammonia over alumina at 300–400°C. Pyridine derivatives are thus formed (61, 117, 122, 123, 124, 125). The reaction is generally formulated as follows:

$3RCH_2CHO + NH_3 \rightarrow$  $+ H_2 + 3H_2O$

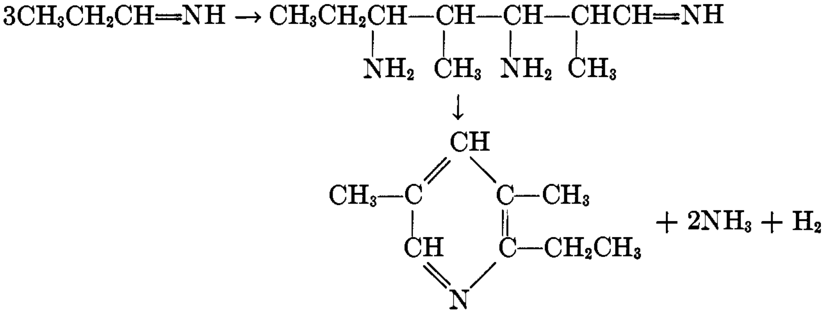
Thus with acetaldehyde the main product is α-picoline; with propionaldehyde it is 2-ethyl-3,5-dimethylpyridine; with butyraldehyde it is 2-propyl-3,5-diethylpyridine; with isovaleraldehyde one obtains 2-isobutyl-3,5-diisopropylpyridine; and with heptaldehyde one obtains 2-hexyl-3,5-diamylpyridine. However, more highly alkylated pyridines are also observed as by-products, owing presumably to the fact that the aliphatic aldehyde aldolizes during the course of the reaction, and the aldolization product then reacts with ammonia. Thus, with acetaldehyde the formation of methylethylpyridine and of β-collidine was observed in addition to α- and γ-picoline.

The Tschitschibabin reaction may also be effected by heating aldehyde ammonias. In the case of butyraldehyde ammonia, the expected 2-propyl-3,5-diethylpyridine is obtained, along with a substantial yield of a more complex substance, to which the following structure has been assigned and which is formed from the former substance by an aldol condensation with an additional molecule of butyraldehyde (61):



Strain (117) has represented the course of the Tschitschibabin reaction (in the case of propionaldehyde) as follows:

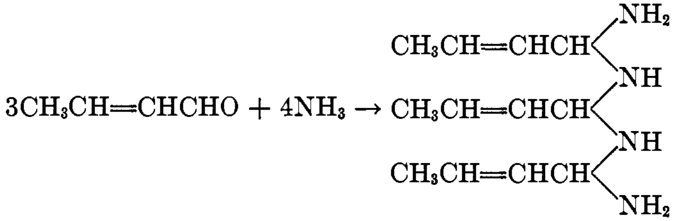
$$CH_3CH_2CHO + NH_3 \rightarrow CH_3CH_2CH{=}NH + H_2O$$



$$3CH_3CH_2CH{=}NH \rightarrow CH_3CH_2\underset{NH_2}{CH}-\underset{CH_3}{CH}-\underset{NH_2}{CH}-\underset{CH_3}{CH}CH{=}NH$$

Thus the first step is presumably the formation of an imine, the second step is an aldol-like trimerization of the imine, and the third step is ring-closure with concomitant loss of ammonia and hydrogen.

The case of crotonaldehyde is somewhat distinctive. A compound of uncertain structure is formed, which has been given the name "tricrotylidenetetramine" and the supposed formula $C_{12}H_{24}N_4$. Delépine (24) has suggested that this reaction be represented as follows:



$$3CH_3CH{=}CHCHO + 4NH_3 \rightarrow \begin{array}{ll} & NH_2 \\ CH_3CH{=}CHCH< & \\ & NH \\ CH_3CH{=}CHCH< & \\ & NH \\ CH_3CH{=}CHCH< & \\ & NH_2 \end{array}$$

If this representation is accurate, tricrotylidenetetramine is closely related structurally to the well-known and technically valuable polyethylene polyamines.

C. *Aliphatic aldehydes and aliphatic amines*

1. Aliphatic aldehydes and aliphatic monoamines

It has previously been indicated that aliphatic amines can be methylated by heating with formaldehyde in the presence of acids. However, if the reaction is carried out at room temperature and in the presence of alkali, it takes another course; addition results and the corresponding methylol derivatives can be isolated. Both primary and secondary aliphatic amines react in this way (64).

$$RNH_2 + CH_2O \xrightarrow{OH^-} RNHCH_2OH$$

$$R_2NH + CH_2O \xrightarrow{OH^-} R_2NCH_2OH$$

The methylolamines derived from methyl-, ethyl-, propyl-, isobutyl-, isoamyl-, and benzyl-amines and from piperidine are colorless liquids. They can be condensed with a second molecule of amine to give bis(alkylamino)- or bis(dialkylamino)-methanes.

$$RNHCH_2OH + R'NH_2 \rightarrow RNHCH_2NHR' + H_2O$$

$$R_2NCH_2OH + R'_2NH \rightarrow R_2NCH_2NR'_2 + H_2O$$

The bis(alkylamino)methanes can also be formed directly from the amine and formaldehyde (70).

When distilled over solid potassium hydroxide, the methylolalkylamines lose water to give the corresponding alkylmethylenimines (or Schiff bases), usually as the cyclic trimers (14, 41, 47, 63).

$$3RNHCH_2OH \rightarrow (R\underset{|}{N}{-}CH_2{-})_3 + 3H_2O$$

The Schiff bases derived from the higher aliphatic aldehydes are sometimes sufficiently stable to be isolated as the monomers. Examples are ethylideneëthylimine, $C_2H_5N{=}CHCH_3$, b.p. 48°C. (65), and propylidenepropylimine, $CH_3CH_2CH_2N{=}CHCH_2CH_3$, b.p. 102°C. (16).

Secondary aliphatic amines may be caused to condense in a similar fashion with higher aliphatic aldehydes, by treating them with solid potassium carbonate. The products correspond to the bis(dialkylamino)-methanes described above (85). These ditertiary amines usually lose one molecule of amine on distillation, giving rise to α,β-unsaturated amines (enamines), e.g.,

$$2C_5H_{10}NH + CH_3CH_2CH_2CHO \xrightarrow{K_2CO_3}$$

Piperidine

$$(C_5H_{10}N)_2CHCH_2CH_2CH_3 + H_2O$$

$$\downarrow$$

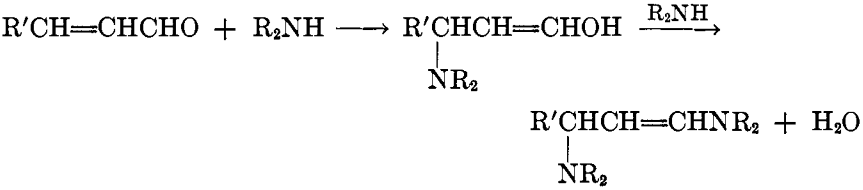
$$C_5H_{10}NCH{=}CHCH_2CH_3 + C_5H_{10}NH$$

Diethylamine and methylaniline behave similarly. Among the aldehydes which react readily are propionaldehyde, butyraldehyde, acetaldehyde, and hydrocinnamaldehyde. In the case of phenylacetaldehyde and dibenzylamine, the unsaturated amine, dibenzylstyrylamine, is formed spontaneously. This change may be represented stoichiometrically as follows:

$$C_6H_5CH_2CHO + (C_6H_5CH_2)_2NH \rightarrow (C_6H_5CH_2)_2NCH{=}CHC_6H_5 + H_2O$$

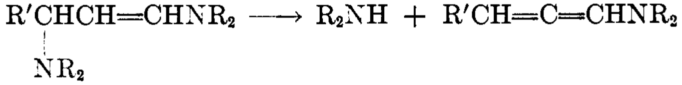
It is not known whether aldehyde ammonias are formed as intermediates, or whether the amine condenses directly with the aldehyde through the enol form of the latter.

With α,β-unsaturated aldehydes, such as acrolein, crotonaldehyde, cinnamaldehyde, and citral, crystalline condensation products are obtained only at temperatures as low as −10° to −20°C.; at higher temperatures, resins or complex aldol-like condensation products result (86). The crystalline products thus obtained may be represented as resulting from a 1,4-addition to the conjugated system, followed by condensation with a second molecule of amine.



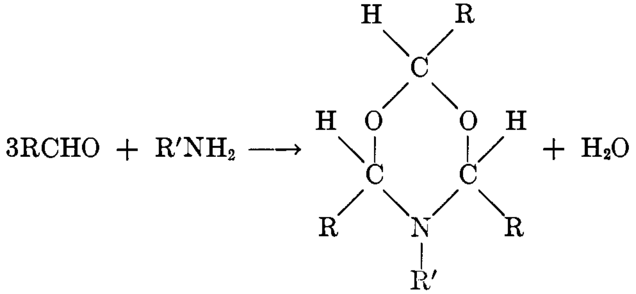
$$R'CH{=}CHCHO + R_2NH \longrightarrow \underset{\displaystyle NR_2}{R'CH}CH{=}CHOH \xrightarrow{R_2NH} \underset{\displaystyle NR_2}{R'CH}CH{=}CHNR_2 + H_2O$$

The unsaturated ditertiary amines decompose on distillation into a molecule of secondary amine and a molecule of a dialkylaminoallene.



$$R'\underset{\displaystyle NR_2}{CH}CH{=}CHNR_2 \longrightarrow R_2NH + R'CH{=}C{=}CHNR_2$$

A somewhat unusual type of reaction has been observed to occur when ethylamine or allylamine reacts with formaldehyde or acetaldehyde at ice-bath temperature. Cyclic compounds are produced which correspond to copolymerization products of two molecules of the aldehyde with one molecule of the monomeric alkylidenimine (4).



The mechanism of this condensation has not been elucidated.

2. Aliphatic aldehydes and aliphatic diamines and polyamines

Ethylenediamine, trimethylenediamine, tetramethylenediamine, and pentamethylenediamine react with formaldehyde in alkaline solution to give products whose exact structure has not been determined, but which correspond to condensation products of 2 moles of aldehyde with 1 mole of diamine, according to the following equation (6, 7):

$$NH_2(CH_2)_nNH_2 + 2CH_2O \rightarrow -CH_2-\underset{|}{N}(-CH_2)_n-\underset{|}{N}-CH_2- + 2H_2O$$

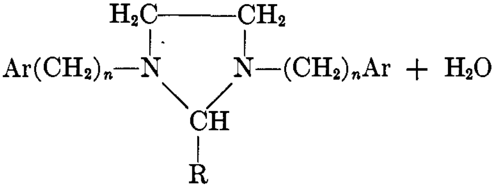
The product derived from ethylenediamine is a crystalline solid, having a molecular weight in benzene twice that of the monomeric unit shown above. Those derived from the three- and four-carbon diamines are liquids, boiling between 200° and 300°C., and are of indefinite molecular weight. That derived from the five-carbon diamine is a high-melting solid, which suggests that it may be polymeric.

The reaction of isobutyraldehyde on ethylenediamine gives rise to a similar condensation product, which has been given the structure of diisobutylideneëthylenediamine, $(CH_3)_2CHCH{=}NCH_2CH_2N{=}CHCH(CH_3)_2$ (69).

1,2-Bis(benzylamino)ethane, 1,2-bis(*p*-methylbenzylamino)ethane, 1,2-

bis(β-phenylethylamino)ethane, 1,2-bis(isobutylamino)ethane, and 1,2-bis(furfurylamino)ethane (all of which may be considered as aliphatic diamines, since the amino groups are not attached directly to an aromatic nucleus) react with aldehydes to give tetrahydroimidazoles (78, 102). The general reaction involved may be represented by the following equation:

$$Ar(CH_2)_nNHCH_2CH_2NH(CH_2)_nAr + RCHO \longrightarrow$$



The aliphatic aldehydes which enter into this reaction include formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, valeraldehyde, and caprylaldehyde. Apparently the closure of the five-membered heterocyclic ring is greatly facilitated when the nitrogen atoms which enter into the reaction are secondary.

III. REACTION OF AROMATIC ALDEHYDES WITH AMMONIA AND WITH ALIPHATIC AMINES

A. Aromatic aldehydes and ammonia

Aromatic aldehydes in general react with aqueous or alcoholic ammonia at room temperature to give the so-called "hydroamides." These are high-melting, crystalline substances formed by combination of three molecules of the aldehyde and two molecules of ammonia, as follows:

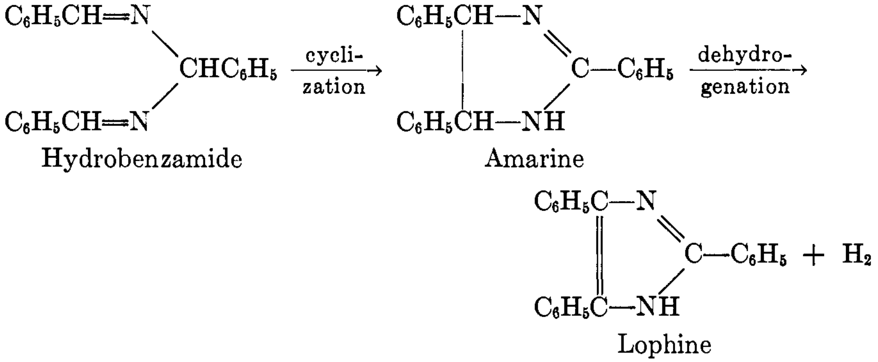
$$3ArCHO + 2NH_3 \rightarrow ArCH(N{=}CHAr)_2 + 3H_2O$$

In the cases of benzaldehyde and *p*-methylbenzaldehyde, an intermediate, crystalline addition compound, consisting of two molecules of the aldehyde and one molecule of ammonia, has been isolated by Francis by carrying out the reaction at low temperatures (48). When warmed, the addition compound breaks up into the hydroamide, aldehyde, and water. The mechanism of the reaction may therefore be represented as follows:

$$2ArCHO + NH_3 \rightarrow ArCHOHNHCHOHAr$$

$$2ArCHOHNHCHOHAr \rightarrow (ArCH{=}N)_2CHAr + ArCHO + 3H_2O$$

Certain hydroamides, when heated in the neighborhood of 130°C. for a few hours, are cyclized to the corresponding 2,4,5-triaryldihydroimidazoles (9, 22, 25, 45, 157). Heating to a still higher temperature results in dehydrogenation to the corresponding triarylimidazole. These changes are illustrated, for the case of hydrobenzamide, as follows:



Exactly similar relationships obtain in the cases of hydroanisamide and hydrofurfuramide. In the case of cinnamaldehyde, the dihydroimidazole is formed directly upon treatment of the aldehyde with aqueous ammonia. Hydrosalicylamide, on the other hand, does not readily rearrange to the amarine structure. *p*-Hydroxybenzaldehyde does not give a stable hydroamide.

1. Reaction kinetics

The kinetics of the aromatic aldehyde–ammonia reaction were investigated by Dobler (30), who found them to be in accord with a bimolecular mechanism in the case of ammonia and benzaldehyde. There was an induction period which extended for about 100 min. at 20°C. A marked falling off of the reaction velocity was noted at about 48 per cent reaction, an observation which was attributed to the increased influence of the reverse reaction. Francis' mechanism (outlined above) was used as a working hypothesis; it was assumed that the first step—formation of the bis(phenylmethylol)amine—was a fast reaction, and that the rate-controlling step was the subsequent bimolecular decomposition of this intermediate into hydrobenzamide and benzaldehyde. The assumption could then be made that the induction period was due to the building up of the bis(phenylmethylol)amine. However, during this period the reaction should follow a trimolecular course (if Francis' mechanism is strictly valid), which was not observed to be the case. The effect of increasing the temperature was found to be a marked decrease in the concentration of hydrobenzamide present at equilibrium; above about 57°C. very little of this product would be formed.

Reaction velocity constants were determined for a number of other aldehydes and found to increase in the following order: anisaldehyde, *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, benzaldehyde, *m*-xylylaldehyde, *m*-nitrobenzaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, and cinnamaldehyde. There was a sevenfold spread in rates from anisaldehyde to *p*-chlorobenzaldehyde, while cinnamaldehyde reacted with an apparent speed twice that of *p*-chlorobenzaldehyde. Dobler did not take into account the fact that cinnamaldehyde goes directly to the dihydroimidazole structure on treatment with aqueous ammonia.

B. Aromatic aldehydes and aliphatic amines

The products most easily isolated when aromatic aldehydes are caused to condense with aliphatic amines are the Schiff bases. The "aldol" is probably first formed, but is rarely capable of isolation. Table 1 shows examples of this type of Schiff base.

Aliphatic diamines (and some polyamines) react readily with aromatic aldehydes. Diprimary amines usually give bis(arylidene)imines (87, 118, 126).

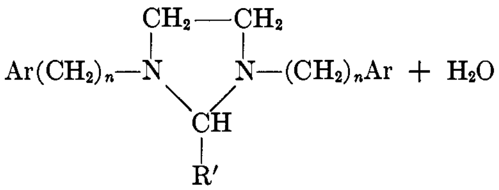
$$ArCHO + NH_2(CH_2)_nNH_2 \rightarrow ArCH{=}N(CH_2)_nN{=}CHAr + 2H_2O$$

The following are a few examples:

	MELTING POINT °C.
1,2-Bis(benzylidenimino)ethane	53–4
1,2-Bis(*p*-isopropylbenzylidenimino)ethane	63–4
1,2-Bis(cinnamylidenimino)ethane	109–10
1,2-Bis(*o*-hydroxybenzylidenimino)ethane	125–6
1,2-Bis(*o*-methoxybenzylidenimino)ethane	113
1,2-Bis(*p*-methoxybenzylidenimino)ethane	110–11

The reaction of aromatic aldehydes on aliphatic 1,2-disecondary amines readily leads to ring closure, with the formation of tetrahydroimidazoles (78, 102, 126). The general reaction involved is analogous to that which occurs with aliphatic aldehydes (page 306).

$Ar(CH_2)_nNHCH_2CH_2NH(CH_2)_nAr + Ar'CHO \longrightarrow$



Tetrahydroimidazoles have thus been prepared from 1,2-bis(benzylamino)ethane, 1,2-bis(β-phenylethylamino)ethane, 1,2-bis(*p*-methoxybenzylamino)ethane, 1,2-bis(isobutylamino)ethane, and 1,2-bis(furfurylamino)ethane with the following aldehydes: benzaldehyde, *p*-tolualdehyde, *p*-methoxybenzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehydes, *o*-, *m*-, and *p*-chlorobenzaldehydes, salicylaldehyde, *p*-hydroxybenzaldehyde, *p*-hydroxy-*m*-methoxybenzaldehyde, piperonal, phenylacetaldehyde, furfural, α-methylfurfural, α-methoxyfurfural, and α-hydroxymethylfurfural. Most of these tetrahydroimidazoles are colorless oils boiling in the neighborhood of 200°C. at about 20 mm. A few of them are crystalline solids.

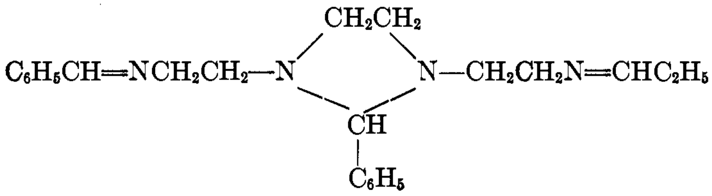
TABLE 1

Schiff bases formed by the condensation of aromatic aldehydes with aliphatic amines

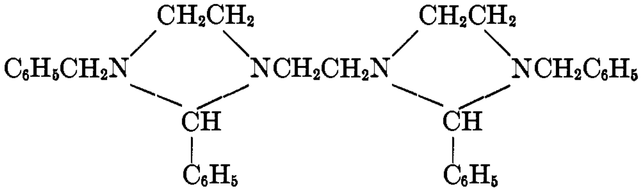
SCHIFF BASE	BOILING POINT	MELTING POINT	REFERENCE
	°C.	*°C.*	
Benzylidenemethylimine	180		(161)
Benzylideneëthylimine	195		(161)
Benzylidenepropylimine	208–10		(161)
Benzylideneisobutylimine	217–18 (35 mm.)		(161)
Benzylideneisoamylimine*			(107)
Benzylideneallylimine	96 (12 mm.)		(4)
Benzylidene-α-methyldecylimine	197–8 (17 mm.)		(99)
Benzylidene-β,β-diethoxyethylimine	156 (12 mm.)		(44)
Benzylidene-β,β-diethoxypropylimine	157 (11 mm.)		(158)
2,5-Dichlorobenzylidenemethylimine		52	(54)
o-Nitrobenzylidenemethylimine	145 (23 mm.)		(1)
p-Isopropylbenzylidenemethylimine	122 (14 mm.)		(112)
Cinnamylideneëthylimine	143–5 (20 mm.)		(1)
o-Hydroxybenzylidenemethylimine	229		(26)
o-Hydroxybenzylideneëthylimine	237		(26)
o-Hydroxybenzylidene-β-bromoethylimine		56–7	(53)
o-Hydroxybenzylidene-β,β-diethoxyethylimine	188 (15 mm.)		(62)
m-Hydroxybenzylidene-β,β-diethoxyethylimine		71	(52)
m-Methoxybenzylidene-β,β-diethoxyethylimine	191 (15 mm.)		(52)
m-Ethoxybenzylidene-β,β-diethoxyethylimine	220 (35 mm.)		(52)
p-Methoxybenzylidene-β,β-diethoxyethylimine	190 (12 mm.)		(62)

* A heavy oil.

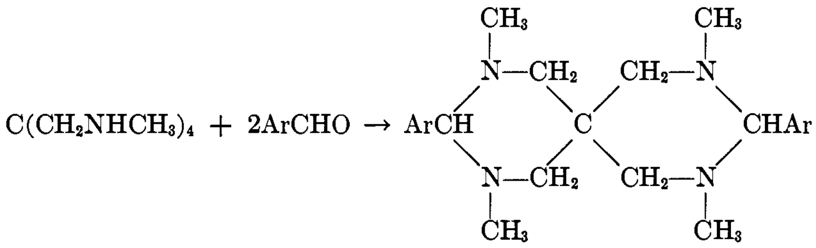
van Alphen has shown that when the reaction is carried out with aliphatic 1,2-disecondary amines which also bear terminal primary amino groups, 3 moles of the aldehyde are required and the product is a bis(arylideniminoalkyl)tetrahydroimidazole (126). Thus, triethylenetetramine and benzaldehyde give a compound of the following structure:



This substance was reduced with sodium and alcohol, and the benzylidene group hydrolyzed with acid. The resulting tetrasecondary amine was again treated with benzaldehyde, giving the following interesting compound, containing two tetrahydroimidazole rings:



van Alphen (127) also prepared a series of very interesting spiro compounds by causing aromatic aldehydes to react with tetrakis(methylaminomethyl) methane.



The aldehydes used in this series of syntheses were benzaldehyde, anisaldehyde, *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, and piperonal. The spiro hexahydro-1,3-diazines are crystalline solids.

IV. REACTION OF ALIPHATIC ALDEHYDES WITH AROMATIC AMINES

A large part of the literature in the field of amine-aldehyde reactions is concerned with the action of aliphatic aldehydes (especially formaldehyde) on aromatic amines. To avoid confusion, it seems desirable at this point to consider some of the individual reactions separately.

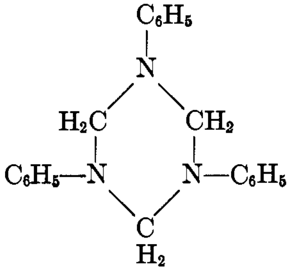
A. *Formaldehyde*

1. Formaldehyde and aromatic monoamines

(*a*) *Aniline.* The literature on this reaction goes back at least seventy years. Much confusion obtained for many years, and many contradictions have not yet been reconciled. An explanation lies in the fact that both crystalline and resinous substances are formed when aniline is treated with formaldehyde. At present we shall consider only the crystalline substances, and devote a separate section to the resins later.

When aniline is treated with formaldehyde in dilute, neutral aqueous solution, products of indefinite composition are obtained unless the conditions are carefully controlled. Under favorable conditions, a compound of the empirical composition C_7H_7N and having a melting point of 140°C. may be isolated (6, 70, 100, 101, 119, 136, 152).

It is now generally recognized that this substance, known as anhydroformaldehyde aniline, is a trimer of the hypothetical Schiff base, methyleneaniline, $C_6H_5N{=}CH_2$, and has a stable six-membered ring structure—namely, that of triphenyltrimethylenetriamine,



However, it is apparently capable of dissociating at higher temperatures, and shows a molecular weight in camphor which is only about twice that of the monomer (93). It is stated that the molecular weight of the vapor corresponds to that of the monomer (70).

Neither the initial "aldol" nor the Schiff base has ever been isolated. However, in alkaline solution one or the other of these must have a transitory existence, for the product which is then isolated is bis(phenylamino)-methane, $(C_6H_5NH)_2CH_2$, (m.p. 64–5°C.), which would result from the further reaction of either of these hypothetical substances with a second mole of aniline (35). Bis(phenylamino)methane is also sometimes found in neutral solution, along with anhydroformaldehyde aniline (37).

The reaction takes a much more complicated course in acid solution, and it is under such conditions that the technically useful aniline-formaldehyde resins are obtained. Among the intermediate substances which are formed in acid solution are the following: aminobenzylaniline,

$NH_2C_6H_4CH_2NHC_6H_5$; diaminodiphenylmethane, $NH_2C_6H_4CH_2C_6H_4NH_2$[2]; and anhydroaminobenzyl alcohol, $(\text{—}NHC_6H_4CH_2\text{—})_x$ (141). More light will be thrown on some phases of this problem when the action of formaldehyde on *p*-toluidine and similar bases is discussed.

(*b*) *Toluidines.* In neutral solution, anhydroformaldehyde *o*-toluidine, $(o\text{-}CH_3C_6H_4\underset{|}{N}CH_2\text{—})_x$, is formed from *o*-toluidine and formaldehyde (x is probably 3) (152). Under carefully controlled conditions, or in the presence of alkali, the product is bis(*o*-tolylamino)methane (m.p. 52°C.) (35). In acid solution products of indeterminate structure usually result (74, 95). If half a mole of formaldehyde is used in the presence of dilute acid, the chief product is 4,4′-diamino-3,3′-dimethyldiphenylmethane (m.p. 158°C.) (141).

In neutral solution, under ordinary circumstances, anhydroformaldehyde *m*-toluidine, $(m\text{-}CH_3C_6H_4\underset{|}{N}CH_2\text{—})_x$, is formed from formaldehyde and *m*-toluidine. In the presence of alkali, bis(*o*-tolylamino)methane (b.p. 220–8°C. at 58 mm.) is obtained (7). In acid solution, with half a mole of formaldehyde, 4,4′-diamino-2,2′-dimethyldiphenylmethane (m.p. 123°C.) is obtained. Under more drastic conditions, resins result (141).

In neutral solution, under ordinary conditions, formaldehyde and *p*-toluidine form more or less indefinite products, among which is anhydroformaldehyde *p*-toluidine, $(p\text{-}CH_3C_6H_4\underset{|}{N}CH_2\text{—})_x$ (m.p. 127–8°C.), in which x is probably 3 (6, 57, 79, 93, 152). In the presence of alkali, bis(*p*-tolylamino)methane is formed (m.p. 89°C.) (35, 37).

A considerable amount of attention has been devoted to the study of the reaction between *p*-toluidine and formaldehyde in acid solution, especially by Wagner and coworkers (42, 114, 143). The great interest in this particular problem first arose from the isolation by Troeger (121) of a base of the formula $C_{17}H_{18}N_2$, since known as "Troeger's base." The same base was obtained by Löb, during the electrolytic reduction of *p*-nitrotoluene in acid solution in the presence of formaldehyde (79), although the identity of the two substances was not realized until later (56). A number of other substances are produced at the same time as Troeger's base (42, 75, 84). Among these the following have definitely been identified: *N*-methyl-*p*-toluidine, *N*,*N*-dimethyl-*p*-toluidine, 1-(*p*-tolylaminomethyl)-2-hydroxy-3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline, and 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline. The follow-

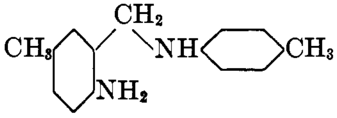
---

[2] *p*,*p*′-Diaminodiphenylmethane may easily be prepared by reacting aniline with half a mole of formaldehyde in weakly acid solution (142).

ing mechanism has been proposed to account for the products observed (42, 114, 149):

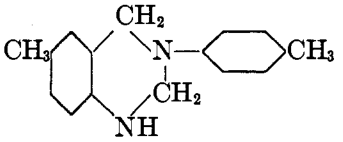
$$(a)\quad 2CH_3C_6H_4NH_2 + CH_2O \rightarrow \underset{\text{I}}{CH_3C_6H_4NHCH_2NHC_6H_4CH_3} + H_2O$$

$$(b)\quad \text{I} + CH_3C_6H_4NH_2 + CH_3C_6H_4NH_3Cl \xrightarrow{\text{rearrangement}}$$



II

$$(c)\quad \text{II} + \text{I} \rightarrow$$

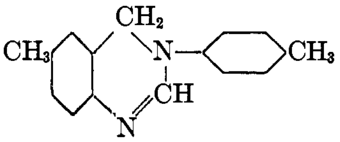


$+ 2CH_3C_6H_4NH_2$

3-*p*-Tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline

III

$$(d)\quad \text{III} + \text{I} \xrightarrow{H^+}$$

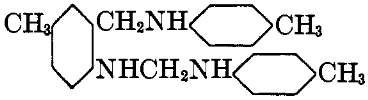


3-*p*-Tolyl-6-methyl-3,4-dihydroquinazoline

IV

$$+ \underset{N\text{-methyl-}p\text{-toluidine}}{CH_3C_6H_4NHCH_3} + \underset{p\text{-Toluidine}}{CH_3C_6H_4NH_2}$$

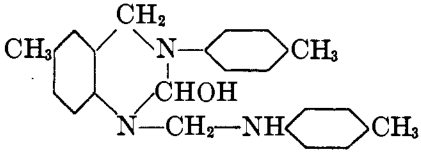
$$(e)\quad \text{II} + CH_2O + NH_2C_6H_4CH_3 \rightarrow$$



$+ H_2O$

V

$$(f)\quad \text{V} + HCOOH \rightarrow$$



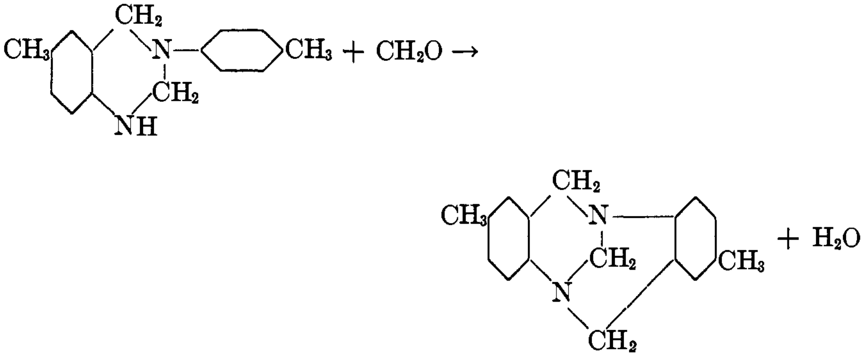
$+ H_2O$

1-(*p*-Tolylaminomethyl)-2-hydroxy-3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline

VI

(The formic acid required for the last step may be formed during the reaction by oxidation of part of the formaldehyde present in the reaction mixture.)

The structure of Troeger's base has recently been established by Spielman (115), who has likewise accomplished its synthesis from 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline and formaldehyde in acid solution.



Troeger's base

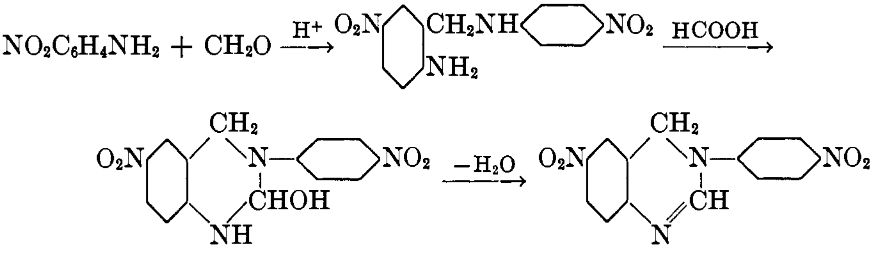
The mechanism by which the base is formed from *p*-toluidine probably involves this step also (141).

(*c*) *Nitroanilines.* The bis(nitrophenylamino)methanes are produced when the nitroanilines are boiled with formaldehyde in the presence of aqueous alcohol (101). The melting points of the *o*-, *m*-, and *p*-isomers are 195°, 213°, and 232°C., respectively.

When heated with formaldehyde and concentrated hydrochloric acid, *o*-nitroaniline is converted to a polymeric substance having the composition of an anhydro-*m*-nitro-*p*-aminobenzyl alcohol, $(C_7H_6N_2O_2)_x$. The same substance is obtained by treating bis(*o*-nitrophenylamino)methane with hydrochloric acid, a mole of *o*-nitroaniline being eliminated in the transformation (91).

$$x\mathrm{CH_2(NHC_6H_4NO_2)_2} \xrightarrow{\mathrm{HCl}} (\mathrm{C_7H_6N_2O_2})_x + x\mathrm{NH_2C_6H_4NO_2}$$

The reaction of *p*-nitroaniline with formaldehyde in the presence of acid is somewhat more complex. A bis(phenylamino)methane is not isolated in this case, but its semidine rearrangement product is: namely, 4-nitrophenylamino-2′-amino-5′-nitrophenylmethane (92). In the presence of formic acid, this condenses further to give 2-hydroxy-3-(*p*-nitrophenyl)-6-nitro-1,2,3,4-tetrahydroquinazoline, which, in turn, readily undergoes dehydration to 3-(*p*-nitrophenyl)-6-nitro-3,4-dihydroquinazoline (84).



Under more severe conditions complex substances are formed, which correspond approximately to polymeric dehydration products of the crystalline intermediates mentioned above (92).

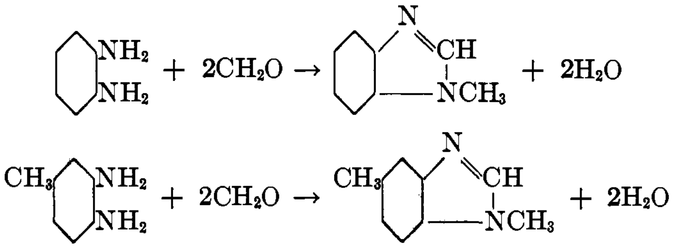
(*d*) *Anisidines and phenetidines.* The *o*- and *p*-anisidines condense with alcoholic formaldehyde in the presence of alkali to give the corresponding bis(methoxyphenylamino)methanes, m.p. 86° and 66°C. In the absence of alkali, however, *p*-anisidine gives the cyclic trimer of methylene-*p*-anisidine, m.p. 132°C. (7). In the case of *p*-phenetidine, bis(*p*-ethoxyphenylamino)methane, m.p. 75°C., is formed, either in the presence or in the absence of alkali (7, 144). In the presence of acid, the products include *N*-methyl-*p*-phenetidine and 3-(*p*-ethoxyphenyl)-6-ethoxy-3,4-dihydroquinazoline (84). The dihydroquinazolines may be obtained from *p*-anisidine and *p*-phenetidine by rearranging the diphenylaminomethanes to the corresponding semidine bases (by heating with the amine and its hydrochloride) and reacting this product with formic acid (144).

(*e*) *Aminobenzoic acids.* The isomeric (*o*-, *m*-, and *p*-) bis(carboxyphenylamino)methanes (m.p. 158°, 129°, and 167°C.) are obtained by treating the aminobenzoic acids with formaldehyde in alcohol (7). The formation of resins was also noted, especially in the case of *m*-aminobenzoic acid.

(*f*) *Chloro- and bromo-anilines.* The isomeric chloroanilines give the corresponding *o*-, *m*-, and *p*-bis(chlorophenylamino)methanes (m.p. 84°, 73°, and 65°C.) when treated with formaldehyde and alkali in alcohol (7). Without the alkali, the trimeric methylenechlorophenylimines were obtained from *m*- and *p*-chloroanilines. Bis(*p*-bromophenylamino)methane may be similarly prepared (144). In the presence of acid, however, the main products obtained from *p*-chloro- and *p*-bromo-anilines are the 3,4-dihydroquinazolines, m.p. 192° and 205.8°C., provided the temperature is kept below room temperature (145). At a higher temperature (70°C.) the main product obtained from *p*-bromoaniline was the ketone 3-(*p*-bromophenyl)-6-bromo-3,4-dihydro-4-quinazolone (12).

2. Formaldehyde and aromatic diamines

A somewhat unusual type of reaction occurs when formaldehyde is mixed with weakly acid solutions of *o*-phenylenediamine or *m*-methyl-*o*-phenylenediamine. The products are *N*-methylbenzoimidazoles, formed by condensation of two molecules of the aldehyde with one molecule of the diamine (46).



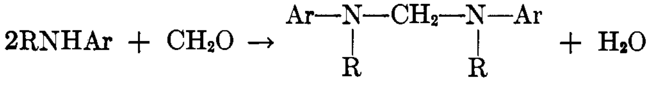
In neutral solution, however, products were obtained which corresponded empirically to dimers of the corresponding Schiff bases (or bis(methyleneimino)benzenes). 1,2-Diaminonaphthalene gave a similar product in neutral solution.

The formation of the "aldol" *p,p'*-bis(hydroxymethylamino)diphenyl, $HOCH_2NHC_6H_4C_6H_4NHCH_2OH$, on treatment of benzidine with formaldehyde in alcohol solution has been reported (71). Earlier, however, the production of the Schiff base, $CH_2{=}NC_6H_4C_6H_4N{=}CH_2$, under these conditions was claimed (108).

3. Formaldehyde and secondary aromatic amines

Secondary aromatic amines do not resinify in the presence of formaldehyde as readily as do the primary amines. Neither do they form the substituted hydroquinazolines. Consequently it is easier in these cases to isolate some of the simpler reaction products.

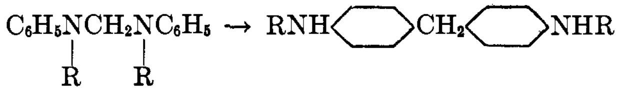
In neutral or slightly alkaline solution the alkyldiphenylaminomethanes are readily obtained, according to the following equation:



$$2RNHAr + CH_2O \rightarrow \underset{\displaystyle R}{\underset{|}{Ar{-}N}}{-}CH_2{-}\underset{\displaystyle R}{\underset{|}{N{-}Ar}} + H_2O$$

Examples are the bases derived from *N*-methylaniline, *N*-ethylaniline, *N*-methyl-*o*-toluidine, and *N*-methyl-*p*-toluidine (129).

When the reaction is carried out in the presence of hot acid, the benzidine type of rearrangement occurs and the *p*-alkylaminodiphenylmethanes are formed.



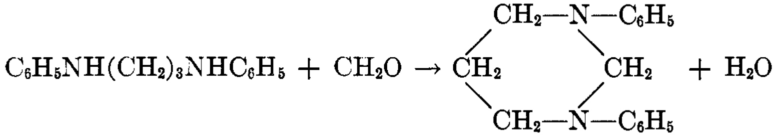
The latter are liquids, boiling in the neighborhood of 250–300°C. at about 10 mm. (55, 129, 141, 142).

The behavior of diphenylamine is very similar. In boiling benzene bis(diphenylamino)methane is obtained; on treatment with dilute acid, this undergoes the benzidine type of rearrangement to give bis(*p*-phenylaminodiphenyl)methane (18).

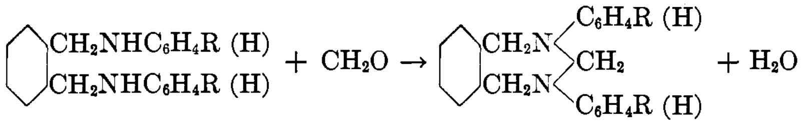
Under somewhat different conditions, the hydrochlorides of anhydro-*p*-alkylaminobenzyl alcohols can be isolated, and these can be converted to the free bases by suspending them in ice-cold alcohol and treating with 20 per cent sodium hydroxide (160). The anhydro-*p*-alkylaminobenzyl alcohols derived from methyl-, ethyl-, *n*-propyl-, *n*-butyl-, isoamyl-, and benzyl-anilines are solids of definite melting points. The molecular weights in benzene correspond almost exactly to those calculated for the trimers, but in camphor the apparent molecular weights are much higher (160). Molecular weights corresponding to those of dimers have also been reported in the cases of anhydromethyl-*p*-aminobenzyl alcohol and anhydroethyl-*p*-aminobenzyl alcohol (51).

In the case of arylated 1,2-diamines, the tetrahydroimidazoles are readily isolated, even when working with acid aqueous or alcoholic solutions. Examples are 1,3-diphenyltetrahydroimidazole (m.p. 124°C.), 1,3-di-(*p*-ethoxyphenyl)tetrahydroimidazole (m.p. 214°C.), 1,3-di-(*m*-tolyl)tetrahydroimidazole (m.p. 100°C.), and 1,3-di(*p*-tolyl)tetrahydroimidazole (m.p. 176°C.) (6, 111). In these cases, then, the results are exactly similar to those obtained with aliphatic 1,2-diamines.

By a similar reaction, 1,3-diphenylhexahydropyrimidine (m.p. 87°C.) is formed when 1,3-bis(phenylamino)propane and formaldehyde are allowed to react in the cold (110, 128).



1,3-Bis(*p*-tolylamino)propane and formaldehyde give the homologous hexahydropyrimidine (m.p. 60–3°C.). Diphenylxylylenediamine and di-*p*-tolylxylylenediamine are said to form the corresponding seven-membered cyclic compounds when heated with formaldehyde (111).

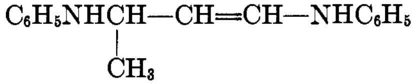


B. *Acetaldehyde*

1. Acetaldehyde and aromatic monoamines

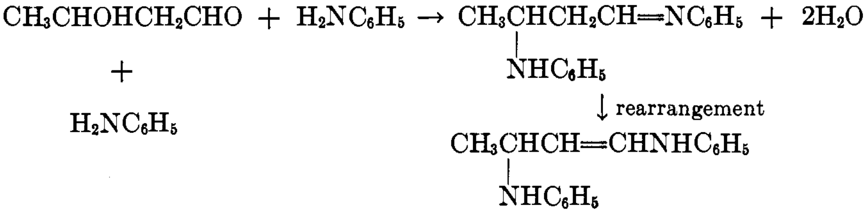
This reaction, like that of aniline and formaldehyde, has been the subject of extensive study over a period of about sixty years. A number of crystalline products have been recognized, as well as the usual amorphous and resinous by-products.

If aniline and acetaldehyde are allowed to react in the cold, either in neutral solution or in the presence of sodium hydroxide, the product obtained is 1,1-bis(phenylamino)ethane, $C_6H_5NHCH(CH_3)NHC_6H_5$, m.p. 51°C. (36, 93). Under less carefully controlled conditions, amorphous and oily products are formed along with crystalline substances (106, 119). When the reaction is carried out in cold alcohol, in the presence of hydrochloric acid, two crystalline substances are found, both of which are dimers of the hypothetical "ethylideneaniline," $C_6H_5N{=}CHCH_3$ (132, 133). The higher melting of these isomers ("Eckstein's base," m.p. 126°C.) has been assigned the following structure:



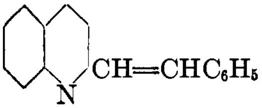
$$\begin{array}{l}C_6H_5NH\underset{\displaystyle CH_3}{\underset{|}{C}}H{-}CH{=}CH{-}NHC_6H_5\end{array}$$

and the assumption is made that the isomeric base (m.p. 85°C.) is a *cis-trans* isomer (38). Both dimeric products may therefore be conceived of as formed by condensation of two molecules of aniline with one molecule of acetaldol, followed by a 1,3-shift of hydrogen (39).



$$\begin{array}{lcl}CH_3CHOHCH_2CHO + H_2NC_6H_5 & \rightarrow & CH_3\underset{\displaystyle NHC_6H_5}{\underset{|}{C}}HCH_2CH{=}NC_6H_5 + 2H_2O \\ + & & \downarrow \text{rearrangement} \\ H_2NC_6H_5 & & CH_3\underset{\displaystyle NHC_6H_5}{\underset{|}{C}}HCH{=}CHNHC_6H_5\end{array}$$

Further complications are noted if aniline hydrochloride and acetaldehyde are allowed to stand in water solution for several weeks. Under these circumstances at least two more amorphous products are formed, both of which correspond empirically to higher polymers of ethylideneaniline (40, 130). These polymers (generally designated as "Schultze's base") are probably derived from Eckstein's base, since the latter can be converted to Schultze's base by treatment with dilute hydrochloric acid at room temperature. Eckstein's base also reacts with benzaldehyde when heated, but the product thus obtained is a definitely crystalline material, and probably has the structure of a benzalquinaldine—namely, α-styrylquinoline (40).



Benzylaniline is also formed during this reaction.

2. Acetaldehyde and other aromatic amines

The diphenylaminoethanes are readily obtained from para-substituted anilines. Thus *p*-nitro- and *p*-chloro-anilines, with acetaldehyde in ether, give 1,1-bis(*p*-nitrophenylamino)ethane and 1,1-bis(*p*-chlorophenylamino) ethane (m.p. 167° and 65°C.) (37).

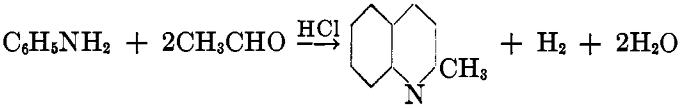
C. Homologs of formaldehyde

1. Homologs of formaldehyde and aromatic amines

Aniline and propionaldehyde form a dimeric product which is probably similar in structure to Eckstein's base (139). Valeraldehyde and aniline also give a dimeric product (134). Butryaldehyde, isobutyraldehyde, isovaleraldehyde, and heptaldehyde form monomeric anhydro products with aniline (presumably of the Schiff base type), as does isovaleraldehyde with *p*-toluidine. Isobutyraldehyde also gives some 1,1-bis(phenylamino)-isobutane (50, 77, 135, 137, 138). Isovaleraldehyde, with *p*-chloroaniline in ether, gives a dimer of the Schiff base, but with *p*-nitroaniline, under the same conditions, 1-bis(*p*-nitrophenylamino)-3-methylbutane, $(CH_3)_2CHCH_2CH(NHC_6H_4NO_2)_2$, is formed (39).

2. The formation of quinoline bases from aliphatic aldehydes and aromatic amines

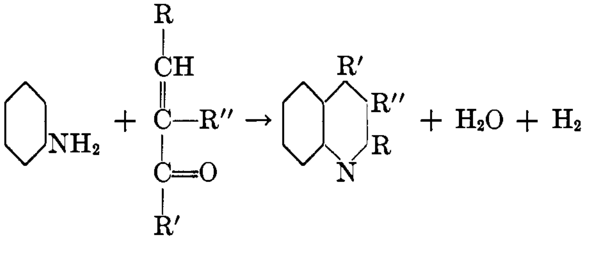
When aromatic amines are heated with aliphatic aldehydes and concentrated hydrochloric acid, a reaction occurs which bears considerable resemblance both to the Skraup quinoline synthesis and to the Tschitschibabin reaction. Ring closure is effected, oxidation and dehydration occur, and a quinoline derivative is formed. In the case of paraldehyde and aniline, the reaction may be represented by the following scheme (31):



The product, α-methylquinoline, or quinaldine, can also be formed from aniline and aldol. The toluidines react in a similar fashion, giving 2,8-, 2,7-, and 2,6-dimethylquinolines, respectively. Among other substituted anilines which react similarly are sulfanilic acid, *o*-aminophenol, *o*-anisidine, *p*-anisidine, cumidine, α-naphthylamine, and β-naphthylamine (the last two giving the corresponding benzoquinaldines) (32).

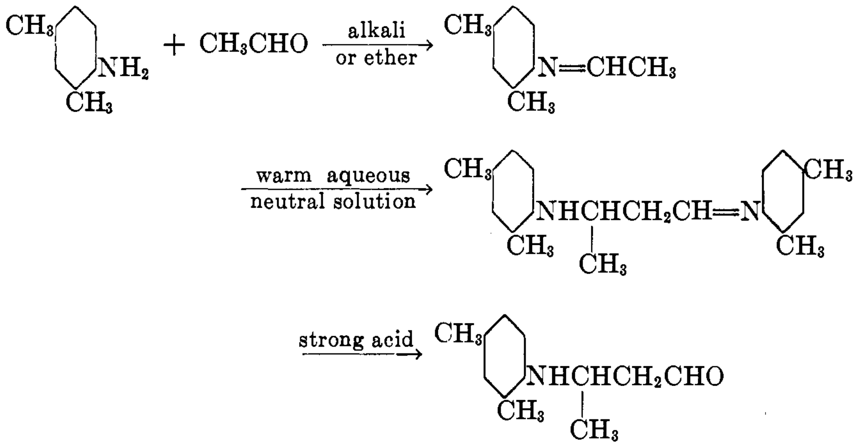
Higher aldehydes react with aniline to give the higher alkylated quinolines. Thus, propionaldehyde yields 2-ethyl-3-methylquinoline; butyraldehyde yields 2-propyl-3-ethylquinoline; isovaleraldehyde yields 2-butyl-3-propylquinoline; and heptaldehyde yields 2-hexyl-3-amylquinoline (33). Tiglic aldehyde, $CH_3CH{=}C(CH_3)CHO$, condenses with aniline to give 2,3-dimethylquinoline, only one molecule of water being eliminated in this case (104). The action of a mixture of propionaldehyde and formaldehyde on aniline leads to a mixture of 3-methylquinoline and 2-ethyl-3-methylquinoline (131). These products would be expected from the action of α-methylacrolein and of 2-methylpenten-2-al upon aniline. The inference is clearly that it is the "crotonaldehyde" of the aldehyde (or mixture of aldehydes) which actually condenses with the amine. The reaction may similarly be carried out with mixtures of aldehydes and ketones (5). A mixture of paraldehyde and acetone thus gives 2,4-dimethylquinoline when heated with aniline; formaldehyde and acetone give 2-methylquinoline; and acetaldehyde and acetophenone give 2-methyl-4-phenylquinoline. (Cinnamaldehyde gives 2-phenylquinoline, rather than 4-phenylquinoline. In this case, something akin to the α,γ-transformation met with in the case of the Claisen rearrangement of allyl phenyl ethers probably occurs.)

A general statement of the quinaldine reaction, as understood when Von Miller was carrying out his classical work on the subject, would be somewhat as follows:

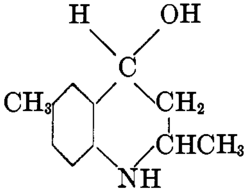


On this view, it should be possible to prepare 2,3,4-trialkyl (or alkyl aryl) derivatives of quinoline by this method. Apparently the validity of this conclusion has not yet been proved or disproved.

Panajotow (97a) found that when *as*-*m*-xylidine is heated with concentrated hydrochloric acid and paraldehyde the product is 2,6,8-trimethylquinoline, as would be expected on the basis of the above scheme. Von Miller and Plöchl (132a) reëxamined this reaction and found that at least three intermediates could be isolated. Thus:

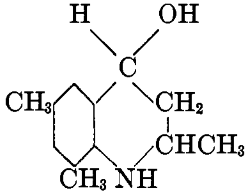


The first is the simple Schiff base; the second is the Schiff base of the third, which, in turn, may be considered to be formed by condensation of one molecule of amine and one molecule of aldol. The intermediate formed in acid solution was found to exist in two stereoisomeric forms. These were later studied by Edwards, Garrod, and Jones (35a), who showed that neither had the above aldehyde structure, and that they were, in fact, *cis–trans* isomers of 2-methyl-4-hydroxy-1,2,3,4-tetrahydroquinoline. The compounds obtained in acid solution in the cases of *p*-toluidine and *as-m*-xylidine therefore have the following structures:



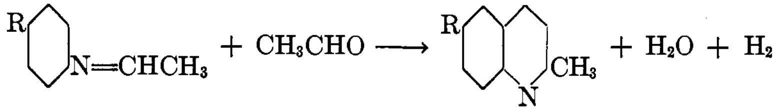
(*cis* and *trans*)

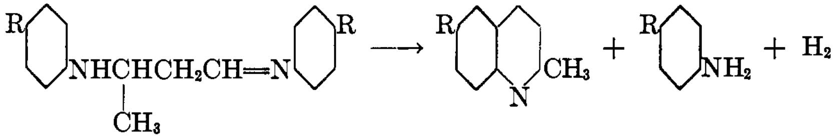
and

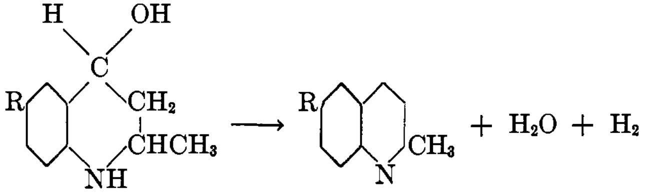


(*cis* and *trans*)

All of the intermediates isolated by Von Miller and Plöchl (132a) may be converted to quinoline derivatives by heating, alone or with acidic agents. The changes involved are represented schematically as follows:

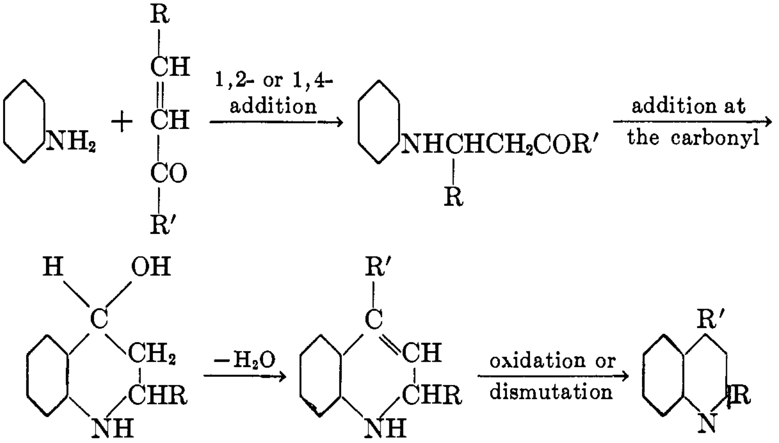






Actually, however, very little, if any, free hydrogen can ever be detected. When the above changes were studied more closely, it was observed that the dihydroquinoline derivative which might be expected if no hydrogen is evolved is converted, by a dismutation reaction, into an equilibrium mixture of a quinoline and a tetrahydroquinoline derivative (65a). Under the conditions of the quinaldine synthesis *per se*, however, tetrahydroquinoline derivatives are not found (93a). Instead the dihydroquinoline is undoubtedly oxidized *in situ*, the oxidizing agents being the simple Schiff bases which are always present during a quinaldine synthesis. (In the case of aniline, for example, ethylideneaniline and crotylideneaniline are presumably present, and are reduced to ethylaniline and *n*-butylaniline by the dihydroquinoline, which is thereby oxidized to quinaldine (93a).)

On the basis of these facts, the mechanism of the quinaldine reaction may best be represented as follows:



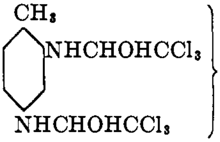
However, this scheme must still be considered as somewhat speculative, since no indisputable proof of it has yet been brought forward.

D. Chloroacetaldehydes and aromatic amines

The initial addition stage (the "aldol" stage) of the amine–aldehyde reaction may be arrested when α-chlorinated acetaldehydes are treated with aromatic amines. The presence of α-chlorine apparently stabilizes the addition compound with respect to both hydrolysis and further reaction with the reagents present. This is especially true in the case of chloral. The α-hydroxy-β-trichloroethylarylamines are therefore conveniently prepared by mixing the reactants in warm inert solvents, such as ether, chloroform, benzene, or toluene. The addition compound usually precipitates under these conditions.

TABLE 2

Addition compounds of chloral and aromatic amines

ADDITION COMPOUND	MELTING POINT	REFERENCE
	°C.	
p-$CH_3C_6H_4NHCHOHCCl_3$	75	(37)
p-$NO_2C_6H_4NHCHOHCCl_3$	128	(37)
2,4-$NO_2(CH_3)C_6H_3NHCHOHCCl_3$	187–188	(155)
3,4-$Cl(CH_3)C_6H_3NHCHOHCCl_3$	182–183	(155)
α-$C_{10}H_7NHCHOHCCl_3$	93–93.5	(105)
β-$C_{10}H_7NHCHOHCCl_3$	101	(105)
o-$NH_2C_6H_4NHCHOHCCl_3$	72	(105)
p-$NH_2C_6H_4NHCHOHCCl_3$	80	(105)
3,4-$NH_2(CH_3)C_6H_3NHCHOHCCl_3$	86	(105)
2,4-$NH_2(CH_3)C_6H_3NHCHOHCCl_3$	67–68	(105)
	56–57	(105)

The α-amino alcohol derived from aniline and chloral was obtained in the form of the double compound with chloral hydrate (m.p. 56.5°C.) (105).

Table 2 shows examples of addition compounds of chloral and aromatic amines.

In the majority of cases, however, the α-amino alcohols condense with a second molecule of amine, even under the mild conditions mentioned above, with the result that the bis(phenylamino)methane is obtained. These condensation products are almost all crystalline solids of fairly high melting points. Examples of this type of condensation product of chloral and aromatic amines are given in table 3. The bis(phenylamino)methanes derived from dichloroacetaldehyde and aniline and from chloroacetaldehyde and *p*-chloroaniline have also been described (37). However, it is stated that 2,4,6-trichloroaniline and 2,6-dichloro-4-nitroaniline do not react with chloral (37).

TABLE 3

Condensation products of chloral and aromatic amines

CONDENSATION PRODUCTS	REFERENCE
Bis(phenylamino)trichloromethylmethane	(37, 109, 146)
Condensation products from chloral and the toluidines	(37, 147, 154)
Condensation products from chloral and the nitroanilines	(37, 156)
Condensation products from chloral and halogenated anilines	(37, 154, 155)
Condensation products from chloral and the anisidines	(154)
Condensation products from chloral and the aminobenzoic acids	(96, 154, 155)
Condensation products from chloral and the nitrotoluidines	(155)
Condensation products from chloral and nitrobromoanilines	(155)

V. REACTION OF AROMATIC ALDEHYDES AND AROMATIC AMINES

A. Aromatic aldehydes and primary aromatic amines

1. Schiff bases

Under ordinary conditions aromatic aldehydes and aromatic amines react very readily to give Schiff bases. These Schiff bases are well-defined, crystalline substances. In general they do not react further with either of the reagents used in their preparation, as do most of the other types of simple intermediates considered thus far. They may accordingly be looked upon as stable representatives of the "crotonaldehyde stage" of the amine–aldehyde condensation.

The aromatic Schiff bases are obtained merely by warming the aldehyde and amine together. However, it is sometimes more convenient to work in a solvent such as alcohol, dilute acetic acid, or glacial acetic acid. Sometimes the reaction is aided by a trace of acid; in other cases the hydrochlorides of the amines can be used in the synthesis.

So many aromatic Schiff bases are described in the literature that it is virtually impossible to list even a representative number of them. Table 4 gives a partial insight into the very great amount of work which has been done in this field.

2. Velocity of formation of Schiff bases

A study was made of the comparative rates of formation of Schiff bases from aniline and substituted anilines and aromatic aldehydes by Oddo and

Tognacchini, using a cryoscopic method to follow the course of the reaction (97). It was noted that for the nitroanilines the speeds of formation were in the order *o* > *m* > *p*. *p*-Tolualdehyde reacted much faster than phenylacetaldehyde, and cinnamaldehyde was much more rapid than either. Cinnamaldehyde was also much more rapid than *m*-nitrocinnamaldehyde. The speed of reaction decreased in the series: cinnamaldehyde, anisaldehyde, vanillin, piperonal. The results were not amenable to a general theoretical interpretation.

TABLE 4

Schiff bases formed from aromatic aldehydes and aromatic amines

SCHIFF BASES FORMED FROM		REFERENCE
Aldehyde	Amine	
Benzaldehyde	Aniline	(8, 15)
Benzaldehyde	Substituted anilines	(13, 14a, 29, 58, 60, 76, 94, 148, 149)
Chlorobenzaldehydes	Aniline or *p*-chloroaniline	(60)
o-Nitrobenzaldehyde	Substituted anilines	(14a, 76, 94, 148)
m-Nitrobenzaldehyde	Substituted anilines	(14a, 60, 94, 113, 148)
p-Nitrobenzaldehyde	Substituted anilines	(14a, 43, 60, 67, 82, 94, 113, 148)
2,4-Dinitrobenzaldehyde	Substituted anilines	(81, 83)
2,4,6-Trinitrobenzaldehyde	Substituted anilines	(80)
2,4,6-Trimethylbenzaldehyde	Aniline; *p*-chloroaniline	(60)
Salicylaldehyde	Substituted anilines	(58, 60, 76, 148)
p-Hydroxybenzaldehyde	Aniline	(29)
o-Methoxybenzaldehyde *p*-Methoxybenzaldehyde	*p*-Aminophenol	(58)
p-Aminobenzaldehyde	Substituted anilines	(94, 150)
p-Dimethylaminobenzaldehyde	Substituted anilines	(94, 151)
p-Diethylaminobenzaldehyde	*p*-Dimethylaminoaniline	(94)
Furfural	Aminophenols	(76)
Terephthalaldehyde	Aminophenols	(76)
Cinnamaldehyde	Aminophenols	(58, 76)
Vanillin	Substituted anilines	(14a, 76)
Piperonal	2-Methyl-5-aminobenzonitrile	(14a)

3. The addition stage

The products of the "aldol" stage of the reaction have been arrested in relatively few instances when both reactants are aromatic. Those isolated include the α-amino alcohol from *m*-aminobenzoic acid and benzaldehyde, *m*-$HOOCC_6H_4NHCHOHC_6H_5$ (59); that from *p*-nitroaniline and benzaldehyde, *p*-$NO_2C_6H_4NHCHOHC_6H_5$ (140); and that from 2,4,6-trinitrobenzaldehyde and aniline, $(NO_2)_3C_6H_2CHOHNHC_6H_5$ (80).

Other aryl-substituted α-amino alcohols have been prepared indirectly by either of two methods. The Schiff bases, on treatment with dry hydrogen chloride in ether or benzene, can be converted to hydrochlorides, which can then be hydrolyzed to the α-amino alcohols by treatment with sodium carbonate solution at low temperatures (60). The α-amino alcohols derived from benzaldehyde and *p*-chloroaniline and *p*-bromoaniline were obtained in this manner.

$$C_6H_5CH{=}NC_6H_4X \xrightarrow{HCl}$$

$$\underset{\displaystyle HCl}{C_6H_5CH{=}NC_6H_4X\cdot} \xrightarrow[Na_2CO_3]{H_2O} C_6H_5CHOHNHC_6H_4X$$

These hydrochlorides may be derivatives of chloromethylamine, i.e., ArCHClNHAr (60), but neither this structure nor the ammonium salt structure pictured above has been established with certainty.

The alternate method for preparing these substances is first to prepare the hydrochloride of the α-amino alcohol by treating the aldehyde with the hydrochloride of the amine in the presence of a trace of mineral acid, and subsequently to treat this hydrochloride with cold sodium carbonate (29).

$$C_6H_5CHO + ClNH_3C_6H_4X \xrightarrow{H^+}$$

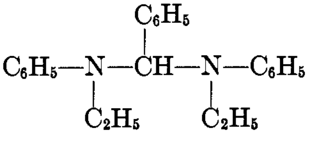
$$\underset{\displaystyle HCl}{C_6H_5CHOHNHC_6H_4X\cdot} \xrightarrow[Na_2CO_3]{H_2O} C_6H_5CHOHNHC_6H_4X$$

The addition products prepared in this way include those from benzaldehyde and *p*-nitroaniline, from salicylaldehyde and aniline, and from *p*-hydroxybenzaldehyde and aniline.

The α-amino alcohols are relatively unstable when both constituents are aromatic in nature. They lose water readily to give the Schiff bases. They cannot be kept for any length of time, for they are readily decomposed into their constituents on standing at room temperature. These two modes of decomposition are probably equilibrium reactions, but they have not yet been studied from that point of view.

B. Aromatic aldehydes and secondary aromatic amines

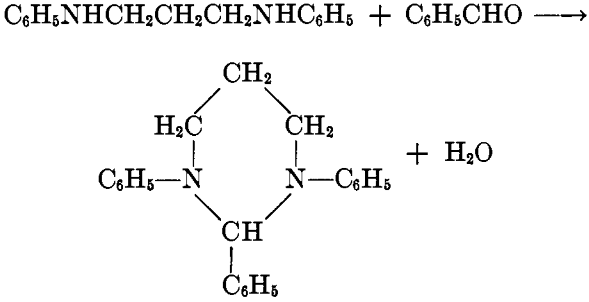
Schiff, in 1864, described the reaction product of *N*-ethylaniline and benzaldehyde (106) to which he assigned the structure,



$$C_6H_5{-}N(C_2H_5){-}CH(C_6H_5){-}N(C_2H_5){-}C_6H_5$$

and described it as a "resin" which showed no definite melting point. A description of a similar product, derived from methylaniline and benzaldehyde, cannot be found in the usual organic reference manuals. Very few, if any, crystalline derivatives of structures similar to that given above have been described.

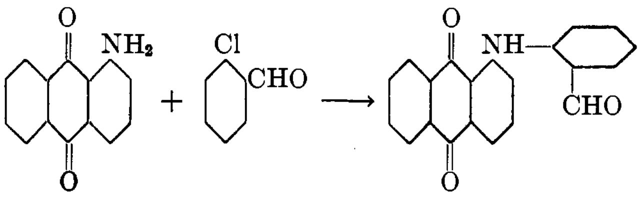
Recently, however, it has been shown (128) that disecondary aromatic-aliphatic amines derived from propane can readily be converted to 1,3-diarylhexahydropyrimidines by treatment with the appropriate aromatic aldehyde in aqueous or alcoholic solution. As an example, 1,2,3-triphenylhexahydropyrimidine is thus formed from 1,3-bis(phenylamino)-propane and benzaldehyde.



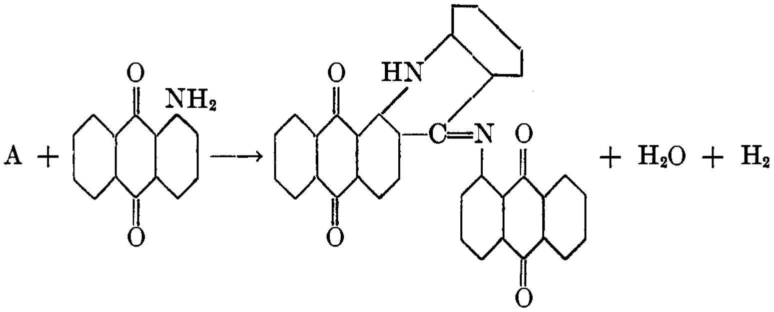
Other aldehydes which react readily are *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, and furfural. However, salicylaldehyde, anisaldehyde, *p*-hydroxybenzaldehyde, and 5-methylfurfural failed to react. 1,3-Bis-(*p*-tolylamino)propane reacted readily with *p*-nitrobenzaldehyde, but failed to react with benzaldehyde.

C. o-Chlorobenzaldehyde and aromatic amines

o-Chlorobenzaldehyde forms numerous Schiff bases, under the conditions outlined above. However, if the amine is heated with an excess of *o*-chlorobenzaldehyde in nitrobenzene or naphthalene, with the addition of a little "Naturkupfer C." and in the presence of sodium carbonate, an anomalous condensation occurs which leads to the formation of acridine derivatives (66, 88, 89, 90). The anomalous condensation is more easily realized in the case of very weakly basic amines, such as the aminoanthraquinones. The first phase of this reaction is a condensation of the Ullmann type, which leaves the aldehyde group intact. The second phase involves another molecule of amine, and effects ring-closure and concomitant oxidation. This may be illustrated, using 1-aminoanthraquinone as an example.

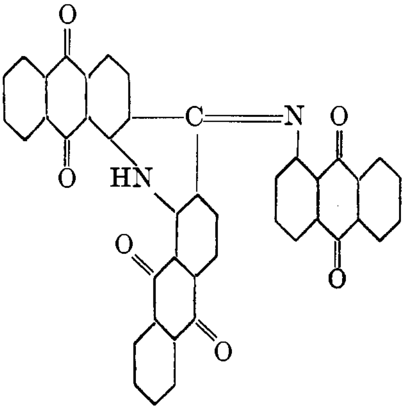


A

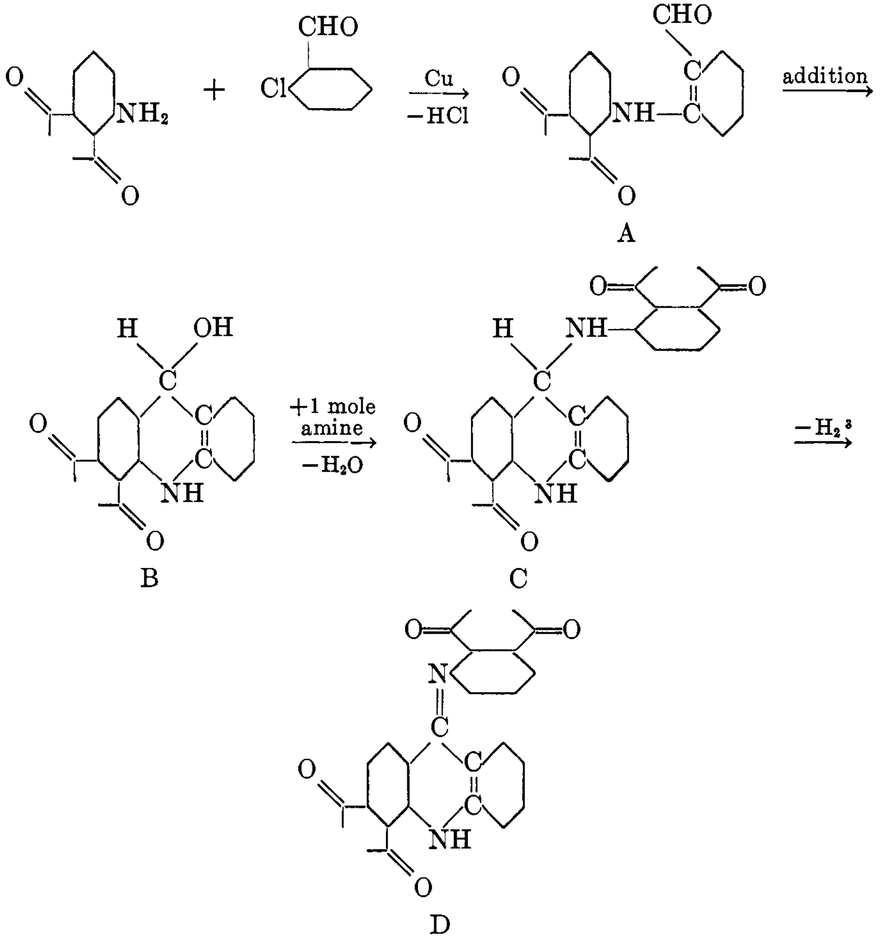


D

The product (D) is therefore a Schiff base derived from aminoanthraquinone and 3,4-phthalylacridone. 2-Aminoanthraquinone and 1-amino-5-chloroanthraquinone react similarly. 1-Aminoanthraquinone reacts with 1-chloroanthraquinone-2-aldehyde under the same conditions to give the Schiff base of 3,4,5,6-diphthalylacridone.



It is perhaps worthy of note that the intermediate A is similar in structure to a dehydrogenation product of the postulated intermediate in the quinaldine synthesis (page 322), and that the product D is, in one sense, a dihydroquinoline derivative. In fact, it has apparently been overlooked previously that this "anomalous" condensation bears a striking external resemblance to the quinaldine reaction. This becomes more apparent if postulated steps in the acridone synthesis are outlined as follows:



The intermediate A and the postulated intermediate B are structurally related to substances which would result in the quinaldine synthesis, if an acetylene aldehyde were used in place of the crotonaldehyde derivative

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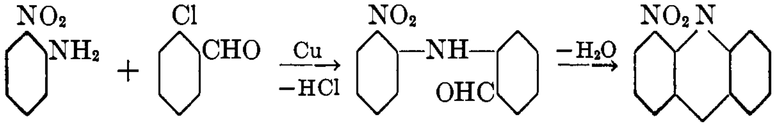
[3] Whether or not hydrogen gas is actually evolved is open to some question.

which is normally employed. The intermediate B, however, cannot lose water as readily as the intermediate formed in the quinaldine reaction and consequently it remains available for condensation with a second molecule of amine, giving C. Oxidation (or dehydrogenation) then gives the dihydroquinoline derivative D. The dihydroquinoline structure is therefore favored by the presence in the intermediate B of the condensed aromatic ring, and is fixed by conversion to the stable Schiff base. This mechanism is, of course, purely speculative, since the work necessary to prove or disprove its adequacy has not been undertaken.

Under the conditions of the above synthesis, the nitramines react in a somewhat more straightforward fashion with *o*-chlorobenzaldehyde. Simple acridines are formed in the second phase of the reaction by what is essentially a dehydration process. This may be illustrated by the case of *o*-nitroaniline, which gives 4-nitroacridine under these conditions (90).



Similarly, 2,4-dinitroaniline gives 2,4-dinitroacridine, 3-nitro-4-toluidine gives 3-nitro-2-methylacridine, and 2-nitro-4-chloroaniline gives 4-nitro-2-chloroacridine.

In many cases, however, the reaction fails to give either acridines or derivatives of acridone. The ordinary Schiff base is then usually obtained. This was observed in the cases of *o*-chlorobenzaldehyde and the following amines: *m*-nitroaniline, *p*-nitroaniline, 4-nitro-1-naphthylamine, 1-nitro-2-naphthylamine, *o*-, *m*-, and *p*-chloroanilines, 2,4-dichloroaniline, 2-chloro-4-toluidine, 2-aminofluorene, 2-aminofluorenone, 2-amino-7-nitrofluorene, 5-nitro-1-naphthylamine, 8-nitro-1-naphthylamine, 5-nitro-2-naphthylamine, and *o*-aminophenol. A similar result was observed in the case of 4-chloroaniline and 2-chloro-4-nitrobenzaldehyde. The reaction was observed to fail altogether in the cases of 2,4,6-trichloroaniline, 2,4-dinitro-1-naphthylamine, and 2,6-dinitroaniline (88, 89, 90).

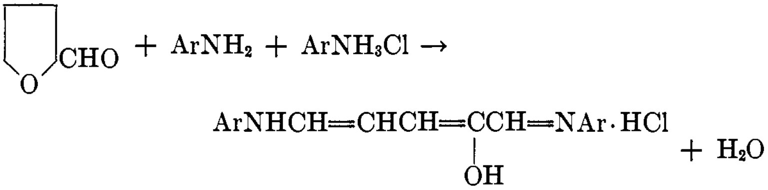
D. Furfural and aromatic amines

Stenhouse first discovered that furfural reacted with aniline in the presence of aniline hydrochloride and with toluidine in the presence of toluidine hydrochloride to give violet-colored salts (116). These reactions may be represented empirically as follows:

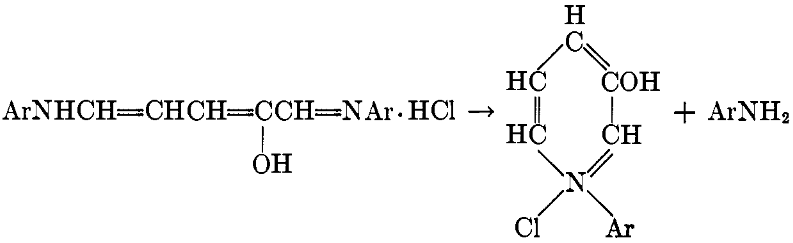
$$C_4H_3O\text{—}CHO + C_6H_5NH_2 + C_6H_5NH_3Cl \rightarrow C_{17}H_{18}N_2O_2\cdot HCl$$

$$C_4H_3O\text{—}CHO + C_7H_7NH_2 + C_7H_7NH_3Cl \rightarrow C_{19}H_{22}N_2O_2\cdot HCl$$

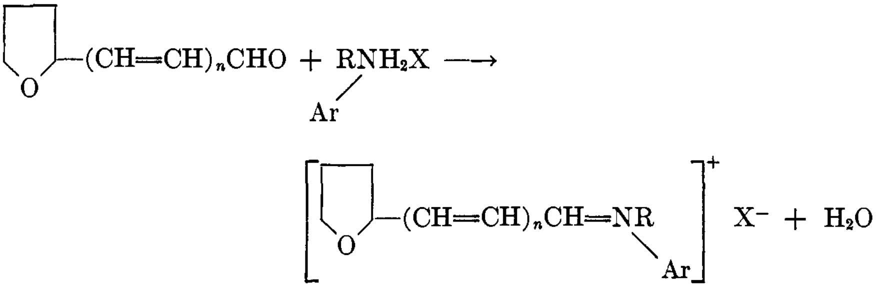
Subsequent investigations (28, 162) proved that these reactions involve scission of the furan ring by addition to it of 1 mole of the aryl amine; and, specifically, that the compound $C_{19}H_{22}N_2O_2 \cdot HCl$ is a hydrated salt of the Schiff base of an open-chain aldehyde, namely, 2-oxy-5-tolylamino-2,4-pentadienaltolylimine hydrochloride. The reaction scheme was therefore amplified as follows:

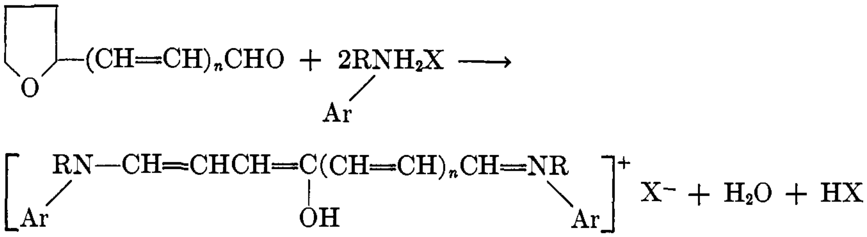


It was found, further, that when the hydrochloride was boiled with alcohol or acetic acid, a ring-closure occurred, leading, however, not to a furfural derivative again, but to a hydroxypyridinium aryl halide.



An elaboration of this investigation demonstrated that furfural could react as above with 2 moles of an arylamine to give an open-chain dye salt; or could react without ring opening with 1 mole of the aryl amine, in which case the product was also a deeply colored salt (72, 73). Similar dyestuffs could be obtained from vinyl homologs of furfural. From these facts the general reaction scheme may be formulated as follows:





(X^- may be any suitable anion, such as halogen or perchlorate)

[In those cases in which R is hydrogen, the 1:1 (closed ring) product is obviously a salt of the Schiff base derived from the amine and furfural (or vinyl homolog). In such cases the salt may be prepared from the Schiff base, merely by suspending the latter in alcohol and treating it with perchloric or other mineral acid. This procedure is, of course, in accord with the general method of preparing salts of Schiff bases previously discussed (60).]

This type of reaction is of quite general applicability. It has been applied to furfural, α-streptomonovinylenefurfural, α-streptodivinylenefurfural, and α-streptotrivinylenefurfural. Among the amines which react readily are *p*-anisidine, methyl-*p*-anisidine, tetrahydroquinoline, dihydro-α-methylindole, methylaniline, tetrahydro-*p*-toluquinoline, thalline, and aniline. It has recently been shown that furan ketones react according to the scheme outlined above (10).

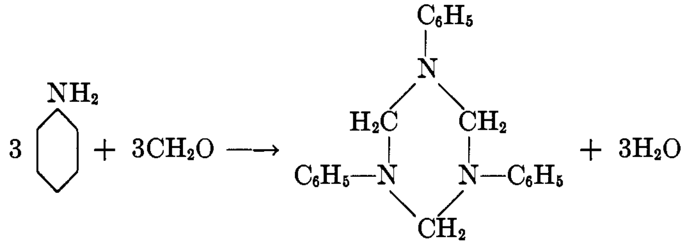
VI. AMINE–ALDEHYDE RESINS

With the exception of the aromatic Schiff bases, which are quite stable substances, almost every other type of aldehyde–amine reaction product is capable of transformation, under the proper conditions, to amorphous or resinous materials of more or less indeterminate structure. The occurrence of such products is, in fact, one of the problems which has continually perplexed workers in this field. The chemistry of the amine–aldehyde resins has been very imperfectly worked out. Relatively brief attention will therefore be paid to this phase of the problem.

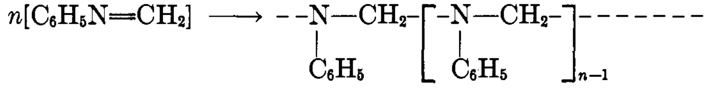
A. Resins obtained from aniline and formaldehyde

This particular subject has recently been discussed by Frey (49).

In neutral or slightly acid solution, the reaction of formaldehyde upon aniline probably goes through the amino alcohol (aldol) and imine (Schiff base) stages. The product usually isolated under these conditions, as has been shown previously, is anhydroformaldehyde aniline trimer.



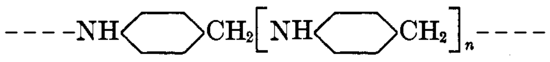
Simultaneously, polymer homologs of anhydroformaldehyde aniline are frequently observed. These probably result from chain-like polymerization of the monomeric Schiff base, much in the manner that polystyrene is formed from styrene monomer.



$$n[C_6H_5N{=}CH_2] \longrightarrow \text{- -}\underset{\displaystyle C_6H_5}{\underset{|}{N}}-CH_2-\left[-\underset{\displaystyle C_6H_5}{\underset{|}{N}}-CH_2-\right]_{n-1}\text{- - - - - - -}$$

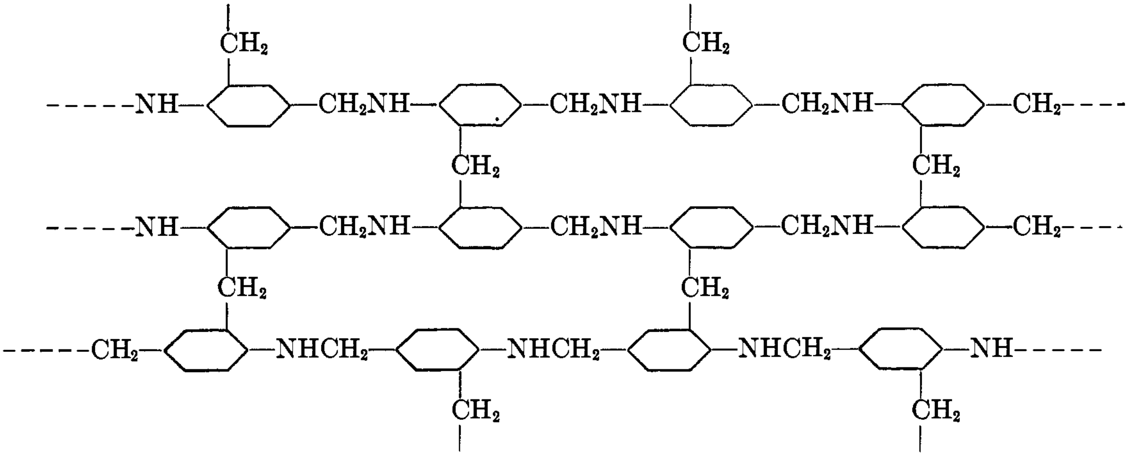
The nature of the groups on the end of the chains has not been determined.

When aniline reacts with an equimolecular proportion of formaldehyde in aqueous solution in the presence of about 1 mole of strong acid, or when anhydroformaldehyde aniline is treated with the equivalent quantity of strong acid, a resin of quite different character is formed. Since this resin may also be obtained by dehydrating aminobenzyl alcohol, it has been referred to as "anhydroaminobenzyl alcohol." By means of reduction studies, it has been proved that the methylene groups are attached to the nitrogen in anhydroformaldehyde aniline, but to the nucleus in anhydroaminobenzyl alcohol. It seems probable that the latter is also a linear polymer and that its structure may be represented as follows:



The nature of the end groups is again an open question, nor is the chain length known with certainty. It is likely that any product actually obtained consists of a mixture of polymer homologs, such as is known to be true in the case of the acid-catalyzed phenol–formaldehyde resins ("Novolaks"). In fact, products of relatively low chain length (n around 5 to 10) are readily obtained by using an excess of aniline, just as in the case of the analogous phenol–formaldehyde resins the use of an excess of phenol leads to products of low chain length. Again, in analogy with the same better known resins, such aniline–formaldehyde resins are permanently fusible and are easily soluble in many organic solvents.

When, however, an excess of formaldehyde is allowed to react upon aniline in acid solution, insoluble infusible products are formed. Hard, resistant materials of exceptional mechanical and electrical properties may thereby be obtained, by application of ordinary technical molding procedure. The structure of the "converted" or "cured" products is unknown, but it is generally supposed that these resins consist of long straight chains which are cross-linked at various points, that is, joined together by methylene groups at random positions in adjacent chains. Frey gives the following as an ideal pattern of this type of "cured" resin. Its similarity to the usual picture for cured or "C stage" Bakelite is worthy of note.



B. *Other amine–aldehyde resins*

Various substituted anilines have been caused to react with formaldehyde to form resins. The status of this particular subject, to 1935, is adequately treated in *The Chemistry of Synthetic Resins*, by Carleton Ellis, pages 686–711. To mention but a few typical examples: *o*-toluidine, *p*-toluidine, α-naphthylamine, β-naphthylamine, and *p*-chloroaniline all give brittle resins with formaldehyde. Monomethylaniline and dimethylaniline give fusible, brittle solids which have been used as copal substitutes. Aniline, the toluidines, naphthylamines, and xylidines have been condensed with acetaldehyde, aldol, crotonaldehyde, etc., to give liquids which may be used in varnishes. Aniline and furfural give dark-colored, brittle resins whose properties vary considerably with the method of preparation, but which have found some use in the lacquer and varnish industry.

A survey of more recent patent literature would show comparatively little important or concerted effort during the last few years. Only a few patents need be cited to illustrate recent trends (163, 164, 165, 166, 167). The first of these provides an example of the technique used at present in the production of aniline–formaldehyde resins. The others describe (*a*) resinous reaction products obtained from aliphatic aldehydes and primary or secondary alkyl or aralkyl amines or secondary heterocyclic bases, which may be used for producing films, lacquers, or shellac substitutes; (*b*) condensation products of aliphatic aldehydes and polyalkylenepolyamines (such as diethylenetriamine and triethylenetetramine) which may be used as waterproofing agents; and (*c*) the reaction products of aliphatic aldehydes and polyaminodiazines, such as 2,4,6-triaminopyrimidine, 2,4-diaminoquinazoline, 2,4,5,6-tetraaminopyrimidine, and 2,4-diamino-5,6-benzoquinazoline. These last-named products are said to combine the excellent chemical and electrical resistance of the aniline–formaldehyde resins with the equally desirable light color and resistance to light of the urea–formaldehyde resins.

Finally, it should be noted that almost any of the amine–aldehyde reactions leads to the formation of tarry or resinous products under certain conditions. Naturally, the properties and structures of these products vary over wide latitudes, depending upon the nature of the reactants, the experimental conditions, and the treatment to which these materials are subjected before they are submitted to evaluating tests.

REFERENCES

(1) ANDREE: Ber. **35**, 424 (1902).
(2) ASCHAN: Ber. **48**, 874 (1915).
(3) BÉHAL AND CHOAY: Ann. chim. [6]**26**, 11 (1892).
(4) BERGMANN AND MIEKELEY: Ber. **57**, 662 (1924).
(5) BEYER: J. prakt. Chem. [2]**33**, 393 (1886).
(6) BISCHOFF: Ber. **31**, 3248 (1898).
(7) BISCHOFF AND REINFELD: Ber. **36**, 35 (1903).
(8) BORODIN: J. prakt. Chem. **75**, 19 (1859).
(9) BORODIN: Ber. **6**, 1253 (1873).
(10) BORSCHE, LEDITSCHKE, AND LANGE: Ber. **71**, 957 (1938).
(11) BUTLEROW: Ann. **115**, 322 (1860).
(12) CAIRNCROSS AND BOGERT: Collection Czechoslov. Chem. Commun. **7**, 58 (1936).
(13) CALM: Ber. **17**, 2938 (1884).
(14) CAMBRIER AND BROCHET: Bull. soc. chim. [3]**13**, 404 (1895).
(14a) CÂNDEA AND MACOVSKI: Bull. soc. chim. [5]**5**, 1487 (1938).
(15) CECH: Ber. **11**, 248 (1878).
(16) CHANCEL: Bull. soc. chim. [3]**11**, 933 (1894).
(17) CHEMISCHE FABRIK V. HEYDEN: German patents 216,072 and 216,073.
(18) CRAIG: J. Am. Chem. Soc. **55**, 3723 (1933).
(19) DELÉPINE: Bull. soc. chim. [3]**13**, 128 (1895).
(20) DELÉPINE: Compt. rend. **125**, 951 (1897).
(21) DELÉPINE: Bull. soc. chim. [3]**19**, 171 (1898).

(22) Delépine: Compt. rend. **125,** 178 (1897); **126,** 343 (1898); **126,** 648 (1898).
(23) Delépine: Compt. rend. **128,** 105 (1899).
(24) Delépine: Compt. rend. **144,** 853 (1907).
(25) Delépine and Rivals: Compt. rend. **129,** 520 (1899).
(26) Dennstedt and Zimmermann: Ber. **21,** 1553 (1888).
(27) Dickenson and Raymond: J. Am. Chem. Soc. **45,** 22 (1923).
(28) Dieckmann and Beck: Ber. **38,** 4122 (1905).
(29) Dimroth and Zoeppritz: Ber. **35,** 984 (1902).
(30) Dobler: Z. physik. Chem. **101,** 1 (1922).
(31) Doebner and Von Miller: Ber. **16,** 2464 (1883).
(32) Doebner and Von Miller: Ber. **17,** 1698 (1884).
(33) Doebner and Von Miller: Ber. **17,** 1712 (1884).
(34) Duden and Scharf: Ann. **288,** 218 (1895).
(35) Eberhardt and Welter: Ber. **27,** 1804 (1894).
(35a) Edwards, Garrod, and Jones: J. Chem. Soc. **101,** 1376 (1912).
(36) Eibner: Ber. **30,** 1444 (1897).
(37) Eibner: Ann. **302,** 334 (1898).
(38) Eibner: Ann. **318,** 58 (1901).
(39) Eibner: Ann. **328,** 121 (1903).
(40) Eibner and Koch: Z. angew. Chem. **39,** 1514 (1926).
(41) Einhorn and Prettner: Ann. **334,** 217 (1904).
(42) Eisner and Wagner: J. Am. Chem. Soc. **56,** 1938 (1934).
(43) Fischer: Ber. **14,** 248 (1881).
(44) Fischer: Ber. **26,** 467 (1893).
(45) Fischer and Prause: J. prakt. Chem. [2]**77,** 129 (1908).
(46) Fischer and Wreszinske: Ber. **25,** 2711 (1892).
(47) Franchimont and Van Epps: Rec. trav. chim. **15,** 169 (1896).
(48) Francis: Ber. **42,** 2216 (1909).
(49) Frey: Helv. Chim. Acta **18,** 491–513 (1935).
(50) Friedjung and Mosler: Monatsh. **22,** 460 (1901).
(51) Friedländer: Monatsh. **23,** 973 (1902).
(52) Fritsch: Ann. **286,** 6 (1895).
(53) Gabriel and Leupold: Ber. **31,** 2832 (1898).
(54) Gnehm and Bänziger: Ber. **29,** 876 (1886).
(55) Gnehm and Blumer: Ann. **304,** 115 (1899).
(56) Goecke: Z. Elektrochem. **9,** 470 (1903).
(57) Grünhagen: Ann. **256,** 288 (1889).
(58) Haegele: Ber. **25,** 2753 (1892).
(59) Hantzch and Kraft: Ber. **24,** 3521 (1891).
(60) Hantzch and Schwab: Ber. **34,** 822 (1901).
(61) Haskelberg: Chemistry & Industry **54,** 261 (1935).
(62) Heller: Ber. **27,** 3097 (1894).
(63) Henry: Bull. acad. roy. belg. [3]**26,** 206 (1893); **28,** 359 (1894); **29,** 26 (1895).
(64) Henry: Bull. acad. roy. Belg. [3]**29,** 355 (1895).
(65) Henry: Compt. rend. **120,** 839 (1895).
(65a) Jones and Evans: J. Chem. Soc. **99,** 334 (1911).
(66) Kalischer and Mayer: Ber. **49,** 1994 (1916).
(67) King and Lowy: J. Am. Chem. Soc. **46,** 757 (1924).
(68) Knudsen: Ber. **47,** 2700 (1914).
(69) Kolda: Monatsh. **19,** 610 (1898).
(70) Kolotov: Bull. soc. chim. [2]**43,** 112 (1885).

(71) Kondo and Ishida: J. Pharm. Soc. Japan **489**, 979 (1922); Chem. Abstracts **17**, 1456 (1923).

(72) König: J. prakt. Chem. [2]**88**, 193 (1913).

(73) König, Hey, Schulze, Silberkneit, and Trautmann: Ber. **67**, 1274 (1934).

(74) Kroneberg: J. Russ. Phys.-Chem. Soc. **48**, 305 (1916); Chem. Abstracts **11**, 582 (1917).

(75) Lepetit, Maffei, and Maimeri: Gazz. chim. ital. **57**, 862 (1927).

(76) Levi: Gazz. chim. ital. **59**, 544 (1929).

(77) Lippmann and Strecker: Ber. **12**, 831 (1879).

(78) Lob: Rec. trav. chim. **55**, 859 (1936).

(79) Löb: Z. Elektrochem. **4**, 428 (1898).

(80) Lowy and Baly: J. Am. Chem. Soc. **43**, 341 (1921).

(81) Lowy and Downey: J. Am. Chem. Soc. **43**, 346 (1921).

(82) Lowy and King: J. Am. Chem. Soc. **43**, 625 (1921).

(83) Lowy and Wescott: J. Am. Chem. Soc. **42**, 849 (1920).

(84) Maffei: Gazz. chim. ital. **58**, 261 (1928).

(85) Mannich and Davidsen: Ber. **69**, 2106 (1936).

(86) Mannich, Handke, and Roth: Ber. **69**, 2112 (1936).

(87) Mason: Ber. **20**, 270 (1887).

(88) Mayer and Bausa: Ber. **54**, 16 (1921).

(89) Mayer and Levis: Ber. **52**, 1641 (1919).

(90) Mayer and Stein: Ber. **50**, 1306 (1917).

(91) Meyer and Rohmer: Ber. **33**, 250 (1900).

(92) Meyer and Stillich: Ber. **35**, 739 (1902).

(93) Miller and Wagner: J. Am. Chem. Soc. **54**, 3698 (1932).

(93a) Mills, Harris, and Lambourne: J. Chem. Soc. **119**, 1294 (1921).

(94) Möhlau: Ber. **31**, 2250 (1898).

(95) Nastyukov and Kroneberg: J. Russ. Phys.-Chem. Soc. **44**, 1200 (1912); Chem. Abstracts **7**, 983 (1913).

(96) Niementowski and Orzechowski: Ber. **35**, 3898 (1902).

(97) Oddo and Tognacchini: Gazz. chim. ital. **52**, **II**, 347 (1922).

(97a) Panajatow: Ber. **20**, 32 (1887).

(98) Plöchl: Ber. **21**, 2117 (1888).

(99) Ponzio: Gazz. chim. ital. **24**, **II**, 280 (1894).

(100) Pratesi: Gazz. chim. ital. **14**, 351 (1884).

(101) Pulvermacher: Ber. **25**, 2762 (1892).

(102) Rameau: Rec. trav. chim. **57**, 194 (1938).

(103) Reinking, Dehnel, and Labhardt: Ber. **38**, 1077 (1905).

(104) Rohde: Ber. **20**, 1911 (1887).

(105) Rügheimer: Ber. **39**, 1653 (1906).

(106) Schiff: Ann. Chem. Pharm. Suppl. **3**, 343 (1864).

(107) Schiff: Ann. **140**, 93 (1867).

(108) Schiff: Ber. **25**, 1936 (1892).

(109) Schiff and Amato: Gazz. chim. ital. **1**, **I**, 376 (1871).

(110) Scholtz: Ber. **32**, 2256 (1899).

(111) Scholtz and Jaross: Ber. **34**, 1504 (1901).

(112) Schwabbauer: Ber. **35**, 413 (1902).

(113) Shibato and Okuyama: Bull. Chem. Soc. Japan **11**, 122 (1936).

(114) Simons: J. Am. Chem. Soc. **59**, 518 (1937).

(115) Spielman: J. Am. Chem. Soc. **57**, 583 (1935).

(116) Stenhouse: Ann. **156**, 199 (1870).

(117) Strain: J. Am. Chem. Soc. **54**, 1221 (1932).

(118) Strache: Ber. **21**, 2361 (1888).
(119) Tollens: Ber. **17**, 653 (1884).
(120) Tollens and Mayer: Ber. **21**, 1570 (1888).
(121) Troeger: J. prakt. Chem. [2]**36**, 225 (1887).
(122) Tschitschibabin: J. Russ. Phys.-Chem. Soc. **37**, 1229 (1905).
(123) Tschitschibabin: J. prakt. Chem. [2]**107**, 122, 129, 132 (1924).
(124) Tschitschibabin and Aparina: J. prakt. Chem. [2]**107**, 138, 145, 154 (1924).
(125) Tschitschibabin and Moschkin: J. prakt. Chem. [2]**107**, 109 (1924).
(126) van Alphen: Rec. trav. chim. **54**, 93 (1935); **55**, 412, 669 (1936).
(127) van Alphen: Rec. trav. chim. **57**, 271 (1938).
(128) Veer: Rec. trav. chim. **57**, 994 (1938).
(129) von Braun: Ber. **41**, 2145 (1908).
(130) Von Miller: Ber. **25**, 2072 (1892).
(131) Von Miller and Kinkelin: Ber. **20**, 1916 (1887).
(132) Von Miller and Plöchl: Ber. **27**, 1296 (1894).
(132a) Von Miller and Plöchl: Ber. **29**, 1462 (1896).
(133) Von Miller and Plöchl with Eckstein: Ber. **25**, 2029 (1892).
(134) Von Miller and Plöchl with Eibner: Ber. **25**, 2041 (1892).
(135) Von Miller and Plöchl with Friedlander: Ber. **25**, 2049 (1892).
(136) Von Miller and Plöchl with Hofer: Ber. **25**, 2028 (1892).
(137) Von Miller and Plöchl with Krempelhuber: Ber. **25**, 2050 (1892).
(138) Von Miller and Plöchl with Lettermayer: Ber. **25**, 2039 (1892).
(139) Von Miller and Plöchl with Senders: Ber. **25**, 2033 (1892).
(140) Von Miller and Rohde: Ber. **25**, 2053 (1892).
(141) Wagner: J. Am. Chem. Soc. **55**, 724 (1933).
(142) Wagner: J. Am. Chem. Soc. **56**, 1944 (1934).
(143) Wagner: J. Am. Chem. Soc. **57**, 1296 (1935).
(144) Wagner: J. Org. Chem. **2**, 157 (1937).
(145) Wagner and Eisner: J. Am. Chem. Soc. **59**, 879 (1937).
(146) Wallach: Ber. **4**, 668 (1871).
(147) Wallach: Ann. **173**, 274 (1874).
(148) Walther and Bamberg: J. prakt. Chem. [2]**71**, 153 (1905).
(149) Walther and Bamberg: J. prakt. Chem. [2]**73**, 209 (1906).
(150) Walther and Kausch: J. prakt. Chem. [2]**56**, 111 (1897).
(151) Weil: Ber. **27**, 3317 (1894).
(152) Wellington and Tollens: Ber. **18**, 3298 (1885).
(153) Werner: J. Chem. Soc. **111**, 844 (1917).
(154) Wheeler: J. Am. Chem. Soc. **30**, 136 (1908).
(155) Wheeler and Jordan: J. Am. Chem. Soc. **31**, 937 (1909).
(156) Wheeler and Weller: J. Am. Chem. Soc. **24**, 1063 (1902).
(157) Winans and Adkins: J. Am. Chem. Soc. **55**, 2051 (1933).
(158) Wohl and Wohlberg: Ber. **34**, 1922 (1901).
(159) Wyckoff and Corey: Z. Krist. **89**, 462 (1934).
(160) Young and Wagner: J. Am. Chem. Soc. **59**, 854 (1937).
(161) Zaunschirm: Ann. **245**, 281 (1888).
(162) Zincke and Muhlhausen: Ber. **38**, 3824 (1905).

Recent patents

(163) I. G. Farbenindustrie, A. G.: British patent 474,034.
(164) I. G. Farbenindustrie, A. G.: British patent 474,601.
(165) I. G. Farbenindustrie, A. G.: French patent 817,153.
(166) Sutter (To Société pour l'industrie chimique á Bâle): U. S. patent 2,097,109.
(167) I. G. Farbenindustrie, A. G.: German patent 667,542.