[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# Hydrogenation–Dehydrogenation Reactions Involving Some Compounds of Ammono-aldehyde, Ammono-acetal and Aquo-ammono-aldehyde Types

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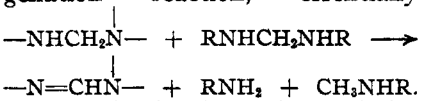
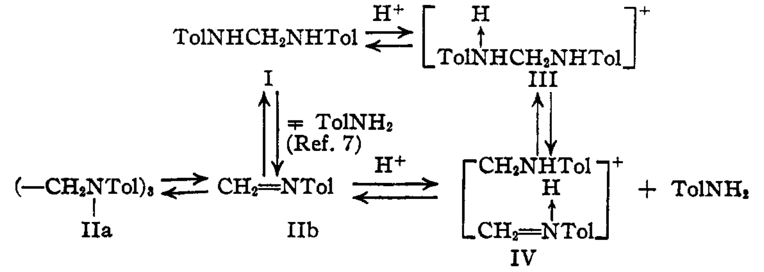
In an earlier paper from this Laboratory Simons[3] showed that the incidental formation of methyl-*p*-toluidine which accompanies conversion of methylene-bis-*p*-toluidine (I) to 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline (VII) by warming with amine salt results by a complementary hydrogenation–dehydrogenation reaction, essentially



$$\text{—NHCH}_2\underset{|}{\text{N}}\text{— + RNHCH}_2\text{NHR} \longrightarrow \text{—N=CH}\overset{|}{\text{N}}\text{— + RNH}_2\text{ + CH}_3\text{NHR.}$$

Methylation has been observed also during interaction of *p*-substituted amines with formaldehyde in aqueous acid solution[4,5] to form dihydroquinazolines and other products, but the propriety of extending Simons' explanation to such cases is doubtful, as are explanations suggested by Maffei[4] and by Eisner and Wagner.[5] The formal resemblance of Simons' reaction to a crossed Cannizzaro reaction is obvious, and recalls some other hydrogenation–dehydrogenation reactions involving compounds of ammonoaldehyde type.[6]

This paper presents the results of a further study of the oxidation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline (VI) to the corresponding dihydroquinazoline (VII) by substances of aldehyde or acetal type in presence of acid, and an interpretation and rationalization of the findings. Though the reaction (at lower temperatures) requires presence of acid the environment is prevailingly basic, and the function of the acid is believed to be the cleavage of the methylene-bis-amines (compounds which can be regarded as ammono-aldehyde "hydrates" or ammono-acetals) to aldehydic structures, *i. e.*, to induce a reaction which is preliminary to the pseudo-Cannizzaro reaction which follows. It has been found that trimeric methylene-*p*-toluidine can function as hydrogen acceptor; in this case the acid may operate in a similar manner to open the triazine ring. These preliminary steps are shown in the scheme.



$$\begin{tikzcd}
 & \underset{\text{I}}{\text{TolNHCH}_2\text{NHTol}} \arrow[r, shift left, "\text{H}^+"] \arrow[d, shift left, "\mp\ \text{TolNH}_2\ (\text{Ref. }7)"] & \underset{\text{III}}{\left[\text{Tol}\overset{\text{H}}{\overset{\uparrow}{\text{N}}}\text{HCH}_2\text{NHTol}\right]^+} \arrow[l, shift left] \arrow[d, shift left] & \\
\underset{\text{IIa}}{(\text{—CH}_2\underset{|}{\text{N}}\text{Tol})_3} \arrow[r, shift left] & \underset{\text{IIb}}{\text{CH}_2\text{=NTol}} \arrow[l, shift left] \arrow[u, shift left] \arrow[r, shift left, "\text{H}^+"] & \underset{\text{IV}}{\left[\begin{array}{c}\text{CH}_2\text{NHTol}\\ \text{H}\\ \uparrow\\ \text{CH}_2\text{=NTol}\end{array}\right]^+} \arrow[l, shift left] \arrow[u, shift left] & + \text{TolNH}_2
\end{tikzcd}$$

In acid-induced reactions the hydrogen acceptor is believed to be the Schiff base IIb or its cation IV, obtainable from the trimer or from the methylene-bis-amine *via* the Schiff base monomer, or from the methylene-bis-amine via its cation III, as shown in the scheme. In thermally induced reactions the hydrogen acceptor may be IIb. The several subsequent reactions which may be initiated in presence of acid were established in their proper relationships by Simons[3]: (1) formation of the *o*-aminobenzylarylamine base V,[8] presumably from IV and *p*-toluidine by ortho-coupling, (2) conversion of V to the diphenylmethane base VIII by action of acid in absence of I or II,[9] a reaction not encountered under the conditions of the present study, (3) conversion of V to the tetrahydroquinazoline VI, a reaction whose reversibility[3] in presence of acid was confirmed in the present study, though the reaction is not sensibly reversible in absence of acid,[10] and (4) the hydrogenation–dehydrogenation reaction which is the principal subject of study. These interrelated reactions are shown in the accompanying scheme. The extent of reaction 4 was estimated from the quantity of VII formed, and the nature of the reaction was inferred from the presence of methylated amine. The possibility cannot be excluded that the amine products of reaction 4 could enter the reaction system, with eventual formation of dimethylated amine of which, however, little or none has been encountered. The presence and amount of unmethylated amine, some of which may be liberated by incidental hydrolysis, are regarded as not diagnostic. To test the possibility that a small quantity of water, operating cyclically, might generate formaldehyde by hydrolysis of I or II and so modify the reaction series, an ex-

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[1] This paper is constructed from the doctoral dissertation of Paul J. McLaughlin, University of Pennsylvania, 1943.

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[3] Simons, THIS JOURNAL, **59**, 518 (1937).

[4] Maffei, *Gazz. chim. ital.*, **58**, 261 (1928).

[5] Eisner and Wagner, THIS JOURNAL, **56**, 1938 (1934).

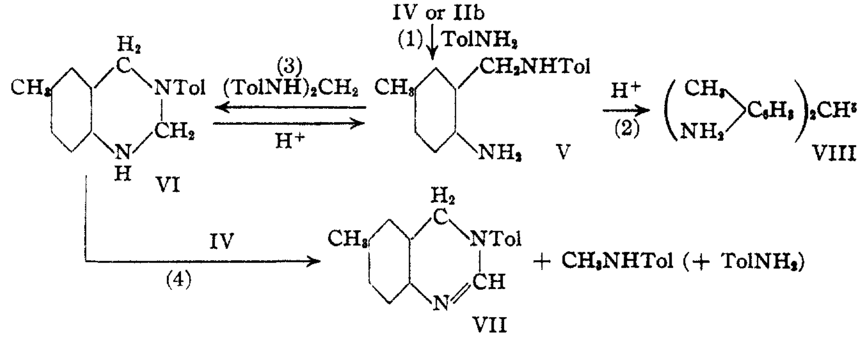
[6] E. C. Franklin, "The Nitrogen System of Compounds," Reinhold Publishing Corp., New York, N. Y., 1935, p. 246; Mills, Harris and Lambourne, *J. Chem. Soc.*, **119**, 1294 (1921); Strain, THIS JOURNAL, **49**, 1558 (1927); **50**, 2218 (1928); Hinsberg and Koller, *Ber.*, **29**, 1499 (1896); Wheeler, *Am. Chem. J.*, **17**, 400 (1895); Fischer and Wrezinski, *Ber.*, **25**, 2711 (1892); Bischoff, *ibid.*, **31**, 3254 (1898); Cuisa and Zerbini, *Gazz. chim. ital.*, **50**, 1294 (1921); Cuisa and Musajo, *ibid.*, **59**, 796 (1929); Robinson and Bogert, *J. Org. Chem.*, **1**, 65 (1936); Crippa and Maffei, *Gazz. chim. ital.*, **71**, 194 (1941).

[7] Bischoff and Reinfeld, *Ber.*, **36**, 41 (1903).

[8] T. R. Miller and Wagner, THIS JOURNAL, **60**, 1738 (1938).

[9] Wagner, *ibid.*, **56**, 1944 (1934).

[10] Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).



periment was performed under anhydrous conditions and was found to give a normal yield of VII and a nearly equivalent amount of methylated amine (Table I, expt. 6). It has shown experimentally (Table I, expts. 3, 4, 5) that the quantities of V and VI decreased with the duration of the reaction, while the quantities of VII and methylated amine increased; these results are consistent with the view that reaction 4 is irreversible.

Reaction 4 was realized with compound VI using as the second aldehydic reactant methylene-bis-*p*-toluidine, trimeric methylene-*p*-toluidine, methylene-bis-piperidine, and benzalaniline, and as the sources of acid *p*-toluidine hydrochloride, piperidine hydrochloride, trimethylamine hydrochloride, the hydrochloride of VII, and ammonium chloride. The salts named appeared to vary with respect to the effectiveness of each in promoting reaction 3 (ring opening–ring closure) and reaction 4 (hydrogenation–dehydrogenation). In experiments with salts of tertiary amines (trimethylamine and VII), which are not eligible to participate in ring opening with formation of V and I, both V and VII were formed (Table I, expts. 2, 5); the ring opening in each of these cases must be attributed to operation of the amines formed in reaction 4. The amine salts used all proved to be more effective than ammonium chloride with respect to reactions 3 and 4 (Table I, expts. 1–10), the order of decreasing effectiveness being *p*-toluidine hydrochloride, trimethylamine hydrochloride, the hydrochloride of VII, piperidine hydrochloride, and ammonium chloride. The comparative activities of these salts as proton donors should be related in an inverse sense to the dissociation constants of the bases represented. Results with *p*-toluidine hydrochloride, trimethylamine hydrochloride and piperidine hydrochloride are consistent with this view; the basicity of VII is not known. The low activity of ammonium chloride thus appears to be anomalous, but may be attributable to the low solubility of this salt in alcohol or in molten amine mixtures. Actually the identity of the salt used is not preserved, for the acid so introduced may be assumed to become distributed among all bases present in a manner determined jointly by the relative strengths and concentrations of the bases and by the relative solubilities of their salts in the reaction mixture.

The possibility that oxidation of VI to VII might be caused by ready loss of hydrogen[11] was tested (expt. 23) by heating VI in contact with air; no VII precipitable as picrate was present. The possibility that picric acid, used to precipitate VII in the experiments, might serve to some extent as oxidant was excluded by the negative result of an experiment (expt. 24) to test this point. Reaction 4 was found to proceed slowly in absence of added acid at a relatively high temperature (expt. 12), indicating that for such conditions an alternate mechanism, involving only thermal effects, must be admitted.

The hypothesis that the hydrogenation–dehydrogenation reaction is analogous to the Cannizzaro reaction was further tested by experiments in which the abilities of compounds of ammono-aldehyde or aldehyde types to serve as hydrogen acceptors were contrasted with those of similar nonaldehydic ammono-carbonyl or carbonyl compounds. The pairs of compounds tested were diphenylformamidine and diphenylacetamidine, formyl-*p*-toluidine and acetanilide, and formamide and acetamide. The first named of each pair possesses an aldehydic structure, and in each case only this compound was found to oxidize VI to VII (expts. 14–22). The behavior of diphenylformamidine, a derivative of ammono-formic acid and also an aldehyde in the sense that formic acid is an aldehyde, is of interest. Dains[12] reported diphenylformamidine to condense with reactive methylene compounds after the manner of aldehydes, and the conversion of VI to VII by formic acid has been recorded.[13] In the oxidation of VI to VII by diphenylformamidine the results showed the reaction to proceed in two stages, essentially

$$\text{PhNHCH{=}NPh} \xrightarrow{\text{VI}} \left\{\begin{array}{l}\text{VII}\\ \text{PhNHCH}_2\text{NHPh}\end{array}\right. \xrightarrow{\text{VI}} \left\{\begin{array}{l}\text{VII}\\ \text{PhNH}_2 + \text{CH}_3\text{NHPh.}\end{array}\right.$$

In the experiments reported in Table I (expts. 14, 15, 16) the reactants were used in this over-all proportion. The reaction was favorably affected by presence of acid (expt. 14), but diphenylformamidine, form-*p*-toluidide and formamide all reacted in absence of added acid but at somewhat elevated temperatures (105–210°; expts. 15, 16, 18, 21). These conversions may be wholly thermal, or they may be induced in part by the acid characters of the compounds named; similar

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(11) Mason, *Ber.*, **20**, 267 (1887); *J. Chem. Soc.*, **55**, 99 (1889); Lankelma and Sharnoff, THIS JOURNAL, **53**, 2654 (1931).

(12) Dains, *Ber.*, **35**, 2496 (1902).

(13) Wagner, *J. Org. Chem.*, **2**, 165 (1937).

TABLE I

HYDROGENATION–DEHYDROGENATION REACTIONS INVOLVING 3-*p*-TOLYL-6-METHYL-1,2,3,4-TETRAHYDROQUINAZOLINE (VI) AND HYDROGEN ACCEPTORS

| | | | | | | Steam-vol. amines | |
|---|---|---|---|---|---|---|---|
| | Acceptor[a] | Acid[b] | Conditions[c] | VII, % | V, % | Methylated base, % | Unmethylated base, % |
| 1 | Methylene-bis-*p*-toluidine | $TolNH_2 \cdot HCl$ | 60°, 3 hr., in EtOH | 62 | 9 | 50 | 40 |
| 2 | Methylene-bis-*p*-toluidine | VII·HCl | 78°, 3.5 hr., in EtOH | 51 | 11 | 25 | 56 |
| 3 | Methylene-bis-*p*-toluidine | $Me_3NHCl$[d] | 78°, 3 hr., in EtOH | 69 | 0 | 28 | 42 |
| 4 | Methylene-bis-*p*-toluidine | $Me_3NHCl$[d] | 78°, 2 hr., in EtOH | 55 | 0 | | 52 |
| 5 | Methylene-bis-*p*-toluidine | $Me_3NHCl$[d] | 78°, 0.5 hr., in EtOH | 11 | 9 | | |
| 6 | Methylene-bis-*p*-toluidine | $TolNH_2 \cdot HCl$ | 85°, 3 hr., anhydrous conditions[e] | 54 | +[f] | 49 | 37 |
| 7 | Trimeric methylene-*p*-toluidine | $TolNH_2 \cdot HCl$ | 60°, 2 hr., in EtOH | 52 | 10 | | |
| 8 | Methylene-bis-piperidine | $TolNH_2 \cdot HCl$ | 60°, 3 hr., in EtOH | 91 | 5 | | |
| 9 | Methylene-bis-piperidine | Piperidine HCl· | 60°, 2 hr., in EtOH | 38 | 29 | [g] | |
| 10 | Methylene-bis-piperidine | $NH_4Cl$ | 60°, 2 hr., then 100°, 1 hr. | 33 | 0 | | |
| 11 | Methylene-bis-piperidine | None | 65°, 2 hr., in MeOH | 0 | | | |
| 12 | Methylene-bis-piperidine | None | 195°, 4 hrs. | 32 | | | |
| 13 | Benzalaniline | $PhNH_2 \cdot HCl$ | 60°, 2 hr., in EtOH | 61[h] | | | |
| 14 | Diphenylformamidine[i] | $PhNH_2 \cdot HCl$ | 60°, 2 hr., in EtOH | 61 | 3 | | |
| 15 | Diphenylformamidine[i] | None | 105°, 2 hr. | 30 | | | |
| 16 | Diphenylformamidine[i] | None | 210°, 1.5 hr. | 53 | | | |
| 17 | Diphenylacetamidine | None | 190°, 2 hr. | 0 | | | |
| 18 | Form-*p*-toluidide | None | 170°, 2 hr. | 30 | | | |
| 19 | Acetanilide | None | 170°, 2 hr. | 0 | | | |
| 20 | Acetanilide | $PhNH_2 \cdot HCl$ | 170°, 2 hr. | 0 | | | |
| 21 | Formamide | None | 150°, 2 hr. | 21 | | | |
| 22 | Acetamide | None | 140°, 2 hr. | 0 | | | |
| 23 | None[j] | None | 150°, 2 hr. | 0 | | | |
| 24 | Picric acid[k] | None | 10°, 6 hr. | 0 | | | |

[a] In most cases 0.005 mole each of VI and acceptor. [b] In experiments involving use of acid (amine salt or $NH_4Cl$) the amount was two molar equivalents with respect to the other reactants, unless specified otherwise. [c] When alcohol was used as solvent, the amount was 50 ml. [d] 0.009 mol. [e] All reagents were dried over sulfuric acid in a desiccator for a week. The glass apparatus was kept in an oven at 135° for four days. The return condenser was protected by a calcium chloride tube. No solvent was used. [f] Benzaldehyde gave a small precipitate, but the m. p. (162°) and the m. p. of a mixture with the benzal derivative of V (106°) indicates probable formation of some diphenylmethane base in the reaction.[3] [g] Presence of methyl piperidine was suggested by the nature of the picrate obtained following removal of piperidine as benzenesulfonyl derivative. Results of attempts to identify and determine methylpiperidine as hydrochloride were not satisfactory. The steam volatile bases were apparently only piperidine and methylpiperidine, for the refractive index of the mixture, redistilled over sodium, was $n^{20}_D$ 1.4453, the values for pure specimens of piperidine and methylpiperidine being 1.4532 and 1.4376, respectively. [h] Only VII was determined, as the isolation of benzylaniline presented difficulties not wholly overcome. [i] The amount of diphenylformamidine was 0.5 equivalent with respect to the amount of VI. [j] Experiment to test possible thermal dehydrogenation of VI to form VII. The mass, after heating, was dissolved in ethanol, and picric acid solution was added. No precipitate appeared. [k] Experiment to test possible formation of some VII by oxidation of residual VI by picric acid added to precipitate VII. A solution of 0.6 g. of VI in 25 ml. of ethanol was treated with 15 ml. of a saturated solution of picric acid in ethanol, and the liquid was chilled in the refrigerator. After six hours only a scanty precipitate of picric acid had separated.

effects have been observed in certain reactions studied recently.[14]

The experimental results available show that the following structure types, all of which are aldehydic, can function as hydrogen acceptors in the reaction studied: (1) $-\overset{|}{N}CH_2\overset{|}{N}-$ (methylene-bis-amines), (2) $-N{=}CH-$ (methylene-amine, Schiff base), (3) $-NHCHO$ (formylamine), (4) $-NHCH{=}N-$ (substituted formamidine), and (5) formic acid. The following structures, respectively, homologous with 3 and 4 but lacking aldehydic structural characteristics, were found to be incapable of serving as hydrogen acceptors: $CH_3CONH-$ and $-NHC(CH_3){=}N-$. It is concluded that, within the scope of this study, possession of a structure of aldehydic type is necessary in order that a compound may function as a dehydrogenating agent in the oxidation of VI to VII, and that the action is promoted at moderate temperatures by presence of acid or, in its absence and less effectively, by considerably higher temperatures.

## Experimental

**Starting Materials.**—Methylene-bis-*p*-toluidine was prepared by the method of Eberhardt and Welter,[15] and methylene-bis-piperidine as described by Ehrenberg.[16]

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(14) E. L. Höljes, Jr., Thesis, University of Pennsylvania, 1943.

(15) Eberhardt and Welter, *Ber.*, **27**, 1808 (1894).

(16) Ehrenberg, *J. prakt. Chem.*, [2] **36**, 117 (1887).

The tetrahydroquinazoline VI was made from *o*-amino-*m*-xylyl-*p*-toluidine (V),[8] prepared by the method of Miller and Wagner,[8] and the dihydroquinazoline VII was made from *p*-toluidine, formalin and formic acid.[13] Trimeric methylene-*p*-toluidine was prepared as described by Miller and Wagner,[17] and diphenylformamidine and diphenylacetamidine were made by the methods of Walther[18] and Sen and Ray,[19] respectively.

**General Procedures.**—For reactions at lower temperatures the reactants (0.005 mole each of tetrahydroquinazoline VI and hydrogen acceptor and 0.011 mole of amine salt in most experiments) were dissolved in ethanol (50 ml.) in a round-bottomed flask (200 ml.) fitted with a short return condenser, and the mixture was heated on a steam-bath. For reactions at higher temperatures the reactants, in a test-tube (25 × 200 mm.) provided with a short return condenser, were heated in a sand-bath. In each procedure temperatures were observed by means of a thermometer with its bulb in the reaction mixture. At the end of the heating period any acid present was neutralized with sodium hydroxide solution and the mixture was submitted to steam distillation to remove volatile amines.

**Analysis of Reaction Mixtures.**—The amines in the steam distillate were extracted in ether. The amines were fixed by conversion to hydrochlorides and the ether was removed by evaporation. The residue was analyzed by the Hinsberg–Kessler procedure[20] modified in one particular. Following the precipitation of the benzenesulfonamides these were dissolved in ether, and the solution was shaken with 10% sodium hydroxide solution to remove the monosulfonamide of any primary amine present. This improved the separation of primary and secondary amines; after the sodium and alcohol treatment the amount of primary amine derivative recovered was small, but the melting point of the secondary amine derivative was better than that observed when the unmodified procedure was used. The sulfonamides of the several amines were identified by mixed melting point tests.

For the analysis of the solid residue in the steam distillation flask a procedure similar to that of Simons[3] was used. The solid was separated by filtration and was dissolved in 25 ml. of ethanol. The solution was heated to boiling, 3 ml. of benzaldehyde was added, and the mixture was kept for ten hours in a refrigerator (about 10°), after which any precipitated benzal derivative of compound V was removed by filtration, dried, weighed and identified by mixed melting point test. The filtrate from the benzal derivative was heated to boiling and was treated with 15 ml. of a saturated solution of picric acid in ethanol. The mixture was chilled, and the picrate of VII was collected, dried, weighed, and identified by mixed melting point test and by its rather unique sensitivity to light, which changes its color from bright yellow to deep orange-red.

The accuracy of this separation procedure, tested by analysis of mixtures of known amounts of the substances named, is indicated by the following recoveries: dihydroquinazoline VII, 87%; *o*-amino-*m*-xylyl-*p*-toluidine (V), 89%; *p*-toluidine, 96%; N-methyl-*p*-toluidine, 82%. Appropriate corrections were thereafter applied to analytical data for reactions involving VI and I or trimeric II.

In the hope of avoiding the rather troublesome isolation and purification of the benzenesulfonyl derivative of methyl-*p*-toluidine a zinc chloride separation based on that of Frankland[21] was submitted to trial. The precipitate of *p*-toluidine zincichloride was found to be chalky and to occlude methyl-*p*-toluidine, recovery of which (as nitrosamine) was variable and did not exceed 79%. Trials of the 3-nitrophthalic anhydride procedure of Alexander and McElvain,[22] designed for use in qualitative analysis, showed the yields of the derivatives of both amines to be far from quantitative.

The separation of piperidine and methylpiperidine by the Hinsberg–Kessler procedure was satisfactory, but the determination of the latter as picrate proved to be inaccurate. Haase[23] reported methylpiperidine picrate to melt at 148°. Several yields of picrate obtained in the separations failed to melt at this temperature, the melting points being indefinite and diverse. The normal (1:1) picrate resulted only when methylpiperidine and picric acid were brought together in exactly equivalent amounts in alcohol. The product was a compound which melted sharply at 228° cor. as first precipitated, and at the same temperature after recrystallization from 95% ethanol; the yield was 87%. The use of methylpiperidine and picric acid in other proportions gave products which melted badly, and which are believed to be loose compounds of the 1:1 picrate and picric acid. Thus methylpiperidine and 2.5 equivalents of picric acid gave a product which melted in the range 146–180° as obtained, and in the range 147–179° after recrystallization; the yield was 118% of the amount calculated for the 1:1 picrate.

Significant data for the hydrogenation–dehydrogenation experiments are presented in Table I.

## Summary

Study of the dehydrogenation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by action of methylene-bis-amine in presence of acid and at temperatures ordinarily not above 100°, the methylene-bis-amine being cleaved by hydrogenation to yield amine and methylated amine, was extended by use of methylene-bis-*p*-toluidine, trimeric methylene-*p*-toluidine and methylene-bis-piperidine with the acids *p*-toluidine hydrochloride, piperidine hydrochloride, trimethylamine hydrochloride and ammonium chloride. The results confirm the opinion that the over-all reaction is an acid catalyzed hydrogenation–dehydrogenation involving two compounds of ammono-aldehydic type, with formation of compounds of ammono-acidic and ammono-alcoholic types, the essential change having at least a formal resemblance to a crossed Cannizzaro reaction. This interpretation was supported by the demonstration that only compounds which possess an aldehydic structure are able to participate in the oxidation–reduction reaction. The structurally aldehydic compounds diphenylformamidine, form-*p*-toluidide, formamide and benzalaniline all reacted; the analogous non-aldehydic compounds diphenylacetamidine, acetanilide and acetamide failed to react.

The function of the acid appears to be the formation, either by cleavage of a methylene-bis-amine (considered as an ammono-acetal) or from a Schiff base (taken as such or derived from the methylene-bis-amine), of a reactive cation capable of serving as a hydrogen acceptor. Higher temperatures (*circa* 200°) force the reaction in absence of added acid. A general reaction scheme for the acid-induced reaction is presented which appears to be consistent with the observed facts.

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(17) J. G. Miller and Wagner, THIS JOURNAL, **54**, 3698 (1932).

(18) Walther, *J. prakt. Chem.*, [2] **53**, 475 (1896).

(19) Sen and Ray, *J. Chem. Soc.*, 646 (1926).

(20) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1916, p. 24.

(21) Frankland, *J. Chem. Soc.*, **115**, 198 (1919).

(22) Alexander and McElvain, THIS JOURNAL, **60**, 2285 (1938).

(23) Haase, *Ber.*, **37**, 3233 (1904).