small amount of high-boiling condensation products. The ether acid is not formed.

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THE ALKYLATION OF PRIMARY AMINES WITH ALUMINUM ALKOXIDES TO GIVE SECONDARY AMINES FREE FROM TERTIARY AMINES

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The direct alkylation of a primary amine with any of the usual alkylating agents results in the formation of tertiary as well as secondary amines. However, John Ulric Nef[1] alkylated aniline and acetanilide with sodium ethoxide in a sealed tube at 250–305°, and obtained ethyl aniline entirely free from diethyl aniline. The yield with aniline was 20% of that calculated and 40% with the acetanilide. We have duplicated Nef's results and extended the method to the use of aluminum alkoxides with a great increase in yield, smoothness of reaction and quality of product. It has been possible to obtain a mixture of bases consisting of 94% of ethyl aniline and 6% of aniline by the direct alkylation of aniline with aluminum ethoxide.

Aluminum alkoxides possess at least three advantages in alkylation over the sodium compounds: (1) They may be used as alkylating agents at least 100° above the temperature at which sodium alkoxides decompose. (2) The by-product of the reaction, alumina, is without effect upon the other products of the reaction as contrasted with the tar and acid-forming propensities of sodium hydroxide; hence the yields are higher and the products water-white. (3) They give better results with the free amine than with the acetyl derivative; hence the preparation of the latter is avoided. Nef explained the better results with the anilide than with the free amine by assuming that the reaction came to a definite equilibrium and that the sodium hydroxide produced worked against the further production of ethyl aniline. He said that when acetanilide was used the acetic acid produced by the reaction removed the sodium hydroxide and displaced the equilibrium in favor of the formation of ethyl aniline. With aluminum ethoxide a much better yield was obtained with aniline than with acetanilide. If the assumption of Nef is true, it should apply here equally well. It seems more plausible to regard the low yield with the sodium compounds as due to the strong alkali which causes decomposition of the remainder of the alkoxide with the formation of fatty acids. The

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[1] Nef, *Ann.*, **318**, 138 (1901).

presence of these fatty acids was reported by Nef and confirmed by us. The fatty acid corresponding to the alkoxide was always formed when the sodium compounds were used. No organic acids have been detected in any experiment in which aluminum alkoxides were used.

Nef of course assumed that the ethoxide dissociated to give a metallic hydroxide and ethylidene which then added to the aniline to give ethyl aniline. He explained that the reason alkylation with ethyl bromide, for example, gives diethyl aniline is that in this case the ethylidene may add to a *salt* of ethyl aniline. When sodium ethoxide is used as the alkylating agent the ethyl aniline first formed cannot form a salt, hence cannot add ethylidene. The truth of these assumptions is certainly far from established and to us this reaction fails to give any support to the idea of dissociation preceding reaction. Nef emphasized that the alkylation proceeds only above the so-called "dissociation point" (250°) of sodium ethoxide. In our opinion sodium ethoxide "dissociates" entirely too much and the limiting factor in its use is this very tendency which may more properly be called decomposition. Aluminum alkoxides are much more stable and are good alkylating agents. Further work upon the mechanism of the reaction will be taken up later. It may be said in passing, however, that an olefin such as amylene does not add to aniline in the presence of aluminum hydroxide under the conditions of alkylation; hence, it seems that the formation of an olefin is not an intermediate step in the alkylation.

Tests for tertiary amines in many different reaction products were made with nitrous acid[2] and with benzenesulfonyl chloride.[3] The faintest trace of tertiary amines was obtained in some cases; in others there was no detectable amount of such amines. This statement refers to the alkylations which were made at 350° or lower. Alkylations at higher temperatures in a few cases gave traces of solid tertiary amines which were apparently the result of reaction between two or more molecules of aromatic amines. The evidence is conclusive that aluminum alkoxides do not form tertiary amines from primary or from secondary amines except in barely detectable amounts, if at all.

In studying the alkylation it was desired to have a rapid and accurate method of determining the percentage of secondary amine present in a given mixture of primary and secondary amines. Such a method was found in the titration of the bases with a 0.5 *N* solution of hydrochloric acid, using congo red paper as an indicator. The neutralization equivalent was calculated from the data obtained. It represents the mean molecular weight and is obtained by dividing the weight of the sample titra-

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[2] Mulliken, "A Method for the Identification of Pure Organic Compounds," John Wiley and Co., New York, **1916**, Vol. II, pp. 17, 47.

[3] Ref. 2, p. 23.

ted by the number of cubic centimeters of 0.001 N acid required. The values for the neutralization equivalent are accurate to within one unit, and the percentage composition calculated from them to within 2%. In the important cases the percentage of secondary amine was checked by fractionations of the mixed bases.

The calculation of the composition of a mixture of two bases from the neutralization equivalent is easily made by use of the equation derived below. If N is the neutralization equivalent, x the number of molecules of the base of smaller molecular weight, y of the other, A the molecular weight of x and B that of y, $N = (Ax + By)/(x + y)$. If P equals the percentage of one base, then $100 - P$ equals the percentage of the other, and $x = P/A$, and $y = (100 - P)/B$. If these values for x and y be substituted in the first equation, and it is solved for P, it will be found that $P = \frac{100\,A\,(B - N)}{N\,(B - A)}$. The truth of this equation has been experimentally demonstrated by the titration not only of known mixtures of aniline and ethyl aniline but of mixtures of oxalic and benzoic acids. The equation would seem to be of considerable general value since it may be used in the calculation of the percentage composition of a mixture of any two pure, titratable substances such as acids, bases, aldehydes, etc. By its use one avoids the easily made error of assuming that if the neutralization equivalent (mean molecular weight) is midway between the molecular weights of the two components they are present in equal amounts. In the case of a 50% mixture of oxalic acid and benzoic acid such an assumption leads to an error of about 8%.

Results.—Since in this work we were primarily interested in the extent to which a given amine may be alkylated, we refer below to the degree of alkylation, having reference to the percentage of secondary amine in the recovered bases. In general the recovery of bases was about 75% of that calculated. Eight g. of sodium ethoxide heated with 15 g. of acetanilide for four hours at 275° alkylated to the extent of 43%. The product was colored and some outward pressure was found in the cold bomb. Under the same conditions 7 g. of aluminum ethoxide gave 31% of the secondary amine. When an equivalent amount of aniline (12 g.) was substituted for the acetanilide the sodium derivative gave 26% and the aluminum compound 60% of ethyl aniline. Acetanilide always gives an ester and a certain amount of tar. Sodium ethoxide heated alone or with ethyl aniline always exploded the bomb at about 275°, within a few minutes. Aluminum ethoxide under the same conditions is slowly converted to alumina and ethyl ether.[4]

Aniline was alkylated with aluminum ethoxide at 275°, 325°, 350°, 375° and 400°. The degree of alkylation (and of recovered bases) increased

[4] Child and Adkins, This Journal, **45**, 3013 (1913).

with temperature to a maximum of 90% at 350°. Higher temperatures gave small amounts of hydrocarbons, phenols, and ammonia and a considerable lowering of yield of bases and degree of alkylation. In the above experiments the reagents were in the proportion of 1 mole of ethoxide (7 g.) to 3 of aniline (12 g.). An increase in the weight of the former to 8 g. increased the degree of alkylation by 2%. Further increase in the amount of alkoxide or in the time of heating beyond four hours was disadvantageous.

An experiment using 24 g. of the ethoxide and 36 g. of aniline (this quantity being as much as could conveniently be sealed in the bomb) was made at 350°; 36.5 g. of bases was recovered, 91% of which was ethyl aniline. Retreatment of this mixture of bases with 8 g. of ethoxide at 275° increased the percentage of the secondary amine to 94%, the highest value obtained in this work. Other experiments with pure ethyl aniline and with mixtures high in that amine indicated that when the re-alkylation was carried out at 350°, unsaturated hydrocarbons and a small amount of a solid tertiary amine, probably triphenyl amine were formed. The alkylations with aluminum ethoxide are characterized by the formation of small amounts of ether[5] and a water-white mixture of bases. The reaction product is homogeneous when warm, but large crystals of an aluminum compound separate as the mixture cools. There is no outward pressure in the cold bomb; in fact, the pressure is less than atmospheric.

One experiment was made in which aluminum anilide, $(C_6H_5NH)_3Al$, and ethyl alcohol were heated together in a bomb at 275°. Since according to Crossley these two compounds react to give aluminum ethoxide and aniline, results similar to those above should be obtained. In this case there was 32% alkylation.

With the optimum conditions as found for ethyl aniline, the following amines were prepared, the degree of alkylation being given after the name of the amine: *n*-butyl aniline (77%), *iso*butyl aniline (74%), *n*-butyl *p*-toluidine (59%), ethyl *p*-toluidine (49%), *iso*butyl *p*-toluidine (51%), ethyl-*n*-pentyl amine (50%), *n*-butyl-*n*-pentyl amine (35%), (alkylation at 300° in this last case). Undoubtedly greatly improved alkylations could be made if the optimum conditions for the formation of each amine were as carefully sought as were those for ethyl aniline.

Reagents.—Aluminum ethoxide, *n*-butoxide and *iso*butoxide were prepared as previously described.[6] Aluminum anilide was made as suggested by M. L. Crossley.[7] The process is the same as that used with the alcohols, except that since the compound is not volatile it must be somewhat purified by washing with anhydrous ether. Butyl

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[5] Ref. 4, p. 3014.

[6] Adkins, THIS JOURNAL, **44**, 2178 (1922).

[7] At the Pittsburgh meeting of the American Chemical Society, Sept., **1922**.

bromide,[8] butyl cyanide,[9] and *n*-pentyl amine[10] were prepared as described by Adams, Kamm and Marvel. The sodium ethoxide was prepared as described by Nef.[1]

Apparatus.—The alkylations were carried out in Pyrex bomb tubes having a diameter of about 30 mm., a wall thickness of 2 to 3 mm. and a length of 30 to 70 cm. The tubes were heated in an electric tube-furnace having a length of 80 cm. The temperature was controlled within 2° or 3° by means of a standard commercial controller and recorder. About one hour was required to bring the furnace up to heat and two hours to cool it. The time of heating recorded does not include these three hours.

Isolation of the Bases.—Three methods were used for the recovery of the bases after the reactions had been completed. The first of these consisted of opening the tube and washing out the contents with 250 cc. of 10% hydrochloric acid which dissolved the contents completely except for a little tar-like material found in some runs. The acid solution was extracted once with ether in order to remove any neutral or acid insoluble material and then 90 g. of sodium hydroxide was added which set the bases free from their hydrochlorides and redissolved the greater part of the precipitated aluminum hydroxide. This alkaline solution was extracted repeatedly with ether until all the bases obtainable had been removed. The ether solution was evaporated to a small volume and the bases were recovered in a pure state by distillation under diminished pressure. This method gave considerable trouble due to the fact that it was impossible to get all of the aluminum hydroxide dissolved in the small amount of alkaline solution, and a large volume of ether was required to remove the amines completely. Therefore the second procedure was adopted. This consisted of washing out the contents of the bomb with acid as described above but instead of extracting with ether, the acid solution was subjected to steam distillation which completely removed all neutral and acidic volatile substances. The large excess of hydrochloric acid was found necessary in order to prevent the hydrolysis of the salts of some of the bases during the first steam distillation. Ninety g. of sodium hydroxide was now added and the steam distillation repeated from the alkaline solution. The basic oil was easily separated and the aqueous layer extracted once with ether. The ether and amines were concentrated and vacuum distilled as described under the first procedure. The disadvantage of this method is that it is not applicable to compounds such as the butyl toluidines which are not sufficiently volatile to be recovered by steam distillation. For these compounds a third procedure was adopted. In experiments in which the proportions of the reacting substances and the temperature were properly adjusted, the products upon cooling separated into two phases, a liquid and solid. The solid phase appeared in the form of crystals while the liquid consisted of the mixture of amines with a little alcohol and ether. The tubes were opened and the liquid portion was carefully poured off leaving the solid material in the tube. This was extracted repeatedly with ether and the latter decanted off each time. The basic oil and the ether washings were combined and shaken with a solution of hydrochloric acid, which was then made alkaline and the bases were shaken out with ether and distilled as described in the first procedure. Due to the volatility and solubility of some of the aliphatic amines in water they were distilled with steam into an acid solution and the solution of the hydrochlorides was evaporated to dryness. This solid material was treated with a concentrated solution of sodium hydroxide, and the bases were separated and distilled.

A mixture of bases obtained by one procedure was titrated and run through another procedure and again titrated. In this way it was found that the various procedures described above could be used interchangeably. It was also found that the efficiency

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[8] Kamm and Marvel, THIS JOURNAL, **42**, 305 (1920).

[9] Adams and Marvel, *ibid.*, **42**, 311 (1920).

[10] Ref. 9, p. 314.

of the recovery of the bases had little effect upon the composition of the primary and secondary amines because in any loss due to inefficient extraction both were lost approximately in the proportion in which they were originally present.

Titration of the Bases.—One hundred-cc. glass-stoppered Erlenmeyer flasks were tared and 1 g. samples weighed into them. Fifty cc. of distilled water was added. These samples were titrated with 0.5 *N* hydrochloric acid, using congo red paper as an indicator. The greater part of the standard acid was run into the flask before the indicator paper was added. After the addition of the acid the flask was gently rotated to permit the base to dissolve. A bit of the test paper was added, the flask tightly stoppered and shaken vigorously. If nearly the required amount of acid had been added the solution was clear, if not, it was turbid due to the undissolved base. The flask was unstoppered, 0.5 cc. of standard acid added and the shaking repeated. This operation was repeated until the end-point was reached. It was found necessary to add a new piece of congo red paper from time to time as the first one was not sensitive to slight acidity. When the end-point was reached, purple spots appeared upon the paper. After the shaking, the paper became uniform in color. A purple color midway between the acid blue and the alkaline red was selected as the end-point. The acid should be standardized against pure aniline using a procedure similar to that described above. The congo red paper was prepared by immersing filter paper for 5 minutes in a 1% aqueous solution of congo red and drying. By following the procedure described above and by comparing the end-point with a standard color, it has been possible in samples of a mixture of aniline and ethyl aniline to check duplicate determinations of the neutralization equivalent within one whole number.

Summary

1. Either aromatic or aliphatic primary amines may be alkylated to secondary amines free from tertiary amines by aluminum alkoxides at 250–350° in sealed tubes.

2. A water-white reaction product containing 94% of ethyl aniline and 6% of aniline was obtained by the direct alkylation of aniline with aluminum ethoxide.

3. *n*-Butyl aniline, *iso*butyl aniline, *n*-butyl *p*-toluidine, ethyl *p*-toluidine, *iso*butyl *p*-toluidine, ethyl-*n*-pentyl amine and *n*-butyl-*n*-pentyl amine have been prepared from the corresponding primary amines and aluminum alkoxides.

4. An algebraic equation has been derived for the calculation of the percentage composition of a mixture of any two pure, titratable substances such as two bases, acids or aldehydes.

5. The fact that primary amines may be alkylated by alkoxides without the formation of tertiary amines was used by Nef in substantiation of his speculations on dissociation as a precursor to reaction. The further study of this reaction has brought to light facts that are not in harmony with Nef's views.

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