

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Condensations of Aromatic Amines with Formaldehyde in Media Containing Acid. I. Para-Toluidine¹

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The products formed by condensations of *p*-toluidine with formaldehyde in presence of acid^{1a} include the base of substituted aminobenzyl-aniline type (*o*-amino-*m*-xylyl-*p*-toluidine),² the so-called higher condensation products or resins, and the diphenylmethane base (2,2'-diamino-5,5'-dimethyldiphenylmethane) reported by Eberhardt and Welter,³ but obtained in small yield and not since studied. No derivative of the substituted anhydroaminobenzyl alcohol type⁴ has been described. In aqueous solution containing acid the reaction appears to follow a somewhat different course, marked by the formation of a number of compounds of unknown constitution. Troeger,⁵ by interaction of *p*-toluidine with methylal in concentrated hydrochloric acid, obtained a base C₁₇H₁₈N₂, m. p. 134°. Löb,⁶ by electrolytic reduction of *p*-nitrotoluene in presence of formaldehyde in acid solution, obtained a product later claimed by Goecke⁷ to be Troeger's base, but with formula C₁₆H₁₈N₂. The compound was again obtained, from a saturated solution of *p*-toluidine hydrochloride and formaldehyde at 60°, by Lepetit, Maffei and Maimeri,⁸ who verified Troeger's formula C₁₇H₁₈N₂. In the same work there were isolated also the following products: a base C₁₇H₁₆ON₂ of m. p. 140°, a base C₁₆H₁₆N₂ of m. p. 158°, a base C₁₇H₂₀ON₂ of m. p. 97-98°, and some methyl-*p*-toluidine.

This paper presents results of a study of the condensation of *p*-toluidine and formaldehyde in cold dilute hydrochloric acid solution. The products isolated include the bases of m. p. 135, 140 and 158° mentioned above (the base of m. p. 97-98° was not found), a steam-volatile mixture

found to consist of *p*-toluidine, methyl-*p*-toluidine, and dimethyl-*p*-toluidine, and the usual resins. Structure determinations of the first three have been undertaken, leading to the complete identification of the base of m. p. 158° as 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline, and to tentative formulas for the other two. These bases will subsequently be designated as base I (m. p. 140°), base II (m. p. 135°) and base III (m. p. 160°).

The incidental methylation of *p*-toluidine by formaldehyde without added reducing agent represents a type of methylation first observed by Plöchl, later by Fischer and Wreszinski, and Meyer and Stillich,⁹ and developed into a useful method for preparation of methylamines by Werner.¹⁰ In the present study the methylated bases volatile with steam accounted generally for more than 5% of the toluidine taken. The influence of various proportions of formaldehyde and *p*-toluidine upon the methylation was determined for molar ratios from 1:1 to 5:1. Total methylation was not greatly increased by a large excess of formaldehyde, but exhaustive methylation increased markedly, the steam-volatile oil consisting entirely of dimethyl-*p*-toluidine with two equivalents or more of formaldehyde.

Experimental

General.—In analyses reported below, carbon and hydrogen were determined by a micro procedure similar to that of Niederl and Whitman,¹¹ nitrogen by the macro-Kjeldahl method with boric acid absorption,¹² chlorine by the sodium peroxide bomb, and molecular weights cryoscopically in benzene; all results are averages of two to five determinations. Solvent ligroin was the commercial 70-90° material.

Condensation and Isolation Procedure.—Condensations were effected at or below room temperature, in the presence of excess dilute hydrochloric acid, and using (except in methylation experiments) slightly more than one equivalent of formaldehyde taken as a 37% solution. The solid products which precipitated were filtered off at intervals, the reaction being allowed to proceed so long as separation

(1) Thesis submitted by Abner Eisner to the Graduate School of the University of Pennsylvania in partial satisfaction of the requirements for the degree of Doctor of Philosophy, 1934.

(1a) This is intended to include reactions in which the preformed initial products (di-*p*-toluidinomethane or methylene-*p*-toluidine) are treated with *p*-toluidine and *p*-toluidine hydrochloride.

(2) German Patent 105,797; *Friedl.*, 5, 84.

(3) Eberhardt and Welter, *Ber.*, 27, 1812 (1894).

(4) Friedländer, *Monatsh.*, 23, 973 (1902); Wagner, *This Journal*, 55, 724 (1933).

(5) Troeger, *J. prakt. Chem.*, [2] 36, 227 (1886); see also German Patent 122,474; *Friedl.*, 6, 82.

(6) Löb, *Z. Elektrochem.*, 4, 428 (1897).

(7) Goecke, *ibid.*, 9, 470 (1903).

(8) Lepetit and Maimeri, *Atti accad. Lincei*, [5] 26, 558 (1917); Lepetit, Maffei and Maimeri, *Gazz. chim. ital.*, 57, 867 (1927).

(9) Plöchl, *Ber.*, 21, 2117 (1888); Fischer and Wreszinski, *ibid.*, 25, 2711 (1892); Meyer and Stillich, *ibid.*, 35, 739 (1902).

(10) Werner, *J. Chem. Soc.*, 111, 844 (1917).

(11) Niederl and Whitman, *Mikrochemie*, 11, 274 (1932).

(12) Meeker and Wagner, *Ind. Eng. Chem., Anal. Ed.*, 5, 396 (1933).

of solid continued (in some cases three weeks or more). As the condensation products could be isolated only with considerable loss, due to difficulties in separation, the yields obtained have perhaps little significance. The following outline of an experiment illustrates the method and results.

A solution of 88 g. of *p*-toluidine in 300 cc. of 3.3 *N* hydrochloric acid was treated with 75 cc. of 37% formaldehyde (1.1 equiv.). The liquid became deep red in color, and a heavy red oil separated, later disappearing. During three days there were removed several crops of a pale blue salt (16.8 g.), found to be the hydrochloride of base I. A white crystalline deposit (6.0 g.) was filtered off the next day; this was found to be the hydrochloride of base II. During the ensuing two weeks there were removed at intervals successively smaller crops of a red-tinted solid (21.7 g.), found to be largely a mixture of the hydrochlorides of bases II and III.

The deep red reaction liquid was made alkaline and steam-distilled. The steam-volatile oil was removed in ether, dried and distilled. It boiled 195–215° (6.6 g.), and on analysis was found to consist of about 30% *p*-toluidine, 45% methyl-*p*-toluidine and 25% dimethyl-*p*-toluidine.

The yellow residue not volatile with steam was extracted in ether, dried and recovered as a resinous solid (34.6 g.). A portion was distilled under reduced pressure, and yielded a little oil boiling below 70° at 4 mm., found to be a mixture of *p*-toluidine, methyl-*p*-toluidine and dimethyl-*p*-toluidine, and then a main fraction boiling 219–221° at 4 mm., composed mainly of base III (about 30% of the resin), with a small quantity of base II.

In this experiment there were eventually obtained, by the isolation procedures outlined below, 10.4 g. of base I, 10.5 g. of base II, and 4.5 g. of base III, with more of the last present in the residue not volatile with steam.

Individual Products: Isolation, Properties and Behavior on Reduction¹³

Base I.—The pale blue salt, washed with cold water or alcohol (to remove some of the red-tinted salt often present) was twice crystallized from hot alcohol, yielding a creamy white product of m. p. 248°; a third crystallization failed to raise the melting point. To isolate the base, the concentrated solution of the salt in hot alcohol was treated with alcoholic potash, water added and the liquid chilled. The product (m. p. 139°) was recrystallized from ligroin as colorless needles showing oblique extinction and melting 139–140° corr. This base is soluble in ether, benzene, alcohol, acetone and in fairly strong hydrochloric acid.

Anal. Found: C, 77.95; H, 7.07; N, 10.85; O (diff.), 4.13, mol. wt., 359. These values yield the formula $C_{24}H_{27}ON_3$; mol. wt., 373.

The hydrochloride was prepared by hydrogen chloride in dry ether, melted at 246°, and was found to be identical with the salt obtained from aqueous solution.

Anal. Calcd. for $C_{24}H_{27}ON_3 \cdot HCl$: N, 10.25; Cl, 8.66. Found: N, 10.24; Cl, 8.56.

The picrate, made in alcohol solution by excess picric acid, and recrystallized from alcohol, melted at 203° corr.

(13) Reductions were undertaken to obtain evidence as to structure.

Attempts to prepare a nitrosamine were unsuccessful, using nitrous acid or amyl nitrite in aqueous, alcoholic or glacial acetic acid solution. The base appeared to be decomposed in part by dilute acid, and in any case the product was scanty, colored, and could not be satisfactorily purified; the (aqueous) filtrate coupled strongly with alkaline β -naphthol.

Reduction.—Hot reduction with zinc dust and 3 *N* sulfuric acid, the clear liquid being made alkaline and steam-distilled, yielded a small amount of oil found on analysis¹⁴ to contain *p*-toluidine and methyl-*p*-toluidine.

A stronger reduction, using tin and hot hydrochloric acid, with enough alcohol to keep the liquid clear, gave 2.3 g. of steam-volatile oil from 10 g. of the hydrochloride. The Hinsberg-Kessler separation showed the presence of primary and secondary amines, and a small quantity of tertiary base. The primary amine derivative (2.4 g.) crystallized from alcohol, melted like a mixture (95–105°). It was therefore hydrolyzed by concd. hydrochloric acid at 200° in a sealed tube, and the steam-distilled bases benzoylated by the Schotten-Baumann method.¹⁵ Fractional crystallization of the product from alcohol and dilute alcohol yielded mostly impure benzoyl-*p*-toluidine (m. p. 145–146°), and finally a small first fraction (about 0.1 g.) of m. p. 167–168°, raised to 174–175° by recrystallization. A mixed melting point test with an authentic specimen of 4-benzoylamino-1,3-xylene (m. p. 191°) gave the result 185–186°; addition of benzoyl-*p*-toluidine (m. p. 158°) to the mixture changed the melting range to 148–174°. It may therefore be concluded that *unsym-m*-xylylidine is a minor product of the reduction of base I; this is important to the structure determination discussed later.

Base II (Troeger's Base).—The white crystalline product obtained separately in the condensation experiment described above was the hydrochloride of base II. After crystallization from hot dilute hydrochloric acid it melted at 215°. In general base II was obtained from the red-tinted salt which separated principally during the later stages of the condensations. This was dissolved in hot water, digested with charcoal, and the filtered and cooled solution precipitated slowly by alkali.¹⁶ The dried base was dissolved in hot ligroin, and on cooling to room temperature there separated most of base III. Concentration and chilling of the filtrate yielded base II in impure condition. It was recrystallized from ligroin or dilute alcohol.

Base II was obtained as colorless needles showing parallel extinction; m. p. 135° corr. It is soluble in ether, benzene, acetone, ligroin and dil. hydrochloric acid.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.60; H, 7.20; N, 11.20; mol. wt., 250. Found: C, 81.75; H, 7.17; N, 10.91; mol. wt., 251.

The hydrochloride was prepared both by hydrogen chloride in ether, and in aqueous hydrochloric acid, melting

(14) Miller and Wagner, *THIS JOURNAL*, **54**, 3698 (1932).

(15) The conversion of the benzenesulfonyl derivatives to benzoyl derivatives was made because previous work had shown *p*-toluidine and *unsym-m*-xylylidine (the primary bases most probably present) to be not separable by fractional crystallization (on a small scale) from alcohol, but satisfactorily separable as their benzoyl derivatives.

(16) The red color of the crude salt was apparently due to the same dye-like by-product which colored the condensation liquid. The color was discharged by alkali.

in either case at 215° obs., but showing an anomalous composition.

Anal. (a) Salt made in water, N, 9.32; (b) made in ether, N, 9.32. Calcd. for $C_{17}H_{18}N_2 \cdot 2HCl$: N, 8.67; for $C_{17}H_{18}N_2 \cdot HCl$: N, 9.80.

Troeger obtained a hydrochloride of m. p. 213°, and stated it to contain $2H_2O$, which in view of the above results appears unlikely.

The picrate, made in alcohol and crystallized from alcohol, melted at 172.6° corr. (Troeger reported a picrate of m. p. 186°).

The nitrosamine, made by Troeger in acetic acid, and reported to melt at 260–264°, was in the present study obtained from dilute hydrochloric acid solution; the m. p. 253° corr. was not raised by crystallization from alcohol. Analysis confirmed Troeger's conclusion that the derivative is the dinitrosamine.¹⁷

Anal. Calcd. for $C_{17}H_{18}O_2N_4$: C, 66.20; H, 5.19. Found: C, 66.10; H, 5.33.

Reduction of base II was attempted by use of zinc dust and hot 6 *N* sulfuric acid, but without splitting off any basic product volatile with steam. This confirms Goecke's finding that the base was resistant to reduction by tin and hydrochloric acid.

Base III.—This compound was obtained mostly from the red-tinted salt precipitated during the condensations; its separation from base II (more soluble in ligroin) is outlined above. Some was obtained from the resinous residues not volatile with steam, by recrystallizing from ligroin the portion boiling about 220° at 4 mm. The base crystallizes from ligroin or alcohol as hexagonal plates of m. p. 162.5° corr. Between crossed nicols the crystals show considerable color; extinction is parallel. The compound dissolves in ether, benzene, acetone, alcohol, ligroin and dilute hydrochloric acid.

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 81.36; H, 6.78; N, 11.86; mol. wt., 236. Found: C, 81.65; H, 6.92; N, 11.88; mol. wt., 237.

The hydrochloride, made by passing hydrogen chloride into the ether solution of the base, melted with decomposition at about 212°. Nitrogen 8.94; calcd. for $C_{18}H_{18}N_2 \cdot 2HCl$, N, 9.12.

The picrate, made in alcohol and crystallized from alcohol, melted at 210° corr.

Reduction.—Reduction by zinc dust and hot dilute sulfuric acid was only partially effective, some *p*-toluidine being recovered. Reduction by tin and hydrochloric acid gave 2.1 g. of steam-volatile oil from 4 g. of base III. Analysis by the Hinsberg–Kessler procedure showed absence of tertiary base. The secondary amine derivative was an oil (1.2 g.) from which no solid product could be obtained. The primary amine derivative (2.8 g.) melted badly and was obviously a mixture. Fractional crystallization from alcohol gave no indication that a separation by this means would be practicable. The material was therefore hydrolyzed by heating under pressure with hydrochloric acid (see reduction of base I), and the steam-volatile bases benzoylated. Fractional crystallization of the mixed benzoyl compounds yielded eventually the

(17) Troeger's values for carbon and nitrogen were satisfactory, but those for hydrogen were inconsistent with the formula.

benzoyl derivative of *p*-toluidine (m. p. 152–153° corr.) and that of 4-amino-1,3-xylene (m. p. 192–193° corr.). Identifications were confirmed by mixed melting point tests using derivatives prepared from authentic specimens of the two amines.

Incidental Methylation of *p*-Toluidine During Condensation with Formaldehyde in Acid Solution.—As the formation of dimethyl-*p*-toluidine was unexpected, some experiments were made to test the effect of various proportions of formaldehyde and toluidine upon the methylation. Results are summarized in the table.

TABLE I
METHYLATION OF *p*-TOLUIDINE HYDROCHLORIDE BY FORMALDEHYDE

Formaldehyde: molar ratio $CH_2O:C_6H_7N$	Composition of steam-volatile products ^a			Amine-H replaced by CH_3 , %
	<i>p</i> -Tolui- dine, %	Methyl- <i>p</i> - toluidine, %	Dimethyl- <i>p</i> -toluidine, %	
1	68	27	0	2.3
1.2	36	30	12	3.0
1.2	31 ^b	40 ^b	11	3.6
1.5	3	20	77	7.7
2.0	0	0	100	6.7
2.5	0	0	100	8.5
5	0	0	100	9.1

^a Analyzed by Hinsberg–Kessler method, with dimethyl-*p*-toluidine precipitated and weighed as picrate. ^b Separated as above, using *p*-toluenesulfonylchloride.

The effect of increase in the proportion of formaldehyde was not so much an increase in the number of *p*-toluidine molecules methylated as an increase in the thoroughness of methylation of the molecules affected. There was also an increase in total methylation with increasing amount of formaldehyde, but the two were not proportional. It appears that the number of molecules which are methylated is determined by the relative velocities of the reactions in progress in the condensation liquid, and that methyl-*p*-toluidine is again methylated more easily than it condenses in other ways with formaldehyde. So far as is now known the methylated toluidines survive, for they have not been identified as component units in the di- or tri-nuclear bases (I, II, III) obtained as final products.

The mechanism of methylation by formaldehyde in absence of added reducing agent, proposed by Werner,¹⁰ involves generation of nascent hydrogen by interaction of water and formaldehyde: $HCHO + H_2O = HCOOH + 2H$, an assumption supported by the appearance of formic acid in Werner's method. This mechanism seems to be acceptable in the present case,

for as appears later the formation of base III involves presence of formic acid as a reactant. Furthermore the presence of some formic acid in the condensation liquid was shown experimentally.

A solution of 36 g. of *p*-toluidine in 150 cc. of 3 *N* sulfuric acid was treated with 63 cc. of 37% formaldehyde, all air replaced by nitrogen, and the tightly stoppered flask allowed to stand at room temperature for ten days. The mixture was steam-distilled as long as the distillate was acidic (1250 cc.). The distillate gave a negative test with barium chloride. An aliquot was titrated, indicating a total acidity equivalent to 17.7 cc. of decinormal alkali. A blank titration on the formaldehyde used indicated a total acidity from this source equivalent to 12.0 cc. of decinormal alkali. To identify the volatile acid it was steam-distilled and retained by a suspension of calcium carbonate,¹⁸ excess calcium carbonate filtered off, the liquid evaporated to small volume, and tested with Schiff's reagent with negative result. Magnesium turnings and hydrochloric acid were added, and after about two hours the (nearly neutral) liquid was tested with Schiff's reagent. A strongly positive result showed presence of formaldehyde formed by reduction of formic acid.¹⁹

If nascent hydrogen is available, as thus appears probable,²⁰ methylation is to be expected, for it has been shown that methylated products are obtained by hydrogenation of the initial condensation products of formaldehyde with aniline, *o*-toluidine and *p*-toluidine,²¹ with alkyl anilines,²² and by hydrogenation of isolated simple condensation products such as di-*p*-toluidinomethane²³ and methylene-*p*-toluidine.¹⁴ Maffei²⁴ assumed methylation to be effected by methyl alcohol produced from formaldehyde by oxidation-reduction, but both the Cannizzaro reaction in acid solution and the ability of aqueous methyl alcohol to methylate an aromatic amine in the cold appear improbable.

Structures

Base III.—This compound was stated by Maffei,²⁴ on the basis of coincident melting points, to be the substituted dihydroquinazoline reported

(18) Cf. "Methods of Analysis," Assoc. Official Agric. Chemists, Washington, D. C., 3d, ed., 1930, p. 347.

(19) See Rosenthaler, "Der Nachweis organischer Verbindungen," F. Enke, Stuttgart, 2d, ed., 1923, p. 283.

(20) There may be considered here also the reducing action of formic acid as used by Clarke, Gillespie and Weisshaus [THIS JOURNAL, **58**, 4571 (1933)] in the methylation of aliphatic amines by formaldehyde, though the amount of formic acid available must be inconsiderable compared with the excess these workers used. It may be added that this method of methylation is at least partially successful with *p*-toluidine, an attempt to prepare base III from *p*-toluidine, formaldehyde and excess of 90% formic acid yielding considerable methylated material (mainly dimethyl-*p*-toluidine), the reaction evolving carbon dioxide.

(21) Eisner and Wagner, unpublished results.

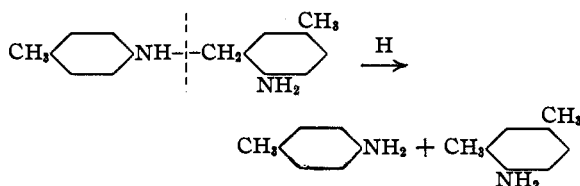
(22) Wagner, THIS JOURNAL, **55**, 724 (1933).

(23) Wagner, unpublished results.

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

by v. Walther and Bamberg.²⁵ The formation of a dihydroquinazoline derivative as a product of the condensation of a *para*-substituted amine with formaldehyde in presence of acid was later established by Maffei²⁶ in the case of *p*-phenetidine, one product being shown by independent synthesis to be 3-*p*-ethoxyphenyl-6-ethoxy-3,4-dihydroquinazoline. As no similarly complete proof of the identity of base III was available, Maffei's assumption regarding it was tested and found correct as follows.

The base C₁₆H₁₆N₂, designated 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline, was prepared from *o*-amino-*m*-xylyl-*p*-toluidine and 90% formic acid, as described by v. Walther and Bamberg, and by mixed melting point test found to be identical with base III. The structure assigned by v. Walther and Bamberg cannot be accepted unreservedly, as it was not determined but was inferred from that of the precursor *o*-amino-*m*-xylyl-*p*-toluidine, whose structure further has not been determined but has been assumed from collateral evidence.²⁷ It therefore seemed desirable to establish definitely the structure of the latter. This was done by the method of reduction used in previous work for rupture of certain carbon-nitrogen bonds.^{14,28} The only products obtained were *p*-toluidine and 4-amino-1,3-xylene. This cleavage constitutes a simple but satisfactory proof of structure



Cleavage of *o*-Amino-*m*-xylyl-*p*-toluidine.—This base was made from pure methylene-*p*-toluidine, *p*-toluidine and *p*-toluidine hydrochloride stirred with nitrobenzene for fifty hours at 20°;²⁹ m. p. 88° corr.

Anal. Calcd. for C₁₅H₁₅N₂: N, 12.39; mol. wt., 226. Found: N, 12.37; mol. wt., 227.

Hot reduction of 4.5 g. of the base yielded 3.4 g. of steam-volatile oil, of which 2.8 g. boiled 202–212°. It was benzoylated, and the product crystallized fractionally from alcohol, yielding 2.0 g. of the less soluble, and 2.2 g. of the more soluble, derivative. Two recrystallizations of the former brought the m. p. to 194.5° corr. (benzoyl deriva-

(25) V. Walther and Bamberg, *J. prakt. Chem.*, [2] **73**, 209 (1906).

(26) Maffei, *Gazz. chim. ital.*, **59**, 3 (1929).

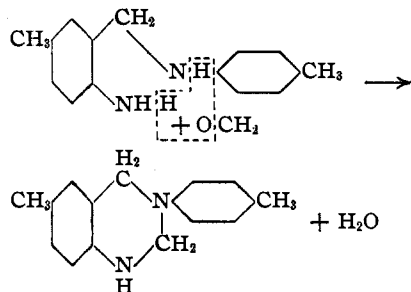
(27) Cohn and Fischer, *Ber.*, **33**, 2586 (1900); v. Walther and Bamberg, *J. prakt. Chem.*, [2] **71**, 153 (1905).

(28) Wagner, THIS JOURNAL, **54**, 660 (1932); **55**, 727 (1933).

(29) German Patent 105,797; *Friedl.*, **5**, 84.

tive of 4-amino-1,3-xylene); the latter on recrystallization melted at 152° (benzoyl derivative of *p*-toluidine).

The structure of base III, obtainable from *o*-amino-*m*-xylyl-*p*-toluidine by ring-closure with formic acid, is thus indicated, and is confirmed as follows. V. Walther and Bamberg found that reduction with sodium and alcohol saturated the 1,2-double bond of their methyltolylidihydroquinazoline, yielding the corresponding tetrahydroquinazoline, m. p. 138°. Base III when thus reduced gave a product of m. p. 141°. Methyl-*p*-tolyltetrahydroquinazoline was then synthesized by condensation of *o*-amino-*m*-xylyl-*p*-toluidine with formaldehyde under conditions previously found to favor di-imine formation, *viz.*, in alcohol solution containing alkali.³⁰ Under other conditions v. Walther and Bamberg obtained only a smeary product, but using the procedure given below the yield of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline (m. p. 141°) was nearly the theoretical



This synthesis shows clearly the structure of the product, which by mixed melting point test was found to be identical with the compound of m. p. 141° obtained by reduction of base III.

Synthesis of 3-*p*-Tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline.—A warm solution of 5 g. of *o*-amino-*m*-xylyl-*p*-toluidine and 1 g. of potassium hydroxide in 25 cc. of alcohol was treated with 1.7 cc. of 37% formaldehyde. The liquid soon set to a mass of crystals. The product was brought into solution by addition of more alcohol (about 100 cc. in all), a little water was added, and on chilling 5.2 g. (98.6%) of yellowish crystals separated. After recrystallization the compound melted at 141°; the melting point was not changed by admixture of the reduction product of base III.

p-Tolylmethyltetrahydroquinazoline was obtained from alcohol as pale yellow scales.

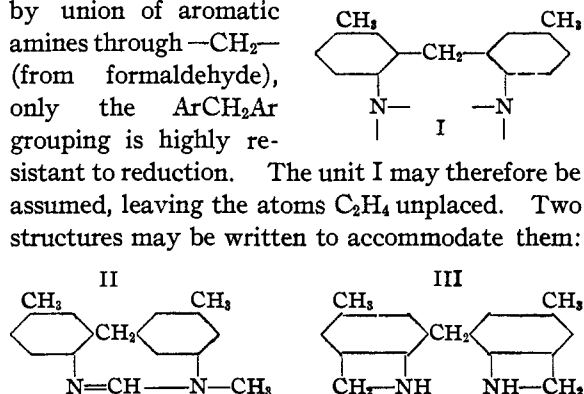
Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.67; H, 7.65; N, 11.77; mol. wt., 238. Found: C, 80.95; H, 7.56; N, 11.79; mol. wt., 235.

The identity of base III as 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline is thus established. This

(30) Eberhardt and Welter, *Ref. 3*; *cf.* Eibner, *Ann.*, **328**, 125 (1903).

structure is consistent with the behavior of the compound on reduction, the products obtained being the two primary amines to be expected (*p*-toluidine and 4-amino-1,3-xylene), apparently two secondary amines (not isolated), and no tertiary amine.

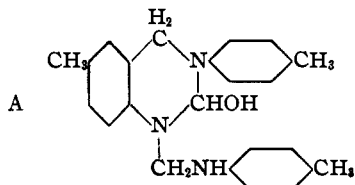
Base II (Troeger's Base).—This compound was represented by Troeger to be $(CH_3C_6H_4-N=CH)_2CH_2$, and by Löb and Goecke as perhaps a polymeric methylene-*p*-toluidine $C_{16}H_{18}N_2$. The formula, however, is undoubtedly $C_{17}H_{18}N_2$, and the fact that the compound yields no steam-volatile bases on attempted reduction at once excludes the proposed structures. The stability of the molecule suggests the diphenylmethane structure, for of all the structure types obtained by union of aromatic amines through $-CH_2-$ (from formaldehyde), only the $ArCH_2Ar$ grouping is highly resistant to reduction. The unit I may therefore be assumed, leaving the atoms C_2H_4 unplaced. Two structures may be written to accommodate them:



As shown above, the base yields a dinitrosamine; Troeger obtained also a rather refractory acetyl compound. Formula III, which represents the base as a di-secondary amine, satisfactorily accounts for the formation of these derivatives while formula II, containing only tertiary nitrogen, is excluded. The assumption of an anhydro-*o*-aminobenzyl alcohol condition encounters the objection that no simple compound of this kind obtained from *p*-toluidine has been reported. A structure similar to III was assigned by Meyer and Stillich⁹ to a diphenylmethane base obtained from *p*-nitraniline, but no acceptable proof of structure was offered. In view of the evidence, however, Troeger's base may be assigned structure III, representing the compound as methylene-3,3'-bis(5-methyl-anhydro-2-aminobenzyl alcohol), or methylene-6,6'-bis-(4-methyl benzoazetine).

Base I.—No structure has been proposed for this compound, represented by Lepetit, Maffei and Maimeri as $C_{17}H_{16}ON_2$ (mol. wt., 264;

found, 300). As shown above the formula is $C_{24}H_{27}ON_3$, requiring presence of three toluidine residues and three additional carbon atoms, of which at least two must be linking atoms. The formation of a monohydrochloride $C_{24}H_{27}ON_3 \cdot HCl$ shows one nitrogen to be more basic than the other two, a condition which should be represented in the structure. Fairly strong reduction split off only *p*-toluidine and methyl-*p*-toluidine, a large part of the molecule being apparently resistant. These results indicate presence of the grouping $>N^bCH_2^aNHC_6H_4CH_3$, which by cleavage at *a* would yield *p*-toluidine, and by cleavage at *b*, methyl-*p*-toluidine. The greater stability of the rest of the molecule suggests that it may be a unit of either the diphenylmethane or the quinazoline type, of which the first is wholly resistant to ordinary reduction, while the quinazoline heterocycle, as shown for base III, is capable of cleavage. Stronger reduction of base I gave as one product a primary amine identified with a fair degree of certainty as 4-amino-1,3-xylene, formation of which excludes the diphenylmethane structure, but is consistent with the quinazoline structure. With the group $-CH_2NHC_6H_4CH_3$ attached to nitrogen in position 1 of the quinazoline unit,³¹ and the unplaced 2H and O assigned to position 2, the provisional formula is A.



This structure accounts for the cleavage products obtained by reduction, and for the lowered basicity of two nitrogen atoms, as the $>NCH(OH)N<$ grouping presents the same association of functions found in the ethanolamines, which are compounds of low alkalinity. In quinazoline ring-closures of the types considered here (by formaldehyde or formic acid) the 2-hydroxyl compound is intermediate. In the case of formation of base III from *p*-toluidine, the intermediate 2-hydroxyl compound loses water spontaneously and has not been isolated. The corresponding compound from *p*-nitraniline is more stable; it

(31) The quinazoline unit referred to is of course the one derivable from *o*-amino-*m*-xylyl-*p*-toluidine, *i. e.*, 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline.

was obtained by Meyer and Stillich,⁹ and shown by Maffei²⁴ to be 2-hydroxy-3-*p*-nitrophenyl-6-nitro-1,2,3,4-tetrahydroquinazoline. In the present case the persistence of the 2-hydroxyl group is due to absence of hydrogen on the neighboring nitrogen atoms. The formation of base I from *o*-amino-*m*-xylyl-*p*-toluidine during the condensations would seem to involve first the coupling of *o*-amino-*m*-xylyl-*p*-toluidine and *p*-toluidine by di-imine condensation,³² with subsequent ring-closure by formic acid (reacting as an aldehyde), with introduction of the group $>CHOH$.

Base I is accordingly represented as 1-(*p*-toluidinomethyl)-2-hydroxy-3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline. This structure is tentative, for while it seems to be consistent with the facts now known, certain conclusions in the structure proof are reasoned, and lack experimental support.

Summary

1. Condensation of *p*-toluidine with formaldehyde in aqueous solution containing hydrochloric acid yields three well-defined polynuclear bases, of m. p. 135, 140 and 162°, respectively, as well as methyl-*p*-toluidine and dimethyl-*p*-toluidine, and considerable quantities of resins. Methods of isolation and properties of the first three bases are reported, and also the effect of various molar ratios of formaldehyde and toluidine upon the extent of the methylation.

2. The methylation of *p*-toluidine and the formation of bases II and III appear to be caused, respectively, by nascent hydrogen and formic acid made available by interaction of formaldehyde and water. Presence of formic acid in the condensation liquid was demonstrated.

3. Structure determinations of the polynuclear bases mentioned, by methods which included their behavior upon strong reduction, led to the conclusive identification of the base of m. p. 162° as 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline, and to tentative formulas for the other two. As incidental steps the structure of *o*-amino-*m*-xylyl-*p*-toluidine was established, and the compound 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline was synthesized.

PHILADELPHIA, PA.

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(32) This would involve the $-NH_2$ group of *o*-amino-*m*-xylyl-*p*-toluidine, as shown by v. Walther and Bamberg [*J. prakt. Chem.*, [2] 71, 153 (1905)] for other condensations of this base with aldehydes.