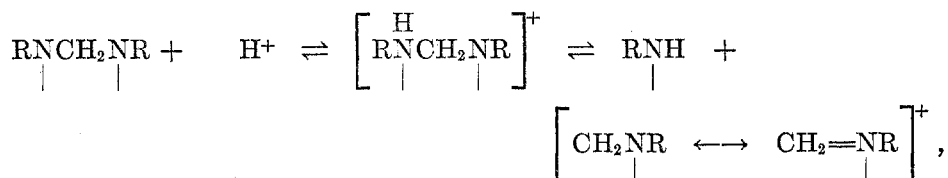


THE ACTION OF ACIDS ON ALKYLIDENE-BIS-AMINES¹

WILLIAM C. HUNT² AND E. C. WAGNER

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It has been suggested (1-3,) that acid-catalyzed reactions of carbonyl compounds and amines may be induced by addition of proton to a primary condensation product (alkylolamine, alkylidene-*bis*-amine, or Schiff base) followed, in the case of a methylene-*bis*-amine, by elimination of amine to form a carbenium-ammonium ion of high activity, *e.g.*,



and that this is the entity involved in reactions yielding products in which the grouping—CH₂NR is present.³ In this way is readily explicable the transformations of methylene-*bis*-primary-amines to Schiff bases (respectively nitrogen-system hemiacetals and aldehydes) induced by acids present sometimes in incidental traces.⁴ This change is implicit in the equation given above, for the carbenium-ammonium ion represented, if from a primary amine, is that of the Schiff base. The hydrogen atom associated with nitrogen is available as proton for another cycle, so that the Schiff base forms in quantity, the change being substantially irreversible owing to the tendency of the Schiff base to polymerize. Experiments⁵ showed that presence of acid induces this change, which is inhibited by presence of base (sodium hydroxide, triethylamine). The nature of the group R in (RNH)₂CH₂ affects the susceptibility of the compound to loss of

¹ Paper constructed from Ph.D. thesis of William C. Hunt, University of Pennsylvania, 1951.

² Present address: Mellon Institute of Industrial Research, Pittsburgh, Pa.

³ Alkylolamines can yield similar results by addition of proton and loss of water. Schiff bases yield the carbonium ions directly: $\left[\begin{array}{c} \text{RC}=\text{NR}' \\ | \quad | \quad | \\ \text{H} \quad \text{H} \quad \text{H} \end{array} \right]^+$. The essential result

with alkylolamines and alkylidene-*bis*-amines is cleavage of a C—N bond. In the case of a methylene-*bis*-amine a second similar cleavage can occur, yielding amine salt or compounds linked thru a methylene group.

⁴ Eibner (4) described the preparation of methylene-*bis*-amines without an attempt to control the slight acidity due to aldehyde or alcohol. Bischoff and Reinfeld (5) found that some alkylidene-*bis*-amines so prepared are contaminated with the corresponding Schiff bases, and that this is prevented by presence of alkali; it is now common practice to prepare methylene-*bis*-amines from primary amines in the presence of added alkali. A striking example of sensitivity to acid is afforded by methylene-*bis-p*-anisidine, satisfactory preparation of which requires presence of alkali during formation, isolation, and purification.

⁵ Unpublished results of experiments by Wm. J. Steele, University of Pennsylvania, 1950-1951.

amine and formation of Schiff base. The order found experimentally for several compounds of the type $(\text{ArNH})_2\text{CH}_2$ is *p*-anisyl > *p*-tolyl > phenyl > *p*-chlorophenyl > *p*-bromophenyl; it is similar to the order of decreasing negativities reported by Kharasch (6).

The view that $-\text{NCH}_2-$ bonds may be cleaved as outlined by protons present in small amounts and heavily buffered by large excesses of basic materials implies an initial actual or momentary salt-formation. In this study attention is directed to (a) the establishment of the reality of salts of methylene-*bis*-amines,⁶ and (b) the results of preliminary experiments to determine the natures of such salts and of their decompositions.

Salts of methylene-bis-amines previously reported. Claims of the preparation of salts of methylene-*bis*-amines are sufficiently numerous to indicate that formation of isolable salts with acids is a characteristic of the class. Trials showed a number of these claims to be fallacious; there emerged finally only one reported salt (methylene-*bis*-piperidine hydriodide) that could be authenticated. In most cases examined the product was either the amine salt (mistaken for the methylene-*bis*-amine salt because elementary analysis does not permit a distinction and because no comparisons with separately prepared amine salts were made) or a secondary product. In the interest of accuracy it seems necessary to outline the essential findings of our investigation of previous claims.

The picrates of methylene-*bis*-*o*-nitroaniline and methylene-*bis*-*m*-nitroaniline reported by Pulvermacher (8) to form in acidic aqueous solution were found to be picric acid precipitated by the acid present. The supposed chloroplatinate of methylene-*bis*-*m*-nitroaniline prepared in aqueous acid solution (8) showed a platinum content between the values for the amine salt and the methylene-*bis*-amine salt. Later it was found that methylene-*bis*-nitroanilines are readily cleaved by aqueous hydrochloric acid.

The six salts of methylene-*bis*-benzylamine⁷ (hydrochloride, hydrobromide, hydriodide, phosphate, oxalate, picrate) reported by Kempff (9) include no compound that is the salt claimed. All the products obtained in repetition of the work are the corresponding benzylamine salts, identified by melting point and mixture melting point tests using authentic specimens of the amine salts (Table III).

Grünhagen's claims (10) that interaction of methylene chloride with *o*- and *p*-toluidines yielded the corresponding methylene-*bis*-*p*-toluidine hydrochlorides must be judged invalid because (a) the base of m.p. 135° recovered in the ex-

⁶ Similar examinations of Schiff bases and of alkylolamines are deferred for possible later study. Methyleneamines are prone to polymerize, which complicates the processes of salt- and ion-formation. One such salt, however, is reported herein, *viz.*, the monohydriodide of trimeric methylenebenzylamine. Methylolamines appear to be less promising for study owing to difficulties in obtaining them pure, and because of their hemiacetal character and probable sensitivity to cleavage by acids. Only a few salts of hydroxyalkylamines have been reported (7), and the status of these compounds has not been tested.

⁷ The compound designated by Kempff (9) as methylene-*bis*-benzylamine (m.p. 45–46°) is actually the Schiff base, shown to be trimeric and probably cyclic. The hydriodide is also probably cyclic, as action of alkali caused separation of the trimeric Schiff base.

periment with *o*-toluidine cannot have been methylene-*bis*-*o*-toluidine, which melts at 52°, and (b) repetition of the experiment with *p*-toluidine yielded 6-methyl-3-*p*-tolyl-3,4-dihydroquinazoline (hydrochloride), known to be formed from methylene-*bis*-*p*-toluidine by a reaction sequence induced by acid (11). Several workers claimed recovery of methylene-*bis*-amine from the supposed salt by treatment of the acidic reaction mixture (not the isolated salt) with alkali. This test is clearly incompetent, and vitiates claims made by Lermontoff (12) and by Houben and Arnold (13). Other claims (14–18) are inadequately supported or represent procedures now known to cleave the methylene-*bis*-amines rapidly and completely. Two compounds designated by Houben and Arnold to be methylene-*bis*-amines (13) were certainly other compounds.⁸

Ehrenberg (14), avoiding presence of water, obtained from hydrogen chloride and methylene-*bis*-piperidine in dry ligroin a product that was apparently a mixture of the mono- and di-hydrochlorides, and from the *isolated* salt recovered methylene-*bis*-piperidine by action of alkali. These results were confirmed and by improvement in procedure there was obtained the monohydrochloride in a fair state of purity. Schmidt and Kohler (21) obtained from piperidine and methylene iodide a salt that was unquestionably methylene-*bis*-piperidine hydriodide, as shown by analysis and by recovery of methylene-*bis*-piperidine from the isolated salt; these results have been confirmed.

Preparation of some methylene-bis-amine salts. Five new salts were prepared from methylene-*bis*-piperidine and methylene-*bis*-morpholine by limited applications of the following procedures: (a) treatment of methylene-*bis*-amine with concentrated aqueous hydriodic acid or hydrobromic acid in the cold; (b) treatment of methylene-*bis*-amine with anhydrous acid (hydrochloric, hydrobromic, picric) in a dry inert solvent (benzene, ligroin); (c) interaction of amine and methylene iodide (21). In earlier experiments treatment with gaseous acids was uncontrolled, but later there was used an apparatus (Figure 1) which permitted introduction of gases in measured amounts. Data for the six salts now known appear in Table I.

These salts do not possess the characteristics of compounds wholly pure and stable. Analyses and melting points are in most cases sufficiently good only to distinguish each salt from other compounds with which it might be confused.

Factors which affect the stabilities of methylene-bis-amine salts. Attempts to obtain salts of methylene-*bis*-arylamines or methylene-*bis*-alkylamines were unsuccessful and it seems clear that formation of stable and isolable salts under ordinary conditions is by no means general among methylene-*bis*-amines. Experiments under varied conditions to study the decompositions of methylene-*bis*-amines by acids yielded the results summarized in Table II.

Methylene-*bis*-amines from *p*-toluidine, *o*-nitroaniline, and *m*-nitroaniline

⁸ The product designated as methylene-*bis*-*N*-ethylaniline (m.p. 145°) was clearly not this compound, shown by von Braun (19) to melt at 79°. The product designated as methylene-*bis*-*p*-bromoaniline was something else, for the compound named melts at 92° (20). The product designated by Houben and Arnold (13) as methylene-*bis*-*m*-bromoaniline (m.p. 135°) seems doubtful, for the *p*-isomer melts at 92°.

yielded with acids either the amine salts or secondary products. Methylene-*bis*-amines from diethylamine, diisobutylamine, and *n*-amylamine were cleaved by aqueous hydriodic acid (unlike methylene-*bis*-piperidine and methylene-*bis*-morpholine) and yielded only the amine salts. Insolubility of a methylene-*bis*-amine salt probably favors its survival; the most general preparative method employs dry acid and dry inert solvent. Incidental observations reveal that temperature and time may require control. Thus methylene-*bis*-piperidine hydriodide, obtainable from methylene-*bis*-piperidine and aqueous hydriodic

TABLE I
SALTS OF METHYLENE-*bis*-AMINES

SALT: Methylene- <i>bis</i> -	METHOD OF PREP. ^a	M.P. °C.	ANALYSIS ^b	M.P. OF AMINE SALT ^c	M.- <i>bis</i> -AMINE RECOVERED
Piperidine-HI	A, B	123-124.5	Iodine ^d : Calc'd, 40.9. Found, 42.2.	168-170	+
Piperidine-HBr	A, D	144-196	Bromine: Calc'd, 30.4. Found, 29.9.	233-235 d.	+
Piperidine-HCl	D	150-215 d.	Chlorine: Calc'd, 16.2. Found, 15.9.	237 d.	+
Piperidine picrate	C	110-112	—	145 d.	+
Morpholine-HI	A	120.5-124.5	Iodine: Calc'd, 40.4. Found, 41.4.	213-215	Not attempted
Morpholine picrate	C	104-106	—	150.5-152	Not attempted
Morpholine-HCl ^e	D	None	Found: ^{e,f} Cl., 19.4. N, 11.7		

^a Methods of preparation: A. Concentrated aqueous acid in the cold; B. Amine and methylene iodide (21); C. Dry benzene solution of picric acid added to dry benzene solution of methylene-*bis*-amine; D. Measured gaseous acid passed into solution of methylene-*bis*-amine in dry ligroin. ^b Footnote 10. ^c Amine salts prepared by same procedure as methylene-*bis*-amine salts. These melting points are included to establish the fact that the product in column 1 is not the amine salt. ^d Schmidt and Kohler's value: C, 42.86; H, 7.35; I, 40.73. ^e Previously obtained by Lieberman and Wagner (2) as a similarly indefinite product. Calculated analysis: for $\text{CH}_2(\text{NC}_4\text{H}_8\text{O})_2 \cdot \text{HCl}$, Cl, 15.9, N, 12.6; for $\text{CH}_2(\text{NC}_4\text{H}_8\text{O})_2 \cdot 2\text{HCl}$, Cl, 27.4, N, 10.8; for $\text{HNC}_4\text{H}_8\text{O} \cdot \text{HCl}$, Cl, 28.7, N, 11.3. ^f See footnote 9.

acid at room temperature or after brief refluxing, is decomposed by prolonged heating, and the hydrobromide, obtainable in the cold, does not survive heating. In these cases decomposition appears to be hydrolytic. Susceptibility of methylene-*bis*-amines to hydrolysis is doubtless general but is perhaps not uniformly so high as has been believed. It is shown below that cleavage by acids under anhydrous and mild conditions may be more rapid and complete than cleavage by water.

An interesting and unexpected effect is that of dry alcohols, apparently not recognized hitherto. When reactants are such that certain secondary reactions known to occur in alcohol are excluded, it was found that action of acid in presence of alcohol in general caused cleavage to yield amine salts. Thus methylene-

bis-piperidine in dry ligroin yields with hydrogen chloride an isolable salt, but in dry ethanol, or in ligroin containing an equivalent (or more) of ethanol, gaseous

TABLE II
ACTIONS OF ACIDS ON METHYLENE-*bis*-AMINES

COMPOUND	ACID ^a	RATIO ACID: COMP.	SOLVENT ^b	CONDITIONS	PRODUCT	
Methylene- <i>bis</i> -piperidine = MbP	HCl 36%	1	EtOH + Et ₂ O	0°; 2-5 min.	Pip.HCl	
	HCl 18%	1	EtOH + Et ₂ O	0°; 2-5 min.	Pip.HCl	
	MbP	HBr 47%	1	EtOH	B.p.; 2 hrs.	Pip.HBr
	MbP	HI 57%	1	EtOH	B.p.; 2 hrs.	Pip.HI
	MbP	HCl gas	2	Dry ligroin + 2 eq. abs. EtOH	Room temp.; 2-5 min.	Pip.HCl
	MbP	HCl gas	2	Abs. MeOH	Room temp.; 2-5 min.	Pip.HCl
	MbP	HCl gas	1	Abs. MeOH	Room temp.; 2-5 min.	Pip.HCl
	MbP	Picric	2	Abs. MeOH	Room temp.; 2-5 min.	Pip. picrate
	Methylene- <i>bis</i> -morpholine = MbM	Picric	2	EtOH	B.p.; 2-5 min.	Morph. picrate
MbM		Picric	1	Abs. EtOH	Room temp.; 2-5 min.	Morph. picrate
MbM		Picric	1	None	Warm	Morph. picrate ^c
MbM		Picric	1	C ₆ H ₆ + 2 eq. EtOH	Room temp.; 2-5 min.	Morph. picrate
MbM		Picric	1	EtOH + 1 eq. LiOH	B.p.; 2-5 min.	Morph. picrate
Methylene- <i>bis</i> -diethylamine		HI 57%	1	EtOH	0°	Et ₂ NH·HI
	HI 57%	1	EtOH	0°	Bu ₂ NH·HI	
	HI 57%	1	EtOH	0°	Am ₂ NH·HI	
Methylene- <i>bis</i> - <i>p</i> -toluidine = MbT	HCl 36%	1	EtOH	B.p.; 5 min.	Tolylmethyl-quinazoline-HCl	
	MbT	HBr 36%	1	EtOH	B.p.; 5 min.	Same-HBr
	MbT	HI 36%	1	EtOH	B.p.; 5 min.	Same-HI
	MbT	Picric	1	Abs. EtOH	Warm; 2-5 min.	Same-picrate
	MbT	HCl gas	Excess	Abs. EtOH	Warm ^d ; 15 min.	<i>p</i> -Toluidine·HCl
Methylene- <i>bis</i> - <i>o</i> -nitroaniline	HCl 36%	Excess	Water	100°; 3 hrs.	<i>o</i> -Nitroaniline-HCl	

TABLE II—*Continued*

COMPOUND	ACID ^a	RATIO ACID: COMP.	SOLVENT ^b	CONDITIONS	PRODUCT
Methylene - <i>bis</i> - <i>m</i> -nitroaniline	Picric	1	EtOH + 2 ggt. conc'd HCl	B.p.; 5 min.	<i>m</i> -Nitroaniline picrate
Methylene - <i>bis</i> - <i>m</i> -nitroaniline	HCl 18%	Excess	Water	Warm; 5 min.	<i>m</i> -Nitroaniline- HCl
Methylene - <i>bis</i> - pi- peridine = MbP	HCl 36%	2	Water	Room temp.; 15 min.	Piperidine-HCl
MbP	HCl gas	2	Dry ligroin + 2 eq. abs. EtOH	Room temp.; 15 min.	Piperidine-HCl
MbP	HCl gas	2	Dry ligroin + 2 eq. <i>n</i> - BuOH	Room temp.; 15 min.	Piperidine-HCl

^a Acids for which strengths are given are aqueous. ^b EtOH refers to 95% ethanol. ^c Product crystallized from ethanol. ^d Not cooled; warmed by heat of absorption of HCl.

hydrogen chloride causes complete cleavage even at 0°. Similarly methylene-*bis*-morpholine yields a picrate in dry benzene, but under anhydrous conditions in ethanol or in benzene containing ethanol and picric acid it is cleaved in a few minutes at room temperature. This sensitivity involves also the character of the acid, for in presence of alcohol methylene-*bis*-piperidine and methylene-*bis*-morpholine yield hydrobromides and hydriodides but not hydrochlorides.

The natures of cleavages in dry inert solvents or in presence of alcohol, and the identities of the products (other than amine salt), are not yet established by rigidly controlled experiments. Cleavage by hydrogen halide in dry benzene or ligroin can involve apparently only the formation of methylene halide. Cleavage in presence of alcohol may involve this as a reactant, with the methylene-*bis*-amine functioning as an ammono-aldehyde to yield acetal. Several early attempts to isolate such products were unsuccessful. Decomposition of benzylidene-*bis*-piperidine in dry ligroin containing ethanol or butanol and hydrogen chloride (equivalent to the amine represented) yielded recognizable amounts of benzaldehyde, suggesting decomposition of a hemiacetal by hydrogen chloride.

With respect to salt-formation by methylene-*bis*-amines the facts that emerge clearly are that such salts exist and probably form initially in any case but may not persist, owing to cleavage induced by acid and made irreversible by fixation of the amine as amine salt, or to involvement in secondary reactions. If this is correct, it should follow that the stability of a methylene-*bis*-amine salt should be related in an inverse sense to the catalytic effectiveness of the acid present in promoting reactions. To test this inference there were made comparative experiments on the conversion of methylene-*bis*-*p*-toluidine to 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline (11, 1) in the presence of hydriodic, hydrobromic, or hydrochloric acid in equivalent amounts. The yields of dihydroquinazoline in five minutes were respectively 19%, 24%, and 26%. This transformation is some-

what complicated, but each of the steps involved is acid-catalyzed and the only considerable variable is the identity of the acid. The results indicate that hydriodic acid, which forms the most stable methylene-*bis*-amine salts, is the weakest catalyst, and that hydrochloric acid, which forms the least stable salts, is the most effective catalyst.

EXPERIMENTAL

General. Piperidine, diethylamine, and morpholine were redistilled (b.p. 105–106°, 55–56°, 126–128°). Hydrobromic and hydriodic acids were the constant-boiling mixtures; the former was redistilled in glass. Hydrogen chloride and hydrogen bromide were taken from pressure cylinders and were bubbled thru two sulfuric acid bottles. The ligroin (Eastman No. 950) was kept over sodium. Melting points are corrected values. New compounds are indicated by asterisk.

Methylene-bis-amines. Methylene-*bis*-morpholine, made by the method of Henry (22), boiled at 136° (20 mm.). Methylene-*bis*-piperidine (b.p. 113–114° at 19 mm.), methylene-*bis*-diethylamine (b.p. 54–55° at 8 mm.), methylene-*bis*-diisobutylamine (b.p. 93° at 1 mm.), and methylene-*bis*-di-*n*-amylamine (b.p. 163° at 4 mm.) were made by Ehrenberg's method (14), with some changes in isolation and purification. Methylene-*bis*-diethylamine, reported to boil at 168–169° with decomposition, was identified by analysis.⁹

Anal. Calc'd for C₉H₂₂N₂; N, 17.7; Mol. wt., 158.

Found: N, 17.8; Mol. wt. (cryoscopic in benzene), 161.

* Methylene-*bis*-di-*n*-amylamine.

Anal. Calc'd for C₂₁H₄₄N₂; N, 8.57; Mol. wt., 326.

Found: N, 8.40; Mol. wt. 334.

Attempts to prepare methylene-*bis*-amines from *n*-butylamine and *n*-amylamine by the same procedure (14) yielded materials of wide boiling ranges (to 196° at 11 mm.), believed to be polymerized Schiff bases. Methylene-*bis*-nitroanilines (*o*- and *p*-; m.p. 190–192°, 212.4–213.2°) were made by the method of Pulvermacher (8) and were crystallized from ethanol. Other aromatic methylene-*bis*-amines (from aniline, *p*-toluidine, *p*-anisidine, *p*-chloroaniline, and *p*-bromoaniline) were made as described by Bischoff and Reinhold (5) and were recrystallized from ether containing a few drops of triethylamine; they melted respectively at 56.3–57.0°, 85.9–87.9°, 66°, 59–60°, and 92°. Benzylidene-*bis*-piperidine, m.p. 82.8–83.8°, was made by the method of Laun (23). Trimeric methylene benzylamine, prepared by Ehrenberg's procedure (14), was isolated by distillation. The crude material (b.p. 225–230° at atmospheric pressure; 140–160° at 15 mm.) was either dried over sulfuric acid for several weeks and then washed with ethanol, or it was dissolved in hot ethanol and recovered by adding water to turbidity and chilling. The product melted at 45–46°.

Preparation of salts of methylene-bis-amines. (Table I). *A. In aqueous solution.* Salts made by action of aqueous acids were isolated by continued chilling of the concentrated solutions, washed with cold ether and dried *in vacuo* over calcium chloride.

Methylene-bis-piperidine hydriodide (21) resulted when methylene-*bis*-piperidine (1.6 g.) in ethanol (2 ml.) was treated with one equivalent of hydriodic acid (either 57% or 27%) either with chilling or at 80° for 15 minutes; m.p. 123–124.5°. Analysis¹⁰ showed the compound to be the monohydriodide. Piperidine hydriodide, similarly prepared, melted at 167–170°. Treatment of methylene-*bis*-piperidine hydriodide with aqueous sodium carbonate yielded methylene-*bis*-piperidine, b.p. 232°.

* *Methylene-bis-morpholine hydriodide.* To a chilled solution of 1.64 g. (0.0088 mole) of methylene-*bis*-morpholine in 3 ml. of ethanol was added 1.2 ml. of 57% hydriodic acid. After 3 days at –10° the mixture yielded crystalline crusts of the salt, m.p. 120.5–124.5°.

⁹ Analyses by Sarah M. Woods.

The value for iodine (Table I) is wide of the requirements for the dihydriodide or for morpholine hydriodide which last, similarly made, melted at 213–215°.

* *Methylene-bis-piperidine hydrobromide* was obtained by adding 1.6 g. (0.0088 mole) of methylene-*bis*-piperidine to 1 ml. of 47% hydrobromic acid (one equiv.) at ice-bath temperature or at 100° for 15 minutes. The separated salt showed no m.p., but if introduced into the bath already at 140° it melted sharply at 144° with gas-evolution, leaving a residue that melted at 197–200°. Piperidine hydrobromide, similarly prepared, decomposed at 233–235°. The formation of both the hydriodide and the hydrobromide of methylene-*bis*-piperidine in hot aqueous mixture indicates a considerable resistance of this methylene-*bis*-amine to hydrolysis. Treatment of the hydrobromide with aqueous sodium carbonate yielded methylene-*bis*-piperidine (b.p. 232°).

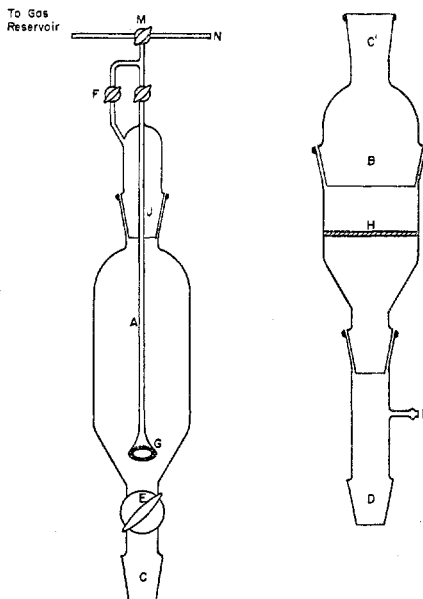


FIGURE 1. APPARATUS FOR OPERATIONS IN A CLOSED SYSTEM

B. In non-aqueous media. In preliminary experiments a solution of the methylene-*bis*-amine in dry ligroin or benzene was treated with gaseous acid bubbled unmeasured into the solution. This procedure was improved by use of the apparatus shown in Figure 1, designed to permit introduction of gaseous acids in metered amounts, recycling of unabsorbed gas, and filtration of solid products, all in a closed system with moisture excluded. Whenever the use of a definite volume of gas is specified it is to be understood that this outfit was used.

The apparatus AB (joined at C') is wholly of glass, with standard-taper connections. It includes also a gas-measuring buret (100 ml. in 0.2 ml.) provided with a mercury leveling tube and reservoir for forcing gases into the reaction chamber A, and a round-bottom flask attached at D to receive the filtrate. Stopcock E is 60 mm. in diameter, and the bore in the plug is 25 mm. in diameter. G is a sintered glass gas-diffuser, and H is a sintered glass filter plate of 75 mm. diameter sealed to the wall of B. Chamber A is of 1 liter capacity, and the filter is of 500 ml. capacity.

To use the apparatus it was flooded for several hours with air dried by passage thru two sulfuric acid bottles and three calcium chloride towers. The alkylidene-*bis*-amine and solvent were introduced rapidly by breaking the connection at J briefly; enough solvent

was used to fill A to the top. The gas was admitted slowly, and any unabsorbed gas was released thru F, returned to the gas buret, and was again forced into A thru G. The precipitated salt was allowed to settle and was then drawn into the filtering chamber by opening stopcock E, turning three-way stopcock M to the position for admitting (at N) air drawn thru three calcium chloride towers, and by applying suction at L. The walls of A and the precipitate on the filter were washed with dry solvent, and the filter was detached and transferred to a vacuum desiccator.

* *Methylene-bis-piperidine hydrochloride*. Repetition of Ehrenberg's experiment (14) using dry ligroin and unmeasured hydrogen chloride yielded a mixture of salts from which methylene-bis-piperidine was recovered by the action of aqueous sodium carbonate. The monohydrochloride was obtained by passing 100 ml. of hydrogen chloride (0.0041 mole) into a solution of 0.75 g. (0.0041 mole) of methylene-bis-piperidine in dry ligroin. The salt was dried over calcium chloride in a desiccator containing paraffin shavings. Treatment with aqueous sodium carbonate regenerated methylene-bis-piperidine which was isolated and identified.

Methylene-bis-morpholine hydrochloride. In this experiment the salt was prepared, filtered, and washed within an air-tight dry-box, provided with a pair of long rubber gloves attached to holes in the sides and with a glass window to permit manipulations within the box. The apparatus was set up in the box, which was allowed to stand for 3 days with the gas inlet protected by a trap charged with phosphorus pentoxide. Dry unmeasured hydrogen chloride (from a liquid generator) was passed into a solution of methylene-bis-morpholine in toluene (dried by distillation and by passage thru a column of silica gel). The product showed no m.p. and yielded analytical values (Table I) that indicate the material to be not a chemical individual, confirming results obtained earlier (2).

* *Methylene-bis-piperidine hydrobromide*, made by the action of 100 ml. (0.0041 mole) of hydrogen bromide on 0.75 g. (0.0041 mole) of methylene-bis-piperidine in dry ligroin, is identical with the salt made in the wet way.

* *Methylene-bis-piperidine picrate*. A mixture of 0.19 g. (0.001 mole) of methylene-bis-piperidine in the minimum of benzene and 0.46 g. (0.002 mole) of dry picric acid as a saturated solution in benzene was boiled briefly and then chilled. The yellow crystalline product melted at 110–112°. Mixture m.p. tests showed the compound to be neither picric acid nor piperidine picrate, and treatment with sodium carbonate solution regenerated methylene-bis-piperidine, recovered from the ether extract (b.p. 235°).

Methylene-bis-morpholine picrate was made in the same manner. It melted at 104–106° and was shown by mixture m.p. tests to be neither picric acid nor morpholine picrate, but it was not more fully characterized.

* *Trimeric methylenebenzylamine hydriodide*. Repetition of parts of Kempff's work (9) disclosed that the compounds he designated as methylene-bis-benzylamine salts are benzylamine salts; the collected evidence appears in Table III. The alleged methylene-bis-benzylamine was made by Ehrenberg's procedure (14) and by treatment with 57% hydriodic acid yielded, after prolonged chilling, a crystalline product of m.p. 106.1–106.5°. The analytical results for this compound are wide of the requirements for methylene-bis-benzylamine hydriodide or benzylamine hydriodide (excluded also by the m.p.), agreeing more closely with those for the monohydriodide of trimeric methylenebenzylamine.

Anal.^{9,10} Calc'd for $(C_6H_5CH_2NCH_2)_3 \cdot HI$: C, 59.38; H, 5.81; N, 8.66; I, 26.2.

Found: C, 58.70; H, 6.12; N, 8.57; I, 28.2.

As a test of structure the salt was submitted to cleavage by reduction (24), yielding dimethylbenzylamine (methiodide, m.p. 179°), methyl benzylamine (benzenesulfonamide,

¹⁰ Analysis for halogen: A sample of about 1 g. (± 0.01 g.) was dissolved in water containing nitric acid, and excess of 10% silver nitrate solution was added. After boiling and then cooling the mixture the silver halide was collected in a sintered-glass crucible, washed with water acidulated with nitric acid, then with acetone, and finally with ether, dried at 110° and weighed. The accuracy of this procedure was shown by trial to be $\pm 2\%$.

m.p. 92.9–93.9°), and some benzylamine (benzenesulfonamide, m.p. 86.7–87.7°); formation of secondary and tertiary amines in quantity indicates the probability of a cyclic structure. That Kempff's supposed methylene-*bis*-benzylamine is the trimeric Schiff base is supported by molecular weight values (determined cryoscopically in benzene) of 322 and 325; those required for methylene-*bis*-benzylamine and trimeric methylenebenzylamine are respectively 226 and 357. The hydriodide, by treatment with aqueous sodium carbonate, followed by ether extraction, evaporation of the ether, and crystallization of the residue from absolute ethanol, yielded methylenebenzylamine, m.p. 45–46°. It seems certain that the product made and isolated as described by Kempff is trimeric methylenebenzylamine, and that this compound forms a fairly definite hydriodide.

Acid-induced cleavages and reactions other than formation of alkylidene-bis-amine salts. Repetition of Grünhagen's experiment (10) with methylene chloride and *p*-toluidine (the latter used in excess to combine with the HCl of reaction) heated in a sealed tube at 100° for 36 hours, yielded a product of m.p. 161.2°, identified by mixture m.p. test as 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline.

TABLE III
ACTION OF ACIDS ON TRIMERIC METHYLENEBENZYLAMINE^a

ACID	PRODUCT		BENZYLAMINE SALT ^c M.P., °C.	MIXTURE M.P., °C.
	Cryst. from	M.P., °C. ^b		
HCl dil.....	Water	253	251–253	253–254
HBr dil.....	EtOH + water	220.4–222.4	222.0–222.8	219.9–222.4
HI dil.....	Benzene	176.6–178.8	178.9–179.7	176.2–178.7
H ₃ PO ₄ aq.....	Reaction mixture	236 d.	236.5 d.	239 d.
Oxalic in EtOH....	Abs. EtOH	175–176 d.	172.6–173.1 d.	171.8–172.8 d.
Picric.....	Reaction mixture (H ₂ O)	201.1–201.4	200.3–201.3	200–200.5

^a Conditions were in general those of Kempff's experiments (9). ^b Melting points are "observed" values. ^c Benzylamine salts were prepared from benzylamine and the acids under conditions similar to those in the experiments with methylenebenzylamine.

Repetition of Pulvermacher's experiment (8) in which methylene-*bis*-*o*- (and *m*-)nitroaniline, dissolved in dilute hydrochloric acid, was treated with picric acid in equivalent amount, showed the product of m.p. 120° to be picric acid. Repetition of the procedure claimed to yield the chloroplatinate of methylene-*bis*-*m*-nitroaniline (8) yielded, after chilling the acid reaction liquid for several days, golden yellow crystals which, dried *in vacuo*, melted indefinitely above 225°. Pulvermacher's analysis (Pt, 27.93) is excellent for the chloroplatinate claimed (calc'd Pt, 27.9), but our analysis⁹ yielded the result Pt, 28.1, affording no certain distinction between this salt and *m*-nitroaniline chloroplatinate (Pt, 28.4). Further the susceptibility of methylene-*bis*-*m*-nitroaniline to cleavage under the conditions of Pulvermacher's experiment is shown by the fact that treatment with dilute aqueous hydrochloric acid caused hydrolysis without heating, yielding *m*-nitroaniline.

Table II presents the experimental conditions and results of most of the experiments described below.

Experiments with methylene-bis-piperidine. The alleged chloroaurate, prepared by the procedure of Schmidt and Kohler (21) (m.p. 214.1–214.6°) in aqueous hydrochloric acid, was found to contain 45.93% of gold, a value between that for methylene-*bis*-piperidine dichloroaurate (45.73) and for piperidine chloroaurate (46.35). Attempts to isolate methylene-*bis*-piperidine from the product, either by treatment with piperidine in benzene solution or by action of aqueous sodium carbonate, were unsuccessful. The procedure for the preparation of the hydriodide and the hydrobromide of methylene-*bis*-piperidine (action of con-

concentrated aqueous acids at the boiling points of the solutions) yielded in both cases the amine salt.

The effect of alcohol is shown by the following results. 1. Methylene-*bis*-piperidine in 95% ethanol was treated with 36% hydrochloric acid, and ether was added to precipitate the product, which was piperidine hydrochloride (m.p. 237°); the use of 18% acid led to the same result. 2. Methylene-*bis*-piperidine in methanol (dried by magnesium) was treated with one equivalent of hydrogen chloride (720.5 ml. of hydrogen chloride for 5.28 g. of base) and the mixture was concentrated to a small volume and cooled, yielding piperidine hydrochloride (m.p. 237°). A similar experiment in which 2 equivalents of hydrogen chloride were used gave the same result. 3. Methylene-*bis*-piperidine, treated at room temperature with a solution of 2 equivalents of picric acid in dry methanol, yielded piperidine picrate, (m.p. 149.5–150.5°), identified by mixture m.p. test. 4. Treatment of methylene-*bis*-piperidine in absolute ethanol with 2 equivalents of hydrogen chloride yielded piperidine hydrochloride, m.p. 233°. The significance of these results appears when it is recalled that in the absence of alcohol methylene-*bis*-piperidine yields by similar procedures an isolable hydrochloride, hydrobromide, and picrate.

Cleavage of methylene-bis-morpholine by picric acid. 1. To 10 ml. of a saturated solution of picric acid in 95% ethanol was added 0.40 g. (0.0022 mole) of methylene-*bis*-morpholine, and the mixture was heated to boiling and then chilled, yielding crystals of m.p. 150.2–151.7°, shown to be identical with morpholine picrate made in the same way from morpholine and picric acid. 2. In a similar experiment under anhydrous conditions there were used ethanol dried by passing thru a column of silica gel, picric acid dried *in vacuo* over calcium chloride, methylene-*bis*-morpholine distilled just before use, and an oven-dried reaction vessel. The product from equivalent amounts of methylene-*bis*-morpholine and picric acid was morpholine picrate, m.p. 150.2–151.7°, identified by mixture m.p. test. 3. In a similar experiment with dry benzene as solvent and in the presence of 2 equivalents of dry ethanol (1 equivalent with respect to the amine represented) total cleavage occurred, yielding morpholine picrate. It is to be noted that in the absence of alcohol the product is methylene-*bis*-morpholine picrate.

Cleavages of other methylene-bis-amines. Methylene-bis-diethylamine. A chilled solution of 3.2 g. (0.02 mole) of methylene-*bis*-diethylamine in 2 ml. of ethanol was treated with 5.45 g. of 47% hydriodic acid (1 equiv.) and the mixture was concentrated by evaporation at room temperature under reduced pressure, yielding crystals of m.p. 172.4–172.9°, a value not changed by admixture with diethylamine hydriodide prepared in the same way from its components. *Methylene-bis-diisobutylamine* in similar manner yielded colorless plates which did not melt when heated to 300°. Analysis for iodine¹⁰ showed the product to be diisobutylamine hydriodide (I calc'd 49.3; found, 49.0); a specimen from amine and acid resembled it in appearance and failure to melt.

Methylene-bis-di-n-amylamine, treated in the same manner with an equivalent of hydriodic acid, yielded colorless crystals that remained solid at 300°, resembling di-*n*-amylamine hydriodide separately prepared. Analysis¹⁰ showed 45.4% iodine; the values for diamylamine hydriodide and methylene-*bis*-diamylamine hydriodide are respectively 44.6 and 28.0%.

Reactions of methylene-bis-arylamines. 1. Treatment of methylene-*bis-p*-toluidine in absolute ethanol with unmeasured but excessive hydrogen chloride, followed by addition of ether and chilling, yielded *p*-toluidine hydrochloride (m.p. 242.2°), from which *p*-toluidine was separated and identified. 2. Methylene-*bis-p*-toluidine (2.0 g., 0.0088 mole) in 1 ml. of ethanol was treated at 0° with 1.2 ml. of 57% hydriodic acid (0.0088 mole of HI); addition of ether and chilling for several hours led to separation of 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline hydriodide (m.p. 191.4–196.4°), identified by recovery of the quinazoline (m.p. 159°) and by analysis¹⁰ (Iodine: calc'd 35.8; found 35.3). 3. Methylene-*bis-p*-toluidine was treated with an equivalent of picric acid in the minimal absolute ethanol and the solution was warmed and then chilled. The separated picrate (m.p. 204°) was readily recognized as that of tolylmethyl-dihydroquinazoline (mixture m.p. test, and charac-

teristic reddening on exposure to light). It will be noted that in experiment 1 the combined effects of ethanol and excess of hydrogen chloride led to total cleavage, but that in experiments 2 and 3, with ethanol present and acid decreased to one equivalent, total cleavage gave place to the reaction sequence leading to the dihydroquinazoline. 4. Methylene-*bis*-*m*-nitroaniline was added to a solution of one equivalent of picric acid as a saturated solution in ethanol, followed by 2 drops of conc'd hydrochloric acid, and the solution was heated to boiling. The product that separated on chilling was *m*-nitroaniline picrate, m.p. 147.8–149.3°, identified by mixture m.p. test.

Experiments with benzylidene-bis-piperidine. In the following experiments attempts were made to isolate by-products formed by the action of acid and alcohol jointly. 1. Benzylidene-*bis*-piperidine (10.34 g., 0.04 mole) in dry ligroin containing 3.68 g. (0.08 mole, 1 equivalent with respect to amine represented) of absolute ethanol was treated with 1981 ml. of hydrogen chloride (0.08 mole). The product was piperidine hydrochloride (9.5 g., 98%), m.p. 238–240°d. 2. A similar experiment in the presence of butanol yielded, from 2.6 g. (0.01 mole) of benzylidene-*bis*-piperidine, 1.48 g. (0.02 mole) of butanol (dried over magnesium sulfate) and 498 ml. (0.02 mole) of hydrogen chloride, 2.45 g. of piperidine hydrochloride (99.6%). No acetal was found upon fractionating the mother-liquors in these experiments, but benzaldehyde was present in small amounts. As conditions during reaction and isolation were anhydrous it appears that the formation of benzaldehyde was not hydrolytic though, as the following experiment shows, benzylidene-*bis*-piperidine is easily hydrolyzed. 3. Benzylidene-*bis*-piperidine (2.59 g., 0.01 mole) was dissolved in 50 ml. of water at room temperature containing 4.9 ml. of conc'd hydrochloric acid (0.05 mole), and the liquid was extracted with ether. Distillation of the dried ether extract yielded 0.97 g. (92.4%) of benzaldehyde.

Conversion of methylene-bis-amines to Schiff bases. The relative sensitivities of five methylene-*bis*-amines to Schiff base formation under the influence of the acidity (inherent plus incidental) of laboratory alcohol were tested comparatively as follows. A solution of 1.0 g. of methylene-*bis*-amine in 9.5 ml. of 95% ethanol and 0.5 ml. of water in a test tube was kept in a bath maintained at 80°, and the time required for the appearance of a turbidity due to Schiff base (found in preliminary experiments to be virtually insoluble in the diluted alcohol) was noted. Methylene-*bis*-*p*-anisidine gave a dense turbidity in less than a minute; methylene-*bis*-aniline and methylene-*bis*-*p*-toluidine gave a scanty turbidity in 1 to 1.5 minute; methylene-*bis*-*p*-chloroaniline and methylene-*bis*-*p*-bromoaniline gave no turbidity in 90 minutes, when the test was concluded.

Relationship between the stabilities of methylene-bis-amine salts and the activities of their acids in acid-induced reactions. Simons (11) showed the conversion of methylene-*bis*-*p*-toluidine to 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline to be induced at different rates by hydrochloric acid free or variously combined or buffered, and elaborated a procedure for the isolation and estimation of the several possible products of such actions. Similar experiments were made using the three acids HCl, HBr, and HI, of which the first yields the least stable, and the last the most stable, methylene-*bis*-amine salts. In each experiment 2.26 g. (0.01 mole) of methylene-*bis*-*p*-toluidine was dissolved in 10 m. of 95% ethanol and to the solution was added 0.01 mole of 36% HCl, HBr, or HI. Each mixture was refluxed for 5 minutes and was then examined by Simons' procedure. The amounts of tolylmethyl-dihydroquinazoline, isolated and weighed as the picrate, were as follows: with HCl, 0.00258 mole; with HBr, 0.00239 mole; with HI, 0.00191 mole. When a similar reaction mixture, containing HCl, was not refluxed but was worked up as soon as the reactants were in solution, no dihydroquinazoline was obtained, but a trace of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline was detected.

SUMMARY

A study of the formation of salts of methylene-*bis*-amines and of the actions of acids on methylene-*bis*-amines produced the following findings. 1. Most

methylene-*bis*-amines are decomposed by acids, in the presence or absence of water or alcohol, with formation of the corresponding amine salts. 2. Of the methylene-*bis*-amines tested only methylene-*bis*-piperidine and methylene-*bis*-morpholine yielded isolable salts with acids (hydrochloric, hydrobromic, hydriodic, picric). The hydriodide and hydrobromide of methylene-*bis*-piperidine can be prepared in aqueous media. Hydrochlorides and picrates require anhydrous conditions and are decomposed by alcohol or water, yielding amine salts. 3. Methylene-*bis*-amines representing aromatic amines do not yield stable or isolable salts with the acids named, but are decomposed in either of two ways: (a) in absence of any molecule with which the grouping ArNCH_2 can condense by displacement of hydrogen (H^+), acid causes complete cleavage with formation of arylamine salt; (b) in presence of a molecule capable of coupling with the unit ArNCH_2 there may be initiated reaction sequences leading to other products, *e.g.*, dihydroquinazolines. 4. It is concluded that with acids methylene-*bis*-amines form salts which in some cases are sufficiently stable to persist, but which in general may not be isolable owing to decomposition involving the carbenium-ammonium ion $\left[\begin{array}{c} \text{RNCH}_2 \leftrightarrow \text{RN}=\text{CH}_2 \\ | \qquad \qquad | \\ \text{---} \qquad \qquad \text{---} \end{array} \right]^+$. The susceptibility of the NCH_2 linkage to cleavage by acids is general and in some cases pronounced, and is explainable by an hypothesis which is outlined.

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