# **184.** *An Experimental Study of the Alkylation of Aromatic Amines using* (1) *Aluminium Alkoxides and* (2) *Alumina with Alcohols.*

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The alkylation of aniline salts and complexes by means of aluminium alkoxides has been explored, and the influence of various anions and cations present on the rate of alkylation roughly examined. The vapour-phase methylation of methylaniline with methanol in the presence of alumina has also been studied in some detail, together with the effect on the rate of *N*-alkylation and on the tendency towards nuclear alkylation of the addition to the catalyst of various metallic salts.

The demand for *N*-alkylated amines for war purposes led the authors to a review of alternative methods of alkylation which might be preferable in some respects to those at present used industrially. Some of the experimental results obtained with two such methods are described here. Not enough evidence is available to indicate whether the two processes under consideration differ fundamentally from one another or whether either or both of them involve the same reacting entities as the other known alkylation processes. It would therefore be premature to introduce a theoretical discussion at this stage. The catalytic action of alumina presents many points of interest which have often been discussed in the literature. Further information will no doubt be gained from a strictly quantitative study of the vapour-phase alkylation process. Requirements of such a study include rigid temperature control and a constant rate of passage of the reaction mixture over the catalyst. The considerable mechanical difficulties involved in meeting these requirements are gradually being overcome and it is hoped that the experimental results eventually obtained will be precise enough to justify theoretical treatment. Meanwhile, many of the facts brought to light during our preliminary studies seem to be of sufficient interest to describe here.

(1) *Alkylation of Aniline Salts and Complexes with Aluminium Alkoxides.*—Lazier and Adkins (*J. Amer. Chem. Soc.*, **1924**, **46**, 741) described the successful alkylation of aniline by heating it with the requisite aluminium alkoxide in a sealed tube at 250—350°. It is possible, however, to alkylate salts of aniline or aniline–metallic salt complexes under atmospheric pressure with aluminium alkoxides at considerably lower temperatures than those needed for aniline itself. The following table summarises a series of experiments in which various aniline salts were mixed with four times the amount of aluminium ethoxide required for complete diethylation and heated under a reflux condenser for several hours. The ease of alkylation of the iodide is remarkable but is in agreement with a recorded observation that the direct action between alcohols and aniline is catalysed by iodides (Brit. Pat. 145,743).

| Salt. | Temp. | Time, hours. | Primary base in product, %. |
|---|---|---|---|
| $Ph{\cdot}NH_3Cl$ | 184° | 5 | 91·8 |
| $Ph{\cdot}NH_3Br$ | 184 | 5 | 46·7 |
| $Ph{\cdot}NH_3I$ | 184 | 5 | 2·4 * |
| $Ph{\cdot}NH_3Br$ | 198 | 5½ | 6·3 |
| $(Ph{\cdot}NH_3)_3PO_4$ | 198 | 5½ | 91·3 |
| $(Ph{\cdot}NH_3)_2SO_4$ | 240 | 5 | 30·0 |

* Tertiary base 18·6%.

Complexes of aniline with metallic salts can also be ethylated by a similar procedure, but the reaction does not take place as readily as with the anilinium salts :

| Complex. | Temp. | Time, hours. | Primary base in product, %. |
|---|---|---|---|
| $CdSO_4,2Ph{\cdot}NH_2$ | 240° | 5 | 69·8 |
| $ZnSO_4,2Ph{\cdot}NH_2$ | 240 | 5 | 80·3 |
| $ZnCl_2,2Ph{\cdot}NH_2$ | 240 | 5 | 56·2 |
| $ZnBr_2,2PH{\cdot}NH_2$ | 240 | 5 | 41·8 |
| $NiCl_2,2Ph{\cdot}NH_2$ | 240 | 5 | 90·3 |

It is evident that both cations and anions have an influence on the rate of alkylation.

The addition of sodium halides to reaction mixtures containing anilinium halides generally increased the rate of alkylation :

| Anilinium salt. | Added salt. | Temp. | Time, hours. | Primary base in product, %. |
|---|---|---|---|---|
| $Ph{\cdot}NH_3Cl$ .............. | NaCl (1 mol.) | 184° | 5 | 44·1 |
| $Ph{\cdot}NH_3Cl$ .............. | NaCl (2 mols.) | 184 | 5 | 27·4 |
| $Ph{\cdot}NH_3Br$ .............. | NaBr (1 mol.) | 183 | 5 | 43·6 |
| $Ph{\cdot}NH_3Br$ .............. | NaBr (1·5 mols.) | 184 | 5 | 34·3 |

Some experiments on the *n*-butylation of aniline hydrochloride were made in which the different sodium halides were used as catalysts :

| | | | Composition of basic product : | | |
|---|---|---|---|---|---|
| Na halide per mol. of $Ph{\cdot}NH_3Cl$. | Temp. | Time, hours. | Primary, %. | Secondary, %. | Tertiary, %. |
| NaCl (1 mol.) ........................ | 198° | 16 | 65·1 | 34·9 | — |
| NaBr (1 mol.) ........................ | 198 | 10 | 43·3 | 48·7 | 8·0 |
| NaI (1 mol.) .......................... | 198 | 10 | 3·3 | 64·0 | 32·7 |

The following routine was adopted for isolating and examining the products from all experiments. The reaction mixture was mixed with a concentrated solution of sodium hydroxide and steam-distilled until no further oil came over. The distillate was extracted thoroughly with ether, and the ethereal solution dried with sodium sulphate. After removal of the ether the bases were distilled. If the distillation temperature indicated that no high-boiling fraction was present, the absence of important amounts of tertiary amine was assumed and no attempt was made to estimate it. Aniline in the product was determined by taking advantage of the fact that it forms a stable complex $CdCl_2,Ph{\cdot}NH_2$ precipitated when it is shaken with a saturated aqueous solution of cadmium chloride. The secondary and tertiary bases do not form water-stable complexes with cadmium chloride. For the actual estimation about 1 g. of the mixed bases was weighed in a 25-ml. graduated flask and 20 ml. of light petroleum (b. p. 40—60°) added with just sufficient 1 : 4-dioxan to form a homogeneous solution. The volume was then made up to 25 ml. with more light petroleum. Then 2 ml. of this solution, or more if the aniline content was low, were run into a small separating funnel and shaken with 3 ml. of saturated cadmium chloride solution. The white complex salt was immediately precipitated together with some cadmium chloride. Generally, most of the precipitate adhered to the wall of the funnel. The liquid was run off through a fritted-glass filter, and the precipitate remaining, partly in the funnel and partly on the filter, was washed with a little light petroleum. The precipitate was then dissolved in 10% hydrochloric acid and titrated with standard bromide–bromate solution and thiosulphate, and the result calculated as aniline. When the preliminary distillation showed the presence of much tertiary amine the above procedure was supplemented by an acetylation of the total bases with a known weight of acetic anhydride and determination of the amount unused after half an hour by decomposition with water and titration with alkali.

(2) *The Vapour-phase Methylation of* N-*Methylaniline by Methanol in the Presence of an Alumina Catalyst.*—Mailhe and de Godon (*Compt. rend.*, 1918, **166**, 467, 564; 1920, **171**, 1154; 1921, **172**, 1417) successfully alkylated aromatic amines by passing the mixed vapour of the amine and the requisite alcohol over a heated alumina catalyst. The reaction was further studied by Schujkin, Balandin, and others (*J. Gen. Chem. Russ.*, 1934, **4**, 1444; *J. Physical Chem.*, 1935, **39**, 1192), especially in respect of the effect of other oxides in admixture with the catalyst. In general, the other oxides diminished the activity of the catalyst, but were sometimes beneficial in inhibiting side reactions.

The large-scale manufacture of alkylated anilines by vapour-phase catalytic methods was successfully practised during the war. With suitably chosen catalysts, much lower temperatures than those specified by the above-mentioned workers (350—400°) were effective in bringing about a high degree of alkylation. It was, therefore, of interest to study the reaction more closely and especially to search for promoters which would increase the activity of the catalyst. To enable large numbers of experiments to be performed in reasonable time, their scale was kept as small as possible. The methods used for the analysis of the products were chosen for their rapidity and reproducibility rather than for their absolute accuracy. The experiments here described were exploratory and only roughly quantitative and were intended to give the preliminary information needed for planning more strictly quantitative work on the reaction. However, they themselves led to definite and interesting conclusions, which justify their description at this stage.

The apparatus used was simple. The liquid mixture of alcohol and amine (with any miscible promoting agent, if used) was placed in a feed chamber terminating in a capillary which projected well into the catalyst tube. A finely adjustable pressure of nitrogen was maintained above the reaction mixture to regulate its speed of introduction, and a by-pass also admitted a regulated stream of nitrogen into the catalyst tube. The tube itself was 35 cm. long and 13 mm. in diameter and terminated in a beak to facilitate the collection of the products in a small flask. The temperature of the catalyst mass was observed by means of a thermometer immersed in it. The tube was heated in an electric furnace.

To avoid unnecessary complications in the analysis of the products, attention was concentrated on the second stage of the methylation of aniline, namely, the conversion of *N*-methyl- into *NN*-dimethylaniline. Accompanying this reaction there is also some nuclear alkylation, the amount of which varies considerably according to the catalyst and experimental conditions used. The principal nuclear alkylation product to be expected is *N*-methyl-*p*-toluidine because it is known that in the large-scale methylation and ethylation of aniline the nuclear by-products consist mainly of *N*-methyl-*p*-toluidine and *N*:*p*-diethylaniline respectively [private communication from F. Kaufler and (Miss) J. Fildes]. A rapid, approximate method of determining the amounts of *N*-methylaniline, *N*-methyl-*p*-toluidine, and *NN*-dimethylaniline in the presence of one another depends on a combination of acetylation and refractive-index measurement. The secondary bases can be determined by quantitative acetylation, and the sum of *N*-methyl-*p*-toluidine and *NN*-dimethylaniline by measurement of the refractivity of the mixed bases. The refractive indices ($n_D^{20°}$) of the three bases are: *N*-methylaniline, 1·5714; *NN*-dimethylaniline, 1·5587; *N*-methyl-*p*-toluidine, 1·5582.

The catalytic activity of alumina, it is well known, varies greatly with the method of preparation. For these experiments, with a few exceptions specifically mentioned, the catalyst was made by decomposing aluminium *n*-butoxide with water, and drying and heating the product at 400° for 2 hours. It was then broken up and sifted, the fraction passing a 10-mesh and retained by a 20-mesh sieve being used. The weight of catalyst used for each experiment was 3 g., occupying approximately 10 c.c.

When the effect of a promoter in the catalyst itself was being examined, a quantity equivalent to 0·5 g. of sodium iodide was dissolved in methanol or aqueous methanol and mixed with 3 g. of the alumina, the solvent being then removed by heating on a water-bath.

For each of the experiments tabulated below, a reaction mixture containing 2 g. of *N*-methylaniline and 0·6 g. of methanol was introduced during 3½ hours into the catalyst tube, heated at 250° unless otherwise specifically mentioned.

In view of the accelerating effect of iodides in the alkylation of aniline salts by aluminium alkoxides mentioned above, a series of experiments were made using iodine or iodides in the reaction mixture. The percentage of acetylatable bases in the product was determined and calculated as monomethylaniline. The same charge of catalyst was used for the whole series of 11 experiments.

| Amt. of iodine or iodide added. | Acetylatable bases expressed as NHPhMe, % | Amt. of iodine or iodide added. | Acetylatable bases expressed as NHPhMe, %. |
|---|---|---|---|
| (None) | 73·0 | None | 59·0 |
| 0·5% $CH_3I$ | 67·5 | None | 64·0 |
| 0·9% $CH_3I$ | 57·2 | None | 70·0 |
| 1·0% $NH_2PhMeI$ | 46·5 | 1% I | 56·5 |
| 1·5% $NH_2PhMeI$ | 46·5 | 1% I | 49·3 |
| None | 52·0 | | |

These results show that iodine and iodides have a strongly accelerating effect on the reaction and that the effect is retained by the catalyst for some time.

When *N*-methylanilinium chloride is added to the reaction mixture there is not a marked increase in *N*-alkylation but a certain amount of nuclear alkylation takes place. The catalyst in this group of experiments was that used on the manufacturing scale for the methylation of aniline.

| $NH_2PhMeCl$ added, %. | NHPhMe in product, %, from refractivity. | Acetylatable bases, %, calc. as NHPhMe. | Diff. due to nuclear alkylation. |
|---|---|---|---|
| None | 43 | 42 | − 1 |
| None | 42 | 43 | 1 |
| None | 45 | 49 | 4 |
| 5% | 38 | 43 | 5 |
| None | 25 | 40 | 15 |
| None | 31 | 43 | 12 |
| None | 38 | 44 | 6 |
| None | 38 | 45 | 7 |
| 2½% | 38 | 44 | 6 |
| 2½% | 39 | 41 | 2 |
| 2¾% | 38 | 53 | 15 |
| None | 38 | 47 | 9 |
| None | 37 | 43 | 6 |
| None | 43 | 42 | −1 |

It is clear from the above two series of experiments that a lag must be expected when a promoter is introduced with the reaction mixture, the promoted catalyst not showing its full activity for some time. The second series also shows what degree of accuracy is to be expected from the method described for estimation of nuclear alkylation.

A third series of experiments shows the effect of adding to the catalyst itself various salts which might be expected to have some effect in increasing the activity of the catalyst or in promoting nuclear alkylation. Each group of four experiments, three at 250° and one at 290°, was done with one charge of catalyst, a fresh charge being then introduced for the next group.

| Temp. | Salt added. | NHPhMe, %, from refractivity. | Acetylatable bases, %, as NHPhMe. | Diff. (nuclear alkylation). | Temp. | Salt added. | NHPhMe, from refractivity. | Acetylatable bases, %, as NHPhMe. | Diff. (nuclear alkylation). |
|---|---|---|---|---|---|---|---|---|---|
| 250° | None | 34·2 | 38·0 | 3·8 | 250° | $CoCl_2$ | 10·3 | 13·1 | 2·8 |
| 250 | None | 38·9 | 45·3 | 6·4 | 250 | $CoCl_2$ | 9·9 | 19·0 | 9·1 |
| 250 | None | 41·2 | 41·9 | 0·7 | 250 | $CoCl_2$ | 7·5 | 23·6 | 16·1 |
| 290 | None | 16·4 | 19·4 | 3·0 | 290 | $CoCl_2$ | 17·9 | 70·9 | 53·0 |
| 250 | NaCl | 32·7 | 27·6 | − 5·1 | 250 | $MnCl_2$ | 10·4 | 11·1 | 0·7 |
| 250 | NaCl | 32·7 | 31·8 | − 0·9 | 250 | $MnCl_2$ | 6·8 | 20·4 | 13·6 |
| 250 | NaCl | 33·5 | 35·1 | 1·6 | 250 | $MnCl_2$ | 9·0 | 25·2 | 16·2 |
| 290 | NaCl | 15·0 | 30·0 | 15·0 | 290 | $MnCl_2$ | 0·0 | 60·6 | 60·6 |
| 250 | NaBr | 10·4 | 10·2 | − 0·2 | 250 | $ZnCl_2$ | 19·5 | 21·9 | 2·4 |
| 250 | NaBr | 11·8 | 21·2 | 9·4 | 250 | $ZnCl_2$ | 18·0 | — | — |
| 250 | NaBr | 10·3 | 21·4 | 11·1 | 250 | $ZnCl_2$ | 10·4 | 35·5 | 25·1 |
| 290 | NaBr | 0·6 | 58·4 | 57·8 | 290 | $ZnCl_2$ | 6·8 | 71·1 | 64·3 |
| 250 | NaI | 17·7 | 15·6 | − 2·1 | 250 | $CdCl_2$ | 9·8 | 13·0 | 3·2 |
| 250 | NaI | 17·7 | 17·9 | 0·2 | 250 | $CdCl_2$ | 3·5 | 23·8 | 20·3 |
| 250 | NaI | 13·3 | 11·7 | − 1·6 | 250 | $CdCl_2$ | 0·5 | 41·3 | 40·8 |
| 290 | NaI | 4·5 | 65·1 | 60·6 | 290 | $CdCl_2$ | 42·0 | 71·4 | 29·4 |
| 250 | $NiCl_2$ | 13·4 | 16·7 | 3·3 | 250 | $FeCl_3$ | 4·5 | 25·0 | 20·5 |
| 250 | $NiCl_2$ | 15·6 | 22·2 | 6·6 | 250 | $FeCl_3$ | 15·0 | 43·7 | 28·7 |
| 250 | $NiCl_2$ | 22·5 | 26·3 | 3·8 | 250 | $FeCl_3$ | 16·4 | 40·5 | 24·1 |
| 290 | $NiCl_2$ | 14·0 | 56·0 | 42·0 | 290 | $FeCl_3$ | 15·6 | 58·2 | 42·6 |
| 250 | $CuCl_2$ | 11·2 | 43·3 | 32·1 | 250 | $SnCl_2$ | 9·0 | 21·8 | 22·8 |

Although the figures in the above table show certain obvious irregularities, and minor variations in the values in cols. 3 and 5 cannot be regarded as having any real significance, yet there are major trends which lead to useful conclusions. All the salts used, except sodium chloride, increased the activity of the catalyst at 250°. Raising the temperature from 250° to 290° increased the rate of alkylation with pure alumina and when sodium halides, manganese chloride, or zinc chloride was present; but cobalt and cadmium chlorides definitely depressed the rate of alkylation at the higher temperature. Whilst with pure alumina there is no significant amount of nuclear alkylation even at 290°, yet most of the added salts promoted nuclear alkylation at that temperature and sometimes at 250° also.

The practical experience gained with the simple apparatus showed clearly that for a quantitative study of the kinetics of the alkylation reaction it would require much modification. This work has been undertaken and will be described in a later paper.

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