[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE B. F. GOODRICH COMPANY]

The Reaction of Acetone with Aniline

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Previous work from other laboratories has indicated that *p,p'*-diamino-2,2-diphenylpropane[1] and its reaction products are formed from acetone and aniline under the influence of relatively high concentrations of aqueous hydrochloric acid. On the other hand, under conditions that are usually suitable for forming quinolines from aniline and carbonyl compounds, the absence of water in the reaction mixture is advantageous to the formation of a compound that has been called acetone anil (I) by Knoevenagel,[2] 2,2,4-trimethyl-1,2-dihydroquinoline (II) by Reddelien and Thurm[3] and 3-methyl-2-isopropenylindoline (III) by Kalnin.[4] Several other investigators have accepted the dihydroquinoline formulation.[5,6]

This paper reviews some of the properties of the "alleged acetone anil" which are significant with respect to the proof of its structure. Such properties, some of which are here reported for the first time, indicate that the compound may be 2,2,4-trimethyl-1,2-dihydroquinoline, but the possibility that it is 2,4,4-trimethyl-1,4-dihydroquinoline is not excluded so far as chemical evidence is concerned. A further study of the reaction of acetone with aniline under conditions suitable for investigating the by-products of the dihydroquinoline synthesis is also reported. This study indicated that the by-products are due mainly to the polymerization of the original "anil" and to *p,p'*-diamino-2,2-diphenylpropane and its reaction products.

Some Reactions of the "Alleged Acetone Anil"

The "alleged acetone anil" is stable in the absence of catalysts up to relatively high temperatures. However, with a small amount of hydrochloric acid at about 100°, it polymerizes to a mixture of a dimer with higher polymers. The dimer can be separated by distillation in the absence of catalysts and is a soft resin, the acetyl derivative of which is a crystalline solid. The higher polymers are brittle resins and cannot be distilled readily. The dimer as well as the higher polymers can be depolymerized by simply distilling slowly at reduced pressure in the presence of a trace of strong acid. Attempts to reduce the polymers catalytically over nickel have led to the formation of the reduction products of the monomer, yet with copper chromite catalyst and at low temperature it is possible to cause depolymerization without reduction. During the polymerization of the monomer or the depolymerization of the polymers there is nothing to indicate a rearrangement of an indole to a quinoline. Kalnin has suggested for even the mildest reactions that the "anil" undergoes such a change.

The most convincing evidence in regard to structure lies in the application of the Freund[7] reaction which Kalnin, however, has not interpreted properly. With 2,4-dimethylquinoline methiodide, methylmagnesium iodide produces in 77% yield a compound with the elementary composition of a tetramethyldihydroquinoline. The picrate of this derivative, in agreement with Kalnin, was found to be substantially identical with the picrate of the N-methyl derivative of the "alleged acetone anil." In addition, the zinci hydrochlorides of the two N-methyl derivatives have been found to be substantially identical. This proof of structure would be rigorous were it not for the possibility of the Freund reaction forming a 1,4-dihydroquinoline. It should perhaps be mentioned that the Freund reaction when applied to the acridine series forms a variety of products.[8]

It has been established in this investigation that the 2,4-dimethylquinoline produced by the acid decomposition of the "alleged acetone anil" is very impure. Moreover, a probably significant by-product is 2,3,4-trimethylquinoline,[9] the formation of which can be accounted for by Equation 1 if the usual Reddelien and Thurm formula for the "anil" is accepted. In support of Equation 1, it was found that the "anil" from methyl ethyl ketone on acid decomposition

(1) For example, see von Braun, *Ann.*, **472**, 1 (1929).

(2) Knoevenagel, *et al.*, *Ber.*, **56**, 2414 (1923), and previous papers.

(3) Reddelien and Thurm, *ibid.*, **65**, 1513 (1932).

(4) Kalnin, *Ann.*, **523**, 118 (1936).

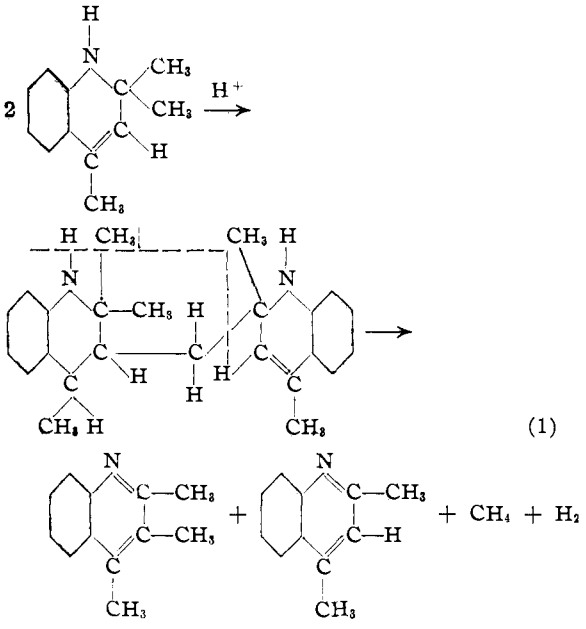
(5) Cliffe, *J. Chem. Soc.*, 1327 (1933), and references therein contained.

(6) Humphrey and Dunbrook, Paper presented at the Kansas City meeting of The American Chemical Society, April, 1936.

(7) Freund, *Ber.*, **37**, 4666 (1904).

(8) Semon and Craig, THIS JOURNAL, **58**, 1278 (1936).

(9) The isolation and identification of this compound was conducted by R. V. Yohe, who also prepared the acetyl derivative of the dimer of the "alleged anil." The author is grateful to Dr. Yohe for permission to include the results of his work in this paper.



(1)

yielded 2,3,4-trimethylquinoline among other products. This would be expected if this "anil" is 2,3,4-trimethyl-2-ethyl-1,2-dihydroquinoline which loses ethane when heated with hydrochloric acid. For identification purposes, 2,3,4-trimethylquinoline was synthesized by a separate set of reactions.

The intermediate product isolated by Kalnin is probably a higher polymer than that represented as a dimer in Equation 1, but since under the influence of acid polymerization or depolymerization may occur, depending on conditions, the simultaneous formation of the quinolines can be represented by this equation, though some methane is probably split out directly from the monomer and from higher polymers.

A smoother method of preparing 2,4-dimethylquinoline is here reported which consists of merely distilling the "anil" with sodamide. This may be represented as the simple splitting out of methane, the formation of which is nearly quantitative. The presence of a relatively small concentration of N-sodium derivatives is sufficient to cause the formation of 2,4-dimethylquinoline. The dimer is definitely not an intermediate in this case since methane is not formed from it except at high temperatures and then in only about 50% of the amount that is formed from an equal weight of the monomer. Also it has been found that the dihydro derivative of the monomer (that is, 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline according to Reddelien) is very stable in the presence of N-sodium derivatives. This seems to support the formula for the dimer given in Equation 2, since one portion of the molecule contains a labile dihydroquinoline structure, and the other portion a stable tetrahydroquinoline structure, the whole molecule being more stable than a simple dihydroquinoline.

The hydrochloride of the "alleged anil," if properly crystallized from hydrochloric acid and dried at reduced pressure, melts at 214–216°. It hydrolyzes with water but not as readily as does the hydrochloride, say, of diphenylamine.

The reaction of the "anil" with formaldehyde according to Cliffe gives a resin to which he assigned the structure of 6,6-methylene-*bis*-(2,2,4-trimethyl-1,2-dihydroquinoline). The compound has now been obtained as a crystalline solid by distilling it and probably has the structure assigned by him.

p,p'-Diamino-2,2-diphenylpropane as an Intermediate in the Formation of Impurities in the Synthesis of the "Alleged Acetone Anil."—In addition to 2,4-dimethylquinoline and the dihydroquinoline polymers, the following compounds can be isolated as by-products of the synthesis of the "alleged anil" under various conditions of reaction: diphenylamine, p,p'-diamino-2,2-diphenylpropane, *p*-cumidine, phenyl-*p*-cumylamine, 5,5-dimethylacridane and 5-methylacridine. As ordinarily conducted at temperatures from 120 to 150° the only one formed in appreciable amount is diphenylamine.

The formation of diphenylamine at such low temperatures is rather surprising since aniline does not lose ammonia in the presence of hydrochloric acid very rapidly below 200°. When, however, acetone was passed through a mixture of aniline and aniline hydrochloride at 180–190°, diphenylamine was found to be one of the main reaction products, but it was not difficult to isolate the other substances mentioned above. In order to investigate the formation of diphenylamine as related to p,p'-diamino-2,2-diphenylpropane, one mole of this substance was heated with eight moles of aniline and five moles of aniline hydrochloride. As a result, 2.2 moles of diphenylamine was formed. This could be explained on the basis of Equation 2 if it is assumed that the p,p'-diamino-2,2-diphenylpropane loses ammonia by reacting with aniline more easily than does aniline alone. A further requirement is that the dianilino derivative produced

must actually decompose into diphenylamine according to Equation 3 or its equivalent. The *p*-isopropenyl derivative

$$(H_2N—C_6H_4\text{-}p)_2C(CH_3)_2 + 2C_6H_5—NH_2 \xrightarrow{H^+} C_6H_5—NH—C_6H_4\text{-}p)_2C(CH_3)_2 + 2NH_3 \quad (2)$$

$$(C_6H_5—NH—C_6H_4\text{-}p)_2C(CH_3)_2 \xrightarrow{H^+} C_6H_5—NH—C_6H_4\text{-}p—C(CH_3)CH_2 + C_6H_5—NH—C_6H_5 \quad (3)$$

could then react with aniline as in Equation 4 to reform the dianilino derivative.

$$C_6H_5—NH—C_6H_4\text{-}p—C(CH_3)CH_2 + 2C_6H_5—NH_2 \xrightarrow{H^+} (C_6H_5—NH—C_6H_4\text{-}p—C_6H_4\text{-}p—NH_2) \xrightarrow{C_6H_5—NH_2} (C_6H_5—NH—C_6H_4\text{-}p)_2C(CH_3)_2 + NH_3 \quad (4)$$

In order to find support for this mechanism it was necessary to prepare *p,p'*-dianilino-2,2-diphenylpropane and study its reactions. The compound was prepared by two separate methods. One of these involved the reaction (Ullmann) of *o*-chlorobenzoic acid with *p,p'*-diamino-2,2-diphenylpropane and the other the reaction of acetone, *p*-isopropenyldiphenylamine or *p,p'*-diamino-2,2-diphenylpropane with diphenylamine. While studying the latter method with acetone it was found possible to isolate the dianilino derivative in good yield if the reaction was conducted at not above approximately 150°. At 170–180° *p*-isopropenyldiphenylamine of Equation 3 was isolated but at 210–300° the main product was 5,5-dimethylacridane. The yield of the dianilino derivative by this method is favored by an excess of diphenylamine which, through a mass action effect, seems to stabilize the diphenylpropane portion of the molecule. When *p,p'*-dianilino-2,2-diphenylpropane was distilled at reduced pressure with a trace of a strong acid diphenylamine and *p*-isopropenyldiphenylamine were obtained in fair yield. This is similar to the results von Braun[1] obtained with *p,p'*-diamino-2,2-diphenylpropane.

Further support for the mechanism of Equations 2 and 3 was sought in attempts to isolate *p,p'*-dianilino-2,2-diphenylpropane from the acetone–aniline reaction mixtures. These attempts were not successful. However, when *p,p'*-diamino-2,2-diphenylpropane was heated with an excess of diphenylamine in the presence of hydrochloric acid the products, among others, were aniline, the expected dianilino derivative and 2,4-dimethylquinoline. The reaction evidently is reversible even to the formation of quinoline derivatives.

The reaction of acetone and diphenylamine under conditions suitable for producing 5,5-dimethylacridane was studied in some detail. Best yields were found when an excess of diphenylamine was used. At 260° none of the *p*-isopropenyldiphenylamine was obtained and the reaction of the dianilino derivative to form the acridane appeared to be complete. Among the side products are 5-methylacridine and acridine, both of which can be isolated as their double compounds with 5,5-dimethylacridane or more conveniently by extraction with dilute acids. This method of making 5,5-dimethylacridane always produces a certain amount of phenyl-*p*-cumylamine presumably formed from *p*-isopropenyldiphenylamine before rearrangement has occurred. This can be construed as evidence that the isopropenyl derivative is an intermediate in the rearrangement.

The structure of the phenyl-*p*-cumylamine was established by the Ullmann reaction from *p*-cumidine. The structure of the *p*-isopropenyldiphenylamine was established by reduction to phenyl-*p*-cumylamine. The structure and properties of the 5,5-dimethylacridane were discussed at considerable length in a previous communication.[3]

Acknowledgment should be made to Dr. W. L. Semon under whose direction the work was conducted and to other members of the laboratory staff for their assistance.

Experimental

The Preparation of the "Alleged Anil."—The directions of Reddelien were followed in essential details. A reaction temperature of 100° was used and a trace of concentrated hydrochloric acid (0.03 mole per cent. on the aniline). The yield for 50 moles of aniline which absorbed 61.8 moles of acetone during five and one-half hours amounted to 20.3 moles (3507 g.) of crude product after the excess aniline was removed by distillation. By further distillation this product was found to contain a trace of aniline, 68% of crude "alleged acetone anil" (m. p. approximately 16–21°), and 31% of a resin.

The crude "anil" could be prepared in a nearly pure state (m. p. 24–25°) by fractional distillation but it was most easily purified by the preparation of the hydrochloride. Ten grams was dissolved in 75 ml. of ether. Five ml. of concentrated hydrochloric acid was then added with stirring. This caused an almost immediate precipitation of the hydrochloride which was filtered off and dried at reduced pressure. The yield of solid, m. p. 212–213°, amounted to 9.7 g. One gram of slightly impure product was obtained by concentrating the filtrate to 15

ml. and adding 3 ml. of concentrated hydrochloric acid. By repeated crystallization from dilute hydrochloric acid the melting point was raised to 214–216°.

Anal. Calcd. for $C_{12}H_{15}N \cdot HCl$: Cl, 16.9. Found by NaOH titration using phenolphthalein as the indicator: 17.0, 17.1.

The addition of water to the hydrochloride produced an oil through partial hydrolysis. A large quantity of the hydrochloride was recrystallized from dilute hydrochloric acid and then decomposed with dilute sodium hydroxide. The nearly colorless oil that resulted was distilled under reduced pressure. It had a melting point of 26–27° and boiled at 255–260° at 743 mm. pressure with traces of decomposition.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.18; H, 8.73; N, 8.09; mol. wt., 173. Found:[10] C, 82.79, 82.98, 83.11; H, 8.70, 8.53, 8.56; N, 8.46, 8.47, 8.52; mol. wt. in freezing benzene, 166, 175.

The Polymerization of the Monomer and Depolymerization of the Polymers.—One mole (173 g.) of the crude monomer (m. p. 16–21°) was mixed with 0.1 mole of concentrated hydrochloric acid (8.3 ml.) and allowed to stand at 100–105° for sixteen hours. The mixture was then dissolved in benzene, extracted with dilute sodium hydroxide and distilled at reduced pressure. Forty-five grams of unreacted monomer, b. p. 88–92° at 2.5 mm., m. p. 15–20°, distilled first. After an intermediate fraction, 38 g. of product of b. p. 215–220° at 2.5 mm. was obtained. The residue, which could not be distilled without decomposition at this pressure, weighed 68 g. The fraction of b. p. 215–220° at 2.5 mm. was a soft clear resin at room temperature. It was very soluble in acetone, alcohol, and benzene, but much less so in petroleum ether. The same compound, though less pure, was obtained by distilling the resin from the preparation of the monomer described above.

Anal. Calcd. for $(C_{12}H_{15}N)_2$: C, 83.18; H, 8.73; N, 8.09, mol. wt., 346. Found: C, 82.95; H, 8.73; N, 8.54; mol. wt. in freezing benzene, 321, 333.

By reaction with a large excess of refluxing acetic anhydride a diacetyl derivative was formed that crystallized readily from alcohol. It melted at 185–186°.

Anal. Calcd. for $(C_{12}H_{14}NCOCH_3)_2$: C, 78.09; H, 7.96; N, 6.51; mol. wt., 430. Found: C, 77.77; H, 8.33; N, 6.61; mol. wt. in freezing benzene, 408.

The dimer or the residue from the polymerization of the monomer or the residue from the preparation of the monomer can be depolymerized by slow distillation in the presence of a trace of strong acid at reduced pressure. For this purpose phosphoric acid is an ideal catalyst although von Braun[1] (p. 11) is of the opinion that it is not as good as other stronger acids for this type of reaction. The 68 g. of residue from the above described preparation of the monomer was distilled slowly at 3 mm. pressure with 1 ml. of 85% phosphoric acid. The distillate amounted to 42 g. On refractionation 27.5 g. of it distilled between 74 and 79° at 1.5 mm. pressure. The product melted at 16–21° and was purified by means of the hydrochloride which melted at 213–215° alone or mixed with the hydrochloride prepared from the original monomer.

The Reduction of the Polymers.—One hundred grams of the distilled dimer, b. p. 215–220° at 2.5 mm., was dissolved in 100 g. of benzene. The solution was shaken with 10 g. of copper chromite (Adkins) catalyst under a hydrogen pressure of 125 atmospheres. No hydrogen was absorbed during two hours at 180–200°. The product was distilled and gave 77 g. of the monomer boiling below 125° at 4 mm. pressure and 15 g. of unchanged dimer. The monomer was identified by the melting point of the hydrochloride and of the phenyl isocyanate derivative (m. p. 128–129°).

The use of nickel formate as the catalyst likewise caused depolymerization but also brought about partial reduction. The use of a more active catalyst such as Raney nickel caused complete depolymerization and complete reduction as well. Two hundred and fifty grams of a crude mixture containing approximately 40% of the monomeric "acetone anil" and 60% of the polymers was shaken with 20 g. of Raney nickel catalyst and 10 atmospheres of hydrogen for five hours at 250–280°. From 228 g. of the product that was worked up, 196 g. distilled between 100 and 110° at 5 mm. This fraction had a setting point of 28° and melted at 39–40° when recrystallized from petroleum ether. The melting point was not depressed when the sample was mixed with the dihydro derivative prepared by the direct reduction of the "alleged acetone anil."

The Reaction of Methylmagnesium Iodide with 2,4-Dimethylquinoline Methiodide.—2,4-Dimethylquinoline methiodide was prepared by allowing a mixture of 2,4-dimethylquinoline, methyl iodide and petroleum ether to stand for a long time. The product melted at 263–265° with decomposition. Kalnin reported a melting point of 251–252° and suggested that the products with lower melting points prepared by previous investigators were impure due to the use of impure 2,4-dimethylquinoline. The 2,4-dimethylquinoline used in this preparation was purified by means of the zinci hydrochloride as described in a subsequent paragraph.

A Grignard solution was prepared from 7.2 g. (0.3 mole) of magnesium turnings, 42.3 g. (0.3 mole) of methyl iodide and 200 cc. of dry ether. To this was added 18.5 g. (0.062 mole) of 2,4-dimethylquinoline methiodide. The reaction was not vigorous. The mixture was allowed to stand overnight and was then hydrolyzed with dilute acetic acid and ice. The ether layer was dried over potassium carbonate and was then distilled. A yield of 9 g. (77%) of an oil distilling at 105–115° at 1.5 mm. was obtained. This oil was converted to the zinci hydrochloride[11] by mixing with 5 ml. of concentrated hydrochloric acid, 4 g. of zinc chloride and 26 ml. of water. Granular crystals soon appeared. These were filtered off after standing for thirty minutes and were washed with 15 ml. of water. They were finally air dried for eight hours. The yield was 13 g., m. p. 195–197°.

Anal. Calcd. for $(C_{13}H_{17}N \cdot HCl)_2 \cdot ZnCl_2$: Zn, 11.26; equiv. wt., 145. Found: Zn, 11.05, 11.09; equiv. wt. by titration with standard NaOH using phenolphthalein as indicator, 147, 147.

Some of the zinci hydrochloride was decomposed with

(10) One set of the elementary analyses was performed by Dr. Ing. A. Schoeller, Berlin, Germany. The other two were conducted by Mr. E. W. D. Huffman, Boulder, Colo.

(11) Craig, THIS JOURNAL, **55**, 3727 (1933).

excess sodium hydroxide. The oil that formed was extracted with benzene and the picrate from it prepared in alcoholic solution. This derivative melted at 147–148° in agreement with Cliffe and other investigators.

For identification and purification the zinci hydrochloride and the picrate of the N-methyl derivative of the "alleged acetone anil" were also prepared. The picrate was found to be a better derivative for purification than the zinci hydrochloride possibly because the hydrochloride of the "alleged anil" is sparingly soluble while its picrate is very soluble. The melting point of the zinci hydrochloride was 193–195° or at 194–196° when mixed with the double salt of the product from the Grignard reaction. The picrate melted at 147–148° alone and no depression was observed when it was mixed with the picrate of the oil from the Grignard reaction.

The Formation of Quinolines from the "Alleged Acetone Anil."—By the action of metallic amides at about 200° the main product produced was 2,4-dimethylquinoline. One-tenth mole (17.3 g.) of the crude "anil" was heated in an oil-bath with 0.05 mole (1.95 g.) of coarsely ground sodamide. The evolution of ammonia was complete at about 150°. The temperature was gradually raised to 210° during one hour. The total volume of gas evolved measured over water amounted to 2250 ml. at 27° and 745 mm. or to 0.086 mole. The product consisted of a mixture of 2,4-dimethylquinoline and its sodium salt. Alcohol (100 ml.) and 4,5-ml. of concentrated hydrochloric acid were added. The sodium chloride that precipitated was filtered off and 25 g. of 90% picric acid dissolved in hot alcohol was added. The picrate was filtered when the solution had cooled: yield, 33 g. (86%); melting point 191–193°.

In another experiment 346 g. (2 moles) of the "alleged acetone anil" was refluxed with a solution freshly prepared from 4.6 g. (0.2 mole) of metallic sodium and 56 g. (0.6 mole) of aniline with the aid of reduced copper powder as the catalyst. The temperature of the solution during the refluxing was 220–230°. The evolution of gas, presumably methane, appeared complete after five hours. After the mixture had cooled it was washed with water and distilled. Most of the aniline could be separated by distillation, but in order to obtain a pure product it was necessary to prepare the picrate as in the above experiment or to prepare the zinci hydrochloride which will now be described. The main fraction which distilled at approximately 90° at 1 mm. pressure weighed 261 g. It was dissolved in dilute hydrochloric acid. The weakly acid solution was then extracted with benzene to remove diphenylamine and unreacted starting material. The addition of zinc chloride precipitated the slightly soluble zinci hydrochloride.[12] In order to decompose the double salt and at the same time not to have an intractable precipitate of zinc hydroxide to contend with, a mixture of sodium hydroxide and sodium cyanide dissolved in water was added. The oil that separated was distilled. It was colorless: yield, 209 g. (67%).

As reported by Bergstrom[13] the sodium salt of 2,4-dimethylquinoline decomposes when heated. Hence an excess of amines over the sodium used is advantageous to the method of preparation just described. Magnesium nitride, magnesium anilide and methylmagnesium iodide were also satisfactory reagents for causing the decomposition. Earlier methods[14] for the preparation of 2,4-dimethylquinoline are more troublesome and usually yield impure products.

In order to test for the decomposition of the "alleged acetone anil" by the acid method, 346 g. (2 equivalents) of a mixture containing approximately 40% of monomeric "anil" and 60% of its polymers were heated to reflux with 130 g. (1 mole) of aniline hydrochloride. No gas was evolved during one hour's heating. One mole (210 g.) of the hydrochloride of the "alleged anil" was then added and refluxing was continued. A combustible gas was evolved vigorously at first but after five and one-half hours the evolution had nearly ceased. The mixture was allowed to cool and then nearly neutralized with dilute sodium hydroxide and finally neutralized completely with dilute sodium carbonate solution. The oil layer was distilled at reduced pressure. After an aniline fraction weighing 125 g., a fraction distilled between 90 and 130° at 2 mm. which amounted to 343 g. The residue weighed 129 g. The main fraction was treated with zinc chloride and hydrochloric acid according to the procedure just given. As a result 101 g. of fairly pure 2,4-dimethylquinoline was obtained. The filtrate on being made alkaline in the presence of sodium cyanide gave an oil that was distilled. The oil contained unreacted "acetone anil" and 2,4-dimethylquinoline among other products. The last fraction weighed 24 g. and distilled at 128–135° at 3.5 mm. It partially crystallized on being cooled. Recrystallization from hexane gave crystals melting at 91–92°. The same compound was found in the reaction product of methyl ethyl ketone (4 moles) with aniline (4 moles) in the presence of hydrochloric acid (1 mole) which was prepared by heating in a glass-lined autoclave for six hours at 200–215°.

Anal. Calcd. for $C_{11}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.37; H, 7.68; N, 8.07.

The analysis agrees with the composition of a trimethylquinoline and the compound was identified as 2,3,4-trimethylquinoline by the melting point and mixed melting point with an authentic specimen which was prepared by the method of von Braun,[15] *et al.*, from methylated acetylacetone and aniline. The melting point of the picrate (216–218°) was identical with that of the picrates of the above described specimens and no depression was observed when the derivatives were mixed.

An attempt was made to decompose the dihydro derivative of the "alleged acetone anil" with sodamide. Forty-eight grams (0.27 mole) of the dihydro derivative, m. p. 40°, was heated with 0.5 g. (0.013 mole) of sodamide. Ammonia was liberated as the sodamide dissolved, but no other gas was liberated during refluxing at 245° for thirty minutes. The recovered starting material had a melting point of 40°.

Fifty grams of the dimer of the "anil" boiling at 215–220° at 2.5 mm. was heated with 0.5 g. of sodamide. No reaction occurred below 200° except the formation of the sodium salt and the liberation of ammonia. After twenty

(12) British Patent 276,156; *Chem. Zentr.*, **99**, II, 2287 (1928).

(13) Bergstrom, THIS JOURNAL, **53**, 4065 (1931).

(14) (a) Kalnin, *Ann.*, **523**, 127 (1936); (b) Heou-Feo, *Bull. soc. chim.*, [5] **2**, 95 (1935).

(15) Von Braun, Gmelin and Petzold, *Ber.*, **57**, 387 (1924).

minutes of heating at 350° the reaction appeared to be complete, but the temperature was raised momentarily to 410°. The mixture was then cooled and fractionated at reduced pressure. After 4.5 g. of forerunnings a fraction weighing 33.5 g. distilled at approximately 220–225° at 2.5 mm. The residue weighed 8 g. On redistilling the main fraction it was found to boil at 215–220° at 2.5 mm.

Anal. Calcd. for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 82.95; H, 8.08; N, 8.44.

6,6′-Methylene-*bis*-(2,2,4-trimethyl-1,2-dihydroquinoline).—A reaction was conducted with 173 g. (1 mole) of the "alleged anil" and 20.8 g. (0.25 mole) of 36% formalin in alcoholic solution in the presence of a trace of hydrochloric acid. The reaction was similar to the reaction of formaldehyde and diphenylamine.[11] After it appeared to be finished the mixture was refluxed for thirty minutes. Two grams of finely powdered potassium carbonate was added and the mixture was distilled. The main fraction distilled at 217–277° at 1 mm. with considerable superheating and weighed 37.5 g. It solidified and was recrystallized from 300 ml. of alcohol: yield 23 g.; m. p. 150–151° or at 153–154° after another recrystallization.

Anal. Calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43; N, 7.82. Found: C, 83.64, 83.68; H, 8.43, 8.78; N, 7.73, 7.77.

The Reaction of Aniline with Acetone at Higher Temperatures.—The method of Reddelien was followed again except for varying his conditions to use a higher temperature and with a higher concentration of hydrochloric acid. A mixture of 744 g. (8 moles) of aniline and 645 g. (5 moles) of aniline hydrochloride was heated to 180–190° and 580 g. (10 moles) of acetone passed through it. The distillate was dried over potassium carbonate and again passed through the mixture. The procedure was repeated several times until the acetone had reacted completely. A combustible gas and ammonia were evolved during the reaction which required about twenty hours. The reaction mixture was washed with water, then with dilute sodium hydroxide and finally again with water. The product was then distilled at reduced pressure in a flask with a short side-arm. A fraction weighing 56 g. distilled below 150° at 1.5 mm. The residue which weighed 720 g. probably contained considerable amounts of the polymers of the "alleged anil" as well as the polymer of *p*-isopropenylaniline which was described by von Braun.[1] The distillate was fractionated systematically several times and, where possible, solids were removed from the various fractions by crystallizing them from hexane. The mother liquors from the crystallizations were then returned to the distillation at the appropriate times. In this manner 112 g. of aniline (b. p. 180–190°), 144 g. of diphenylamine (m. p. 52–54°), 8 g. of 5,5-dimethylacridane (m. p. 120–123°), a trace of the double compound of the acridane with 5-methylacridine (m. p. 122–123°), and a mixture of 2,4-dimethylquinoline with the "alleged acetone anil" were obtained. The 2,4-dimethylquinoline was isolated from this mixture as the zinci hydrochloride. This, on decomposition with alkali, yielded 14 g. of crude 2,4-dimethylquinoline. The filtrate from the zinc salt was made alkaline with sodium hydroxide. The oil that precipitated was then separated and treated with an excess of dilute hydrochloric acid. The hydrochloride of the "alleged acetone anil" that quickly crystallized weighed 49 g. and melted at 209–211°. *p*-Cumidine and phenyl-*p*-cumylamine were not isolated from this mixture although they were probably present. These two compounds as well as the others mentioned in this paragraph were isolated from a reaction mixture produced by heating aniline (2.4 moles), acetone (1 mole) and concentrated hydrochloric acid (0.03 mole) in the presence of considerable amounts of water (5 moles) to 240–250° for eight hours in an autoclave. The *p*-cumidine was identified by the melting point of its acetyl derivative and mixed melting point with an authentic specimen of acetyl-*p*-cumidine. The other compounds isolated were recrystallized and identified by melting points and mixed melting points with authentic specimens.

The Reaction of *p,p′*-Diamino-2,2-diphenylpropane with Aniline.—One mole of *p,p′*-diamino-2,2-diphenylpropane (226 g.), 4.8 moles (628 g.) of aniline hydrochloride and 5 moles (465 g.) of aniline were heated to approximately 195° for fourteen hours. Much ammonia was evolved during this time. The product was distilled after the acid had been removed by extracting with dilute sodium hydroxide. A yield of 373 g. (2.2 moles) of diphenylamine (m. p. 50–52°), 14 g. of phenyl-*p*-cumylamine and a small amount of 2,4-dimethylquinoline was obtained. No *p,p′*-dianilino-2,2-diphenylpropane could be isolated from this run or from others under widely varying conditions of temperature and concentration.

***p,p′*-Dianilino-2,2-diphenylpropane.**—Twelve moles (2028 g.) of diphenylamine, 0.75 mole of acetone (43.5 g.) and 0.6 mole (50 ml.) of concentrated hydrochloric acid were heated at 120–135° for six hours in a glass-lined autoclave. The product was washed with dilute sodium hydroxide and then distilled at reduced pressure in a flask with a short fractionating column. The excess diphenylamine distilled first and was found to have a setting point of 52.5°. There was no intermediate fraction. The product distilled at 270–300° at 2 mm. with considerable superheating. The yield amounted to 173 g. (61%). A residue of 14 g. remained in the distilling flask. The use of equimolecular amounts of acetone and diphenylamine gave a much lower yield of distilled product and a higher yield of residue. The reaction occurs slowly in refluxing acetone and is conveniently conducted by distilling acetone through the reaction mixture between 100–150°. The product that distilled at 270–300° at 2 mm. crystallized on standing. It was recrystallized by pouring the melted product into 160 ml. of alcohol. A yield of 149 g. of colorless crystals, m. p. 98–99°, resulted. A further recrystallization from alcohol raised the melting point to 99–100°. The same compound was formed by heating 0.1 mole (226 g.) of *p,p′*-diamino-2,2-diphenylpropane, 0.5 mole (84.5 g.) of diphenylamine and 0.1 mole (20.6 g.) of diphenylamine hydrochloride to approximately 240° for one and one-half hours. In addition to the dianilino derivative, aniline and 5,5-dimethylacridane were isolated from the resulting reaction product.

Anal. Calcd. for $C_{27}H_{26}N_2$: C, 85.67; H, 6.93; N, 7.40. mol. wt., 378. Found: C, 86.20; H, 7.03; N, 7.06; mol. wt. in freezing benzene, 346, 374.

This compound was also synthesized by the Ullmann

reaction by heating 10 g. of *p,p'*-diamino-2,2-diphenylpropane, 15 g. of *o*-chlorobenzoic acid and 5 g. of potassium carbonate at 150–170° in the presence of a trace of cuprous iodide. The product was worked up in the usual way. The part that distilled at 280–290° at 2 mm. was crystallized from alcohol. The crystals melted at 98° alone or at 98–99° when mixed with the product prepared from diphenylamine by the reactions just described.

***p*-Isopropenyldiphenylamine.**—This compound was obtained when acetone was heated to 160–170° with a large excess of diphenylamine in the presence of hydrochloric acid. A better method involved the slow vacuum distillation of *p,p'*-dianilino-2,2-diphenylpropane in the presence of a strong non-volatile acid such as phosphoric acid. The diamine (42 g.) was distilled with 0.5 g. of 85% phosphoric acid. Diphenylamine distilled first followed by a fraction weighing 20 g. This was recrystallized several times from hexane and then had a melting point of 91–92°.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.07; H, 7.23; N, 6.70. Found: C, 86.44; H, 7.00; N, 6.59.

This compound after several years standing was found to be partially resinified.

Phenyl-*p*-cumylamine.—*p*-Isopropenyldiphenylamine (10 g.) was reduced with sodium and alcohol. The product after crystallization from methanol amounted to 9.5 g. of glistening plates. The melting point was 70–72°.

Anal. Calcd. for $C_{15}H_{17}N$: C, 85.27; H, 8.10; N, 6.63. Found: C, 85.31, 85.20; H, 8.37, 8.29; N, 6.46, 6.55.

For purposes of identification the compound was prepared by the Ullmann reaction from 67.5 g. (0.5 mole) of *p*-cumidine, 39 g. (0.25 mole) of *o*-chlorobenzoic acid, 17 g. of potassium carbonate and a trace of cuprous iodide. The product was purified by distillation (yield 78%, b. p. 165–200° at 15 mm.) and was then crystallized from methanol. The glistening plates thus obtained melted at 71–72° alone or mixed with the compound just described. The compound was prepared in low yield by heating aniline hydrochloride and *p*-cumidine to 300°, by heating *p*-cumidine with its hydrochloride to the same temperature and by the reaction of sodium *p*-cumidide with chlorobenzene. The acetyl derivative of phenyl-*p*-cumylamine was prepared by reaction with acetyl chloride and was recrystallized several times from hexane. It then melted at 94–95°.

The Synthesis of 5,5-Dimethylacridane by the Reaction of Acetone with Diphenylamine.—In the development of this synthesis a series of steel seamless tube autoclaves was used. These held Pyrex tubes, the upper ends of which were open except for a covering of lead foil. The purpose of the lead foil was to retard the corrosion of the autoclaves. The smallest size accommodated a tube 2 cm. in diameter and 50 cm. long while the largest held a tube 15 cm. in diameter and 90 cm. in length. The autoclaves usually were heated in baths of refluxing vapor of suitable liquids. Diphenyl oxide was used for 260°, the temperature at which most of the experiments were conducted; diphenylamine was used for 302° although it had to be replaced frequently due to pyrolysis and oxidation; for temperatures between 180 and 259° mixtures of diphenyl oxide with *o*-dichlorobenzene were used; for lower temperatures chlorobenzene, chlorotoluene, *o*-dichlorobenzene or mixtures of these were found satisfactory. The heating baths were long vertical tubes with the upper ends closed with a removable reflux condenser which usually was a semi-spherical water-bath. The baths were direct fired. The autoclaves were fitted with the annular ring type of closure commonly used for closing hydrogenation autoclaves. A copper ring gasket was used. For the larger size autoclaves a cushion of diphenyl oxide was placed around the glass tubes to prevent them from breaking by mechanical or thermal shock.

In a typical experiment 61.6 moles (10.4 kg.) of diphenylamine, 15.4 moles (893 g.) of acetone and 12.1 moles (979 ml.) of concentrated hydrochloric acid were added alternately in small portions to the large size autoclave. The autoclave was closed and then lowered into the refluxing vapor of the diphenyl oxide bath by means of a suitable hoist. Approximately two hours elapsed before the temperature rose to 250°. It was held at 250–259° for approximately two hours, during which time a pressure of approximately 400 lb. per sq. in. (27 atm.) developed. The autoclave was allowed to cool and was then opened after allowing a small amount of gas, presumably methane, to escape. The color of the product was deep red. It was washed free of acid with boiling dilute sodium hydroxide. This removed most of the color. The product was separated by distillation through a column 5 cm. in diameter and 60 cm. long which was packed with 1.5 cm. glass Raschig rings. The diphenylamine fraction distilled first at 142° at 5 mm. It had a setting point of 50.5° and amounted to 7093 g. Then an intermediate fraction distilled which weighed 806 g. The fraction distilling at 165–175° at 5 mm. was then collected. It weighed 2294 g. It was melted and poured into 2 volumes of hexane. Crystallization started almost immediately. After cooling to room temperature, the crystals were filtered off: yield, 1412 g. (44%); m. p. 120–124°. Recrystallization from hexane several times raised the melting point to 125–126° alone or mixed with an authentic specimen[8] of 5,5-dimethylacridane. The recovered diphenylamine was used in a subsequent experiment. In a series of ten experiments the yield was raised to approximately 60% calculated on the acetone used. The yield was appreciably better in large size reactors than it was in small ones.

The by-products that were isolated from this synthesis were phenyl-*p*-cumylamine and the double compounds[8] of 5,5-dimethylacridane with acridine and 5-methylacridine. The yields of these products increased with the amount of acid used and decreased when a greater excess of diphenylamine was used. They could be isolated by carefully crystallizing suitable fractions from hexane. A more convenient method of obtaining the acridines was to extract them with 10% sulfuric acid. After this was done with the fraction distilling just after diphenylamine the phenyl-*p*-cumylamine could be crystallized readily from methanol in glistening plates. It did not depress the melting point of the reference sample described in a preceding section.

Summary

1. The reaction of acetone with aniline has been studied with respect to the formation of quinoline derivatives and also with respect to the formation of *p,p'*-diamino-2,2-diphenylpropane and its reaction products.

2. The structure of the "alleged acetone anil" has been discussed. In agreement with the Reddelien formulation it was shown to be a trimethyldihydroquinoline.

3. The "anil" was found to polymerize readily. A dimer was isolated. The polymers were depolymerized easily.

4. A rapid method for the preparation of pure 2,4-dimethylquinoline was found which consisted in the decomposition of the "anil" in the presence of a metallic salt of an amine.

5. The acid decomposition of the "anil" was found to be related to its tendency to polymerize. One of the products was found to be 2,3,4-trimethylquinoline. This compound was also formed from the reaction of methyl ethyl ketone and aniline.

6. The following compounds were isolated when the reaction of aniline with acetone was conducted at higher temperatures than are usually used for the synthesis of the "anil": diphenylamine, phenyl-*p*-cumylamine, *p*-cumidine, 5,5-dimethylacridane and 5-methylacridine.

7. The reaction of acetone with diphenylamine was found to be more convenient for the preparation of the 5,5-dimethylacridane. As possible intermediate products in the formation of this compound *p,p'*-dianilino-2,2-diphenylpropane and *p*-isopropenyldiphenylamine were prepared and studied.

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[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkyl and Alkamine Esters of *p*-Aminomandelic Acid and Related Compounds

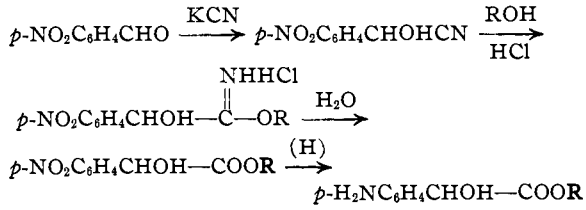
BY L. S. FOSDICK AND G. D. WESSINGER

The esters of *p*-aminobenzoic acid have been studied extensively since the preparation of novocaine.[1]

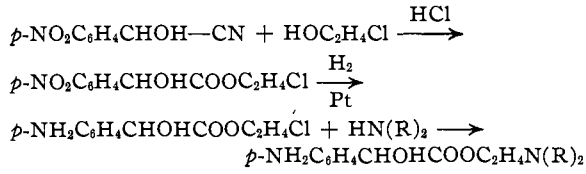
It is interesting to note that practically all of the effective analogs have a carbonyl group conjugated with the double bonds of the aromatic nucleus.[2] The esters of *p*-aminophenylacetic acid, a compound without this system, are quite devoid of anesthetic properties;[3] however, the esters of phenylacetic acid do have slight anesthetic properties.[4] On the other hand, all conjugated systems of this type do not produce anesthesia. The alkamine esters of β-aminocrotonic acid[2] are of this type.

In view of the above theoretical considerations it was thought that perhaps the esters of *p*-aminomandelic acid would be interesting compounds. The anesthetic efficiency should be less than that of novocaine due to the absence of the carbonyl group conjugated with the double bonds of the benzene ring but at the same time the presence of the secondary hydroxyl would make it less toxic.[5]

The normal esters of *p*-nitro- and *p*-aminomandelic acid were prepared by the reactions



The preparations of the alkamine esters are shown by the reactions



The toxicity and anesthetic efficiency were determined on diethylaminoethyl *p*-aminomandelate hydrochloride by Spruth and Olsen through the courtesy of Abbott Laboratories. The M. L. D. on white mice was 1400 mg./kg. compared with novocaine 180–200 mg./kg. The anesthetic efficiency on guinea pig wheals was not complete with a 2% solution while a 1% solution of novocaine gave anesthesia. The guinea pig wheals also produced a slight necrosis. A 2% solution of the same compound on human wheals produced anesthesia lasting twenty-five minutes while the same concentration of novocaine lasted thirty-five minutes. There was no tissue damage.

(1) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).
(2) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).
(3) Pyman, *J. Chem. Soc.*, **111**, 167 (1917).
(4) Kurvahata, Ochiai and Nukita, *Folia Pharmacol. Japn.*, **7**, 408 (1928).
(5) Hartung, *Chem. Rev.*, **9**, 389 (1931).