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

SOME REACTIONS OF METHYLENE-BIS-AMINES AS AMMONO-ALDEHYDES

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The structural analogies between methylene-bis-amines,[2] considered as ammono-aldehydes or ammono-acetals, and the hydrate and acetals of formaldehyde, appear upon comparison of the formulas:

Ammonia System		Water System	
$NH_2 \cdot CH_2 \cdot NH_2$	Diaminomethane (1), known in form of derivatives:	$HO \cdot CH_2 \cdot OH$	Formaldehyde hydrate
$RNH \cdot CH_2 \cdot NHR$	Methylene diamines from primary amines		
$R_2N \cdot CH_2 \cdot NR_2$	Methylene diamines from secondary amines including those from cyclic secondary amines, *e.g.*, piperidine.	$RO \cdot CH_2 \cdot OR$	Formaldehyde acetals

Examples of reactions which validate this structural analogy are probably numerous, though this rationalization is generally not pointed out and may be unrecognized. Methylene imines may probably be considered as functionally equivalent to methylene diamines since Schiff bases of this type, even when trimeric, may be used interchangeably with methylene diamines in certain reactions (2), the two being related as are formaldehyde and formaldehyde hydrate:

$$HO \cdot CH_2 \cdot OH \rightleftharpoons CH_2O + H_2O$$

$$RNH \cdot CH_2 \cdot NHR \rightleftharpoons CH_2{:}NR + RNH_2 \text{ (3).}$$

The use of hexamethylenetetramine in the preparation of phenol-formaldehyde resins (4) involves $-\overset{|}{N} \cdot CH_2 \cdot \overset{|}{N}-$ units and may be considered to be a methylene diamine reaction. The condensation of succinimide and formaldehyde (5) to yield methylene-bis-N,N′-succinimide and tris-(methylenesuccinimido)amine

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[1] This paper is constructed from the thesis submitted by J. R. Feldman to the Graduate School of the University of Pennsylvania in partial satisfaction of the requirements for the degree of Doctor of Philosophy, June 1941.

[2] Throughout this paper the more convenient general term methylene diamine will be used. These compounds have been designated previously as "diimines."

has been duplicated by use of hexamethylenetetramine (6). Methylene diamines can be used instead of formaldehyde in the Knoevenagel reaction (7). Ullmann (8) prepared 10-methyl-7,12-dihydro-1,2-benzacridine (9) from naphthol-2 by interaction with either trioxymethylene and *p*-toluidine or with methylene-bis-*p*-toluidine, and obtained other acridines similarly.

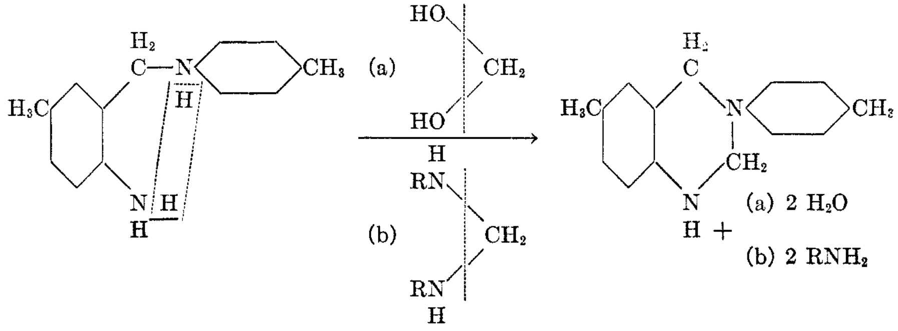
In the experimental demonstration that methylene diamines and formaldehyde (formalin) react in ways essentially identical, the method employed was to use methylene diamines and formalin interchangeably in certain reactions known to be characteristic of formaldehyde. In each group of comparable reactions the main product was the same whether the methylene diamine or formaldehyde was used. The manner of reaction of the methylene diamine was further revealed by the fact that the by-product (corresponding to the water split out in formaldehyde reactions) was the amine represented by the methylene diamine used. In many experiments the liberated amine was recovered and identified, and its amount found to correspond with that of the main product, making it possible to indicate the reaction by equation without assumptions.

The susceptibility to acid hydrolysis which is characteristic of methylene diamines made necessary some precautionary experiments under anhydrous conditions. Though in most cases the products were isolated by direct methods, this did not exclude the possibility that small amounts of water (present for example in the alcohol used as solvent, or even as traces present in chemicals or on apparatus) might operate cyclically to yield formaldehyde as the actual reactant, as well as the amine obtained as by-product. Failure to exclude this possibility would make uncertain any conclusions drawn from the results of the methylene diamine reactions, and the analogy involved would be entirely invalid if it were shown that the methylene diamine reactions could occur only in presence of at least traces of water. Several of the reactions were therefore attempted using materials and apparatus which had been scrupulously dried. It was found that under these conditions the reactions occurred smoothly, and it is concluded that the observed aldehydic behavior of the methylene diamines studied was indicative of an inherent aldehydic character based upon structure.

The methylene diamines used were derived from both primary and secondary amines, *viz.*, methylene-bis-*p*-toluidine (I), methylene-bis-*p*-chloroaniline (II), methylene-bis-*p*-bromoaniline (III), methylene-bis-*p*-anisidine (IV), methylene-bis-ethylaniline (V), methylene-bis-piperidine (VI), and methylene-bis-morpholine (VII). The last three compounds, with no amino hydrogen, are ammonia-system analogs of formaldehyde acetals. Since acetals can be used instead of aldehydes in some reactions (10), it was expected that methylene diamines of these types would show a functional analogy with formaldehyde, and this was found to be the case. In some experiments the trimeric Schiff base methylene-*p*-toluidine (VIII) was used, and yielded in each case the same products as did the corresponding methylene diamine.

The reactions studied, and the results obtained, are outlined below. The reactions, whether in the water system or the ammonia system, are of types which are known to be, or which may be assumed to be, reversible, though reversal may be inconsiderable in reactions leading to ring closures. No effort was made to disclose a reversible character in any of the ammonia-system reactions, and accordingly the reaction diagrams are given without indications of reversibility.

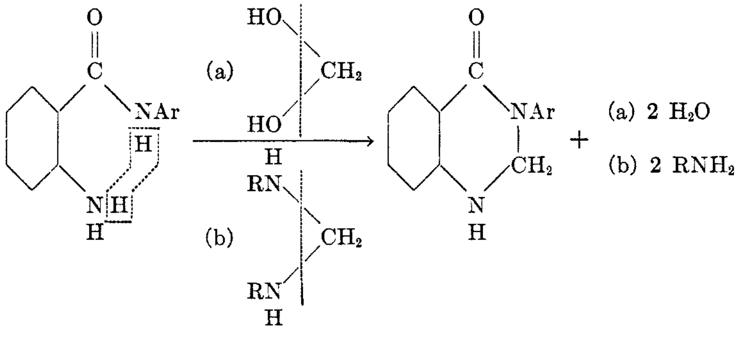
1. *Formation of 3-p-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline from o-amino-m-xylyl-p-toluidine by action of methylene diamines.*



IX X

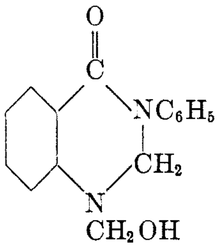
This ring closure, previously effected by means of formaldehyde (11) and also methylene-bis-*p*-toluidine (12), was found to occur when the other methylene diamines named above were used. The reaction took place when the methylene diamine and the aminobenzylamine were heated together in alcohol solution. It was unfavorably affected by presence of sodium ethoxide (*cf.* 2).

2. *Formation of 3-substituted-1,2,3,4-tetrahydroquinazolones from anthranilanilides by action of formaldehyde and of methylene diamines:*



Reaction (a), not previously reported, was found to occur upon treating the anthranilanilide, dissolved in alcohol containing alkali, with excess formalin at temperatures up to about 60°. The resulting tetrahydroquinazolones were identified as such by analysis and by oxidation to the corresponding dihydroquinazolones (13), which had been reported (14) or were synthesized from anthranilic acid and suitable formylamines (15). The anthranilanilides used were N-phenylanthranilamide (XI), N-(*p*-bromophenyl)anthramilamide (XII), and N-(*p*-anisyl)anthranilamide (XIII), and the resulting quinazolones were respectively 3-phenyl-1,2,3,4-tetrahydroquinazolone-4 (XIV), 3-*p*-bromophenyl-1,2,3,4-tetrahydroquinazolone-4 (XV), and 3-*p*-anisyl-1,2,3,4-tetrahydroquinazolone-4 (XVI).

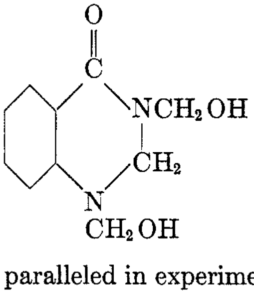
By interaction of anthranilanilide (XI) and formalin at lower temperatures and with the latter in larger excess the tetrahydroquinazolone (XIV, m.p. 175° obs.) was not obtained, but instead a compound of m.p. 109–110°obs. This product, with empirical formula $C_{15}H_{14}N_2O_2$, was identified (see Experimental Part) as 1-methylol-3-phenyl-1,2,3,4-tetrahydroquinazolone-4.



XVII

This compound is similar to certain methylol compounds previously reported (4a), and closely resembles the more stable bases prepared by Miller (16). The cleavage of formaldehyde from methylol compounds is familiar in the depolymerization of linear "polymers" of formaldehyde. Other examples include the condensation of 1-methylolpyrroles to yield dipyrrylmethanes (17), and the elimination of formaldehyde from methylol derivatives of methylene-N,N′-bisbenzamide reported by Einhorn (18).

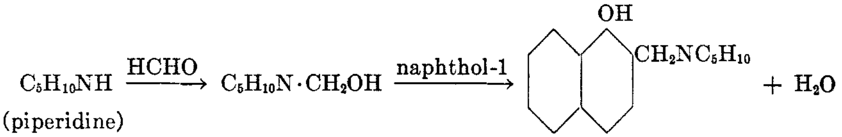
Interaction of anthranilamide and formaldehyde failed to yield the expected tetrahydroquinazolone, but gave a product (m.p. 141°) found by analysis to have the empirical formula $C_{10}H_{12}N_2O_3$. Evidence given in the experimental section indicates this compound to be 1,3-bis-methylol-1,2,3,4-tetrahydroquinazolone-4:



As this reaction could not be paralleled in experiments with anthranilamide and several methylene diamines it was not studied further.

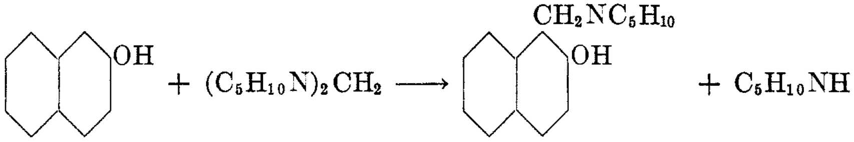
Reaction (b) was caused to occur by heating anthranilanilides and methylene diamines together in absolute alcohol, and was assisted by the presence of sodium ethoxide. This fact, and the favorable effect of alkali in the corresponding formaldehyde reaction (a) are comprehensible if it is noted that in each case the ring closure involves removal of an amino hydrogen and an amido hydrogen, and with respect to the latter change resembles the alkylation of an amide and is promoted by presence of alkali. In the ring closures by methylene diamines this effect must be attributed to the influence of the alkaline agent upon the amide hydrogen rather than upon the methylene diamines, which are relatively quite stable in alkaline environment (4a).[3] The absence of added alkali does not by any means exclude reaction (b), from which it appears that the methylene diamine itself, or the by-product amine, may serve as alkaline promotor.

3. *Formation of aminomethylphenols by interaction of methylene diamines and phenols.* The related water-system reaction is illustrated by the condensation of phenol and formaldehyde as applied in the preparation of resins. Aminomethylphenols have been obtained by interaction of phenols, formaldehyde, and secondary amines by Auwers and Dombrowski (19), Caldwell and Thompson (20), and Bruson and MacMullen (21). The reaction is believed to involve intermediate formation of the methylolamine, and condensation of this with the phenol, *e.g.*,



XVIII

The same final result might be expected if the reactive intermediate were the methylene diamine, the possibility of whose formation cannot well be excluded. Experiments showed that interaction of methylene diamines (or of VIII) with phenols, upon heating in absolute alcohol, yielded compounds identical with those obtainable from formaldehyde, phenols, and amines, the reaction in each case occurring with liberation of half the amine, *e.g.*,



XIX

Reactions of this type were realized with naphthol-1, naphthol-2, and carvacrol. The methylene diamines used were I, II, and VI. The aminomethylphenols obtained were 2-piperidinomethylnaphthol-1 (XVIII), 1-piperidinomethylnaphthol-2 (XIX), 1-*p*-toluidinomethylnaphthol-2 (XX), 1-*p*-chloroanilinomethylnaphthol-2 (XXI), and piperidinomethylcarvacrol (XXII). The reaction occurred also (naphthol-2 and VI) under anhydrous conditions.

The aminomethylphenols prepared were found to exhibit a partially cryptophenolic character. They were insoluble in cold aqueous alkali, but dissolved

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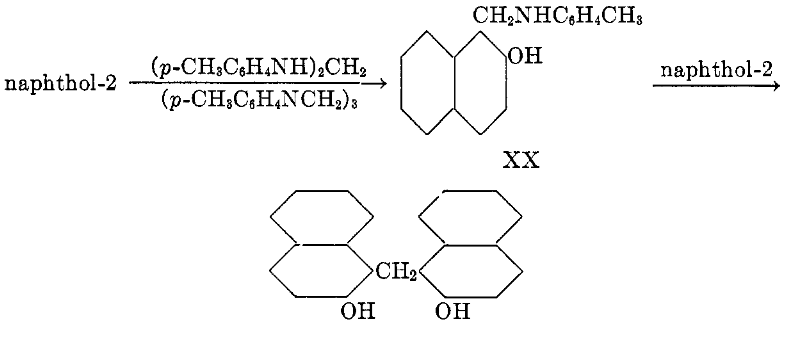
[3] Methylene-bis-piperidine can be distilled over sodium under reduced pressure without noticeable decomposition. Distillation of some methylene diamines leads to partial conversion to the trimeric Schiff bases (3).

on heating: 1-*p*-toluidinomethylnaphthol-2 thus dissolved was recovered with small loss upon acidification of the alkaline solution.

In the presence of alkali (compare the conditions above) the condensation of phenols, formaldehyde, and secondary amines was found by Auwers and Dombrowski (19) to go farther, yielding the bis-(hydroxyaryl)methane compounds. The same final result was obtained in the present study by interaction of naphthol-2 with I and with VIII.

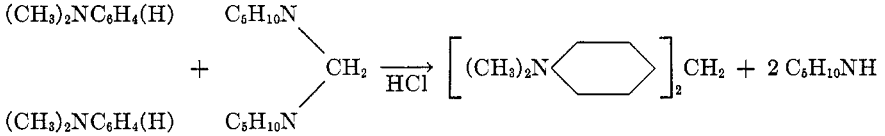


XX

XXIII

In the absence of added alkali, the same reactants yielded a mixture of XX and XXIII, indicating that the amine liberated in formation of the former can function as the alkaline agent needed to promote the second stage of the reaction. In the presence of sodium ethoxide, only the dinaphthylmethane compound (XXIII) was obtained. The over-all reaction is actually of the type considered in the following section, *viz.*, formation of diarylmethane bases from amines and formaldehyde, shown by v. Braun and Kruber (22) to involve an intermediate hydroxymethyl compound. The influence of alkali may perhaps be interpretable in a manner similar to that suggested by Hauser and Breslaw (23) for the coupling of phenols and diazonium compounds.

4. *Formation of 4,4′-dimethylaminodiphenylmethane (XXIV) from dimethylaniline by the action of methylene-bis-piperidine (VI).* The preparation of XXIV from dimethylaniline and either formaldehyde (24) or methylal (10a) is familiar. When dimethylaniline was heated with VI in absolute alcohol no reaction occurred. In the presence of hydrogen chloride the diphenylmethane base formed, with liberation of an equivalent amount of piperidine:

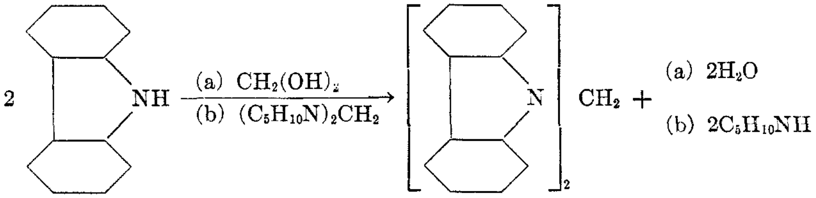


XXIV

5. *Interaction of carbazole with formaldehyde and with methylene-bis-piperidine.* The formation of methylene-bis-carbazole (XXV) by interaction of carbazole and formaldehyde or compounds containing methylene groups attached to oxygen or nitrogen was shown by Votoček and Veselý (25) to occur in acid solution.

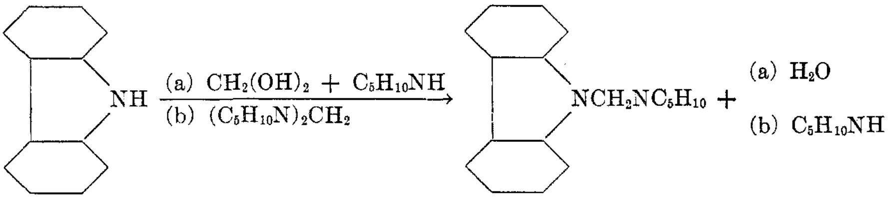
Trials using either formaldehyde or VI in glacial acetic acid yielded the expected methylene-bis-carbazole (XXV). When carbazole, piperidine, and formalin were heated in aqueous alcohol solution, in the absence of acid, the product (99%) was not XXV but 9-piperidinomethylcarbazole (XXVI). The same compound was obtained by heating together carbazole and VI in the absence of solvent or acid. The reactions involved in these experiments may be represented:

In acid solution:



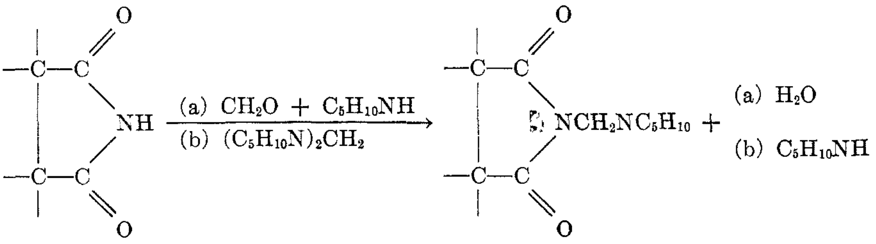
XXV

In absence of acid:



XXVI

6. *Formation of aminomethylimides by interaction of acid imides and methylene diamines.* The water-system equivalent of this reaction is illustrated by the formation of hydroxymethylamides (18) or hydroxymethylimides (26) by action of formaldehyde on amides or imides. Cherbuliez and Sulzer (27) obtained N-piperidinomethylsuccinimide (XXVIII) by interaction of N-hydroxymethylsuccinimide and piperidine, and Sachs (26) found that succinimide, formaldehyde, and piperidine reacted to yield the same compound. The corresponding ammonia-system reaction occurred readily when succinimide or phthalimide was warmed with methylene-bis-piperidine (VI) in absolute alcohol.



phthalimide
or
succinimide

XXVII or XXVIII

In these reactions succinimide and phthalimide (and also carbazole, section 5) may be regarded as weak acids, the acid character of which is increased in basic media (28).

7. *Interaction of methylene diamines and dimethyldihydroresorcinol.* Dimethyldihydroresorcinol ("methone", etc.), used as a reagent for aldehydes (29), was found to react with methylene diamines I, II, III, and IV to give high yields of methylene-bis-4,4-dimethylcyclohexadione-2,6 (methylene-bis-methone: XXIX) identical with the compound obtained from methone and formaldehyde.

EXPERIMENTAL

Analyses. Carbon and hydrogen were determined by a semimicro procedure, nitrogen by semimicro Kjeldahl (37), and halogen by a semimicro adaptation of Robertson's procedure (40a), using alkaline arsenite solution in the receiver (40b).

Starting Compounds. Methylene-bis-amines from *p*-substituted aromatic primary amines were prepared by the method of Bischoff and Reinfeld (3). The products were purified by crystallization from ethanol containing a small amount of potassium hydroxide, excepting methylene-bis-*p*-anisidine, which is extensively converted into the trimeric Schiff base by attempted crystallization from alcohol or ether (31, 2). The first fraction generally contained some trimeric Schiff base, but by diluting and chilling the mother liquor several fractions of pure methylene diamine were obtained. The compounds so prepared were methylene-bis-*p*-toluidine (I, m.p. 93.5–95° obs.), methylene-bis-*p*-chloroaniline (II, m.p. 64–66° obs.), methylene-bis-*p*-anisidine (IV, m.p. 63–65° obs.), and methylene-bis-*p*-bromoaniline (III, m.p. 90–92° obs.).

Methylene-bis-amines from secondary amines. Methylene-bis-ethylaniline (V, m.p. 74–75° obs.) was prepared by the method of v. Braun (32, 33). Methylene-bis-piperidine (VI, b.p. 69–72° at 2 mm.) was obtained in 90% yield by the method of Ehrenberg (34, 7). Methylene-bis-morpholine (VII, b.p. 99–107° at 2 mm.) was obtained similarly and in a yield of 69%. As this compound was not fully characterized by Mason and Zief (35) its identity was confirmed by analysis for nitrogen (calc'd for $C_9H_{18}N_2O_2$: N, 15.03; found: N, 14.99, 14.97).

Anthranilanilides were made by interaction of amines and isatoic anhydride (36). After evolution of carbon dioxide ceased, the mass was extracted with several portions of hot benzene, the solution was decolorized with charcoal, and the pure product obtained by chilling the filtered solution. The compounds so prepared were N-phenylanthranilamide (XI, m.p. 128.5–129°, obs.), N-*p*-bromophenylanthranilamide (XII, m.p. 154–155° obs.), and N-*p*-anisylanthranilamide (XIII, m.p. 123–123.7° obs.). The last-named compound has not been reported previously.

Anal. Calc'd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56.
Found: C, 69.67, 69.52; H, 5.86, 5.72; N, 11.51, 11.49.

REACTIONS

1. *Formation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline (X) from* o*-amino-*m*-xylyl-*p*-toluidine (IX) by action of methylene-bis-amines. General procedure.* About 0.01 mole (2.26 g.) of IX made by the procedure of Miller and Wagner (38), and an equivalent amount of the methylene diamine, were dissolved in 50–90 cc. of absolute ethanol, and the solution was boiled under reflux for an hour or longer. The volume was reduced to 10–15 cc. by removal of alcohol under reduced pressure. The concentrated solution was chilled, and the crude X was separated by filtration. To separate the rest of the X and the amine set free in the reaction (39), the mother liquor was diluted, acidified with dilute hydrochloric acid (1:20), and extracted with ether. The ether extract was evaporated to dryness and the residue of X combined with the main portion for crystallization from ligroin (90–120°). The purified tetrahydroquinazoline was identified by its m.p. (139° to 141°) and by mixed

m.p. test using a specimen prepared by action of formaldehyde on IX (11). The acid extract was evaporated to dryness, and the residue of amine hydrochloride weighed. When the amine was relatively volatile (piperidine, morpholine) it was isolated from the first filtrate: amine and alcohol were distilled, the last traces being removed by codistillation with two 25-cc. portions of toluene, and the distillate was acidified with hydrochloric acid and evaporated to dryness. The essential results of individual reactions are collected into Table I.

Reaction under anhydrous conditions. A mixture of 0.01 mole of IX (previously dried for several weeks over phosphorus pentoxide) and 0.011 mole of VI (distilled *in vacuo* over sodium) in 15 cc. of toluene (distilled through a 3-ball Snyder column and stored over sodium), in an all-glass apparatus which had been dried at 130–135° for forty-eight hours, was refluxed for two hours, with the open end of the condenser protected by calcium chloride and Ascarite tubes. The reaction products were isolated as outlined above; X was purified by crystallization from a mixture of dry toluene and ligroin. The yield of X was 92%; piperidine was recovered quantitatively as hydrochloride.

TABLE I

FORMATION OF 3-*p*-TOLYL-6-METHYL-1,2,3,4-TETRAHYDROQUINAZOLINE (X) FROM *o*-AMINO-*m*-XYLYL-*p*-TOLUIDINE (IX) BY RING CLOSURE WITH METHYLENE DIAMINES

METHYLENE DIAMINE	TETRAHYDRO-QUINAZOLINE (X) % YIELD	AMINE	AMINE %	IDENT.
I	79 (86)[a]	*p*-toluidine	86	Bz-deriv. m.p. 152–153° obs.
II	76 (95)[a]	*p*-chloroaniline	86	Bz-deriv. m.p. 188°
III	77	*p*-bromoaniline	84	Bz-deriv. m.p. 201°
IV	70	*p*-anisidine	99[b]	Bz-deriv. m.p. 154.5–155°
VI	95	piperidine	99	B·HCl, m.p. 242.5–244°
VII	88	morpholine	73	B·HCl, m.p. 168–172°
VII	25[c]	morpholine	—	—
V	95	ethylaniline	—	—

[a] Crude yields in parentheses.

[b] The methylene diamine which escaped reaction with IX was probably decomposed during the isolation procedure, since the instability of this methylene diamine is exceptional (3, 31).

[c] Reaction in the presence of sodium ethoxide.

2. *Formation of 3-substituted tetrahydroquinazolones from anthranilanilides by action of formaldehyde and of methylene diamines. A. Ring closure with formaldehyde. General procedure.* The anthranilanilide (0.005–0.01 mole) was dissolved in 10–20 cc. of ethanol alkaline with sodium hydroxide, 2–5 cc. of 37% formalin (five times the theoretical formaldehyde) was added, and the solution was warmed to about 60° and then chilled. The separated product was crystallized from alcohol.

3-*p*-Bromophenyl-1,2,3,4-tetrahydroquinazolone-4 (XV) was obtained in 82% yield (0.85 g. from 1.00 g. of XII); the m.p. was 194–195° obs., or 199–200° corr.

Anal. Calc'd. for $C_{14}H_{11}BrN_2O$: C, 55.46; H, 3.66; N, 9.24; Br, 26.36; mol. wt., 303.

Found: C, 55.67, 55.85; H, 3.67, 3.63; N, 9.27, 8.98; Br, 26.12, 26.38; mol. wt. (Rast method), 296, 310.

3-*p*-Methoxy-1,2,3,4-tetrahydroquinazolone-4 (XVI) was obtained in 91% yield (1.15 g. from 1.20 g. of XIII). After crystallization from ethanol the compound melted at 185–185.5° obs.

Anal. Calc'd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.56; N, 11.01.

Found: C, 71.00, 70.91; H, 5.76, 5.66; N, 10.83, 10.86.

3-Phenyl-1,2,3,4-tetrahydroquinazolone-4 (XIV) was obtained in 96% yield (2.15 g. from 2.11 g. of XI). The purified compound melted at 176° obs., or 180° corr.

Anal. Calc'd. for $C_{14}H_{12}N_2O$: C, 74.90; H, 5.38; N, 12.49.

Found: C, 75.07, 74.92; H, 5.65, 5.55; N, 12.27, 12.22.

1-Methylol-3-phenyl-1,2,3,4-tetrahydroquinazolone-4 (XVII). When preparation of XIV was attempted at lower temperature and with relatively more formaldehyde, the product was a lower-melting compound eventually identified as XVII. A warm solution of 1.2 g. of XI in 30 cc. of ethanol previously made alkaline to litmus with sodium hydroxide was treated with 5 cc. of 37% formalin, and was then chilled. The crystalline product weighed 0.80 g., and melted at 109–110° obs., or 110–111° corr., in a capillary tube. Dilution of the filtrate with water yielded a second crop (0.35 g.) of m.p. 108° obs., with effervescence. Mixed melting point tests showed that the compound was not impure XIV nor XI. When it was heated slowly on a Fisher-Johns melting point block or in a micro melting point apparatus the compound melted at 105–110° with gas evolution. The mass was then seen to resolidify, and showed no further change until it melted at 172–175° obs., the m.p. of XIV. The following experiment established that the new compound is converted by heat into 3-phenyltetrahydroquinazolone-4 with elimination of formaldehyde.

The compound of m.p. 110° (0.40 g.) was dissolved in 10 cc. of absolute ethanol in a distilling flask, and the alcohol was distilled into a solution of dimethyldihydroresorcinol. Distillation was repeated after addition of more absolute alcohol to the residue, and then twice with 20-cc. portions of water. The combined distillates yielded 0.25 g. of methylene-bis-methone (XXIX) of m.p. 190–191° obs. The residue in the distillation flask (0.25 g.) was XIV, m.p. 176–178° obs., and was identified by mixed m.p. tests.

Anal. Found: C, 71.01, 70.82; H, 5.24, 5.51; N, 11.01, 10.95.

These results are consistent with the molecular formula $C_{15}H_{14}N_2O_2$; Calc'd.: C, 70.85; H, 5.55; N, 11.02.

Interaction of anthranilamide and formaldehyde.[4] Treatment of 12.0 g. of anthranilamide (41) with formaldehyde by the general procedure (150 cc. of 95% ethanol made alkaline with sodium hydroxide; 30 cc. of 37% formalin) yielded 11.0 g. of a colorless crystalline product which melted at 139–141°, with gas evolution. Crystallization from alcohol yielded material of m.p. 141° obs., but was not uniformly satisfactory, as in solution the compound was decomposed by even gentle warming.

In absence of alkali, the interaction of anthranilamide and formaldehyde in ethanol at 70–75° yielded a colorless, viscous product which solidified when the mixture was chilled in ice. The separated substance softened at 65–70° and evolved a gas with the odor of formaldehyde, after which the mass resolidified, and on further heating sublimed around 170°. This product was not examined further.

The compound of m.p. 141° was found to yield formaldehyde on heating or by action of water or of aqueous ammonia. The cold water extract gave a strong test with Schiff's reagent. After concentrating the formaldehyde by distillation of the extract, it was precipitated as the dimethyldihydroresorcinol derivative (m.p. 190–192°) and identified by mixed m.p. test. A similar result was obtained when the compound was dissolved in alcohol and the alcohol distilled: the distillate contained formaldehyde, identified as the methone derivative. Aqueous ammonia dissolved the compound, and after acidification of the mixture with acetic acid and removal of solid material by filtration, the filtrate was treated with Thatcher's reagent (44). The red-orange crystalline product darkened at 110–115°, shrank at 165–170°, and at 210° melted to a dark red liquid, indicating it to be urotropin tetraiodide.

The essential structure of the compound of m.p. 141° was indicated by its conversion to

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[4] The preliminary experiments and analysis are the work of the junior author. For preparative details, and for tests to determine the structure of the product, credit is due S. N. Hall.

3,4-dihydroquinazolone-4 by mild oxidation with potassium permanganate in acetone (see section D below). The product (1.7 g. from 2.5 g. of compound) melted at 210–214°, and at 210–212° obs. after crystallization from water. A mixture with a specimen of 3,4-dihydroquinazolone-4 made by Niementowski synthesis from anthranilic acid and formanilide melted at 209–211°. The picrates (m.p. 206–208°) of the two specimens were likewise identical.

Anal. Found: C, 57.35, 57.72; H, 5.61, 5.81; N, 13.28, 13.33.

These analytical values are consistent with the molecular formula $C_{10}H_{12}N_2O_3$ (Calc'd: C, 57.68; H, 5.81; N, 13.46).

All the foregoing evidence supports the conclusion that the compound is 1,3-bis-methylol-1,2,3,4-tetrahydroquinazolone-4.

B. Ring closure with methylene diamines. General procedure. A solution of the anthranilanilide (0.005–0.01 mole) and an equivalent amount of the methylene diamine in absolute alcohol was heated under reflux for periods of several hours up to twenty-four hours. In some experiments 0.1 g. of sodium was previously dissolved in the alcohol, in order to effect the reaction in presence of sodium ethoxide. The crystalline quinazolone separated when the solution was chilled. The mother liquor generally yielded one or more additional crops of product. The filtrate was evaporated and the residue was subjected to steam distillation. The residue in the flask was crystallized from ethanol in fractions, and the crude tetrahydroquinazolone was recrystallized from alcohol. The steam distillate was filtered to remove unchanged methylene diamine (in part present as trimeric Schiff base), and the filtrate was acidified slightly with 1:20 hydrochloric acid. Evaporation of the acid liquid left the amine as hydrochloride. This was weighed, and the amine was identified. In experiments with VI and VII the liberated piperidine and morpholine were isolated by the procedure outlined under 1. The essential results of individual reactions are collected into Table II.

C. Interaction of anthranilamide and methylene diamines. As shown in section A, the interaction of anthranilamide and formaldehyde yielded a compound other than the expected tetrahydroquinazolone-4. Experiments in which I, IV, and V were used instead of formaldehyde failed to yield any isolable or recognizable products other than unchanged amide, methylene diamine (or Schiff base formed from it), and free amine.

D. Proof of structure of tetrahydroquinazolones. General procedure (13). A solution of 0.003–0.01 mole of the tetrahydroquinazolone in 150–300 cc. of dry acetone was cooled to 0° and treated with 10% more than the calculated amount of potassium permanganate dissolved in acetone, added during two or three hours while stirring and chilling the mixture. Excess of sodium bisulfite was added, and the mixture was kept in a refrigerator for two days, after which it was filtered. The filtrate was freed of acetone by distillation, and the residue was crystallized from ethanol. The essential results of these experiments, and the evidence as to identities of XIV, XV, and XVI, are as follows:

Compound XIV yielded 48% [including tailings recovered as picrate, m.p. 177–178° (42)] of 3-phenyl-3,4-dihydroquinazolone-4, m.p. 138–139° obs. A mixture with a specimen (m.p. 139–140°) made from anthranilic acid and formanilide (15) melted at 138.5–139.5°.

Compound XV yielded 36% of 3-*p*-bromophenyl-3,4-dihydroquinazolone-4, m.p. 189–190° obs. A mixture with a specimen (m.p. 190–191°) made synthetically (15) from anthranilic acid and formyl-*p*-bromoaniline melted at 190–190.5°. As Paal and Koch reported the m.p. to be 174° (14b), the compound was analyzed for bromine. Calc'd for $C_{14}H_9BrN_2O$: Br, 26.54. Found: Br, 26.43, 26.24, 26.59, 26.32.

Compound XVI yielded 87% of 3-*p*-anisyl-3,4-dihydroquinazolone-4, m.p. 193.5–194° obs. A mixture with a specimen made by synthesis (m.p. 193–194°; see below) melted at 193–194°.

3-*p*-Methoxyphenyl-3,4-dihydroquinazolone-4, not previously reported, was prepared (15) by heating anthranilic acid and formyl-*p*-anisidine for ninety minutes at 150°. The product was crystallized successively from alcohol, benzene, and light ligroin. The yield of pure material, m.p. 193–194°, was 28%.

Anal. Calc'd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.80; N, 11.10.

Found: C, 71.12, 71.32; H, 4.73, 4.59; N, 11.28, 11.14.

3-*p*-Bromophenyl-3,4-dihydroquinazolone-4 picrate, prepared from the base and an equivalent amount of picric acid in alcohol, melted at 171–173°. Analysis for bromine gave the values 14.71 and 15.07; calc'd for $C_{20}H_{14}BrN_3O_8$: Br, 15.02.

TABLE II

FORMATION OF 3-ARYL-1,2,3,4-TETRAHYDROQUINAZOLONES FROM ANTHRANILANILIDES BY RING CLOSURE WITH METHYLENE DIAMINES

METHYLENE DIAMINE	PRODUCT								
	3-phenyltetrahydroquinazolone (XIV)			3-*p*-bromophenyltetrahydroquinazolone (XV)			3-*p*-anisyltetrahydroquinazolone (XVI)		
	Conditions[a]	Yield %	Amine %	Conditions[a]	Yield %	Amine %	Conditions[a]	Yield %	Amine %
I	n.s. 115° 5 hrs.	26	30[b]		56			53	63[c]
II					14	—		49	46[d]
III				3.5 hrs.	73	ident.		55	66[e]
IV					70	84		86	92
V	NaOEt	47	—	NaOEt	40	—	NaOEt	22[f]	—
VI	8 hrs.	65	58	5 hrs.	40	—[g]	24 hrs.	52	39[h]
VI	NaOEt	87	78	NaOEt 9 hrs.	71	58	NaOEt	87	ident.
VII	n.s. 145° 2 hrs.	26	33	n.s. 145° 10 hrs.	33[i]	45	n.s. 145° 10 hrs.	39[i]	40
VII				NaOEt	36	38[j]			
VII				18 hrs.	12	10[k]			

[a] Reaction in boiling alcohol, 2 hours, unless other time stated; n.s. = no solvent (fusion); no NaOEt unless stated.

[b] Recovered considerable unchanged XI, and 72% of I.

[c] Recovered unchanged 39% of XIII and 40% of I.

[d] " " 31% of XIII and 53% of II.

[e] " " 33% of III.

[f] " " 31% of XIII.

[g] " " 53% of XII.

[h] " " 29% of XIII.

[i] Nearly half of this yield was obtained by evaporation of the first filtrate and by heating the residue *in vacuo* at 235°.

[j] Recovered unchanged 43% of XII.

[k] " " 29% of XII.

3. Formation of aminomethylphenols and methylene-bis-(hydroxyaryl) compounds by interaction of methylene diamines and phenols. A. Aminomethylphenols. General procedure. A mixture of about 0.02 mole of the phenol (naphthol-1, naphthol-2, or carvacrol), an equivalent amount of the methylene diamine (I, II, or VI) and 20 cc. of absolute ethanol was heated under reflux for fifteen to sixty minutes. The crystalline product separated when the solution was chilled; in some experiments the mother liquor was worked up to obtain additional crops of product, or unchanged methylene diamine. To recover the amine liberated in the reaction, the filtrate was distilled under reduced pressure (to avoid formation of colored resins which otherwise appeared at about 130°), and the uncondensed vapors passed through a trap charged with hydrochloric acid. The distillate and the liquid from the trap were combined and evaporated to dryness. The residue of amine hydrochloride was weighed and the amine identified. The residue from the distillation was recrystallized from alcohol to obtain an additional crop of the aminomethylphenol. Essential results of the experiments are given in Table III.

TABLE III

FORMATION OF AMINOMETHYLPHENOLS FROM PHENOLS BY ACTION OF METHYLENE-BIS-AMINES

PHENOL	METHYLENE DIAMINE	AMINOMETHYLPHENOL			AMINE	
		Name	M.p. °C.	Yield %	%	Ident.
Naphthol-1	VI	2-Piperidinomethyl-naphthol-1 (19)	133.5–134.5	77[a]	97	B·HCl, m.p. 242.4°
Naphthol-2	VI	1-Piperidinomethyl-naphthol-2 (19)	95– 96.5	97	97	B·HCl, m.p. 239–241°
Naphthol-2	VI	1-Piperidinomethyl-naphthol-2	95– 96.5	61[b]	62	
Naphthol-2	I	1-*p*-Toluidinomethyl-naphthol-2	136.5–137	80[c]	84	
Naphthol-2	II	1-*p*-Chloroanilino-methylnaphthol-2	139–141.5	81	95	
Carvacrol	VI	Piperidinomethyl-carvacrol (20)	182–183	24	29	B·HCl, m.p. 235–239°

[a] Reaction at room temperature gave an almost identical result: yield 78%.

[b] Reaction under anhydrous conditions; solvent was dry 90–120° ligroin.

[c] Recovered 15.5% of I, m.p. 88–91°.

1-(N-p-toluidinomethyl)naphthol-2 (XX). The composition of this compound, not previously reported, was determined by analysis.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 81.9; H, 6.51; N, 5.32.
Found: C, 81.9; 81.6; H, 6.47, 6.27; N, 5.19, 5.25.

Compound XX was not dissolved by 10% sodium hydroxide solution cold, but it dissolved on heating. Acidification of the solution produced a gummy precipitate from which, after washings with ether and 10% alkali, most of XX (m.p. 136–137°) was recovered. An ether solution of XX was not affected by shaking with cold aqueous sodium hydroxide solution; the starting material was recovered quantitatively from the ether layer. These results indicate that the *p*-toluidinomethyl group is not attached to oxygen, and that the phenolic character of XX is relatively weak.

1-(N-*p*-chloroanilino)naphthol-2 (XXI), not previously reported, was characterized by analysis.

Anal. Calc'd for $C_{17}H_{14}ClNO$: C, 71.95; H, 4.97; N, 4.94.
Found: C, 72.03, 71.85; H, 5.03, 4.99; N, 4.88, 4.87.

B. 1,1'-Methylene-bis-naphthol-2 (XXIII). This compound (43) was obtained as the sole product when naphthol-2 and VIII (trimeric methylene-*p*-toluidine) were heated in the presence of sodium ethoxide in alcohol solution. A mixture of 2.88 g. (0.02 mole) of naphthol-2, 2.38 g. (0.0067 mole) of VIII, 25 cc. of absolute ethanol and 0.3 g. of sodium ethoxide (0.1 g. of sodium previously dissolved in the alcohol) was heated under reflux for several hours. The solution was saturated with carbon dioxide, and the precipitated sodium carbonate was removed by filtration. Dilution of the filtrate caused the separation of 0.25 g. of XXIII (m.p. 194–195°; identified by mixed m.p. test), after removal of which the filtrate was made acid to litmus by addition of acetic acid and was chilled, yielding 1.3 g. of XXIII (total yield 52%), and a small amount of tarry material.

In the absence of added alkali, the interaction of naphthol-2 and I or VIII formed toluidinomethylnaphthol (XX) as the main product, but smaller amounts of methylene-bis-naphthol (XXIII) were isolated in several experiments, as illustrated by the following. A mixture of 2.20 g. (0.01 mole) of I, 1.58 g. (0.011 mole) of naphthol-2 and 20 cc. of absolute ethanol was heated under reflux for ninety minutes. The reaction mixture yielded 1.55 g. (59%) of XX (toluidinomethylnaphthol, m.p. 136–136.5°; identified by mixed m.p. test), 0.20 g. (22%) of XXIII (methylene-bis-naphthol, m.p. 197–198°), 0.1 g. of unchanged naphthol-2, and 2.3 g. (80%) of *p*-toluidine hydrochloride. To separate these compounds the reaction mixture was chilled, and the crystalline precipitate of XX was removed. The filtrate was diluted with 10% sodium hydroxide solution, the mixture was extracted with ether, and the ether extract was washed with 10% sodium hydroxide and with several portions of water (extract A). The ether solution was then extracted with 1:20 hydrochloric acid (extract B). The extract A was acidified with hydrochloric acid and the mixture was extracted with ether (extract C). Aqueous extract A contained 0.15 g. of XX, and extract C yielded 0.5 g. more, and also the naphthol. Extract B contained the *p*-toluidine as hydrochloride.

4. Formation of 4,4′-dimethylaminodiphenylmethane (XXIV) from dimethylaniline by action of methylene-bis-piperidine. A mixture of 3.63 g. (0.03 mole) of dimethylaniline and 1.82 g. (0.01 mole) of VI was saturated with hydrogen chloride. The resulting solid mass was dissolved in 10 cc. of hot absolute alcohol, and the solution was heated under reflux for several hours. The liquid was made alkaline by addition of an alcohol solution of sodium ethoxide. Piperidine and ethanol were removed by distillation and the removal was completed by codistillation with toluene. The piperidine hydrochloride recovered from the distillate weighed 0.7 g. (29%). The residue in the distillation flask was transferred to a filter and there washed several times with ethanol. The alcohol was removed by distillation, and the residue was submitted to steam distillation to remove remaining dimethylaniline. The residue of crude XXV in the flask was crystallized from dilute alcohol. The yield was 0.55 g. (22%), and the m.p. 88–90° obs. A mixture of the product and a specimen of XXIV made from dimethylaniline and formaldehyde had the same m.p.

When dimethylaniline and I were heated together in the absence of acid there was no evidence that reaction occurred.

5. Interaction of carbazole with formaldehyde and with methylene-bis-piperidine (VI). A. Formation of methylene-bis-carbazole (XXV). I. Carbazole and formaldehyde. A mixture of 1.5 cc. of 37% formalin and 2–3 cc. of glacial acetic acid was added to a hot solution of 3.34 g. (0.02 mole) of carbazole in 50 cc. of glacial acetic acid. The solution was chilled and diluted with water. The colorless needles of XXV were removed (1.15 g., m.p. 301–303° obs.), and a second crop was obtained from the filtrate by further dilution and chilling (0.65 g.; m.p. 296–301°); the total yield was 52%. A third crop melted between 220° and 240° and was probably mostly unchanged carbazole (m.p. 244.8°).

When the same reactants were brought together in the presence of a small amount of conc'd hydrochloric acid, the product was a dense bluish-white solid with no definite m.p. Recrystallization from aniline gave a product which melted at about 255°. Votoček and Veselý (25) obtained a bluish-white compound whether the reaction occurred in presence of acetic or mineral acid, and reported its m.p. to be 280°. It seems probable that their colored product was impure, and that the colorless compound of m.p. 301–303° is XXV.

Anal. Calc'd for $C_{25}H_{18}N_2$: C, 86.68; H, 5.24; N, 8.09.

Found: C, 86.26, 86.25; H, 5.09, 5.16; N, 7.95, 7.98.

II. Formation of XXV from carbazole and methylene-bis-piperidine (VI). In a mixture of 50 cc. of glacial acetic acid and 1.5 cc. of acetic anhydride (to establish anhydrous conditions), 3.34 g. (0.02 mole) of carbazole was dissolved. The solution was heated and 1.82 g. (0.01 mole) of VI was introduced. Reaction occurred at once, and a precipitate of colorless needles appeared. The mixture was saturated with hydrogen chloride, which colored the precipitate pale blue. The product weighed 2.7 g. (77%), and melted at about 258°. After recrystallization from aniline and then from ether the compound weighed 0.7 g. (20%) and melted at 300–305° obs. A mixture with the compound made with formaldehyde melted at 304–305° obs.

B. Formation of 9-(N-piperidinomethyl)carbazole (XXVI). This compound, not previously reported, was obtained by interaction of carbazole and VI, or of carbazole, piperidine, and formaldehyde, in the absence of acid; *cf.* A, above.

I. Formation of XXVI from carbazole, piperidine, and formaldehyde. A mixture of 3.34 g. (0.02 mole) of carbazole, 40 cc. of 85% alcohol, 1.8 cc. of 37% formalin (0.022 mole of formaldehyde), and 1.7 g. (0.02 mole) of piperidine was heated under reflux for thirty minutes on a water-bath. The solution was chilled and the crystalline precipitate was removed (4.45 g.; melted at 95–96° to an opalescent liquid). Progressive dilution of the mother liquor caused separation of two additional crops (0.65 g., m.p. 97–98°; 0.15 g., m.p. 92–95°). The total yield (5.25 g.) was 99%. The first fraction, recrystallized from alcohol, melted at 99–99.5°.

Anal. Calc'd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.59.
Found: C, 81.68, 81.45; H, 7.43, 7.45; N, 10.61, 10.50.

II. Formation of XXVI from carbazole and methylene-bis-piperidine (VI). A mixture of 3.34 g. (0.02 mole) of carbazole and 1.82 g. (0.01 mole) of VI was heated for an hour at 180–185°. These proportions were used because it was expected that this experiment would yield XXV. As the product was XXVI, twice the needed carbazole was present. The isolation procedure gave two crops of XXVI (1.05 g., m.p. 91–93°; 1.2 g., m.p. 95–96°; total yield 43%), 1.55 g. (46%) of unchanged carbazole, and 1.12 g. (47%) of piperidine hydrochloride, m.p. 234–235° obs.

6. Formation of aminomethylimides by interaction of acid imides and methylene-bis-amines. A. N-(N'-piperidinomethyl)phthalimide (XVII). I. Formation from phthalimide, piperidine, and formaldehyde (26). A mixture of 1.7 g. (0.02 mole) of piperidine, 10 cc. of 80% alcohol, 1.7 cc. of 37% formalin (0.022 mole of formaldehyde), and 2.94 g. (0.02 mole) of phthalimide was warmed on a water-bath just long enough to obtain a clear solution, which was immediately chilled. The product XXVII was isolated in two fractions: 4.5 g., m.p. 119–119.5°, and 0.15 g., m.p. 117–118°; total 4.65 g., or 95%. Sachs (26) reported for XXVII the m.p. 117–118°. The yield was decreased to 21% in an experiment in which the reactants were refluxed for fifteen minutes in 50% alcohol (26).

II. Formation of XXVII from phthalimide and VI. A mixture of 2.92 g. (0.02 mole) of phthalimide, 3.64 g. (0.02 mole) of VI, and 20 cc. of absolute ethanol was heated for two hours on a steam-bath. The solution was chilled, and 0.85 g. of XXVII (m.p. 119–119.5°) was removed. The filtrate yielded two additional crops of crystals by progressive dilution with water (3.2 g., m.p. 115–116°; 0.45 g., m.p. 118–119°). The yield of XXVII was 92%. The piperidine hydrochloride weighed 1.9 g. (79%), and melted at 243–244° obs.

B. N-(N'-piperidinomethyl)succinimide (XXVIII). I. Formation from succinimide, piperidine and formaldehyde. A mixture of 1.7 g. (0.02 mole) of piperidine, 10 cc. of 95% alcohol, 1.8 cc. of 37% formalin, and 1.98 g. (0.02 mole) of succinimide was warmed until a clear solution resulted, when 30 cc. of water was added. After several hours the crystalline precipitate was removed. The yield was 1.8 g. (46%) of XXVIII. The m.p. (107–107.5°) duplicates that reported for XXVIII by Cherbuliez and Sulzer, who prepared it (m.p. 106–107°) from N-hydroxymethylsuccinimide (27).

II. Formation of XXVIII from succinimide and VI. A mixture of 1.98 g. (0.02 mole) of succinimide, 3.64 g. (0.02 mole) of VI, and 10 cc. of absolute alcohol was refluxed for fifteen minutes. The isolation procedure, similar to that in A, II above, yielded in several fractions 3.8 g. (97%) of impure XXVIII (melted 98° to 107°). After recrystallization the product weighed 3.5 g. (89%) and melted at 106–107° obs. A mixed m.p. test showed it to be identical with XXVIII made by use of formaldehyde and piperidine. The piperidine liberated in the reaction was recovered as hydrochloride (2.25 g., or 93%).

7. Formation of methylene-bis-methone (XXIX) by interaction of methylene diamines with *dimethyldihydroresorcinol (methone). General procedure.* Methone (1.4 g.; 0.01 mole) and methylene diamine (0.005 mole) were dissolved in 10–15 cc. of absolute alcohol or di-*n*-butyl ether with minimal warming. [By continued heating the yields of XXIX were decreased, with formation of a higher-melting substance, probably the "anhydride" (29a, 30), formation of which is favored in anhydrous solvents.] The solution was chilled, and the product was removed by filtration. The filtrate was diluted with ether (and water, when the reaction solvent was alcohol), and the liquid was extracted with dilute hydrochloric acid. This acid extract was evaporated to recover the amine as hydrochloride. The ether layer was heated under reduced pressure to remove solvents, yielding a second crop of XXIV. In each experiment the product was identified by mixed m.p. test using a specimen made from methone and formaldehyde. In the following summarized results are given in sequence the number of the methylene diamine, the solvent, the yield of XXIX, its m.p., and the yield of amine liberated in the reaction.

I, alcohol, 93%, 187°, —. I, butyl ether, 96%, 188–189°, 97%.

II, alcohol, 99%, 189–190°, 100%. II, butyl ether, 96%, 188–189°, 100%.

III, butyl ether, 96%, 187–188°, —.

IV, butyl ether, 58%, 188–189°, 78%.

In the last experiment the product first isolated was impure (two crops melted 160° to 176°). Purification decreased the indicated initial yield of 99% to 58%.

SUMMARY

The structural analogy between hydrated formaldehyde and methylene-bis-amines, considered as ammonia-system aldehydes, was validated by experimental demonstrations of a clear functional analogy, established by realizing with methylene-bis-amines or formaldehyde, used interchangeably, reactions characteristic of the latter. In each reaction studied both reagents led to the formation of the same principal product; the by-product of the ammonia-system reaction was the liberated amine, corresponding to the water split out when formaldehyde was used.

Methylene diamines of several types (from aromatic primary amines, ethylaniline, piperidine, morpholine) were used, in order to show that the reactions may be attributed to the essentially aldehydic character of the grouping

$$-\overset{|}{N}CH_2\overset{|}{N}-.$$

Several reactions were effected under anhydrous conditions, to exclude the possibility that small amounts of water, operating cyclically, caused hydrolysis of the methylene diamine and liberation of formaldehyde as the actual reactant.

Reactions of formaldehyde and methylene diamines were compared using the following compounds: (a) *o*-amino-*m*-xylyl-*p*-toluidine, (b) N-arylanthranilamides (phenyl, *p*-bromophenyl-, *p*-anisyl), (c) phenols (naphthol-1, naphthol-2, carvacrol), (d) dimethylaniline, (e) carbazole, (f) phthalimide and succinimide, (g) dimethyldihydroresorcinol.

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