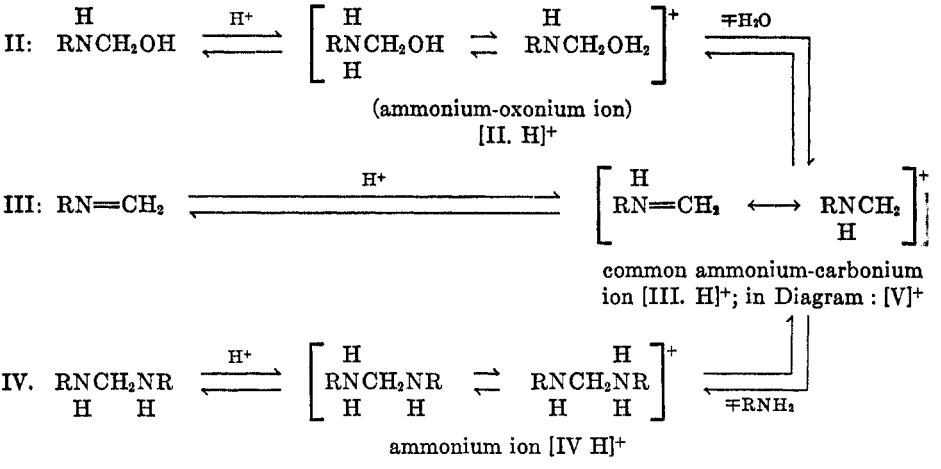
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF PENNSYLVANIA]

A RATIONALIZATION OF ACID-INDUCED REACTIONS OF METHYLENE-BIS-AMINES, METHYLENE-AMINES, AND OF FORMALDEHYDE AND AMINES

E. C. WAGNER

Received April 29, 1954

This paper[1] outlines the manner in which the diverse results of acid-induced reactions of formaldehyde with primary and secondary amines (I, Ia),[2] or of the products of the condensations of such amines with formaldehyde, *viz.*, methylolamines (II), methylene-amines or Schiff bases (III), or methylene-bis-amines (IV), may be unified by means of a single assumption, *viz.*, that these condensation products, by accession of a proton, are convertible to a common cation, as follows (for primary amines):



The oxonium form of $[IIIH]^+$ contains the elements of water properly combined as such, and $[IVH]^+$ contains a molecule of amine as such. By loss of water or of amine respectively there results ammonium-carbonium ion $[V]^+$ (reaction Diagram), *viz.*, $[ArNHCH_2]^+$ which, when the amine represented is secondary, is $[R_2NCH_2]^+$. Stated briefly: II, III, and IV with proton can yield a common cation, which is that of the Schiff base when the amine is primary. In the reaction diagram these relationships are shown as reactions C, C′ and C″, leading to ion $[IIIH]^+$, there designated as ion $[V]^+$. The postulation of a common ion derivable from II, III, or IV by action of acid, and hence also during any action of formaldehyde and I or Ia in presence of acid, provides an obvious explanation of the

[1] Some older references are omitted when they can be reached through papers cited. Attention is directed to a review on the condensations of arylamines with formaldehyde by Morgan (84), and especially to the review by Sprung (85), "A Survey of the Reactions of Aldehydes with Amines."

[2] Compounds represented by Roman numerals are shown in the Reaction Diagram.

familiar fact that in certain reactions promoted by acid there may be used interchangeably the amine I or Ia and formaldehyde, or preformed III or IV.[3] The existence of such ions was conceived on grounds partly speculative or inferential (1). Their importance in certain acid-induced reactions was pointed out by McLaughlin and Wagner (58). They were assumed by Porai-Koshits (2) to be involved in the hydrolysis of alkylidene-bis-amines and of Schiff bases by aqueous acid. The outlined ionic hypothesis has been applied to the Wallach alkylation reaction and to the Mannich reaction (3, 4), and similar ions were postulated recently by Böhme and Kreutzkamp (31b).

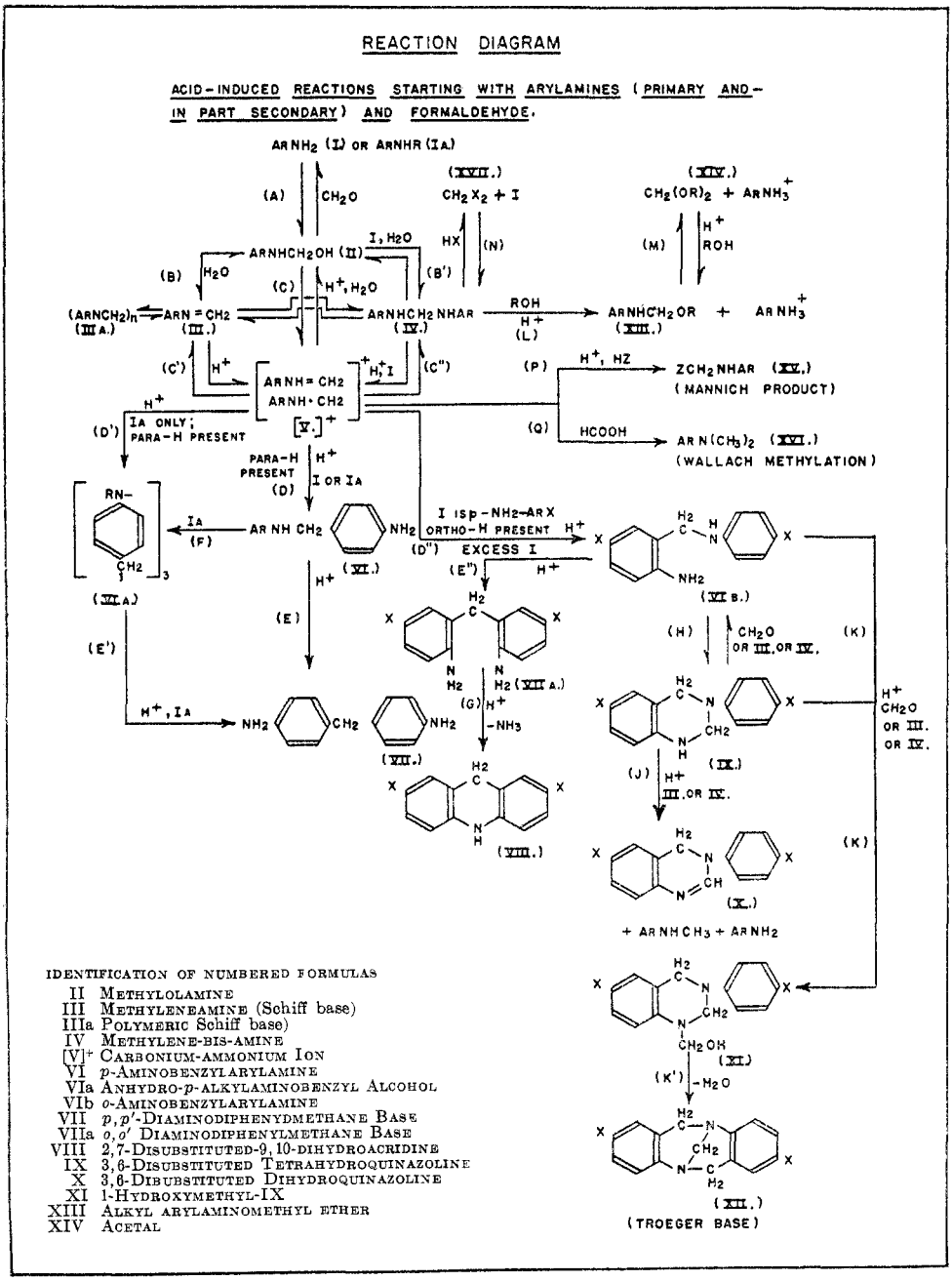
The reactions to be considered are arranged in their determined relationships in the Reaction Diagram. The lettered reactions in most cases have been studied sufficiently to disclose the probable steps and the conditions necessary to ensure them, but not sufficiently to reveal features such as comparative catalytic effects, reaction rates, or orders. Compounds represented in the diagram by Roman numerals are obtainable as products, though this may not be true for all methylolamines (II) or all monomeric Schiff bases (III), nor of course for ion $[V]^+$. Experimental conditions for directing and controlling the lettered reactions are outlined in appropriate places.

Reactions A, B, B′ and *B″* (formation of II, III and IV) are the several primary condensations.[4] *Methylolamines* (II) are rather sparingly represented by isolable products. Those reported include a number from aliphatic primary or secondary amines (5–7). Analogous addition products of amines with chloral or trinitrobenzaldehyde (8–11) are isolable.[5] Hydroxyalkyl amines are in general not very stable; they react with amine to yield IV (reaction B′), and those from primary amines lose water on heating, with conversion to III (reaction B). Alkylolamines are therefore not usually available as starting compounds, though they are generally (and doubtless properly) regarded as the initial condensation products of primary and secondary amines with aldehydes. The relative instability of this class is consistent with the methylene aminohydrin structure, which is that of an aquoammono aldehyde hydrate.

[3] This equivalence in reactions can be explained in a more superficial way as due to the characters of II, III, and IV as nitrogen-system compounds of aldehydic type, *viz.*, II as an aquoammono aldehyde hydrate, III as an ammono-aldehyde, and IV as an ammono-aldehyde hydrate or acetal.

[4] The possibility that condensations of primary and secondary amines with formaldehyde to yield II, III, and IV may be acid-induced is not overlooked, since these, like the reverse hydrolyses, can be represented as ionic reactions. Because acid seems to be not essential to these condensations (compounds of type IV are best made in presence of base), and in sufficient amount may obstruct them, it will be assumed that the initial reaction is additive, yielding II which by loss of water may yield III, by interaction with amine may yield IV which, by loss of amine, may yield III (reactions B, B′, B″). Of these secondary changes those that lead to III are almost certainly acid-induced. It was reported recently that formation of ketimines by condensation of ketones and amines is catalyzed by acid (95).

[5] N-Hydroxymethyl compounds are represented also by the products of the condensations of formaldehyde with urea, melamine, etc., and by certain compounds formed by action of formaldehyde on —NH— groups present in rings (40, 30).



Methylene-amines or Schiff bases (III) derived from formaldehyde and primary amines polymerize spontaneously in most cases.[6] Those from familiar aromatic

[6] Schiff bases from the low aliphatic aldehydes above formaldehyde polymerize also, but some have been claimed to be monomers, *e.g.*, $CH_3CH{=}NC_2H_5$ and $CH_3CH_2CH{=}NC_3H_7$ (86, 87).

primary amines are known only as polymers which may be either sharply definite cyclic trimers[7] containing the *sym*-triazane ring (12, 13a) or indefinite linear aggregates;[8] the two are respectively the nitrogen-system counterparts of trioxan and paraformaldehyde. Trimeric methylene aniline, as deduced from dipole moment (1.174 in CCl_4, 1.180 in C_6H_6, 1.160 in ligroin) by J. G. Miller and R. A. Florentine, exists in the "chair" configuration, while trimeric methylene-*p*-toluidine (dipole moment 2.893, 0.896, 0.873) appears to be a mixture of two forms (13b). Some Schiff base polymers distill by depolymerization, the vapors consisting largely of monomer; the distillate changes into trimer upon standing, and more rapidly in contact with a solvent from which the trimer can crystallize (16). Continued action of strong acids on such condensation products converts them finally to refractory amorphous material, such as the resins obtained from aniline and formaldehyde in presence of hydrochloric acid (14). Monomeric Schiff bases result when formaldehyde and higher aldehydes condense with amines of the type $R_3C{\cdot}NH_2$. The products, *viz.*, $R_3C{\cdot}N{=}CH_2$, are stable and distillable monomers (15); the impedance to polymerization is apparently steric. Aromatic aldehydes appear to yield only monomeric Schiff bases, *e.g.*, benzalaniline, though action of hot strong acid may cause resinification. Schiff bases are ordinarily made by direct condensation of aldehyde and primary amine, but the structure $-\overset{|}{C}{=}N-\overset{|}{C}-$ characteristic of the class can be obtained by regulated oxidation of compounds containing the condition $-\overset{|}{C}H-NH-\overset{|}{C}-$ (19); (see also reaction J).

[7] There appears to be no sound evidence (12, 13, 16) for the actuality of the simple dimers reported by Ingold and Piggott (17) and Hartough, Meisel, Koft, and Schick (18). Interesting examples of Schiff base dimers of a different type are Eckstein's bases, obtained as isomers from acetaldehyde and aniline in cold alcohol in presence of acid (88). The formulas assigned are $CH_3CHCH_2CH{=}NC_6H_5$ and its tautomer (m.p. 85° and 126°). Eibner (89)

$$\begin{array}{l} CH_3CHCH_2CH{=}NC_6H_5 \\ \quad | \\ \quad NHC_6H_5 \end{array}$$

explained the reaction as the condensation of two equivalents of aniline with aldol initially formed from acetaldehyde, and showed that aldol and aniline react to yield Eckstein's bases. It is suggested that the product shown by the formula may result by a nitrogen-system aldol condensation of the nascent Schiff base ethylidene aniline; Eckstein's base is dimeric ethylidene aniline in the same sense that aldol is dimeric acetaldehyde. Heating with acid converts Eckstein's base to quinaldine, a fact of possible significance with respect to the course of the Doebner-Miller quinaldine synthesis. These reactions are explicable by suitable extension of the ionic hypothesis under discussion.

[8] The structures of Schiff bases from formaldehyde and aniline, *p*-toluidine, *p*-aminophenol, and *p*-phenetidine were established by the evidence of molecular weight determinations, which showed them to be trimeric, and of reduction-cleavage, which yielded amine, methylated amine, and dimethylated amine. It seems unlikely that a linear polymer $-N(Ar)-CH_2-N(Ar)-CH_2-N(Ar)-CH_2-$ would exist as a compound of great definiteness, or that the average molecular weights of several such compounds, determined in several solvents, would by coincidence be those of the trimers, so it is concluded that the structure is cyclic. This appears also to be a necessary conclusion from the configuration of trimeric methylene aniline as indicated by the study of its dipole moment by Miller and Florentine (13b).

Methylene-bis-amines (IV) result when aldehydes react with secondary amines, and are formed from primary amines and aldehydes when the ratio of reactants is at least 2:1, and in general when acid is absent. Alkylidene-bis-amines of the type $RNHCH_2NHR$ are best made in presence of alkali or tertiary base (20) in order to exclude conversion to Schiff bases by loss of amine (21, 22). Methylene-bis-amines may be obtained from methylolamines by action of amine (5); mixed methylene-bis-amines can be made in this way. Attempted preparation of mixed compounds by hydrogenation of substituted amidines (23) was only qualitatively successful, the necessary conditions being not yet determined. Interconversions of III and IV are discussed below (reaction B″).

Formation of methylene-bis-amines from amines and methylene halides has been claimed to succeed (24) with aniline and methylene iodide, but not with aniline and methylene chloride (21). Grünhagen's reported preparation of methylene-bis-*p*-toluidine (25) from the amine and methylene chloride was tested by Hunt and Wagner (26), who obtained not the product named but the quinazolline X; they were able, however, to verify Schmidt and Kohler's statement (27) that piperidine and methylene iodide yield methylene-bis-piperidine. It therefore appears that when the amine is aromatic, the liberated acid may lead to secondary changes (Reaction Diagram).

The structures of methylene-bis-amines were established by analysis (including molecular weight values), by the facts that yields from secondary amines (2:1) often exceed 80%, by the fact that reduction cleavage yields only amine and methylated amine (28, 29), and by the consistent duplication of certain reactions of formaldehyde by various methylene-bis-amines (30) which are thus shown to function as N-system aldehydes (hydrates or acetals).

Compounds II, III, and IV are susceptible to hydrolytic cleavage by aqueous acids, yielding the original amine and aldehyde, and this susceptibility, while perhaps rather less pronounced and general than has been supposed (26), must be kept in mind in dealing with these compounds. When the amine represented is aromatic, simple hydrolysis may be complicated by, or even excluded by, more rapid or less reversible reactions shown in the reaction diagram.

Salt-Formation of II, III, and IV; the Ion $[V]^+$. The acid-induced reactions of II, III, and IV are assumed to be initiated by formation of salts of any or all of these condensation products. Evidence as to the reality of such salts is now substantial with respect to methylene-bis-amines (IV), of which six salts have been obtained (27, 26) in isolable form.[9] Salts of hydroxyalkylamines have been reported by Bodendorf and Koralewski (31a)[9] and by Böhme and Kreutzkamp (31b). Methylene-amines, including those in trimeric form, appear to form salts (32, 33). Recent additions to the list of such salts include the hydriodide of trimeric methylene benzylamine (26, 34).

In order that salts of II, III, or IV may qualify as reactants in acid-induced

[9] All early claims of preparations of isolable salts of alkylidene-bis-amines, excepting one, proved to be erroneous (26), the amine salts having been mistaken in most cases for the alkylidene-bis-amine salts. Claims of isolable salts formed from alkylolamines (31) should probably be tested further.

reactions it is not essential that they be isolable or stable, though the demonstrated reality of some such salts relieves the hypothesis of an outright assumption on this point. The acid required may be much less than stoichiometric. It is often introduced as a salt of the amine represented, and in the reaction mixtures the effective concentration of acid may be very low, for the acid is distributed among all the bases present (reactants, intermediates, products), and may be heavily buffered, so that salts of II, III, or IV can exist in such systems in amounts momentarily small. It follows that the salt and the carbonium-ammonium ion $[V]^+$ may have the characters of fleeting intermediates rather than of substances of sensible duration. That this does not prevent reactions both rapid and extensive suggests mobile equilibria and ionic entities of high activity, sufficient to enable them to dislodge as protons, and sometimes in presence of considerable acid, atoms of hydrogen only moderately activated, *e.g.*, hydrogens *ortho* or *para* with respect to N or O, as in aromatic amines intentionally added or liberated during formation of ion $[V]^+$ from IV.

Acid-induced reactions of the types to be discussed are most varied and interesting when the amines represented are primary or secondary aromatic amines with unsubstituted *para* or *ortho* hydrogen. The reaction diagram applies primarily to such amines.

Interconversion of IV and III. Methylene-bis-amines are convertible to Schiff bases by action of formaldehyde (17, 35), and conversion of III to IV by heating with amine has been reported (21).

Application of the outlined hypothesis affords a virtually inevitable explanation for the observed facts with respect to conversion of IV to III, sometimes unexpectedly, by acid[10] which may be only incidental traces of acid present in laboratory solvents, such as alcohol or ether used in preparation or recrystallization (21, 22, 36). The change, when induced by acid is believed to be reaction C″, whereby IV accepts a proton to yield ion $[IVH]^+$ which, by loss of a neutral molecule of amine, is left as ion $[V]^+$. This is the Schiff base ion; its proton is readily ceded to the free amine present and the trimeric Schiff base appears. It seems clear that it was this secondary effect of acid upon IV that led Drazdov (37) to the conclusion that, regardless of the proportions of amine and aldehyde, reaction in acid solution yields the Schiff base III rather than the alkylidene-bis-amine IV. That the conversion of IV to III under such conditions[11] is caused by

[10] Methylene-bis-amines may be cleaved to yield amines and Schiff bases by heat alone, as during distillation (22).

[11] The sensitivity of methylene-bis-*p*-anisidine to acid is exceptional, and this case has been examined more extensively than others. In the absence of added alkali, *p*-anisidine and formaldehyde (as formalin) in 2:1 ratio, yield IV (m.p. 68°) mixed with IIIa (trimer, m.p. 133°). Made in presence of alkali which, during the isolation is "neutralized" by passing in a stream of carbon dioxide, the acidity thus finally established by carbon dioxide suffices to convert IV to III to the extent of over 30% (90). Made in the presence of alkali and isolated directly from the alkaline mixture IV was obtained in 85% yield and there was present no trace of Schiff base. Attempted crystallization of IV from ordinary ethyl alcohol leads to partial conversion to III (22), and laboratory ether was observed to have a like effect (91). By recrystallization of IV from ethanol containing triethylamine the change to III was inhibited and pure IV was obtained (20).

cyclical operation of proton seems certain, for it is prevented by presence of alkali (21) or of triethylamine (26) which can scarcely have any positive effect in stabilizing IV.

Reactions C, C′, and C″ represent the acceptance of a proton by II, III or IV, with conversion of all to ion $[V]^+$, the Schiff base ion. The depolymerization of $(III)_n$, which is of structure type IV, by acid is entirely analogous to cleavage of IV, and finally yields the Schiff base ion $[V]^+$ whether the polymer is cyclic or linear.

Reactions D and D″ are equivalent sequences by which methylene-bis-amines IV or Schiff bases III from either I or Ia are converted reversibly (38) to VI or VIa *viz.*, aminobenzylamines; over-all:

$$C_6H_5NHCH_2NHC_6H_5 \underset{C_6H_5NH_2,\ HCl}{\overset{C_6H_5NH_2}{\rightleftharpoons}} C_6H_5NHCH_2C_6H_4NH_2.$$

The reaction is not an intramolecular rearrangement or isomerization for, if there is present a second aromatic amine with "open" *para-* (or *ortho-*) position this amine, whether primary, secondary or tertiary, may appear as a component of the product VI (39 a, b, c, d). The reaction is therefore recognizable as a proton-induced cleavage of IV followed by attack of ion V at the active nuclear position of amine either detached from $[IVH]^+$ or introduced as amine salt. For the case represented above:

$$C_6H_5NHCH_2NHC_6H_5 \overset{H^+}{\rightleftharpoons} (IV\ H)^+ \rightleftharpoons \left\{\begin{matrix}(C_6H_5NHCH_2)^+ \\ \\ +\ (H)C_6H_4NH_2\end{matrix}\right\} \rightleftharpoons C_6H_5NHCH_2C_6H_4NH_2 + H^+.$$

Schiff bases can be used in the same way, provided sufficient amine is present.

In practice the preparation of compounds of type VI and VIb (40) involves interaction of IV or III with acid (as amine salt) in deficiency, and in presence of a considerable excess of amine. The last restrains reactions E and E″, which are reversible (38), and which, by repetition of the cleavage-coupling operation, change VI and VIb to VII and VIIa (diphenylmethane bases). For preparation of aminobenzylarylamines of type VIb a satisfactory ratio of IV:amine salt:amine is 1:0.5:10. Using a trimeric Schiff base a satisfactory ratio of III_n:amine salt:amine is 1:1.5:33 (40).

The structures of aminobenzylarylamines are indicated by the convertibility of those of type VI to the corresponding diphenylmethane bases VII (in simple cases an isomerization) and by the convertibility of those of type VIIb to corresponding tetrahydroquinazolines (IX) by action of formaldehyde (reaction H) (41) or of formic acid or ethyl orthoformate (42). The structure of *o*-amino-*m*-xylyl-*p*-toluidine (VIb from *p*-toluidine) was confirmed (41) by reduction-cleavage; the only products were *p*-toluidine and 4-amino-1,3-xylene.

Reaction D′. Formation of "Anhydro-p-alkyl-aminobenzyl alcohol"[12] *VIa from secondary arylamine.* This reaction occurs when an N-alkyl-arylamine in aqueous hydrochloric (or other) acid is treated with formalin; the salt of the anhydro-*p*-

[12] So called because obtainable by reduction of *p*-nitrobenzyl alcohols.

alkylaminobenzyl alcohol (crystalline when R is a low alkyl) precipitates. At first represented to be "exochloromethyl" compounds, $ArNRCH_2Cl$ (43–45), they were recognized by Friedländer (46) to be hydrochlorides of anhydroalkylaminobenzyl alcohols, believed to be dimeric, since by reduction they yield alkyl *p*-toluidines. A number of such salts (R = methyl, ethyl, *n*-propyl, *n*-butyl, isoamyl) were found (47) to approximate the formula ($—CH_2C_2H_4NR \cdot HCl$), and the liberated bases (including also R = benzyl) were shown to be trimeric (48).

Friedländer (49, 46) suggested that these compounds are formed by primary nuclear condensation of formaldehyde with Ia, and subsequent coupling of the hydroxymethyl compound with NH of another molecule:

$$RHNC_6H_4(H) + CH_2O \longrightarrow RHNC_6H_4CH_2OH$$

$$3RNC_6H_4CH_2OH \xrightarrow{-H_2O} (RNC_6H_4CH_2—)_3 + 3H_2O.$$

This course for the reaction was excluded by the demonstration (47) that N-alkylamines, when condensed with formaldehyde in acid solution with concurrent reduction, gave good yields (54–87 %) of N,N-methylalkylamines, showing the primary attack of formaldehyde to be on nitrogen. When solid salts of the anhydroalkylarylamines were allowed to separate and were then reduced the products were the corresponding N-alkyl-*p*-toluidines (53–79 %). It is clear therefore that the trimeric anhydroalkylaminobenzyl alcohols are formed by a sequence essentially identical with reaction D, nuclear coupling of the ion $[(H)C_6H_4NR^{\bullet}CH_2]^+$ being secondary:

$$ArNHR \xrightarrow[H^+]{CH_2O} \left[\begin{matrix} ArNR \cdot CH_2 \\ ArNR{=}CH_2 \end{matrix}\right]^+ \xrightarrow{\textit{para}\text{-coupling}} \left[C_6H_4NRCH_2C_6H_4NRCH_2C_6H_4NRCH_2\right] \quad \text{(VIa)}$$

$$\left[\begin{matrix} ArNR \cdot CH_2 \\ ArNR{=}CH_2 \end{matrix}\right]^+ \xrightarrow{[H]} ArNRCH_3 \qquad \text{(VIa)} \xrightarrow{[H]} 3CH_3C_6H_4NHR$$

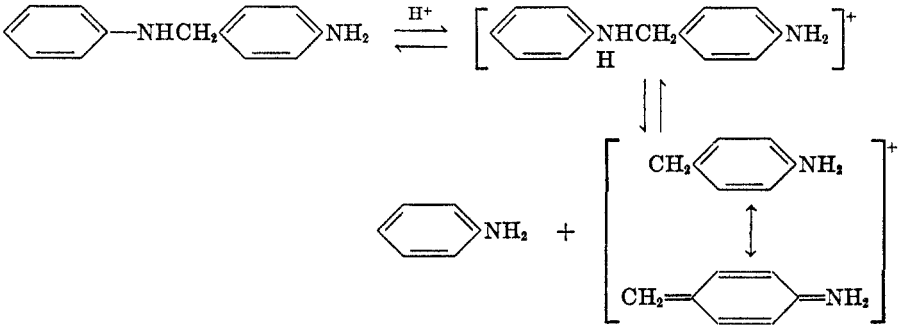
Reduction of VIa severs the N—CH_2 bonds as shown, yielding N-alkyl-*p*-toluidines.

The fact that VIa is of the same structural type as VI and VIb should not be overlooked, as it is obscured by (a) the apparently different ways in which VIa, VI, and VIb are made, (b) the dissimilar names anhydroalkylaminobenzyl alcohols and aminobenzylamines, and (c) the trimeric character of VIa, both VI and VIb being monomeric. The characteristic grouping in all three is $ArNCH_2Ar$; they are all substituted aminobenzylamines.

Reaction F, with reaction D, represents the probable course of reaction D′.

Colorations in acid solutions in which arylamines and formaldehyde react. Reaction mixtures containing aromatic amines and formaldehyde (or their pre-

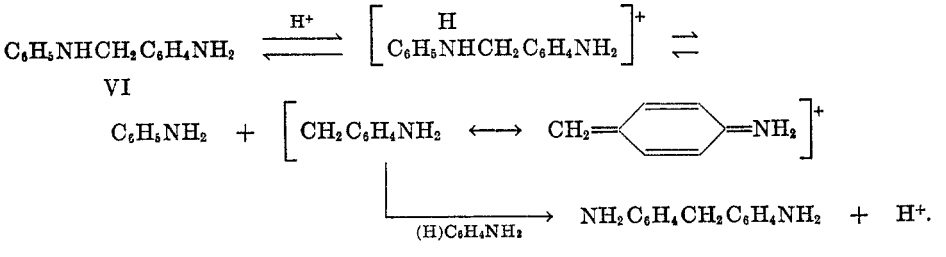
formed condensation products) in presence of acid have generally a pronounced red color, which is bleached when the mixtures are made alkaline. The cause of this coloration has not been ascertained experimentally. A simple surmise, involving only acid and VI, is that action of acid on compounds of type VI yields benzenoid-quinonoid ions:



Similar final results could follow the operation of oxygen or a hydrogen acceptor (*cf.* reaction J) upon compounds of type VI or VII.

Reactions E, E′, and *E″; Conversion of aminobenzylarylamines VI, VIa, VIb to diaminodiphenylmethanes VII and VIIa.* This transformation occurs in presence of acid and is not reversible, the diaminodiphenylmethanes being terminal products. Reactions E and E′ (conversion of VI and VIa to VII) occur readily when III, IV, VI, or VIa is the starting material, and VII is readily obtained in one operation on heating I or Ia and formaldehyde in presence of amine salt or even of free acid in aqueous solution (50–52).

Reactions E, E′, and E″ are not rearrangements for, if reaction occurs in presence of an amine other than that represented by VI, mixed diphenylmethane bases result (53). They are believed to be essentially repetitions of reactions D, D′, and D″, *i.e.*, to involve formation of carbonium ions and coupling of these at active nuclear positions (of amines) with expulsion of proton:



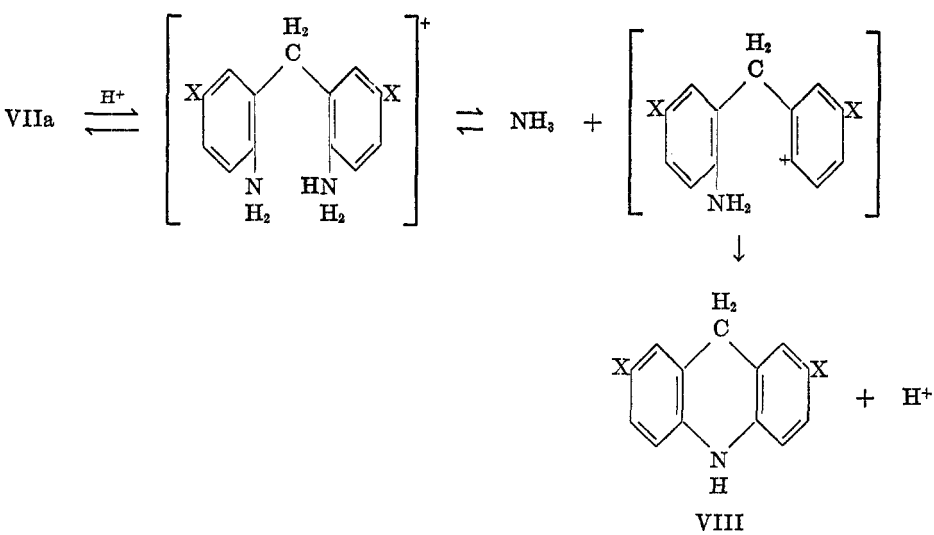
It appears that *para*-hydrogen is more readily displaced in this way than is *ortho*-hydrogen, for conversion of VIb to VIIa is slow and incomplete. When both *ortho*- and *para*-hydrogen are available, *para*-coupling predominates. King (54)

found that *p,p'*-diaminodiphenylmethane (from aniline) contains about 10% of *o,p'*-diaminodiphenylmethane, and it may be that *ortho*-couplings in other cases have been overlooked.

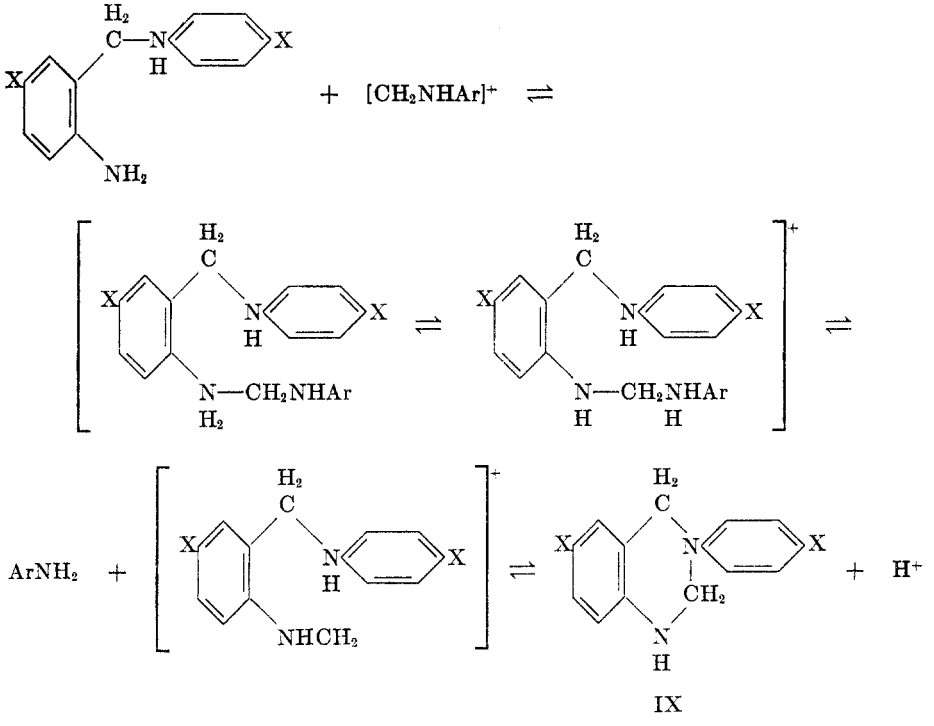
Reaction E′ occurs when anhydroalkylaminobenzyl alcohols (VIa) react with amine salts (55, 56), and is believed to involve formation of ion $[CH_2C_6H_4NHR]^+$, which by nuclear coupling yields $RNHC_6H_4CH_2C_6H_4NHR$.

Reaction E″. Diaminodiphenylmethanes of type VIIa (*o,o'*-) are obtainable with some difficulty, probably because the required second *ortho*-coupling is slow, allowing VIb to become involved in the sequence starting with reaction H. Preparation of base VIIa (X = CH_3) from *p*-toluidine, *p*-toluidine hydrochloride and IV (Ar = *p*-tolyl) (21) was found (52) to give trivial yields (to 16% crude). By use of *p*-toluidine and formalin in aqueous hydrochloric acid there were obtained X, XII and, in one experiment, a trace of VIIa. This diphenylmethane base was obtained in 48% yield, together with much tarry material, by heating VIb (X = CH_3) with twice its weight (each) of *p*-toluidine and *p*-toluidine hydrochloride (9 to 14 hours at 120–130°). That good conditions for its formation are as yet not determined is shown by the foregoing and by the fact that Simons (38), by heating together IX (X = CH_3) and *p*-toluidine hydrochloride in ethanol, obtained small amounts of VIIa, X and methyl-*p*-toluidine (the last a by-product of the formation of X, as explained below).

Reaction G. Conversion of 2,2'-diaminodiphenylmethane to dihydroacridine (VIII). This transformation requires heating VIIa with *p*-toluidine and *p*-toluidine hydrochloride at 200–220° (57). The elimination of ammonia from an activated position may be considered equivalent to elimination of amine from ion $[IVH]^+$, yielding *in situ* a carbonium ion which couples internally with nitrogen (the NH_2 group containing the most reactive hydrogens available) to close the ring:



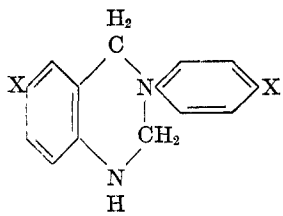
Reaction H. Conversion of o-aminobenzylamine VIb to tetrahydroquinazoline IX. This ring closure occurs readily when VIb is treated with formaldehyde, or with IV or III in presence of acid (30); this condensation may not be exclusively acid-induced, but in one case the normal yield of 88% of IX was decreased to 25% in the presence of sodium ethoxide[13]. Conversion of VIb to IX by ion $[V]^+$ may be represented as follows:



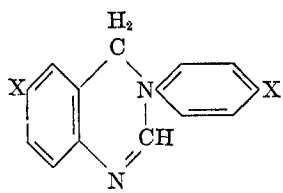
Reaction J. Conversion of tetrahydroquinazoline IX to dihydroquinazoline X. This is a hydrogenation-dehydrogenation reaction (similar to that involved in the Doebner-Miller quinaldine synthesis), the elucidation of which (38, 58) provided an explanation for the presence of methylated amines among the products formed when formaldehyde and *p*-substituted amines react in presence of acid (59, 41, 60), and for the formation of methylamines from formaldehyde and ammonium chloride (61, 62). The over-all reaction is recognizable as a nitrogen-

[13] Analogous ring-closure of anthranilamides, by either formaldehyde or IV, to yield corresponding 4-keto-tetrahydroquinazolines (30), with conversion of —NH to —NCH_2OH, is promoted by the presence of alkali. This ring-closure requires removal of amide-hydrogen, and is actually the alkylation of an amide, a reaction normally promoted by the presence of alkali. It may be presumed that the acidic character of the amide suffices to produce from IV traces of ion $[V]^+$, the situation thus resembling that encountered in the Mannich reaction (4).

system crossed and unidirectional Cannizzaro reaction, with only IX eligible to serve as hydrogen-donor:[14]



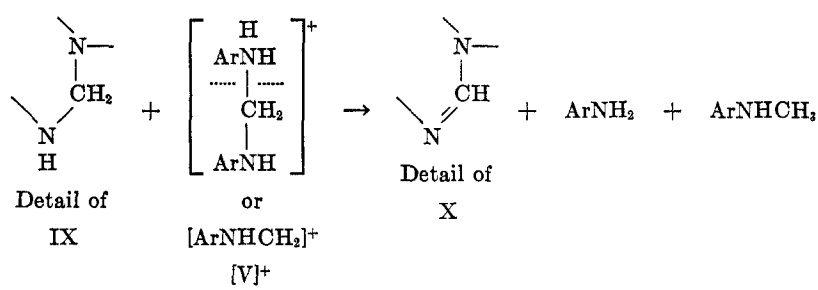
IX + $XC_6H_4NHCH_2NHC_6H_4X$ (IV) $\xrightarrow[\text{Transfer of 2 H}]{H^+}$



X + $XC_6H_4NH_2$ (I) + $XC_6H_4NHCH_3$ (Ia).

The reactants are both of aldehydic type; of the products X, a cyclic amidine, is of acidic type (63), and the amine and methylated amine are nitrogen-system alcohols. The "oxidation" of IX to X was found (58) to be effected also by other hydrogen-acceptors of aldehydic type, *viz.*, III, IV, formamide, formanilide, N,N′-diphenyl-formamidine, or formic acid. The similar but not aldehydic compounds acetamide, acetanilide, and N,N′-diphenylacetamidine failed to convert IX to X.

It is believed that reaction J, when effected under the usual mild conditions that suffice in presence of acid (as amine salt or ammonium chloride) involves operation of ion $[IVH]^+$ or $[V]^+$.[15]



Detail of IX + $[ArNHCH_2]^+$ or $[V]^+$ → Detail of X + $ArNH_2$ + $ArNHCH_3$

Dihydroquinazolines (X), together with other products, are readily obtained in one operation from *p*-substituted amines by condensation with formaldehyde

[14] The reverse would involve opening of the quinazoline ring, for which conditions are not sufficiently severe.

[15] In absence of acid methylene-bis-piperidine did not "oxidize" IX at 65°, but partial oxidation (32%) occurred at 195°. This reaction, like some others normally acid-induced, can be forced in absence of acid by higher temperatures.

in acid solution (59, 41), and under these conditions the products include dimethylated amines, formed *via* ArN—CH_2—NAr.

CH_3 CH_3

Oxidation of IX to X can be effected chemically by potassium permanganate or other oxidants, and X can be reduced to IX by sodium and alcohol or other agents. The direct conversion of VIb to X by a conventional ring-closure is achieved by heating VIb with formic acid or ethyl orthoformate (42). Consideration of the several requirements for formation of X led to a simplified preparative method using as reactants amine, or IV, or trimeric III, with formaldehyde and formic acid (29).

Reaction K. Formation of Troeger's base (XII). This compound, containing the diazocine heterocycle, is formed, perhaps more or less incidentally, under the apparently hit-or-miss conditions that are known to yield it, together with compound X and other products, from *p*-toluidine and formaldehyde in the presence of acid (64–67). The structure[16] was established by Spielman (68), who found that cleavage by hydriodic acid and red phosphorus at 200° yields only 4-amino-1,3-xylene, and that action of formaldehyde on IX effects a simple and direct synthesis of XII.

The steps leading to Troeger's base were shown (69) to comprise in sequence reactions D″, H, and K; the base was obtained by the action of formaldehyde (in ethanol containing hydrochloric acid) on I, III, IV, VIb, or IX. Similar synthesis of several analogs (X = OCH_3 or OC_2H_5) of Troeger's base (70) revealed as probable the penultimate formation of the hydroxymethyl derivative of IX, *viz.*, compound XI which, when X = Cl or Br, resisted ring closure and was obtained as terminal product. The course of the final ring closure thus suggested

involves acceptance of proton by —NCH_2OH to yield an ion of type V, followed by internal coupling with the side-ring to yield Troeger's base; a similar mechanism for ring closure of IX to XII by formaldehyde would appear to be necessary even if compounds of type XI were unknown.

Troeger's base possesses special interest for several reasons: (a) It is the endomethylene derivative of the unknown dimeric anhydro-*o*-aminobenzyl-*p*-toluidine (a compound of type VIa). (b) The endomethylene bridge is displaced by action of acetic anhydride or nitrous acid ($CH_2 \rightarrow CH_2O$ or CO). (c) The ring structure, with multiple CH_2—N linkages, is simultaneously of types VIa and IV, owing its relative stability to cyclization, and recalls the structure of uro-

[16] The structure of Troeger's base was for many years elusive, owing to certain misleading evidence: (a) faulty early analyses, leading to uncertainties in calculation of the empirical formula; (b) failure of attempted cleavage by reduction using tin and hydrochloric acid or zinc dust and sulfuric acid (66, 41), which agents often cleave external C—N bonds; as a consequence a stable diphenylmethane structure was assumed (41); (c) formation of a diacetyl derivative and a dinitrosamine led to representation of the compound as a disecondary amine, which view was corrected when Spielman (68) showed that acetylation or nitrosation of Troeger's base is accompanied by expulsion of the methylene bridge as respectively, formaldehyde or carbon dioxide.

tropin and of the bimolecular bases obtained from 1,2-diamines by the action of formaldehyde in the presence of acid (71, 72). (d) It is unique among trivalent nitrogen compounds in having been resolved (chromatographically, by use of lactose) into optically active isomerides (73).[17]

Reactions L and M represent decompositions of methylene-bis-amines jointly by acid and alcohol to yield substituted aminoethers (XIII) and acetals (XIV). Since reactions leading to compounds of types VI, VII, IX, X, and XII may occur in the presence of alcohol, it had been inferred that no reaction between IV and alcohol occurs. During study of the actions of acids on IV it was found (26) that, when the lettered reactions below L (reaction scheme) are excluded or repressed, some compounds of type IV are rapidly and completely cleaved by acid in presence of alcohol (methanol, ethanol, butanol), even by one equivalent of the alcohol in a large volume of an inert solvent, yielding the corresponding amine salts. The fate of the methylene group in these reactions was revealed later by Browne (34), who isolated acetals (XIV) as products when gaseous acids were used, and the intermediate aminoethers (XIII) when the acid was introduced as pyridine hydrochloride; these products are formed by reactions L, M, and L, respectively.[18] Compounds of type XIII are aquo-ammono-hemiacetals; the examples isolated are compounds of moderate stability. The formations of XIII and XIV are consistent with the aldehydic character of IV, and both changes are explicable by application of the ionic hypothesis:

Reaction L

$$\underset{\text{IV}}{\mathrm{ArNHCH_2NHAr}} \overset{\mathrm{H^+}}{\rightleftharpoons} \begin{cases} [\mathrm{ArNHCH_2}]^+ \\ + \ \mathrm{ArNH_2} \end{cases} \overset{\mathrm{ROH}}{\rightleftharpoons} \underset{\text{XIII}}{\mathrm{ArNHCH_2OR}} + \mathrm{H^+}$$

Reaction M

$$\underset{\text{XIII}}{\mathrm{ArNHCH_2OR}} \overset{\mathrm{H^+}}{\rightleftharpoons} [\mathrm{ArNH_2CH_2OR}]^+ \rightleftharpoons \mathrm{ArNH_2} + [\mathrm{CH_2OR}]^+ \overset{\mathrm{ROH}}{\rightleftharpoons} \underset{\text{XIV}}{\mathrm{ROCH_2OR}} + \mathrm{H^+}$$

Acetals were obtained similarly (34) from Schiff bases, *viz.*, benzalaniline (monomeric), trimeric methylene-isopropylamine and trimeric methylene-*n*-butylamine.

Reaction N, the total cleavage of IV by anhydrous acid to form methylene halide (XVII), is the reverse of a conventional method for preparation of compounds of type IV (24). This preparative method is of doubtful value when the amine represented is aromatic, owing to involvment of the methylene group in

[17] Earlier attempts to resolve Troeger's base by the use of optically active acids (92) failed owing to instability of the salts.

[18] Böhme and Kreutzkamp (31b) obtained evidence for the presence of N-ethoxymethyl piperidine hydrobromide among the products of the interaction of N-methyl-bis-piperidinomethane hydrobromide and ethanol.

nuclear coupling reactions (21) induced by the by-product acid,[19] but it succeeds when the amine represented is non-aromatic, *e.g.*, piperidine (27). Attempts to cleave several methylene-bis-arylamines by action of anhydrous hydrogen chloride or hydrogen bromide, with recovery of the methylene halide, were unsuccessful (34). Methylene-bis-piperidine was converted to resinous products by action of hydrogen bromide under pressure, but yielded no isolable methylene bromide. This study was discontinued because reaction N bears no relationship to the useful transformations shown in the reaction diagram, being a merely retrogressive step.

Reaction P, designated in the reaction diagram as of the Mannich type, has the general form:

$$HZ + \text{II, III, IV } via\ [V]^+ \xrightarrow[(S)]{} \underset{(XV)}{ZCH_2NHR} \xrightarrow[(S')]{HZ} \underset{(XVa)}{ZCH_2Z} + RNH_2,$$

in which HZ is a compound with H (attached to carbon) sufficiently active, and in which step S is the Mannich reaction and step S′ is either optional or inevitable. It can be seen that, in the reaction diagram, reactions D, D′, and D″ may be considered to be of type S and that reactions E, E′, and E″ may be considered to be of type S′, with the active hydrogen involved being that *para* or *ortho* to nitrogen on an aromatic ring. Experimentally realized extensions of reaction P to other compounds of type HZ (4, 30), the isolable products being those indicated, include condensations of III, IV, or formaldehyde with α-naphthol, β-naphthol (XV and XVa), phthalimide (XV and XVa), carbazole (XV and XVa), antipyrine (XV), dibenzoylmethane (XVa), dimethone (XVa), sodium acid sulfite (XV), and hydrogen cyanide (XV), all of which are sufficiently acidic to react without added acid; also dimethylaniline (XV and XVa), which reacts only in presence of added acid. The products from sodium acid sulfite and hydrogen cyanide are the aldehyde bisulfites and their nitrogen-system counterparts the aminonitriles.

In a study of the Mannich reaction (4), using III obtained from dibenzylamine morpholine, and piperidine, the varied effects of acid in promoting or repressing the reactions led to the conclusion that the Mannich reaction involves a dual catalysis in an amphoteric system, in which conditions must be such as to permit simultaneous presence of $[Z]^-$ and $[V]^+$ as the reacting entities. The basic properties of the amine present, and the acidic properties of compound HZ, jointly determine the optimum conditions (which may change as reaction progresses) with respect to the need for added acid or base, in order to maintain a useful rate for the essential action $HZ + [CH_2NR]^+ \rightarrow ZCH_2NR + H^+$.

Compounds formulated $RNHCH_2SO_3Na$ or $R_2NCH_2SO_3Na$, *viz.*, N-substituted aminomethane sulfonates, result (74) when I or Ia and formaldehyde react

[19] Methylene chloride and two equivalents of *p*-toluidine, claimed by Grünhagen (25) to yield the hydrochloride of methylene-bis-*p*-toluidine, were found (26) to yield instead only 6-methyl-3-*p*-tolyl-3,4-dihydroquinazoline (X).

in presence of sodium bisulfite, or when preformed IV or III (which may be trimeric) is treated with sodium bisulfite (75–78). They are the nitrogen-system counterparts of formaldehyde sodium bisulfite, which is known to be a sulfonate (79), as is acetaldehyde sodium bisulfite (80). The formulas assigned are somewhat misleading, for aldehyde (ketone) bisulfites on treatment with excess acid may be decomposed with disengagement of sulfur dioxide, though Knoevenagel (78) reported certain N,N-disubstituted aminomethane sulfonates to yield with equivalent acid the corresponding aminomethane sulfonic acids $R_2NCH_2SO_3H$, represented as dipolar ions $R_2\overset{+}{N}HHSO_3^-$. It is known (1) that aldehyde bisulfites are formed reversibly, and that in solution they undergo successive ionic divisions:

$$RCH(OH)SO_3Na \rightleftharpoons Na^+ + [RCH(OH)SO_3]^- \rightleftharpoons \underset{\downarrow\uparrow}{RCH(OH)}]^+ + {}^-SO_3$$
$$RCHO + H^+.$$

The first dissociation accounts for the salting-out of water-soluble bisulfite compounds by excess sodium bisulfite. As a result of the second dissociation the bisulfite compounds are decomposed by acids, alkalies, and oxidizing agents (e.g., iodine), all of which attack the free sulfite (ion) and not the addition compound, for in each case the over-all rate is determined by the rate of the second dissociation.

Similar relationships were established (1) for N,N-disubstituted aminomethane sulfonates of the type $R_2NCH_2SO_3Na$, which also are attacked by oxidizing agents (iodine, bromine, hydrogen peroxide) at rates determined by the rates of the second dissociation:

$$R_2NCH_2SO_3Na \rightleftharpoons Na^+ + [R_2NCH_2SO_3]^- \rightleftharpoons [R_2NCH_2]^+ + {}^-SO_3.$$

It may be concluded that in aldehyde (ketone) bisulfites and in N-substituted aminoalkane sulfonates the C—S bonds have a quasielectrovalent character:

$$[HOCH_2SO_3]^-Na^+ \rightleftharpoons {}^-SO_3 + [HOCH_2 \leftrightarrow HO{=}CH_2]^+ \rightleftharpoons CH_2O + H^+$$
$$[RNHCH_2SO_3]^-Na^+ \rightleftharpoons {}^-SO_3 + [RNHCH_2 \leftrightarrow RNH{=}CH_2]^+ \rightleftharpoons RN{=}CH_2 + H^+.$$

It will be noted that $[RNHCH_2]^+$ or $[R_2NCH_2]^+$ is ion $[V]^+$, the existence of which has thus been inferred from the results of several divergent experimental approaches.

The nitrogen-system counterparts of the aldehyde (ketone) cyanohydrins are the α-aminonitriles, of which those of types $RNHCH_2CN$ or R_2NCH_2CN may be formed from I or Ia by action of cyanide and formaldehyde, or from $RNCH_2SO_3Na$ by action of cyanide, or from IV or III and hydrogen cyanide. In both series the union C—CN is firmer than the union C—S in corresponding bisulfite compounds, for action of aqueous acid does not cleave them, but yields the corresponding carboxylic acids, *viz.*, α-aminoacids. Stewart and Li (81) represent as irreversible the reaction $R_2NCOH + HCN \rightarrow R_2NCCN + H_2O$, though

formation of cyanohydrin is reversible. These results suggest that $RNHCH_2CN$ and R_2NCH_2CN may yield ion $[V]^+$ sparingly if at all.

Reaction Q (reaction diagram) is an over-all representation of the Wallach alkylation of amines by the use of carbonyl compounds and formic acid (82). When the carbonyl compound is other than formaldehyde (*e.g.*, benzaldehyde, cyclohexanone) the reduction is caused solely by formic acid[20] (3). The alkylation involves primary condensation of amine and carbonyl compound to form II, III, or IV, which in presence of formic acid is thought to be present as the formate of ion $[V]^+$, which by transfer of hydrogen yields alkylated amine and carbon dioxide:

$$[RNHCH_2]^+O\underset{H}{C}{=}O^- \rightarrow RNHCH_3 + CO_2.$$

The role of formic acid is multiple: (a) as an acid it accelerates the reaction;[21] (b) as an aldehyde it serves as the reducing agent in what is apparently a unidirectional quasi-Cannizzaro reaction involving two aldehydic ions; (c) it may assist the reaction as a solvent that prevents stratification. It was found that excess formic acid may impede alkylation by impeding the primary condensation of carbonyl compound and amine. Treatment of preformed IV (benzylidene-bispiperidine) with formic acid led to spontaneous reaction at room temperature and after heating the mixture alkylation reached 100% (3). As this occurred in presence of an amount of formic acid independently shown to retard alkylation when the reactants were benzaldehyde, piperidine, and formic acid, the inference is clear that excess formic acid impedes the primary condensation but not the subsequent reduction. This result establishes the eligibility of IV to function as intermediate and the fact that formic acid is capable of hydrogenating it. That the Wallach alkylation does not necessarily proceed *via* IV was shown in a study of the extension of the method to aromatic amines (83). It was found that certain aromatic amines can be methylated by interaction of formaldehyde, amine, and formic acid, but not by action of formic acid on preformed III or IV; no carbon dioxide was disengaged and no methylation was detected. By a modification of the Wallach procedure, by which previously only mesidine and tribromoaniline had been methylated successfully (other arylamines yielding tars, owing to reactions involving nuclear couplings) there were methylated 17 aromatic amines in yields of 23% to 98%. The course of the Wallach alkylation may therefore involve II, III, or IV, and may be represented:

$$\text{I or Ia} + CH_2O \rightarrow \left\{\begin{matrix}\text{II}\\ \text{III}\\ \text{IV}\end{matrix}\right\} \xrightarrow{HCOOH} [ArNHCH_2]^+O\underset{H}{C}{=}O^- \rightarrow ArNHCH_3 + CO_2.$$

[20] As in the Werner or Eschweiler methods for methylating amines (see discussion of reaction J), formaldehyde serves as a reducing agent (93).

[21] The analogous Leuckart reaction, in which ordinarily free formic acid is not used, was shown to be assisted by presence of the acid (94).

It is considered advisable at present not to exclude a non-ionic path by which II, III, or IV (all aldehydic) may be reduced by formic acid functioning as an aldehyde capable of serving only as hydrogen-donor (3).

SUMMARY

An ionic hypothesis is applied to several series of sequentially related acid-catalyzed reactions of primary and secondary amines (especially aromatic) and formaldehyde, and of their several condensation products the hydroxymethyl-amines, the methylene amines (Schiff bases), and the methylene-*bis*-amines. It is suggested that these apparently diverse sequences of interrelated reactions can be rationalized as consequences of a single essential change initiated by a proton. The steps involved are (a) formation of salts of one or more of the intermediates named, which salts though often fugitive in character provide the cationoid entities $[RNHCH_2 \leftrightarrow RNH{=}CH_2]^+$ or $[R_2NCH_2 \leftrightarrow R_2N{=}CH_2]^+$; (b) the union of the ionic fragment with a reactant by displacement of hydrogen as proton. By means of this conception and some logical extension there are unified and rationalized reactions of formaldehyde and aromatic amines leading to the formation of aminobenzylarylamines, diaminodiphenylmethanes, certain acridines, substituted tetrahydro- and dihydro-quinazolines, Troeger's base and its analogs, aminoethers, acetals, Mannich products, and a number of compounds resulting from the ability of the primary condensation products to show a functionally aldehydic character.

PHILADELPHIA 4, PENNA.

LITERATURE CITED

(1) STEWART AND BRADLEY, *J. Am. Chem. Soc.*, **54**, 4172, 4182 (1932).
(2) PORAI-KOSHITS, *J. Gen. Chem. (Russia)*, **17**, 1774 (1947).
(3) STAPLE AND WAGNER, *J. Org. Chem.*, **14**, 559 (1949).
(4) LIEBERMAN AND WAGNER, *J. Org. Chem.*, **14**, 1001 (1949); *cf.* HELLMANN, HELLMAN, AND LINGENS, *Chem. Ber.*, **86**, 1346 (1953).
(5) HENRY, *Bull. acad. roy. Belg.*, [3] **26**, 206 (1893); **28**, 359 (1895); **29**, 26 (1895).
(6) DIMROTH AND ZOEPPRITZ, *Ber.*, **35**, 984 (1902).
(7) KONDO AND ISHITA, *J. Pharm. Soc. Japan*, # 489, 979 (1922).
(8) EIBNER, *Ann.*, **302**, 334 (1898).
(9) RÜGHEIMER, *Ber.*, **39**, 1653 (1906).
(10) WHEELER AND JORDAN, *J. Am. Chem. Soc.*, **31**, 937 (1909).
(11) LOWY AND BALZ, *J. Am. Chem. Soc.*, **43**, 341 (1921).
(12) WAGNER, *J. Am. Chem. Soc.*, **54**, 660 (1932).
(13) (a) MILLER AND WAGNER, *J. Am. Chem. Soc.*, **54**, 3698 (1932); (b) FLORENTINE AND MILLER, J. G., Ph.D. Thesis, University of Pennsylvania, 1953.
(14) FREY, *Helv. Chim. Acta*, **18**, 491 (1935).
(15) U. S. Patent 2,582,128 (Jan. 8, 1952); *Chem. Abstr.*, **46**, 8146 (1952).
(16) ANGYAL, PENMAN AND WARWICK, Privately communicated, 1953.
(17) INGOLD AND PIGGOTT, *J. Chem. Soc.*, **123**, 2745 (1923).
(18) HARTOUGH, MEISEL, KOFT, AND SCHICK, *J. Am. Chem. Soc.*, **70**, 4013 (1948).
(19) German Patent 92,084; *Frdl.*, **4**, 131.
(20) STEELE, WM., unpublished results, U. of Pa., 1950.
(21) EBERHARDT AND WELTER, *Ber.*, **27**, 1804 (1894).
(22) BISCHOFF AND REINFELD, *Ber.*, **36**, 41 (1903).

(23) FREEMAN, J. H., unpublished results, U. of Pa., 1950.
(24) LERMONTOFF, *Ber.*, **7**, 1255 (1874).
(25) GRÜNHAGEN, *Ann.*, **256**, 286 (1889).
(26) HUNT AND WAGNER, *J. Org. Chem.*, **16**, 1792 (1951).
(27) SCHMIDT AND KOHLER, *Arch. Pharm.*, **240**, 232 (1902).
(28) Reference 13a, page 3705.
(28a) CRAIG, *J. Am. Chem. Soc.*, **55**, 3723 (1933).
(29) WAGNER, *J. Org. Chem.*, **2**, 157 (1937).
(30) FELDMAN AND WAGNER, *J. Org. Chem.*, **7**, 31 (1942).
(31) (a) BODENDORF AND KORALEWSKI, *Arch. Pharm.*, **271**, 101 (1933); (b) BÖHME AND KREUTZKAMP, *Marburg Sitzungsber.*, **76**, 1–37 (1953).
(32) TANASESCU AND SILBERG, *Bull. soc. chim.*, [5], **3**, 224 (1936).
(33) HANTZSCH AND SCHWAB, *Ber.*, **34**, 822 (1901).
(34) BROWNE, Ph.D. Thesis, U. of Pa., 1953.
(35) Reference 29, page 163.
(36) EIBNER, *Ann.*, **302**, 349 (1898); or Reference 8, page 349.
(37) DRAZDOV, *J. Gen. Chem.* (*U.S.S.R.*), **1**, 1171 (1931).
(38) SIMONS, *J. Am. Chem. Soc.*, **59**, 518 (1937).
(39) German Patents 87,934 (*Frdl.*, **4**, 66); 104,230 (*Frdl.*, **5**, 83); 105,797 (*Frdl.*, **5**, 84); 108,064 (*Frdl.*, **5**, 85).
(40) MILLER AND WAGNER, *J. Am. Chem. Soc.*, **60**, 1738 (1938).
(41) EISNER AND WAGNER, *J. Am. Chem. Soc.*, **56**, 1938 (1934).
(42) VON WALTHER AND BAMBERG, *J. prakt. Chem.*, [2], **73**, 209 (1906).
(43) German Patents 96,851; 97,710; *Frdl.*, **5**, 91.
(44) GREEN AND SAUNDERS, *J. Soc. Dyers Colourists*, **29**, 10 (1923).
(45) GOLDSCHMIDT, *Chem. Ztg.*, **24**, 284 (1900); **26**, 606, 967 (1902).
(46) FRIEDLÄNDER, *Monatsh.*, **23**, 973 (1902).
(47) WAGNER, *J. Am. Chem. Soc.*, **55**, 724 (1933).
(48) YOUNG AND WAGNER, *J. Am. Chem. Soc.*, **59**, 854 (1937).
(49) FRIEDLÄNDER AND DINESMANN, *Monatsh.*, **19**, 672 (1898).
(50) VON BRAUN, *Ber.*, **41**, 2145 (1908).
(51) RIVIER AND FARINE, *Helv. Chim. Acta*, **12**, 865 (1929).
(52) WAGNER, *J. Am. Chem. Soc.*, **56**, 1944 (1934).
(53) COHN AND FISCHER, *Ber.*, **33**, 2586 (1900).
(54) KING, *J. Chem. Soc.*, **117**, 988 (1920).
(55) German Patent 96,762; *Frdl.*, **5**, 77.
(56) VON BRAUN AND KRUBER, *Ber.*, **45**, 2977 (1912).
(57) ULLMANN, *Ber.*, **36**, 1018 (1903).
(58) MCLAUGHLIN AND WAGNER, *J. Am. Chem. Soc.*, **66**, 251 (1944).
(59) MAFFEI, *Gazz. chim. ital.*, **58**, 261 (1928).
(60) WAGNER AND EISNER, *J. Am. Chem. Soc.*, **59**, 879 (1937).
(61) WERNER, *J. Chem. Soc.*, **111**, 850 (1917).
(62) *Org. Syntheses*, Coll. Vol. I, 2nd. Ed., 347, 528 (1941).
(63) WAGNER, *J. Org. Chem.*, **5**, 133 (1940).
(64) TROEGER, *J. prakt. Chem.*, [2] **36**, 227 (1887).
(65) LÖB, *Z. Elecktrochem.*, **4**, 428 (1897).
(66) GOECKE, *Z. Elecktrochem.*, **9**, 470 (1903).
(67) German Patent 122,474; *Frdl.*, **6**, 82.
(68) SPIELMAN, *J. Am. Chem. Soc.*, **57**, 583 (1935).
(69) WAGNER, *J. Am. Chem. Soc.*, **57**, 1296 (1935).
(70) MILLER AND WAGNER, *J. Am. Chem. Soc.*, **63**, 832 (1941).
(71) FISCHER AND WREZINSKI, *Ber.*, **25**, 2711 (1892).
(72) BISCHOFF, *Ber.*, **32**, 245 (1898).
(73) PRELOG AND WIELAND, *Helv. Chim. Acta*, **27**, 1127 (1944).

(74) (a) KNOEVENAGEL, *Ber.*, **37**, 4075 (1904). (b) REINKING, DEHNEL, AND LABHARDT, *Ber.*, **38**, 1077 1905).
(75) MILLER AND PLÖCHL, *Ber.*, **25**, 2020 (1892).
(76) EIBNER, *Ann.*, **316**, 89 (1901).
(77) LEPETIT, *Gazz. chim. ital.*, **47**, 197 (1913); *Atti. accad. Lincei*, **26**, 126 (1917).
(78) Reference 74a; p. 4073.
(79) LAUER AND LANGKAMMERER, *J. Am. Chem. Soc.*, **57**, 2360 (1935); RASCHIG, *et al.*, *Ber.*, **59**, 859, 2025 (1926); **61**, 179 (1928); BALZEN, *Ber.*, **60**, 1470 (1927).
(80) SHRINER AND LAND, *J. Org. Chem.*, **6**, 889 (1941).
(81) STEWART AND LI, *J. Am. Chem. Soc.*, **60**, 2782 (1938).
(82) WALLACH, *Ann.*, **343**, 54 (1905).
(83) BORKOWSKI AND WAGNER, *J. Org. Chem.*, **17**, 1128 (1952).
(84) MORGAN, *J. Soc. Chem. Ind.* (*London*), **49**, 245–251 (1930).
(85) SPRUNG, *Chem. Revs.*, **26**, 297–338 (1940).
(86) CHANCEL, *Bull. soc. chim.* (3), **11**, 933 (1894).
(87) HENRY, *Compt. rend.*, **120**, 839 (1895).
(88) VON MILLER PLÖCHL, AND ECKSTEIN, *Ber.*, **25**, 2029 (1892); VON MILLER AND PLÖCHL, *Ber.*, **27**, 1292 (1894).
(89) EIBNER, *Ber.*, **27**, 1281 (1894); *Ann.*, **318**, 58 (1901); **328**, 121 (1903).
(90) MILLER, C. S., unpublished results, U. of Pa., 1937.
(91) WAGNER, unpublished results, U. of Pa., 1936.
(92) SIMONS, unpublished results, U. of Pa., 1935.
(93) CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(94) INGERSOLL, BROWN, KIM, BEAUCHAMP, AND JENNINGS, *J. Am. Chem. Soc.*, **58**, 1808 (1936); CROSSLEY AND MOORE, *J. Org. Chem.*, **9**, 529 (1944).
(95) NORTON, HAURY, DAVIS, MITCHELL, AND BALLARD, *J. Org. Chem.*, **19**, 1054 (1954).