751 cm.$^{-1}$, and penta-substituted benzene structure 874 cm.$^{-1}$.

A portion of the product was converted to the picrate in methanol as solvent. Recrystallization from methanol gave orange needles, m.p. 149° (lit.[6] m.p. 148–148.5°).

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.14; H, 4.29. Found: C, 57.16; H, 4.14.

Action of Mercaptoethanol, Thiophenol, Acetylacetone, Morpholine and Phenol on 2-Methyl-*o*-naphthoquinol-*p*-toluenesulfonimide Acetate.—Attempts to add mercaptoethanol and thiophenol in presence of triethylamine in chloroform solution to 2-methyl-*o*-naphthoquinol-*p*-toluenesulfonimide acetate failed and only 2-methyl-1-*p*-toluenesulfonamidonaphthalene resulted. Acetylacetone with sodium methoxide as catalyst in anhydrous dioxane, morpholine in chloroform, phenol with triethylamine catalyst were unreactive and the starting material was recovered unchanged.

3-Acetoxy-2-methyl-1-*p*-toluenesulfonamidonaphthalene.—An attempt to add benzenesulfinic acid to 2-methyl-*o*-naphthoquinol-*p*-toluenesulfonimide acetate failed, but under the reaction conditions acetic acid reacted with formation of 3-acetoxy-2-methyl-1-*p*-toluenesulfonamidonaphthalene. Omission of the sodium benzenesulfinate in the experiment described would probably not have affected the result.

To a solution of 2.00 g. of 2-methyl-*o*-naphthoquinol-*p*-toluenesulfonimide acetate and 0.92 g. of sodium benzenesulfinite in 80 ml. of glacial acetic acid was added 6 drops of concentrated sulfuric acid. A turbidity was immediately apparent. The mixture was allowed to stand at room temperature for 46 hours and was then concentrated to one half its original volume in a stream of air. The concentrate was poured into water, and a gummy solid was formed. The crude material was recrystallized from ethanol (Darco) to give 1.16 g. (58%) of a slightly-yellow, crystalline solid. Four recrystallizations from glacial acetic acid gave white crystals, m.p. 202–203°.

Anal. Calcd. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.08; H, 5.23; N, 3.52.

The infrared spectrum indicated the presence of the acetoxyl group.

3-Hydroxy-2-methyl-1-*p*-toluenesulfonamidonaphthalene.—An attempt to add hydrogen fluoride to 2-methyl-*o*-naphthoquinol-*p*-toluenesulfonimide acetate in glacial acetic acid as solvent failed. However, the addition of acetic acid apparently was catalyzed and during the separation of the product hydrolysis of the acetoxyl group was effected.

To a solution of 0.50 g. of 2-methyl-*o*-naphthoquinol-*p*-toluenesulfonimide acetate in 20 ml. of glacial acetic acid at *ca.* 50° was added one ml. of 49% hydrofluoric acid. The yellow color disappeared in about 5 minutes. After the mixture had been allowed to stand at room temperature for 9 hours, it was poured into water, and the resulting pink solid was removed by filtration. The crude material was dissolved in ethanol and treated twice with Darco. Enough water was added to the hot ethanolic solution to cause slight turbidity; and, upon cooling, the solution yielded 0.18 g. (41%) of white crystals. Two recrystallizations from aqueous acetic acid gave white crystals, m.p. 197° dec.

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 66.03; H, 5.24; N, 4.28. Found: C, 65.67; H, 5.03; N, 4.19.

The infrared spectrum indicated the presence of a phenolic hydroxyl group: OH stretching band at 3400 cm.$^{-1}$ and C–O deformation band at 1244 cm.$^{-1}$.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Ortho Esters, Imidic Esters and Amidines. VII. N-Alkylformanilides from Alkyl Orthoformates and Primary Aromatic Amines; Rearrangement of Alkyl N-Arylformimidates[1]

BY ROYSTON M. ROBERTS AND PAUL J. VOGT

RECEIVED MARCH 5, 1956

The major product of the reaction of an alkyl orthoformate and a primary aromatic amine in the presence of sulfuric acid catalyst at temperatures above 140° has been shown to be an N-alkylformanilide. Alkyl N-arylformimidates, which are the major products of these same reactants at lower temperatures, undergo molecular rearrangement to N-alkylformanilides at higher temperatures under the influence of sulfuric acid. Good yields of several N-alkylformanilides have been obtained directly from primary aromatic amines and alkyl orthoformates. Since the latter are easily obtained by transesterification of methyl or ethyl orthoformate and since N-alkylformanilides are readily hydrolyzed to N-alkylanilines, this sequence of reactions provides a new convenient synthesis of pure secondary amines of the type Ar-NH-R.

The reaction of ethyl orthoformate with aniline was shown by Wichelhaus[2] in 1869 to produce N,N'-diphenylformamidine. Later, Claisen[3] demonstrated that another product, ethyl N-phenylformimidate, could be obtained in low yield from the same reactants under slightly different conditions. Recently, the mechanism of these reactions has been studied,[4] and it has been shown that excellent yields of ethyl N-phenylformimidate may be obtained by the use of acid catalysts.[5] In the course of these studies, while investigating the use of various acids as catalysts, it was observed that in certain experiments in which sulfuric acid was used low yields of ethyl N-phenylformimidate resulted and significant amounts of a higher-boiling material were produced. This higher-boiling material was easily identified as N-ethylformanilide, which is isomeric with ethyl N-phenylformimidate. After considerable investigation, conditions were established under which good yields of N-ethylformanilide could be obtained. Thus, by varying catalysts and experimental conditions, it is now possible to produce in good yield any one of three different products from the reaction of ethyl orthoformate with aniline!

N,N'-Diphenylformamidine is obtained from the reactants in the absence of an acid catalyst or in the presence of such a catalyst whenever there are present two moles of aniline per mole of ethyl orthoformate, since ethyl N-phenylformimidate,

---

(1) Presented before the Division of Organic Chemistry at the Minneapolis Meeting of the American Chemical Society, September 16, 1955. Taken from the M.A. thesis of Paul J. Vogt, University of Texas, January, 1955.

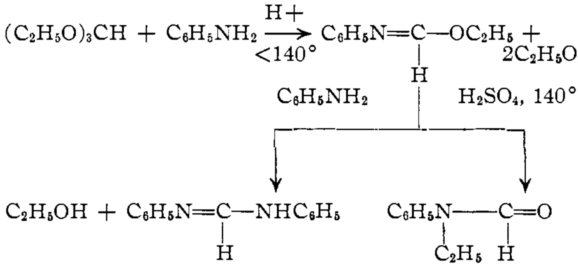
(2) H. Wichelhaus, *Ber.*, **2**, 116 (1869).

(3) L. Claisen, *Ann.*, **287**, 363 (1895).

(4) R. M. Roberts and R. H. DeWolfe, THIS JOURNAL, **76**, 2411 (1954).

(5) (a) R. M. Roberts, *ibid.*, **71**, 3848 (1949); (b) R. M. Roberts and P. J. Vogt, *Org. Syntheses*, **35**, 64 (1955).

which is the primary product,[4] reacts with a second mole of aniline to give N,N′-diphenylformamidine. When aniline and an equimolar or larger amount of ethyl orthoformate react in the presence of hydrochloric, sulfuric, *p*-toluenesulfonic or acetic acid at temperatures up to about 140°, the principal product is ethyl N-phenylformimidate.[5a] It has now been found that when sulfuric acid is the catalyst and the reaction mixture is heated above 140° after the alcohol produced by the reaction has distilled, the major product is N-ethylformanilide. When hydrochloric acid is the catalyst, however, higher temperatures do not result in the formation of any N-ethylformanilide. It seemed obvious from these observations that the production of N-ethylformanilide involved the primary formation of ethyl N-phenylformimidate followed by its rearrangement to the isomer, which was catalyzed by sulfuric acid but not by hydrochloric acid. The relationship between the three products can thus be outlined as



$$(C_2H_5O)_3CH + C_6H_5NH_2 \xrightarrow[<140°]{H+} C_6H_5N{=}\underset{H}{C}{-}OC_2H_5 + 2C_2H_5OH$$

$$C_6H_5NH_2 \longrightarrow C_2H_5OH + C_6H_5N{=}\underset{H}{C}{-}NHC_6H_5 \qquad H_2SO_4,\ 140° \longrightarrow C_6H_5\underset{C_2H_5}{N}{-}\underset{H}{C}{=}O$$

The rearrangement of pure ethyl N-phenylformimidate was next tested. When heated with a catalytic amount of sulfuric acid at 170–180° for a short time, the imidic ester was isomerized to the formanilide in yields of 41–53%. This corresponded to the yield of formanilide obtained directly from equimolar amounts of aniline and ethyl orthoformate. In other experiments, however, 1.5 moles of ortho ester per mole of aniline was used (since this ratio had been found to be advantageous in the preparation of ethyl N-phenylformimidate) and with sulfuric acid catalyst, yields of 75% of N-ethylformanilide were obtained. To check on the influence of excess ortho ester in increasing the yield, experiments were performed in which 0.5 mole of ethyl orthoformate was added to a mole of ethyl N-phenylformimidate and this mixture was heated with sulfuric acid. The yields of rearrangement product were 74–85%, as expected. Apparently the ortho ester aids in the rearrangement reaction in some way, so that it must not be a purely intramolecular reaction. Other evidence related to this was obtained by heating ethyl N-phenylformimidate with sulfuric acid and an ortho ester having different alkyl groups—isoamyl orthoformate. In this case a complex mixture of products was obtained; the highest-boiling fraction was evidently N-isoamylformanilide, for hydrolysis gave N-isoamylaniline in good yield.

Some rearrangement was observed in an experiment in which *p*-toluenesulfonic acid was used as catalyst, but the yield of N-ethylformanilide was only 11%. Less than 3% of the ethyl N-phenylformimidate was recovered; most of the material remained in a dark brown non-volatile residue.

The optimum concentration of sulfuric acid as catalyst for the rearrangement was found to be about 0.04 mole per mole of imidic ester. Lower concentrations resulted in recovery of more unchanged imidic ester and higher concentrations resulted in more high-boiling residue. The rearrangement was most conveniently carried out by heating in an oil-bath at a temperature of 170–180° for 0.5 hr., although equivalent results were obtained by heating at a temperature of about 145° for 2 hr.

Two other alkyl N-arylformimidic esters were shown to rearrange similarly. Methyl N-phenylformimidate was converted into N-methylformanilide in 61% yield and ethyl N-*p*-chlorophenylformimidate was converted into N-ethyl-*p*-chloroformanilide in 63% yield. It was observed that all of these rearrangements are exothermic. Soon after a reaction mixture was placed in an oil-bath at 170–180°, the temperature of the liquid would rise considerably above that of the bath—as high as 244° in one case. During this reaction period a small amount of volatile material distilled out of the reaction mixture. A preliminary examination of this material indicates it to be a mixture of alkyl formate and alcohol. This will be investigated further.

Reports in the literature related to the rearrangements we have observed are conflicting. In 1900 Wislicenus and Goldschmidt[6] claimed that heating ethyl N-phenylformimidate at 230–240° in a sealed tube for 8 hr. converted it into N-ethylformanilide in 65% yield. This experiment was repeated unsuccessfully by Grunfeld,[7] who obtained a complex mixture of decomposition products, none of which was the N-ethylformanilide reported by the earlier workers. Wislicenus and Goldschmidt also reported the conversion of methyl N-phenylbenzimidate into N-methylbenzanilide, and this was repeated without success by Lander,[8] using the conditions described by the earlier workers.[9] However, Lander found that alkyl imidic esters would rearrange to N-alkylamides when heated with alkyl halides as catalysts, and when the alkyl group of the "catalyst" was different from that of the alkyl imidic ester, mixed products were obtained. Since ortho esters may react similarly to alkyl halides as alkylating agents, parallelism between Lander's observations and our own may be seen.

Much later, the thermal rearrangement of methyl N-phenylbenzimidate was accomplished by Chapman,[10] but only by heating to higher temperatures (300–330°) than those used by Wislicenus and Goldschmidt, and even then the yield (25%) was lower than that reported by the earlier workers. This was the only alkyl imidic ester studied by Chapman; the corresponding aryl imidic esters were shown to undergo thermal rearrangement much more readily. The rearrangement was said

---

(6) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1471 (1900).

(7) M. Grunfeld, *Bull. soc. chim* , [5] **3**, 668 (1936)

(8) G. D. Lander, *J. Chem. Soc.*, 406 (1903).

(9) In view of our discovery of the catalysis of the rearrangement by sulfuric acid, a possible explanation may be given of the discrepancy between the results of Wislicenus and Goldschmidt and those of Grunfeld and Lander. The earlier workers may have had traces of sulfuric acid in their reaction mixtures which catalyzed the rearrangement, while in the later experiments no such acid was present.

(10) A. W. Chapman, *J. Chem. Soc.*, 1743 (1927), and preceding papers.

TABLE I

N-ALKYLFORMANILIDES AND N-ALKYLANILINES FROM AROMATIC AMINES AND ALKYL ORTHOFORMATES

		N-Alkylformanilides				Analyses, %[b]		N-Alkylanilines		
Amine	Ortho-formate	Yield,[a] %	B.p., °C. (Mm.)	n_D (t°)	Empirical formula	Carbon: Calcd., found	Hydrogen: Calcd., Found	Yield,[a] %	B.p., °C. (Mm.)	n_D (t°)
Aniline	Methyl	61	150–153 (40)	1.5611 (20)				44[d]	104–105 (40)	1.5701 (22)
	Ethyl	75	153–154 (40)	1.5410 (27)	$C_9H_{11}NO$	72.46 72.62	7.43 7.01	66	92–93 (16)	
	Isoamyl	67	156–158 (15)	1.5173 (25)	$C_{12}H_{17}NO$	75.33 74.87	8.96 9.02	58	149–151 (40)	1.5212 (25)
m-Toluidine	Methyl	74	163–164 (40)	1.5509 (25)	$C_9H_{11}NO$	72.46 72.77	7.43 7.26	67	120–121 (40)	1.5557 (25)
	Ethyl	77	164–165 (40)	1.5362 (25)	$C_{10}H_{13}NO$	73.59 73.05	8.03 7.88	69	125–127 (40)	1.5451 (23)
p-Chloroaniline	Methyl	85	165–166 (20)[c]	. . .	C_8H_8ClNO	56.65 56.50	4.75 4.88	77	141–142 (40)	1.5799 (25)
	Ethyl	86	167–168 (20)	1.5559 (25)	$C_9H_{10}ClNO$	58.86 59.10	5.50 5.43	78	149–150 (40)	1.5661 (25)

[a] Based on aromatic amine taken. [b] Analyses by Clark Microanalytical Lab., Urbana, Ill., and Drs. G. Weiler and F. B. Strauss, Oxford, England. [c] M.p., 51°. [d] See Experimental section.

to be entirely intramolecular, and this has recently been confirmed by more elegant experiments.[11]

It occurred to us that this rearrangement might be very useful in organic synthesis. We had found that primary aromatic amines react with alkyl orthoformates in the presence of sulfuric acid to form alkyl N-arylformimidates which may be isomerized without isolation by a brief heating period into N-alkylformanilides. N-Alkylformanilides may be hydrolyzed readily in almost quantitative yield to N-alkylanilines. Thus it seemed likely that primary aromatic amines generally might be converted quite simply into their secondary N-alkyl derivatives without the tedious separations from tertiary and quaternary by-products and unchanged starting material which are necessary in classical alkylation procedures.[12] Methyl and ethyl orthoformates are commercially available, and other alkyl orthoformates can be obtained readily from them and the alcohols by transesterification.[13] In order to determine the practicality of the procedure described above, we applied it to the alkylation of aniline, *m*-toluidine and *p*-chloroaniline by methyl and ethyl orthoformates. To illustrate the use of a higher orthoformate, we also alkylated aniline with isoamyl orthoformate. The data on the products are given in Table I. The yields based on the primary aromatic amines were quite satisfactory. As can be seen in the Experimental section, the pure secondary amines can be obtained quickly and conveniently, so that the procedure appears promising as a general method for the mono-alkylation of primary aromatic amines, particularly for the introduction of methyl and ethyl groups.

Experimental[14]

Preparation of N-Ethylformanilide from Ethyl Orthoformate and Aniline.—A mixture of 18.6 g. (0.20 mole) of aniline, 44.5 g. (0.30 mole) of ethyl orthoformate and 0.78 g. (0.008 mole) of concentrated sulfuric acid was heated by an oil-bath to reflux for 0.5 hr. and then the ethanol produced (21.8 g.) was distilled through a 10-in. glass helix-packed column as the temperature of the oil-bath was raised to 170–175°. After heating for 0.5 hr. at 175°, the reaction was cooled somewhat and then subjected to vacuum distillation. At 65–67° (40 mm.), 9.1 g. (0.061 mole) of excess ethyl orthoformate was recovered. At 118–120° (40 mm.), 0.3 g. (0.002 mole) of ethyl N-phenylformimidate distilled, then at 150–154° (40 mm.), 22.4 g. (0.15 mole) of N-ethylformanilide distilled, a 75% yield based on aniline. The residue amounted to 5.4 g. of dark brown sirup.

Physical and analytical data on the product are given in Table I. In addition, *microanalysis* for nitrogen was made: calcd. N, 9.39; found, 9.41. Mol. wt., calcd. 149; found (Rast) 159.

A second experiment was carried out as above except that the time of heating at 170–175° was extended to 1 hr. The yield of N-ethylformanilide was 73%.

A third experiment was carried out as the first except that equimolar amounts (0.20 mole) of amine and ortho ester were used. On distillation, no ethyl orthoformate was recovered, the amount of ethyl N-phenylformimidate was 2.6 g. (0.017 mole), and the amount of N-ethylformanilide was 14.4 g. (0.096 mole) or 48% based on aniline. The residue amounted to 9.0 g.

Hydrolysis of N-Ethylformanilide.—An equal volume of 10% hydrochloric acid was added to the amide and the mixture (which was homogeneous at the boiling point) was heated to reflux for 2 hr. The cooled reaction mixture was made basic with 10% sodium hydroxide solution, the organic phase was extracted by ether, the ether solution was dried over potassium hydroxide and was then distilled. N-Ethylaniline, b.p. 92–93° (16 mm.), was obtained in 88% yield based on N-ethylformanilide, corresponding to an over-all yield from aniline of 66%. The b.p. at atmospheric pressure was 205°.

The hydrochloride and picrate of the product were prepared and had the expected melting points. The phenylthiourea was prepared and melted at 71°. The reported value[15] is 89°. A derivative prepared from an authentic sample of N-ethylaniline melted at 71°, undepressed by mixture with the derivative from our product. The phenyl isothiocyanate was checked by reaction with aniline and gave a derivative with the correct melting point. Thus, the value reported in reference 15 must be in error.

Attempts to Obtain N-Ethylformanilide from Aniline and Ethyl Orthoformate Using Aniline Hydrochloride as Catalyst.—Two experiments were carried out in which 0.20 mole of aniline, 0.30 mole of ethyl orthoformate and 0.016 mole of aniline hydrochloride were treated under the condi-

---

(11) K. B. Wiberg and B. I. Rowland, THIS JOURNAL, **77**, 2205 (1955).

(12) See, for example, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 290.

(13) (a) E. R. Alexander and H. M. Busch, THIS JOURNAL, **74**, 554 (1952); (b) R. M. Roberts, T. H. Higgins, Jr., and P. R. Noyes, *ibid.*, **77**, 3801 (1955).

(14) All boiling points are uncorrected.

(15) W. Gebhardt, *Ber.*, **17**, 2090 (1884).

tions described above when sulfuric acid was used as catalyst. In both cases only ethyl N-phenylformimidate was obtained, in yields of 66 and 76%; no higher-boiling material could be induced to distil.

Rearrangement of Ethyl N-Phenylformimidate. A. By Sulfuric Acid.—A mixture of 59.7 g. (0.40 mole) of imidic ester and 1.56 g. (0.016 mole) of concentrated sulfuric acid was heated in an oil-bath at 170–180°. When the temperature of the reaction mixture reached 170°, exothermic reaction took place and the temperature went above the bath temperature—to a maximum of 228°. The flask was kept in the oil-bath for 30 minutes; during this time 2.8 g. of colorless liquid boiling at 52–57° distilled. (Fractions from several runs were collected and redistilled. The major part boiled at 54°, n^{20}_{D} 1.3598. These values check well with the properties of ethyl formate, but a saponification equivalent was high.) After cooling the reaction mixture somewhat, it was subjected to vacuum distillation. At 118–120° (40 mm.) there was recovered 2.7 g. (4.5%) of ethyl N-phenylformimidate and then at 150–154° (40 mm.), 31.6 g. of N-ethylformanilide, corresponding to a 53% yield of rearranged product. The residue (19.0 g.) was dark brown and viscous and smelled of phenyl isocyanide.

Two other very similar experiments gave yields of 41 and 53% rearrangement.

Experiments in which the concentration of sulfuric acid was decreased and other conditions maintained the same resulted in the recovery of a larger amount of unchanged imidic ester and a smaller amount of rearranged product. When the heating period was extended on a reaction mixture having a decreased catalyst concentration, the degree of rearrangement increased, as might be expected. An experiment in which the concentration of catalyst was doubled gave a 26% yield of rearranged product and a large amount of non-volatile residue. Therefore a concentration of 0.04 mole of sulfuric acid per mole of aniline seems to be about optimum.

An experiment in which the temperature of the reaction mixture was kept at about 145° for 2 hr. and which was distilled at a lower pressure so as to avoid heating above 150° gave a yield of 52% of rearranged product.

B. By *p*-Toluenesulfonic Acid.—A mixture of 0.40 mole of imidic ester and 0.016 mole of *p*-toluenesulfonic acid monohydrate was heated in an oil-bath at 175–180° for 1.25 hr. The temperature of the reaction mixture never went above 185°. The yield of recovered imidic ester was less than 3% and of rearranged product 11%. A residue of 43 g. of dark brown non-volatile material remained.

C. By Sulfuric Acid in the Presence of Ethyl Orthoformate.—A mixture of 0.20 mole of imidic ester, 0.10 mole of ortho ester and 0.008 mole of concentrated sulfuric acid was heated in an oil-bath at 175–180° for 0.5 hour. The temperature of the reaction mixture rose to a maximum of 192° during this period and 5.5 g. of material distilled at a head temperature of 62–93°. Vacuum distillation gave 4.5 g. (0.03 mole) of recovered ethyl orthoformate, b.p. 65–67° (40 mm.), a few drops of recovered ethyl N-phenylformimidate and 25.4 g. (0.17 mole) of N-ethylformanilide, b.p. 150–154° (40 mm.). This amounted to an 85% rearrangement based on the imidic ester taken. The residue weighed only 2.8 g.

A second experiment which was identical except for a 0.25 hr. heating period instead of 0.5 hr. gave 0.048 mole of recovered ortho ester, 0.011 mole of recovered imidic ester and 0.148 mole (74%) of rearranged product.

D. By Sulfuric Acid in the Presence of Isoamyl Orthoformate.—A mixture of ethyl N-phenylformimidate (0.40 mole), isoamyl orthoformate[13] (0.20 mole) and concentrated sulfuric acid (0.016 mole) was heated in an oil-bath at 180–190° for 0.5 hr. The temperature of the reaction mixture did not go above 183°; 2.7 g. of distillate came over at a head temperature of 56–62°. Vacuum distillation showed the reaction mixture to be complex; five fractions were collected between 58 and 148° (40 mm.), a sixth at 148–158° (40 mm.) and a seventh at 150–151° (14 mm.). The last two fractions were combined and redistilled and 20.3 g. of N-ethylformanilide, b.p. 150–155° (40 mm.) and 18.7 g. of N-isoamylformanilide, b.p. 150–154° (14 m..), were obtained.

The last fraction was hydrolyzed with 10% hydrochloric acid, yielding 12.1 g. of N-isoamylaniline, b.p. 146–148° (40 mm.). The *p*-toluenesulfonyl derivative was prepared m.p. 80–81° (reported[16] 81–82°). The amount of N-isoamylaniline obtained indicated about a 25% conversion of ethyl N-phenylformimidate into N-isoamylformanilide.

Rearrangement of Other Imidic Esters.—A mixture of 0.182 mole of ethyl *p*-chlorophenylformimidate and 0.008 mole of concentrated sulfuric acid was heated in an oil-bath at 170–175°. As the exothermic reaction took place, the temperature of the reaction mixture rose to 235° and then slowly dropped back while the heating was continued for 30 minutes. A few drops of material distilled at 50–52°. The pressure was reduced and 0.115 mole (63%) of N-ethyl-*p*-chloroformanilide was distilled, b.p. 176–178° (40 mm.). A residue of 8.5 g. remained.

A mixture of 0.157 mole of methyl N-phenylformimidate and 0.008 mole of sulfuric acid was treated similarly. The exothermic reaction raised the temperature to a maximum of 210°. Upon vacuum distillation a few drops of imidic ester were recovered and 0.095 mole (61%) of N-methylformanilide was obtained, b.p. 150–152° (40 mm.).

N-Alkylation of Aniline, *m*-Toluidine and *p*-Chloroaniline by Means of Alkyl Orthoformates.—The procedure applied to the preparation of the compounds listed in Table I is illustrated by description of the alkylation of *p*-chloroaniline by ethyl orthoformate.

A mixture of 53.6 g. (0.50 mole) of *p*-chloroaniline, 111 g. (0.75 mole) of ethyl orthoformate and 2.0 g. (0.02 mole) of concentrated sulfuric acid was placed in a three-necked flask equipped with a thermometer with its bulb in the liquid and a 12-in. glass helix-packed distilling column. The reaction mixture was heated by an oil-bath while ethanol distilled; as the evolution of alcohol slackened, the temperature of the oil-bath was raised to 175–180°. A total of 60.3 g. (1.31 moles) of alcohol was obtained. The reaction mixture was kept in the oil-bath for 0.5 hr., the inside temperature rising to a maximum of 187° and a small amount of material distilling at 50–60°. After cooling somewhat, the reaction mixture was vacuum distilled. At 65–67° (40 mm.) 19.5 g. (0.132 mole) of ethyl orthoformate was recovered, and at 82–83° (40 mm.) 1.6 g. of material distilled, which was undoubtedly ethyl N-*p*-chlorophenylformimidate. The pressure was lowered to 20 mm. and 78.6 (0.43 mole) of N-ethyl-*p*-chloroformanilide distilled at 167–168°, a yield of 86%, based on *p*-chloroaniline. The residue was dark brown and weighed 10.6 g.

A 77.8-g. (0.424 mole) sample of the N-ethyl-*p*-chloroformanilide was hydrolyzed by boiling under reflux with about three times its volume of 10% hydrochloric acid for 1 hr. After cooling, the mixture was neutralized and made basic with 15% potassium hydroxide. The organic layer was removed and the aqueous solution was extracted with ether. The combined organic layer and ether solution was washed with water, dried over calcium chloride and distilled. N-Ethyl-*p*-chloroaniline boiled at 149–150° (40 mm.); 59.8 g. (0.385 mole) was obtained, a yield of 91% on hydrolysis and a yield of 78% based on the amount of primary amine taken.

The *p*-toluenesulfonyl derivative was prepared; it melted at 103–104° (reported[17] 102.5–104°).

In some of the other rearrangements, more heat was evolved and some flooding of the column occurred, but in no case was the reaction violent.

The low yield of N-methylaniline reported in Table I was due largely to incomplete hydrolysis of the formanilide, which was refluxed with acid solution only 30 minutes. It was later found that about an hour is required to complete the hydrolysis.

The purity of all the secondary amines prepared was attested to not only by the boiling points and refractive indices but also by the melting points of characteristic acyl and sulfonyl derivatives which were prepared. One discrepancy from the literature (in addition to that mentioned in connection with N-ethylaniline above) was encountered; the acetyl derivative of N-methyl-*m*-toluidine melted at 75–76° (reported[18] 66°).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.20; H, 7.83.

AUSTIN 12, TEXAS

---

[16] J. Braun and R. Murjahn, *Ber.*, **59**, 1205 (1926).

[17] A. F. Crowther, F. G. Mann and D. Purdie, *J. Chem. Soc.*, 58 (1943).

[18] P. Monnet, F. Reverdin and E. Nolting, *Ber.*, **11**, 2279 (1878).

[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT LABORATORY, SOCONY MOBIL OIL CO., INC.]

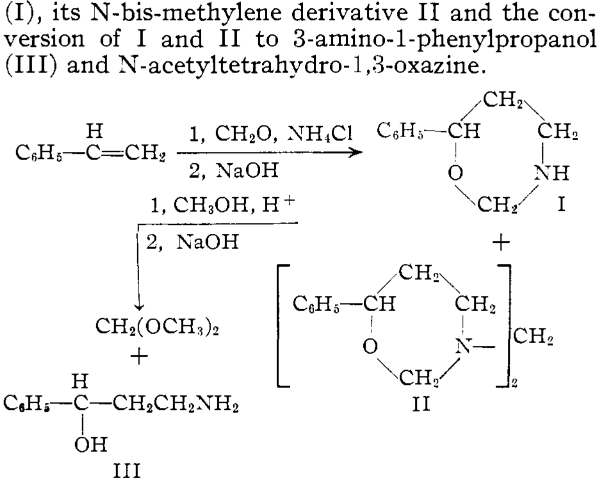
The Aminomethylation of Styrene. A New Synthesis of 3-Amino-1-phenylpropanol[1]

BY S. L. MEISEL, J. J. DICKERT, JR., AND H. D. HARTOUGH

RECEIVED MAY 21, 1956

Styrene condenses with formaldehyde and ammonium chloride to form 6-phenyltetrahydro-1,3-oxazine (I) and bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane (II). Reaction of I or II with methanol and hydrochloric acid yields 3-amino-1-phenylpropanol (III), while reaction with acetic anhydride leads to the N-acetyl derivative of I.

The Prins reaction, which involves the acid-catalyzed addition of formaldehyde to olefins to form unsaturated alcohols, glycols, dioxanes and other oxygenated derivatives, is well known.[2] Recently, this reaction has been extended to include the preparation of amino compounds by adding either ammonium or amine salts to the standard mixture.[3–5] This paper discusses the reactions of styrene, formaldehyde and ammonium chloride to form 6-phenyltetrahydro-1,3-oxazine (I), its N-bis-methylene derivative II and the conversion of I and II to 3-amino-1-phenylpropanol (III) and N-acetyltetrahydro-1,3-oxazine.



Davies and Powell have prepared III previously by the reduction of β-aminopropiophenone and have compared its activity with epinephrine.[6]

The reaction of I or II with acetic anhydride leads to N-acetyltetrahydro-1,3-oxazine.

Experimental

Bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane.—To 104 g. (1 mole) of styrene were added 340 g. (4 moles) of 36% formaldehyde solution and 108 g. (2 moles) of ammonium chloride. The well-stirred mixture was warmed to 75–80° for 40 minutes and cooled. An oily layer of about 60 g. separated. This layer contains unreacted styrene, formaldehyde, 4-phenyl-1,3-dioxane and possibly minor amounts of other products formed in the normal Prins reaction. The aqueous layer was extracted three times with diethyl ether to remove additional oily material and then reacted with 2 moles of sodium hydroxide (as a 40% solution). This caused a separation of an amine and aqueous layer. The aqueous layer was extracted with ether and this extract was combined with the amine layer. Removal of the solvent yielded 88 g. of a light yellow viscous oil. About 70 g. (43% based on styrene charged) of this material crystallized on standing to form bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane. The remaining oil (11%) contained impure 6-phenyltetrahydro-1,3-oxazine. The N-bis-methylene derivative was recrystallized from ethanol to yield a product melting at 125.5–126°.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.56; H, 7.69; N, 8.28; mol. wt., 338. Found: C, 74.11; H, 7.75; N, 8.31; mol. wt. (b.p.), 376.

N-Acetyl-6-phenyltetrahydro-1,3-oxazine.—To 161 g. of a mixture of I and II were added 250 ml. of benzene and 214 g. of acetic anhydride. The reaction mixture was cooled during the addition and then refluxed for 3 hr. Removal of the benzene yielded 164 g. of crude product. Distillation yielded a center cut, 133 g. (65%), b.p. 145–146° (0.5 mm.). This material crystallized on standing and was recrystallized from *n*-heptane; m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.35; H, 7.51; N, 6.87.

3-Amino-1-phenylpropanol.—To 85 g. (0.25 mole) of bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane were added 50 g. of concd. hydrochloric acid, 150 ml. of water and 300 ml. of methanol. The mixture was stirred for 1 hr. at room temperature and then allowed to stand for 16 hr. The reaction mixture was refluxed (69–72°) for 1 hr. and distilled to a reaction temperature of 100° to remove the methylal and excess methanol. After cooling, the reaction mixture was treated with 55 g. of 40% sodium hydroxide. A water-insoluble layer formed and was separated from the reaction mixture. The oil layer was then distilled *in vacuo*. A center cut of 53 g. (70% yield), b.p. 117–119° (1.0 mm.), crystallized on standing. A foreshot of 9 g. and a residue of 13 g. also produced some crystalline material when seeded. The center cut was recrystallized twice from benzene; m.p. 61–62°; lit.[6] 63.5–64°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.61; N, 9.27. Found: C, 70.82; H, 8.54; N, 9.16.

A phenylthiourea derivative of this material was prepared and recrystallized three times from absolute ethanol; m.p. 135–135.5°.

Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 9.79. Found: C, 67.28; H, 6.51; N, 10.29.

Discussion

The mechanism of this reaction is probably similar to those proposed for the Prins reaction[7] and for the aminomethylation of olefins with secondary amines.[4,5] However, they are not entirely comparable reactions. Extremely reactive olefins, such as α-methylstyrene, are needed for the latter reaction. Both our work and that of Hennion, Price and Wolff[4] have shown that styrene condenses readily with ammonia but not with secondary amines. This difference may be related to either the ease of formation or the reactivity of the carbonium ion intermediates, $CH_2NH_2^+$ from ammonia and $R_2NCH_2^+$ from secondary amines.

The condensation of formaldehyde with 3-

---

(1) Presented at the Delaware Valley Regional Meeting, Philadelphia, February 16, 1956.

(2) (a) H. J. Prins, *Proc. Acad. Sci. Amsterdam*, **22**, 51 (1919); (b) C. C. Price, F. L. Benton and C. J. Schmidle, THIS JOURNAL, **71**, 2860 (1949).

(3) H. D. Hartough, J. J. Dickert, Jr., and S. L. Meisel, U. S. Patent 2,647,117, 2,647,118 (*C.A.*, **48**, 8265 (1954)).

(4) G. F. Hennion, C. C. Price and V. C. Wolff, Jr., THIS JOURNAL **77**, 4633 (1955).

(5) C. J. Schmidle and R. C. Mansfield, *ibid.*, **77**, 4636 (1955)

(6) R. E. Davies and G. Powell, *ibid.*, **67**, 1466 (1945).

(7) C. C. Price, "Mechanisms of Reactions at the Carbon–Carbon Double Bond," Interscience Publishers, Inc., New York, N. Y., 1946, p. 45.