# METHYLATION OF AROMATIC AMINES BY THE WALLACH METHOD[1]

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Previous to the demonstration by Clarke, *et al.* (1) and by Emerson, *et al.* (2) that mesidine and tribromoaniline can be methylated by the Wallach procedure (3, 4) attempts to alkylate aromatic amines by this method were unsuccessful, the products being resinous and gluey mixtures (5). Experiments made at intervals during the past ten years (6, 7) showed that in the reaction of formaldehyde and formic acid with *p*-toluidine the first two are consumed and carbon dioxide is evolved but that the main isolable product is 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline, together with small amounts of a steam-volatile oil containing a compound provisionally identified as *o*-hydroxymethyl-N,N-dimethyl-*p*-toluidine, obtained by von Braun and Kruber (8) by action of formaldehyde on dimethyl-*p*-toluidine in aqueous acid solution. By a change in procedure Gaskins (7) was able to obtain small yields of N,N-dimethyl-*p*-toluidine. Aromatic amines with *para*-hydrogen condense with formaldehyde in the presence of aqueous hydrochloric acid to yield finally diphenylmethane bases (thru a series of intermediates) and, as is reported below, the same bases result also in the presence of formic acid, accompanied possibly at all stages by methylation on nitrogen. Since all of these reactions excepting methylation involve nuclear attack at *ortho* or *para* positions and since in the absence of such labile hydrogens normal Wallach methylation occurs (1, 2), it appears certain but has not been demonstrated that nuclear condensations are responsible for the failure of the Wallach procedure when applied to aromatic amines capable of such reactions. This paper presents the results of a study of (a) the nature of the reactions which decrease or exclude simple methylation of aromatic primary and secondary amines by the Wallach procedure, (b) the effects of acids upon nuclear condensations of formaldehyde with aromatic amines $ArNR_2$, (c) the development of a procedure by which some aromatic amines can be methylated by formaldehyde and formic acid, and (d) the effects of conditions upon the methylation reaction as applied to aromatic amines.

The identified products attributable to nuclear condensation of formaldehyde and aromatic amines in the presence of formic acid were found to include fully methylated diphenylmethane bases (from methylaniline, 2,6-dimethylaniline, 2,6-dibromoaniline, *m*-nitroaniline, and dimethyl-*p*-toluidine; not from N,N-dimethyl-2,6-dimethylaniline), 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline from *p*-toluidine, and products not identified from 2,4-xylidine and 2,4-dichloroaniline. Using other aromatic amines no single compounds could be isolated from the

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[1] Paper constructed from the Ph.D. thesis of Walter L. Borkowski, University of Pennsylvania, 1951.

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amorphous and often sticky and viscous reaction products; these mixtures contain the "higher condensation products" (probably polynuclear) reported earlier (9) but not identified. Reactions of these types appear to be acid-catalyzed, resembling the nuclear attack of formaldehyde upon phenol (10). If so, whether initiated by involvement of formaldehyde with hydrogen on nitrogen or on a ring carbon, the reaction progresses with eventual displacement of nuclear hydrogen as proton and it may be expected that the reaction will fail in the complete absence of acid and that in each case an increase in acidity beyond the optimum will retard and at some point perhaps exclude condensation if this follows the course suggested, *viz.*,

$$H_2C{=}O + H^+ \rightleftharpoons [H_2C{=}OH \longleftrightarrow H_2C{-}OH]^+$$
$$\xrightarrow{R_2NC_6H_4H} R_2NC_6H_4CH_2OH + H^+$$

By a similar mechanism involving a second molecule of amine there may be formed diphenylmethane bases. This matter was tested experimentally by studying the effects of acidity (*inter alia*) upon the condensation of several amines of the type $(CH_3)_2NAr$ with formaldehyde in acid media to yield tetramethyldiaminodiphenylmethanes.

*Influence of acidity upon the condensation of some N,N-dimethylarylamines with formaldehyde.* Table I lists the results of experiments in which N,N-dimethylarylamines were treated at steam-bath temperature with formaldehyde (as paraformaldehyde) in presence of hydrochloric, formic, or acetic acids. The product was determined either by isolation or from the material volatile with steam (unchanged amine) following neutralization of the reaction mixtures.

It is shown (Table I) that (a) in the absence of acid, condensation is negligible (3–4%); (b) condensation in the presence of hydrochloric acid is at the maximum (98%) with one equivalent of acid in the mixture, and is decreased by less or more acid (to 30% with 2 equivalents); (c) formic and acetic acids induce condensation, the extent of which increases to the maximum with the amounts of these acids (to 92% with 1.3 and 2 equivalents respectively), decreasing slowly with excess formic acid (to 49% with 8 equivalents) but that the addition of HCl or HBr to mixtures containing effective amounts of formic or acetic acid exerts a marked repressive effect. It is shown further that condensation of dimethylaniline and formaldehyde in the presence of acid (HCl or formic) is rapid and is nearly complete with about the calculated amount of formaldehyde although slightly increased by an excess. The use of formic acid led to the formation, in a 5-minute reaction period, of 92% of *p,p'*-bis(dimethylamino)diphenylmethane that was of better quality and was more easily purified than the product obtained by the usual prolonged heating (6 hours) of dimethylaniline and formalin in aqueous hydrochloric acid (11). The use of enough acid to restrain nuclear condensation may result in slow and incomplete methylation, which also is adversely affected by excess acid (3).

The *rates of methylation* of sixteen primary or secondary aromatic amines were compared, using the familiar Wallach procedure (excess of formaldehyde and formic acid), the evolved carbon dioxide being collected and weighed (3) at four time-intervals. The results (Table II) indicate the extent of methylation, but

TABLE I

Condensation of N,N-Dimethylarylamines with Formaldehyde in the Presence of Acids[3]

| Amine Dimethyl- | HCHO[a] equiv. | Acid | Acid equiv.[b] | Time, min.[c] | Not volatile with steam[d], % |
|---|---|---|---|---|---|
| aniline | 0.5–0.55 | None[e] | 0 | 5 | 2.5[f] |
| aniline | .5–0.55 | F[h] | 0.55 | 15 | 89 |
| aniline | .5–0.55 | F | .55 | 5 | 78 |
| aniline | .5–0.55 | F | .55 | $\frac{1}{4}$ | 61 |
| aniline | .5–0.55 | F | .55 | $\frac{1}{10}$ | 56 |
| aniline | .65 | F | .55 | 5 | 81 |
| aniline | .75 | F | .55 | 5 | 86 |
| aniline | 1.0 | F | .55 | 5 | 87 |
| aniline | 1.0 | None[e] | 0 | 5 | 3[f] |
| aniline | 0.5 | F | 1.1 | 5 | 74[f] |
| aniline | .5 | F | 1.3 | 5 | 92[f] |
| aniline | .5 | F | 2 | 5 | 89[f] |
| aniline | .5 | F | 4 | 5 | 64[f] |
| aniline | .5 | F | 8 | 5 | 49[f] |
| aniline | 1.0 | F | 0.058 | 5 | 12 |
| | | | .097 | | 35 |
| | | | .14 | | 50 |
| | | | .28 | | 62 |
| | | | .55 | | 78 |
| | | | 1.1 | | 92, 82[f] |
| aniline | 0.5 | HCl[g] | 0.05 | 30 | 45[f] |
| aniline | .5 | HCl | .1 | 30 | 35 |
| aniline | .5 | HCl | 1.0 | 30 | 98 |
| aniline | .5 | HCl | 2.0 | 30 | 30 |
| aniline | .5 | HCl | 1.0 | 180 | 48 |
| | | Formic | 2.5 | | |
| aniline | .5 | HCl | 2.0 | 180 | 36 |
| | | Formic | 1.0 | | |
| aniline | .5 | HCl | 2.0 | 180 | 52 |
| | | Formic | 2.5 | | |
| aniline | .5 | HBr | 2.0 | 180 | 48 |
| | | Formic | 2.5 | | |
| aniline | .5 | Acetic | 2.0 | 30 | 92 |
| aniline | .5 | Acetic sat. dry HCl | 5.0 | 30 | 28 |
| *o*-toluidine | 0.55 | Formic | 0.55 | 5 | 0 |
| *o*-toluidine | 1.0 | Formic | 1.0 | 15 | 0 |
| *o*-toluidine | 2.0 | Formic | 2.0 | 60 | 3 |
| *p*-toluidine | 1.0 | Formic | 1.0 | 15 | 7 |
| *p*-toluidine | 2.0 | Formic | 2.0 | 60 | 59 |
| 5-bromo-2-aminotoluene | 2.0 | Formic | 2.0 | 60 | 0 |
| *o*-chloroaniline | 2.0 | Formic | 2.0 | 60 | 23 |

TABLE I—*Continued*

| AMINE Dimethyl- | HCHO[a] EQUIV. | ACID | ACID EQUIV.[b] | TIME, MIN.[c] | NOT VOLATILE WITH STEAM[d], % |
|---|---|---|---|---|---|
| 2,6-xylidine | 2.0 | Formic | 2.0 | 60 | 0 |
| 2,4-xylidine | 2.0 | Formic | 2.0 | 60 | 0 |

[a] Formation of diphenylmethane base requires 0.5 equivalent. Paraformaldehyde used. [b] Not stoichiometrically related. [c] At steam-bath temperature. [d] This material in each case was largely the diphenylmethane base $[(CH_3)_2NAr\text{-}]_2CH_2$. [e] Results were the same when the reaction mixture was at first made slightly alkaline with sodium hydroxide. [f] These results were obtained by Hanna Suss and Joseph Feighan, U. of Penna., 1951. The diphenylmethane base was determined as such. [g] Further results showing effects of hydrochloric acid in Table VI. [h] F = 98% formic acid.

as nuclear condensation may lead to products (also methylated) other than the dimethylated amines the significance of the over-all rates is decreased. It is known however that Wallach methylation is a rapid reaction, and it was observed that with fourteen of the amines tested there was prompt and vigorous evolution of carbon dioxide, and that only 2,6- and 2,4-dinitroaniline failed to react. Since, as appears later, the reactive amines are susceptible to successful methylation by a modified procedure, it is concluded that the results in Table II represent principally normal methylation. As in other Wallach reactions (3) the initially high rate of evolution of carbon dioxide decreases rapidly and is followed by an extended period of evolution at decreasing rate. This fact is responsible for the long periods of heating recommended for Wallach alkylation of non-aromatic amines. Prolonged heating is undesirable in working with aromatic amines, for the extent of methylation increases only slowly and at a diminishing rate with time, but nuclear condensation, even with acidities above the optimum, increases with time (Table I).

The results in Table II indicate (a) that methylation of aromatic amines not readily susceptible to nuclear condensation with formaldehyde is in some cases substantial within 15 to 45 minutes; (b) that the rate of methylation is decreased by the presence of halogen or the nitro group as a nuclear substituent, so that longer periods of heating are advantageous provided the amine is not subject to strong nuclear attack by formaldehyde. This condition is represented by the nitroanilines, and especially by tribromoaniline, the rather slow methylation[3] of which is not in competition with nuclear condensation with formaldehyde.

*Wallach procedure modified for the methylation of aromatic amines.* The results discussed above make plain the fact that control of acidity cannot be expected selectively to repress nuclear attack of formaldehyde upon amines having open *ortho* or *para* positions while permitting satisfactory methylation on nitrogen. By the use of 2,4-xylidine and 2,6-xylidine, each with only one reactive position open (*ortho* and *para* respectively), and therefore with sufficient impedance of nuclear condensation (after methylation) that this does not occur within 60

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[3] The slow methylation of tribromoaniline is perhaps due to the fact that its solubility in the mixture is low.

minutes, (Table I) the problem was solved though in a semiempirical manner involving the order of mixing the reactants.

*Formaldehyde.* In the cases not complicated by nuclear condensations (mesidine, tribromoaniline) methylation was accompanied by evolution of the theoretical amount of carbon dioxide (Table II); it is concluded that formic acid is the only operative reducing agent. Methylaniline, which is attacked very vigorously by formaldehyde and formic acid, yielded as the only isolable product some *p,p'*-bis(dimethylamino)diphenylmethane, requiring with respect to the methylaniline converted to this compound 1.5 equivalents of formaldehyde and 1 equivalent of formic acid, with the liberation of 1 equivalent of carbon dioxide. Since condensations, secondary reactions, and methylations may occur together, the needed amount of formaldehyde for an untried case cannot be estimated, and in general it seems advisable to use formaldehyde in some excess, even though this may somewhat increase the rate of nuclear condensation (Table I).

TABLE II

Time-Yield Relationships of Some Wallach Alkylations[a]

| AMINE | 15 min. | 45 min. | 95 min. | 165 min. |
|---|---|---|---|---|
| Mesidine | 93 | 93 | 94 | 96 |
| Tribromoaniline | 28 | 51 | 63 | 68 |
| *p*-Bromoaniline | 25 | 40 | 59 | 60 |
| *p*-Chloroaniline | 21 | 33 | 40 | 44 |
| *o*-Chloroaniline | 39 | 48 | 54 | 56 |
| 5-Bromo-2-aminotoluene | 24 | 29 | 35 | 39 |
| *o*-Nitroaniline | 15 | 32 | 46 | 54 |
| *m*-Nitroaniline | 34 | 41 | 50 | 56 |
| *p*-Nitroaniline | 27 | 48 | 64 | 66 |
| N-methyl-*p*-nitroaniline | 80 | 83 | 86 | 88 |
| N-methyl-*o*-toluidine | 74 | 76 | 78 | 80 |
| N-methyl-*p*-toluidine | 50 | 54 | 59 | 61 |
| *p*-Toluidine | 8 | 15 | 26 | 33 |
| 2,4-Dichloroaniline | 53 | 61 | 65 | 67 |
| Anthranilic acid | 6 | 10 | 10 | 10 |
| *p*-Aminobenzoic acid | 20 | 34 | 40 | 40 |

[a] Conditions: Ratio of formaldehyde (as paraformaldehyde), formic acid (98%), and amine: 2.8:4.0:1.0. Reactants mixed in the cold and heated on the steam-bath, and the evolved $CO_2$ collected and weighed.

Preliminary experiments showed paraformaldehyde to be preferable to formalin or trioxane. The water in formalin affects methylation adversely (3). Trioxane is not rapidly depolymerized by formic acid at steam-bath temperatures; as a consequence it may be incompletely utilized, some material surviving and appearing as a sublimate during isolation of the product. Paraformaldehyde depolymerizes rapidly in presence of formic acid at steam-bath temperatures; by its use conversion of dimethylaniline to bis(dimethylamino)diphenylmethane was more than half complete in 15 seconds and was nearly quantitative in 5 minutes. The use of the three agents in the methylation of mesidine showed paraformaldehyde to give the highest yields. The relationships between the extent of methylation of 2,4- and 2,6-xylidine using formaldehyde as formalin and as paraformaldehyde are shown by the data in Tables III and IV respectively.

TABLE III

METHYLATION OF 2,4- AND 2,6-XYLIDINES. THE EFFECT OF THE AMOUNT OF FORMALDEHYDE AS FORMALIN[a]

| RATIO $CH_2O$: amine | YIELD OF DIMETHYLATED AMINE | |
|---|---|---|
| | Dimethyl-2,4-xylidine, % | Dimethyl-2,6-xylidine, % |
| 1.5 | 20 | 50 |
| 2.0 | 35 | 50 |
| 3.0 | 35 | 60 |
| 4.0 | 35 | 75 |
| 6.0 | 40 | 75 |
| 10.0 | 30 | 65 |
| 15.0 | 20 | 65 |

[a] Conditions: 3 equivalents of 98% formic acid; formaldehyde taken as 35% formalin; amine added last; time of reaction (steam-bath), 10 minutes.

TABLE IV

METHYLATION OF 2,4- AND 2,6-XYLIDINES. THE EFFECT OF THE AMOUNT OF FORMALDEHYDE AS PARAFORMALDEHYDE AND THE EFFECT OF ADDED WATER[a]

| RATIO $CH_2O$: amine | RATIO $H_2O$: amine | YIELD OF DIMETHYLATED AMINE | |
|---|---|---|---|
| | | Dimethyl-2,4-xylidine, % | Dimethyl-2,6-xylidine, % |
| 2.5 | 0 | 40 | 75 |
| 2.5 | 7.0 | 35 | 60 |
| 2.5 | 19.0 | 25 | 20 |
| 2.5 | 34.0 | 15 | 10 |
| 5.0 | 0 | 45 | 75 |
| 5.0 | 14.0 | 35 | 45 |
| 5.0 | 38.0 | 25 | 25 |

[a] Conditions: 3 equivalents of 98% formic acid; formaldehyde taken as paraformaldehyde; water added as indicated (column 2); reaction time (steam-bath), 10 minutes.

The results in Table III show that an increase in the amount of formaldehyde (as formalin) from 1.5 to 4–6 equivalents increases the extent of methylation. The effect is doubtless potentially greater than is so indicated, for the water introduced with the formalin dilutes all the reactants and impedes methylation (3).

The results in Table IV show the repressive effect of water. By the use of paraformaldehyde and no added water methylations by 2.5 equivalents of formaldehyde were equal to those obtained with 4 to 6 equivalents of formaldehyde taken as formalin (Table III).

The relationship between the amount of *formic acid* and the extent of methylation is shown in Table V.

TABLE V

METHYLATION OF 2,4- AND 2,6-XYLIDINES. THE EFFECT OF THE AMOUNT OF FORMIC ACID[a]

| RATIO HCOOH:amine | RATIO $CH_2O$:amine | YIELD OF DIMETHYLATED AMINE | |
|---|---|---|---|
| | | Dimethyl-2,4-xylidine, % | Dimethyl-2,6-xylidine, % |
| 2.0 | 2.5 | 35 | 50 |
| 2.5 | 2.5 | 40 | 55 |
| 3.0 | 2.5 | 40 | 75 |
| 4.0 | 2.5 | 25 | 75 |
| 6.0 | 2.5 | 15 | 80 |
| 10.0 | 2.5 | — | 70 |
| 2.5 | 5.0 | 40 | |
| 3.0 | 5.0 | 45 | |
| 3.5 | 5.0 | 30 | |
| 4.0 | 5.0 | 25 | |
| 6.0 | 5.0 | 15 | |

[a] Conditions: formaldehyde as paraformaldehyde and 98% formic acid as indicated; amine added last; time of reaction (steam-bath), 10 minutes.

TABLE VI

METHYLATION OF 2,4- AND 2,6-XYLIDINES. EFFECT OF HYDROCHLORIC ACID[a]

| RATIO HCl:amine | FORMALDEHYDE, 2.5 equiv. as | YIELD OF DIMETHYLATED AMINE | |
|---|---|---|---|
| | | Dimethyl-2,4-xylidine, % | Dimethyl-2,6-xylidine, % |
| 0.0 | Formalin | 35 | — |
| .1 | Formalin | 35 | — |
| 1.0 | Formalin | 10 | — |
| 2.0 | Formalin | 5 | — |
| 0.0 | Paraformaldehyde | 40 | 75 |
| .1 | Paraformaldehyde | 30 | 25 |
| 1.0 | Paraformaldehyde | 15 | 6.5 |
| 2.0 | Paraformaldehyde | 5 | 3 |

[a] Conditions: 2.5 equivalents of formaldehyde as shown (column 2); 3.0 equivalents of 98% formic acid; amine added last; time of reaction (steam-bath), 10 minutes.

The results in Table V show that methylation of 2,4-xylidine decreases with increasing concentration of formic acid, while that of 2,6-xylidine increases up to 6 equivalents of formic acid and is only slightly less with 10 equivalents.

The results in Table VI indicate the strongly repressive effect of strong acid upon the methylation of the two xylidines, presumably due to interference with the initial condensation of amine and aldehyde (3).

*Formylation*, shown by Staple and Wagner (3) to retard but not to exclude alkylation by the Wallach procedure, was apparently *not a factor in the* methylations reported here, as application of the Hinsberg test to steam-distillates from the alkalized reaction mixtures failed to reveal the presence of other than tertiary amines.

*The order of mixing reactants.* Comparisons among experiments which differed only in the order of mixing the reactants showed a marked improvement in yield when the amine was introduced last and by drops, the effect being greater for 2,6-xylidine than for 2,4-xylidine; a similar advantage was observed earlier by Gaskins (7), in the methylation of *p*-toluidine, by addition of formic acid last. The results of experiments to test this matter appear in Table VII.

The results (Table VII) for *o*- and *p*-toluidine when the amines were added last are in marked contrast to those by the usual Wallach procedure, which fails with these amines. From the few cases tested comparatively it appears that the methylation of amines with an open *para*-position or with one open *ortho*-position is improved by adding the amine last, although with the final addition of formic acid results are about equally as good and are better than those with the unmodified Wallach procedure. The failure of the *m*-toluidines to methylate is complete, presumably due to condensations involving one or more of the three reactive nuclear positions; the same is true of aniline.

TABLE VII

METHYLATION OF AROMATIC AMINES BY THE WALLACH PROCEDURE.[a] EFFECT OF ORDER OF MIXING THE REACTANTS

| AMINE | YIELDS OF DIMETHYLATED AMINES[b] | | | |
|---|---|---|---|---|
| | Reactants mixed and heated | Formalin added last | Formic acid added last | Amine added last |
| 2,4-Xylidine | 30 | 35 | 40 | 43 |
| 2,6-Xylidine | 30 | 5 | 35 | 60 |
| *o*-Toluidine | — | — | 25 | 40[c] |
| *m*-Toluidine | — | — | 0 | 0 |
| *p*-Toluidine | — | — | 50 | 45 |
| N-Methyl-*o*-toluidine | — | — | 40 | 55[d] |
| N-Methyl-*m*-toluidine | — | — | 0 | 0 |
| N-Methyl-*p*-toluidine | — | — | 95 | 95 |

[a] Conditions: 2.5 equivalents of formaldehyde, as paraformaldehyde; 3.0 equivalents of 98% formic acid; time of reaction 10 minutes. [b] The yields stated represent isolated product and are not necessarily comparable with the results by the usual Wallach procedure and based on $CO_2$ (Table II). [c] Not increased by doubling the paraformaldehyde or formic acid. [d] With paraformaldehyde doubled the yield was 65%.

*Effect of agitation.* The successful methylation of *p*-toluidine when the amine is added last and slowly appears to involve the prompt reaction of the amine as added, the initial reaction product of the amine and formaldehyde being at once reduced by the formic acid. Agitation of the mixture should favor rapid utilization of amine, and should improve the results when the mixture tends to stratify. Table VIII lists the results of some experiments to test the effects of agitation, showing the advantages of (a) the addition of either amine or formic acid last and at a slow rate, and (b) the rapid agitation of the mixture during the final addition of amine or acid.

The findings outlined above permit the selection of experimental conditions by which certain aromatic amines may be satisfactorily methylated by formaldehyde and formic acid. These conditions include the use of 2.5 equivalents of formaldehyde (as paraformaldehyde), the use of not less than 3 equivalents of formic acid, and the addition of the amine last and during a period of 10–15 minutes while stirring the mixture effectively. A brief period of heating on the steam-bath completes the reaction; if the amine is known readily to undergo nuclear condensation with formaldehyde the time of addition of the amine should be decreased and the after-heating omitted. Table IX lists the results obtained with 25 amines, of which 17 were successfully methylated.

TABLE VIII

METHYLATION OF 2,4- AND 2,6-XYLIDINES BY A MODIFIED WALLACH PROCEDURE. EFFECT OF AGITATION[a]

| REACTANT ADDED LAST | TIME OF ADDITION, min. | AGITATION[b] | YIELD OF METHYLATED AMINE | |
|---|---|---|---|---|
| | | | Dimethyl-2,4-xylidine, % | Dimethyl-2,6-xylidine, % |
| Formic acid | 0.25 | Vigorous | 30 | — |
| Formic acid | 10 | Vigorous | 55 | — |
| Formic acid | 40 | Vigorous | 65 | — |
| Amine | 12 | None | 30 | 35 |
| Amine | 12 | Moderate | 40 | 90 |
| Amine | 12 | Vigorous | 45 | 97 |
| Amine | 5[c] | None | 40 | 75 |
| Amine | 12[c] | None | 40 | 75 |
| Amine | 5[c] | Vigorous | 45 | 90[d] |
| Amine | 90[c] | Vigorous | 45 | 85 |

[a] Conditions: 2.5 equivalents of formaldehyde as paraformaldehyde; 3.0 equivalents of 98% formic acid. [b] A mechanical stirrer of the centrifugal type was operated at controlled, uniform speeds. [c] The amine was added as solution in pentane to aid dispersal. [d] No change in yield by doubling the amount of formic acid or by the use of formalin instead of paraformaldehyde.

One fact which appears clearly (Table IX) is that the methylation is successful only when the reactive *ortho* and *para* positions are more or less completely blocked. Aniline, methylaniline, *m*-toluidine, N-methyl-*m*-toluidine, *m*-nitroaniline, N-methyl-*m*-nitroaniline, and the naphthylamines, with all reactive nuclear positions unsubstituted, may undergo methylation complicated by nuclear condensations. Primary amines with one or two reactive positions blocked can be methylated with yields of about 50% when one such position is occupied, ranging to above 90% when two positions are blocked, and approaching the quantitative when 2,4,6-substituents are present. Secondary (N-methyl)amines give higher yields than corresponding primary amines.

*Methylene-bis-arylamines and methylene-arylamines (Schiff bases)*, when treated with formic acid yielded no carbon dioxide and no methylated amine. This result contrasts with that reported by Staple and Wagner (3) for benzylidene-bis-piperidine (100% benzylation), and indicates that methylene-bis-arylamines and methylene-arylamines are not intermediates in the methylation of arylamines; the alternative route *via* the hydroxymethylamines is suggested.

TABLE IX

METHYLATION OF SOME AROMATIC AMINES BY A MODIFIED WALLACH METHOD

| AMINE | YIELD OF DIMETHYLATED AMINE | AMINE | YIELD OF DIMETHYLATED AMINE |
|---|---|---|---|
| Aniline | 0 | *p*-Anisidine | 50 |
| *o*-Toluidine | 40 | Mesidine | 98 |
| *m*-Toluidine | 0 | 2,4-Dichloroaniline | 92 |
| *p*-Toluidine | 50 | 2,6-Dibromoaniline | 92 |
| *o*-Chloroaniline | 23 | *p*-Bromo-*o*-Toluidine | 65 |
| *p*-Chloroaniline | 65 | 2,4,6-tribromoaniline | 98 |
| α-Naphthylamine | 0 | N-Methylaniline | 0 |
| β-Naphthylamine | 0 | N-Methyl-*o*-toluidine | 55 |
| 2,4-Xylidine | 65 | N-Methyl-*m*-toluidine | 0 |
| 2,6-Xylidine | 97 | N-Methyl-*p*-toluidine | 95 |
| Sulfanilic acid | 0 | N-Methyl-2,4-xylidine | 98 |
| *m*-Nitroaniline | 0 | N-Methyl-2,6-xylidine | 98 |
| *p*-Nitroaniline | 50 | | |

## EXPERIMENTAL

Throughout this section the melting point and boiling point values are the observed (uncorrected) readings.

*Nuclear condensations of formaldehyde with aromatic amines in the presence of formic acid.* The results in Table I represent experiments in which the reactants were mixed together and heated on the steam-bath; the reaction mixture was poured into sodium hydroxide-sodium sulfite solution; the volatile material (unchanged or methylated amine) was removed by steam-distillation and was identified. The results of the five experiments which follow indicate that the products not volatile with steam are largely the tetramethyl diphenylmethane bases.

1. *Dimethylaniline*, paraformaldehyde, and 98% formic acid (1:1:1.1), heated for 60 minutes, yielded 92% (crude) of *p,p'*-bis(dimethylamino)diphenylmethane isolated by distillation with steam at 270°; after crystallization from ethanol it melted at 85–86° and was identified by mixture melting point and as the picrate.

2. *Dimethyl-p-toluidine*, paraformaldehyde, and formic acid (1:1:1), heated for 3.5 hours, yielded a trace of steam-volatile oil and a residue [97% crude assuming it to be 2,2'-bis-(dimethylamino)-5,5'-dimethyldiphenylmethane]. By extraction in ether and distillation a product of b.p. 205–208° (16 mm.) was obtained; the b.p. reported for the compound named is 212–214° at 16 mm. (Beilstein).

3. *2,6-Xylidine* was added gradually to a mixture of paraformaldehyde and formic acid (1:3:3), the lively evolution of carbon dioxide was allowed to subside, and the mixture was heated for 30 minutes. Steam-distillation yielded 33% of dimethylxylidine, b.p. 194–199°. The residue was transferred by distillation with superheated steam (63% crude). It was dis-

tilled (54%; 180–200° at 1 mm.), redistilled (170.5° at 0.8 mm.), and recrystallized from pentane; the product then melted at 49.5–50.5°; after solidification it remelted at 60.0–60.5°. Analysis confirmed it as the diphenylmethane base. Found: C, 81.23; H, 9.47.

4. *2,6-Dibromoaniline* (12), trioxane, and 98% formic acid (1:3:8.0), heated for 3 hours, yielded 83% of 4,4′-bis(dimethylamino)-3,3′,5,5′-tetrabromodiphenylmethane. After crystallization from 1:1 dioxane-ethanol it melted at 159–160°. Analysis supported its identification. Found: C, 35.95; H, 3.28.

5. *Meta-nitroaniline*, paraformaldehyde, and 98% formic acid (1:2.6:4) heated for 10.5 hours yielded, after extraction of the reaction mixture with ether, a solid residue of 4,4′-bis(dimethylamino)-2,2′-dinitrodiphenylmethane (35%), m.p. 191.0–191.8°; after crystallization from acetone-hexane the product melted at 191–192°. Analysis: N calc'd, 16.3; N found, 16.7.

*Formation of a substituted dihydroquinazoline from p-toluidine, formaldehyde, and formic acid.* A mixture of *p*-toluidine, paraformaldehyde, and formic acid (1:3:3) evolved carbon dioxide on heating. After 30 minutes on the steam-bath the mixture was made alkaline and was submitted to steam-distillation, yielding only a trace of methylated toluidine. The residue was distilled *in vacuo*, and the fraction obtained near 150° was separated and was extracted with ether; the undissolved residue was 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline, m.p. 156.5–157°. It was identified by mixture m.p. test, as picrate, and by analysis for C, H, and N. The yield of the pure compound was 10%; isolation and purification losses were high.

*Unidentified products by the action of formaldehyde and formic acid on 2,4-xylidine and 2,4-dichloroaniline.* 2,4-Xylidine (0.2 mole) was added to a mixture of paraformaldehyde and 98% formic acid (1:3:3) at such a rate as to control the vigorous reaction, and the mixture was heated for 30 minutes. Steam-distillation of the alkalized mixture yielded 33% of dimethyl-2,4-xylidine. The residue was dissolved in ether, and the ether solution was dried and distilled, yielding at 208–220° (1.5 mm.) 15 g. of a heavy yellow oil, which on redistillation yielded 12 g. boiling 183–203° (1 mm.). This material was again distilled, and the 186–187° (0.8 mm.)-fraction was crystallized from pentane, with chilling in Dry Ice, yielding a product of m.p. 164–166°, not changed by recrystallization from ethanol (165–166°). *Anal.* Found: C, 77.86; H, 7.62; N, 8.79.

In a separate experiment under similar conditions the evolved carbon dioxide was found to correspond to a 36% methylation (in agreement with the 33% dimethylxylidine isolated), indicating that the solid by-product was formed from the unmethylated xylidine and is itself not subject to methylation.

*2,4-Dichloroaniline* (0.6 mole), paraformaldehyde, and formic acid (1:3:3), treated as above, yielded 84% of dimethyl-2,4-dichloroaniline. The material not volatile with steam was extracted with ether, leaving colorless crystals (3 g.) of m.p. 166.5–167.5°, raised by recrystallization from ether-ethanol to 169.5–170.5°, a value not changed by recrystallization of the compound from ethanol. *Anal.* Found: C, 48.59; H, 2.70; N, 7.14. This compound was recovered unchanged after 0.5 g. was boiled with 8 ml. of acetic anhydride for 15 minutes and for 5 minutes longer with 5 ml. of pyridine added; the mixture was poured into water, and the precipitated compound (0.43 g.) was shown by m.p. (169–170°) and by mixture m.p. to be the starting material.

*Rates of methylation as indicated by the carbon dioxide evolved.* The apparatus was essentially that used in similar work by Staple and Wagner (3). In each experiment the amine (0.03 mole), paraformaldehyde (0.084 mole), and 98% formic acid (0.12 mole) (ratio 1:2.8:4) were introduced into the chilled reaction flask, which was joined into the assembly and which rested in a (cold) steam-bath. A slow stream of nitrogen (passed first through a tower packed with soda-lime) was started, and steam was admitted to the bath. Reaction within the flask started within a minute, with the evolution of carbon dioxide which subsided in several minutes and continued thereafter at a diminishing rate. At the time intervals indicated in Table II the gas stream was temporarily increased (during 5 minutes so as to sweep out accumulated carbon dioxide), the Ascarite absorber was rapidly replaced by a fresh absorber, and the first absorber was weighed. These operations were repeated in uniform fashion at each time interval. All the carbon dioxide was absorbed in the single absorber; a second receiver placed in series failed to increase in weight. With several amines that reacted vigorously (*e.g.*, mesidine), as ascertained in preliminary tests, the quantities of reactants were halved, and both the reactants and the reaction flask were chilled before using. The observed time-yield relationships are collected in Table II.

*The Wallach alkylation procedure modified for the methylation of aromatic amines.* The apparatus comprised a 250-ml. 3-necked flask, fitted with a centrifugal stirrer and a dropping-funnel; the third neck was left open to vent the evolved carbon dioxide. Except in preliminary trials in which were studied the effects of stirring and of the order in which reactants were mixed, the paraformaldehyde and the 98% formic acid were mixed and warmed gently (most of the former dissolving), and the amine was introduced gradually, with vigorous stirring. The proportions of amine, formaldehyde, and formic acid were in general 1:2.5:3. An excess of formic acid may sometimes be advisable to prevent stratification, but a large excess may be expected in some cases to decrease the extent of methylation (ref. 3 and Table V). To assist in the dispersal of the amine in the mixture in some experiments the amine was added as a solution in pentane or ether. The reaction mixture was heated on the steam-bath for about 5 minutes (in addition to the 10–15 minutes during addition of the amine). When it was known that the methylated amine was one readily converted by action of formaldehyde to products not volatile with steam, the time of addition of the amine was halved and the after-heating was omitted. The reaction mixture was poured into a chilled solution of sodium hydroxide (1.3 equivalents with respect to formic acid) and sodium sulfite (1.2 equivalents with respect to formaldehyde) and the alkaline mixture was subjected to steam-distillation. Any oil that passed over was extracted in ether and the extract was dried over potassium carbonate. The residue after evaporation of the ether was weighed as a crude product, which was purified by distillation. The efficacy of this isolation procedure was determined by experiments in which dimethylaniline was added to a mixture of formaldehyde, formic acid, sodium hydroxide, and sodium sulfite (as obtained in the modified Wallach procedure outlined above); recovery of dimethylaniline approached the quantitative. The sodium sulfite may be dispensable, as formaldehyde would scarcely survive contact with hot alkali and as the bisulfite addition product, while notably stable (14), may be dissociable by hot alkali. Table IX presents the results by the modified Wallach procedure applied to 26 aromatic amines, of which 17 were successfully methylated.

*Preliminary experiments, using 2,4-xylidine and 2,6-xylidine.* The results of experiments to test the influence of the amount of formaldehyde taken as formalin, and the related influence of water, appear in Tables III and IV. Table V records the effects of variations in the amounts of formic acid, and Table VI shows the strongly repressive effect of strong acid upon methylation. Tables VII and VIII respectively show the effects of the order of mixing the reactants and of agitation.

*Experiments with preformed aldehyde-amine condensation products.* In a series of experiments the methylene-bis-amines from *p*-toluidine, *o*-chloroaniline, and *p*-chloroaniline, and the methylene amines (trimeric Schiff bases) from *p*-toluidine, *p*-chloroaniline, and *p*-bromoaniline (13) were heated with formic acid as in the procedure for the determination of evolved carbon dioxide. In no case was there evolution of carbon dioxide during 30 minutes on the steam-bath.

## SUMMARY

Study of the Wallach procedure for the methylation of amines showed that the unsatisfactory results obtained hitherto with aromatic amines other than mesidine and tribromoaniline are the result of condensations involving formaldehyde and reactive nuclear hydrogen, leading to the formation of varied products some of which themselves may be partially or exhaustively methylated on nitrogen.

Such products were found to include the diphenylmethane bases, a substituted quinazoline, and the "higher condensation products" obtained as amorphous, often gluey, and intractable mixtures. These side reactions appear to be acid-catalyzed; they are negligible in the absence of acid and are impeded by acid in sufficient excess. By a modification of the Wallach procedure seventeen aromatic amines were methylated in yields of 23% to 98%. The aromatic primary or secondary amines successfully methylated all have one or more of the *ortho* or *para* hydrogens replaced. With all reactive positions unsubstituted the nuclear condensations predominate; with one or two reactive positions blocked methylation reaches 90%; with all reactive positions blocked methylation is nearly quantitative.

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