

## SYNTHESIS OF CERTAIN ETHYL, PHENYL, AND NITROPHENYL DERIVATIVES OF UREA<sup>2</sup>

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As part of an investigation (1) of the derivatives which are formed from centralite (1,3-diethyl-1,3-diphenylurea) during the accelerated aging of double base smokeless powder, it was necessary to synthesize a considerable number of derivatives of centralite and of urea. Since certain of these compounds, or the intermediates which are required for their synthesis, apparently have not been described in the literature, we present in this paper methods which we have found to be successful for their synthesis. With one exception, in which a nitration was used, all of the compounds were prepared by the reaction of an amine with either an isocyanate or a substituted carbanilyl chloride. Because only small quantities of the compounds were required, no attempts were made to improve yields or to refine the procedures; however, experience suggested certain possibilities for improvement which are briefly discussed.

### EXPERIMENTAL PART

Stem corrections were applied to melting points all of which were taken in melting-point tubes in an electrically-heated copper block. Micro-analyses were made by the late Dr. G. Oppenheimer and Mr. G. Swinehart. 1,3-Diethyl-1-phenylurea was synthesized by Mr. Floyd Preston.

*1,1-Diphenyl-3-ethylurea.* 1,1-Diphenyl-3-ethylurea was prepared by the reaction of ethyl isocyanate with diphenylamine. Ethyl isocyanate<sup>4</sup> was obtained by the method of Boehmer (2) in which propionyl chloride is reacted with activated sodium azide (3). This reaction may become vigorous unless carefully controlled. An 8-g. portion of recrystallized diphenylamine (Eastman White Label) and an equivalent amount of ethyl isocyanate in 30 ml. of toluene were heated for 13 hrs. in a sealed tube at 150° since the reaction seemed to be sluggish in refluxing toluene. The cooled reaction mixture was boiled with 100 ml. of benzene in order to remove unreacted isocyanate and when the volume had been reduced to 25 ml., 400 ml. of ligroin (60–70°) was added and the solution was cooled. The pink needles which separated were recrystallized 6 times from ligroin to yield a colorless product, m.p. 74.8–75.3°. The yield of purified compound was 4 g. or 37%.

*Anal.* Calc'd for  $C_{15}H_{15}N_2O$ : C, 74.97; H, 6.71; N, 11.66.

Found: C, 75.04; H, 6.55; N, 11.61.

*1,3-Diethyl-1-phenylurea.* The reaction between N-ethylcarbanilyl chloride and ethylamine was used to prepare 1,3-diethyl-1-phenylurea. A 12-g. portion of N-ethylcarbanilyl chloride which had been synthesized by the method of Price (4) was dissolved in 50 ml. of toluene and 11 g. of cold ethylamine (Eastman White Label) was slowly added at 0°. Heat

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<sup>4</sup> Dr. C. E. Schweitzer (private communication) recommends the method of Stotta and Lorenz, *Ber.*, **58**, 1320 (1925) as a more convenient one for the preparation of ethyl isocyanate. Ethyl sulfate, potassium cyanate, and sodium carbonate are heated with caution.

was evolved and a gelatinous precipitate of ethylamine hydrochloride formed immediately. After 15 hrs. at room temperature, the reaction mixture was refluxed for one hr. The solution was separated from the ethylamine hydrochloride and washed 5 times with 50 ml. of water to remove dissolved ethylamine hydrochloride. After the solvent had been removed, the crystalline residue was recrystallized 5 times from ligroin (60–70°) and twice from ethyl ether; Norit was used during two of the recrystallizations from ligroin. The final product was colorless, free of halogen, and melted at 62.5–62.8°. The yield was 1.5 g. (12%).

*Anal.* Calc'd for  $C_{11}H_{16}N_2O$ : C, 68.71; H, 8.39; N, 14.58.

Found: C, 68.59; H, 8.20; N, 14.54.

The yield probably could be improved if dissolved ethylamine hydrochloride were removed from the solution with a paste of sodium carbonate rather than by washing with water because, as was determined later, the compound is appreciably soluble in water.

*1-Phenyl-1,3,3-triethylurea.* This compound was prepared from 12 g. of N-ethylcarbanil chloride (4) and 11 g. of diethylamine (Eastman White Label), each of which was dissolved in 50 ml. of anhydrous toluene. When the solutions were mixed at 0°, heat was evolved and diethylamine hydrochloride precipitated. The temperature was permitted to rise to 60° and after the reaction had slowed, the mixture was refluxed for 30 min. After the filtered solution had been washed once with 3 *N* hydrochloric acid and twice with water, the solvent was evaporated under reduced pressure. The 14.3 g. of yellowish residual oil was then distilled under reduced pressure in an all-glass apparatus and 12.5 of product (yield 88%) was obtained; b.p. 166–167°/27 mm. and m.p. –7 to –8°.

*Anal.* Calc'd for  $C_{13}H_{20}N_2O$ : C, 70.84; H, 9.17; N, 12.72.

Found: C, 71.18; H, 9.19; N, 12.77.

*The anomalous melting point of 1-ethyl-1,3,3-triphenylurea.* This substituted urea has been prepared by Michler (5) who heated N,N-diphenylcarbonyl chloride with 2 equivalents of N-ethylaniline at 130° and by Kaufmann (6) who melted together N-ethylcarbanil chloride and diphenylamine in the presence of zinc dust. Kaufmann's product melted at 80° and it is stated in his paper that Michler's material also had this melting point, while Dains, *et al.* (7) report m.p. 79°.

An initial attempt to prepare the compound by the method of Michler resulted in the isolation of a viscous oil which could not be induced to crystallize. Trial experiments then showed that a purer product could probably be obtained by the following procedure. An 8-g. portion of N,N-diphenylcarbonyl chloride (Eastman White Label recrystallized), 5 g. of redistilled N-ethylaniline, and 5 g. of zinc dust were heated at 110° until the reaction began with the evolution of gas and then at 90–100° for 12 hrs. The viscous reaction mixture was dissolved in 100 ml. of ether, the solid was filtered off, and the solution was washed with two 100-ml. portions of 3 *N* hydrochloric acid and three 100-ml. portions of water. However, the viscous, light yellow liquid which remained after evaporation of the solvent could not be made to crystallize.

Crystals were first obtained from a sample which was distilled in a high vacuum; the fraction which distilled at 137–138° at a pressure of 10–20 microns crystallized when a solution in ligroin (60–70°) was cooled to the temperature of Dry Ice. It is interesting to note that, once these crystals had formed, crude and distilled fractions from the various preparations began to crystallize slowly at their different places in the laboratory even though they were not consciously seeded. However, the solid product was somewhat amorphous in nature and the melting point and character of the solid were not improved by recrystallization. A pure product was finally obtained by dissolving the material from several preparations in anhydrous ether and saturating at 0° with hydrogen chloride gas. The precipitate which formed (probably diphenylamine hydrochloride) was filtered off, excess hydrogen chloride was removed with moist sodium bicarbonate, and the solvent was evaporated. Several recrystallizations were carried out from methanol by adding water at room temperature until a trace of oil separated, seeding, and cooling to 0°. The final product was composed of well-formed, colorless needles which had a constant melting point of 66.0–66.5° and gave the following analysis.

*Anal.* Calc'd for  $C_{21}H_{20}N_2O$ : C, 79.70; H, 6.39; N, 8.86; M.W., 316.

Found: C, 79.94; H, 6.41; N, 9.14; M.W., 325 (Rast micromethod in exaltone).

Because of the complicated series of purifications from several preparations, the calculation of a yield is meaningless.

The melting point  $66.0$ – $66.5^\circ$  is very different than that of  $80^\circ$  which is reported by Michler (5) and Kaufmann (6) and of  $79^\circ$  by Dains, Roberts, and Brewster (7). However, the method of preparation, the analysis, and the molecular weight lead us to believe that our product actually is 1-ethyl-1,3,3-triphenylurea and that the difference in melting points probably is due to polymorphism.

*N-Ethyl-2-nitrocarbanilyl chloride.* *N-Ethyl-2-nitrocarbanilyl chloride* was required as an intermediate in the synthesis of 2-nitrocentralite.<sup>5</sup> A 15-g. sample of 2-nitro-*N*-ethyl-aniline<sup>6</sup> and 10 g. of triethylamine (Eastman White Label) were dissolved in 300 ml. of dry distilled benzene. Phosgene which had been washed with unsaturated cottonseed oil and conc'd sulfuric acid was passed into the solution at  $0^\circ$  for 15 min. At the end of this time, the solution was removed from the ice-bath, allowed to warm to  $40^\circ$ , and then, after the reaction had slowed and the temperature had fallen to  $30^\circ$ , warmed to  $60^\circ$  for 20 min. Phosgene was passed into the solution throughout this time and 5 g. of triethylamine was added during the course of the reaction to replace any which had been lost by vaporization. A white precipitate of triethylamine hydrochloride formed in the solution during the reaction. The benzene solution was washed with three 200-ml. portions of 6 *N* hydrochloric acid and four 200-ml. portions of water and then dried with calcium chloride. Evaporation of the solvent left a residue of 24 g. of dark yellow oil which solidified slowly when 100 ml. of ligroin ( $60$ – $70^\circ$ ) was added and the mixture was cooled to  $0^\circ$ . Recrystallization from 50 ml. of warm ether to which 150 ml. of ligroin was added yielded 15.5 g. (yield 75%) of light yellow product, m.p.  $46.5$ – $47.5^\circ$ . A small portion was recrystallized three times to m.p.  $47.5$ – $48.0^\circ$  and this material gave the following analysis.

*Anal.* Calc'd for  $C_{21}H_{20}ClN_2O_2$ : C, 47.27; H, 3.94; N, 12.24; Cl, 15.53.

Found: C, 47.13; H, 4.16; N, 11.86, 11.84; Cl, 15.62.

While phosgene was being passed into the solution during the above preparation, a white solid formed in the air above the solution and, indeed, the first reaction in the solution was the formation of a white solid at a rate much more rapid than the main reaction which resulted in the formation of hydrogen chloride and the eventual formation of triethylamine hydrochloride. It seems probable that this white substance is a *complex of phosgene and triethylamine*: the literature apparently does not contain information about such a complex although some data are available concerning complexes or reaction products of phosgene and other tertiary amines. We have not had occasion to study the properties of this material further but we should like to point out that if it is a reasonably stable complex, it might prove useful in organic syntheses as a convenient, solid, concentrated source of phosgene. Its formation during the preparation of *N*-ethyl-2-nitrocarbanilyl chloride apparently did not interfere with the main reaction.

*2-Nitrocentralite.* When the solution of 8 g. of *N*-ethyl-2-nitrocarbanilyl chloride and 10 g. of *N*-ethylaniline (Eastman White Label) in 25 ml. of dried benzene was refluxed for 2 hrs., it became very dark red in color and both a red-black and a colorless precipitate formed. The mixture was diluted with 100 ml. of benzene and the nearly black solution was washed successively with 100 ml. of water, 100 ml. of 3 *N* hydrochloric acid, and three 100-ml. portions of water. The final washings were almost colorless and the brownish-orange benzene solution, after drying and treatment with 2 g. of Norit, became bright yellow-orange in color. The oil which remained after removal of the solvent could not be induced to crystallize until it had been purified chromatographically. The general chromatographic procedures have been described elsewhere (8) but the specific details of this purification will

<sup>5</sup> In the convention of *Chemical Abstracts*, "Centralite" refers to 1,3-diethyl-1,3-diphenylurea. Hence, 2-nitrocentralite is 1,3-diethyl-3-(2-nitrophenyl)-1-phenylurea.

<sup>6</sup> Obtained from Dr. R. L. Shriner.

be given. The 2.2 g. of crude 2-nitrocentralite was dissolved in 80 ml. of 1:4 benzene-ligroin<sup>7</sup> and placed on a 7 × 25-cm. column of 2:1 silicic acid-Celite (by weight) which had been pre-washed with V ml.<sup>8</sup> of ether and 2 V ml. of ligroin (60–70°). By development with 2 V ml. of a 5% solution of ether in ligroin, a dark yellow impurity, probably 2-nitro-N-ethylaniline, was washed into the filtrate. After the receiver had been changed, the 2-nitrocentralite was washed into the filtrate with 2 V ml. of 1:1 ether-ligroin. The solvent was evaporated and the residual red oil was taken up in 50 ml. of boiling ligroin (30–60°). The crystals which were formed when the solution was cooled in an ice-salt bath and the vessel was scratched were recrystallized three times to give one gram (yield 9%) of light yellow stubby needles which had a constant melting point of 56–57°. The following analysis was obtained.

*Anal.* Calc'd for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: C, 65.18; H, 6.06; N, 13.42; M.W., 313.

Found: C, 65.41, 65.44; H, 6.09, 6.17; N, 13.67, 13.65; M.W., 322 (Rast micro-method in exaltone).

The yield of 2-nitrocentralite was small because the main reaction took another course which produced a highly colored red compound. Although the compound which melted at 56–57° was not the main product, there was little doubt that it was 2-nitrocentralite because of the excellent agreement of the analysis and molecular weight determination with the calculated value. Furthermore, the physical and chromatographic properties were those which would be expected of 2-nitrocentralite on the basis of the behavior of related compounds (1).

*N-Ethyl-4-nitrocarbanilyl chloride.* N-Ethyl-4-nitrocarbanilyl chloride was required as an intermediate in the preparation of 4-nitrocentralite. A 25-g. sample of 4-nitro-N-ethylaniline<sup>9</sup> which had been prepared by the methods of Weller (11) and Nölting and Collin (12) and 20 g. of dimethylaniline (Eastman White Label) were dissolved in 400 ml. of dry, distilled benzene and phosgene was passed through the solution essentially as in the preparation of N-ethyl-2-nitrocarbanilyl chloride. At the end of the reaction, the clear red benzene solution was decanted from a second phase which was then dissolved in benzene. Both solutions were washed thoroughly with 6 N hydrochloric acid and with water, dried, and combined, and the solvent was then removed under reduced pressure. The yellow crystalline residue was dissolved in 50 ml. of hot acetone and crystallized by the addition of 50 ml. of ligroin (60–70°) and subsequent cooling to 5°. The yellow crystals weighed 15 g. and melted at 115–116°; the mother liquor yielded 6.5 g. of somewhat darker material, a total yield of 63%. Recrystallization of the lighter-colored sample produced a material which melted at 115.8–116.5° and gave the following analysis.

*Anal.* Calc'd for C<sub>9</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 47.27; H, 3.94; N, 12.24; Cl, 15.53.

Found: C, 48.27; H, 4.48; N, 12.33; Cl, 14.34.

The analytical results were not entirely satisfactory but the product was a satisfactory intermediate for the preparation of 4-nitrocentralite and hence was not purified further.

Probably it would be better to use triethylamine instead of dimethylaniline to remove hydrogen chloride during the reaction of phosgene with 4-nitro-N-ethylaniline since dimethylaniline can react with phosgene to form Michler's ketone. Triethylamine was used in the preparation of N-ethyl-2-nitrocarbanilyl chloride as a result of the experience with this preparation.

*4-Nitrocentralite.* Lécorché and Jovinet (13) have prepared a mononitrocentralite by

<sup>7</sup> The compositions of solvents are in terms of the ratios of the volumes of the constituents.

<sup>8</sup> "V ml." is defined as the volume of solvent which is required to wet completely the column of adsorbent.

<sup>9</sup> N-Ethylacetanilide which is required as an intermediate in the preparation of 4-nitro-N-ethylaniline is much more easily prepared by the acetylation of N-ethylaniline by general procedures as described by Shriner and Fuson (9) than by ethylation of acetanilide (10).

nitration of centralite. Since a less ambiguous procedure was desired, the compound has been prepared by the reaction of *N*-ethyl-4-nitrocarbanilyl chloride with *N*-ethylaniline. An attempt to prepare 4-nitrocentralite by the reaction of *N*-ethylcarbanilyl chloride with 4-nitro-*N*-ethylaniline was unsuccessful.

The mixture of 6 g. of *N*-ethyl-4-nitrocarbanilyl chloride and 9 g. of distilled *N*-ethylaniline (Eastman White Label) in 25 ml. of purified xylene was refluxed for 2 hrs. About 100 ml. of ether and 100 ml. of water were added to the cooled reaction mixture, the phases were separated, and the organic phase was thoroughly washed with 3 *N* hydrochloric acid and with water. After evaporation of the solvent under reduced pressure the 4-nitrocentralite was in the form of a yellow oil which could not be induced to crystallize from benzene, ligroin, ether, acetone, or chloroform and consequently it was purified by recrystallization in the form of the ethanol complex as suggested by Lécorché and Jovinet (13). The entire material was dissolved in 35 ml. of absolute ethanol, 40 ml. of ligroin (30–60°) was added, and crystallization was induced by seeding and vigorous scratching of the vessel. Three similar recrystallizations yielded 4 g. of pale yellow, superficially dry needles which quickly lost alcohol in air and became sticky. When the complex was heated under vacuum at 70°, a honey-like oil of 4-nitrocentralite was obtained which could not be crystallized although Lécorché and Jovinet did obtain crystals which melted at 43°. The oil gave the following analysis.

*Anal.* Calc'd for  $C_{17}H_{19}N_3O_3$ : C, 65.18; H, 6.06; N, 13.42.

Found: C, 65.19; H, 6.22; N, 13.66.

*2,4,4'-Trinitrocentralite.* [*1,3-Diethyl-1-(4-nitrophenyl)-3-(2,4-dinitrophenyl)urea*]. It was necessary to prepare 2,4,4'-trinitrocentralite by nitration since experience with the preparation of 4-nitrocentralite gave little hope that the compound could be prepared unambiguously by reaction of nitro-*N*-ethylcarbanilyl chlorides with nitro-*N*-ethylanilines. A 5-g. portion of 4,4'-dinitrocentralite<sup>6</sup> was dissolved in 8.2 ml. of conc'd sulfuric acid. To this solution, 5.6 ml. of a mixture of 25 ml. of conc'd sulfuric acid, 3.4 ml. of water, and 5.0 ml. of 70% nitric acid was slowly added in the course of 30 min. so that the temperature did not rise above 45°. After the addition was complete, the red solution was warmed to 55°, allowed to stand for 10 min. (during which time gas began to be evolved), cooled in an ice-bath, and then poured onto 300 g. of crushed ice. The yellow solid which separated was filtered, washed well with water, and dried. After digestion of the crude material with 100 ml. of boiling 95% ethanol, an undissolved portion remained which proved to be 2,2',4,4'-tetranitrocentralite and when the solution was cooled to room temperature, the first crystals were mainly tetranitrocentralite. These crystals were filtered off and the solution was allowed to stand overnight during which time 2.8 g. of yellow platelets were deposited. Two recrystallizations of the platelets from 95% ethanol gave a product which melted at 147.5–148.5°. 4,4'-Dinitrocentralite melts at 147–148° (14) but a mixture of the product and 4,4'-dinitrocentralite melted at 125–135°. Five recrystallizations from absolute ethanol raised the melting point to a nearly constant value of 151.5–152.3°. The yield of purified material was 0.5 g. or 9% and from it the following analytical results were obtained.

*Anal.* Calc'd for  $C_{17}H_{17}N_5O_7$ : C, 50.60; H, 4.27; N, 17.36; M.W., 403.

Found: C, 50.87; H, 4.36; N, 17.44; M.W., 394 (in camphor).

In addition to the analysis, other experiments were made to show that the compound actually is trinitrocentralite. After hydrolysis with 65% sulfuric acid, the hydrolytic products were separated chromatographically and determined spectrophotometrically. By this means, 112% of the expected 4-nitro-*N*-ethylaniline and 85% of the expected 2,4-dinitro-*N*-ethylaniline were found. Further experimentation showed that the low yield of the dinitro compound is caused by some destruction during the hydrolysis and to a somewhat incomplete chromatographic separation from 4-nitro-*N*-ethylaniline which in turn causes an apparent yield of this compound which is greater than the theoretical. In addition, the chromatographic properties of 2,4,4'-trinitrocentralite on silicic acid-Celite were found to be different from those of 4,4'-dinitrocentralite and 2,2',4,4'-tetranitrocentralite. Hence, it is probable that the compound which melts at 151.5–152.3° is 2,4,4'-trinitrocentralite.

*1-Ethyl-1-(4-nitrophenyl)-3-phenylurea. (4-Nitro-N-ethylcarbanilide).* Since the reaction between phenyl isocyanate and 4-nitro-N-ethylaniline did not proceed in refluxing benzene or even when the compounds were heated together, 1-ethyl-1-(4-nitrophenyl)-3-phenylurea was prepared by refluxing the solution of 5 g. of N-ethyl-4-nitrocarbanilyl chloride and 4.1 g. of aniline (General Chemical Co.) in 25 ml. of chloroform for 3 hrs. A 50-ml. portion of chloroform was added to the cooled reaction mixture and the solution was washed twice with 100 ml. of 3 N hydrochloric acid and twice with 50 ml. of water. After the chloroform phase had been dried, it was heated to boiling, 75 ml. of ligroin (60–70°) was added, and the solution was cooled to 0°. The pale yellow needles which separated were recrystallized once from a mixture of 70 ml. of ethanol and 25 ml. of water and twice from a mixture of 60 ml. of chloroform and 50 ml. of ligroin. The final product had a constant melting point of 156.0–156.7°, weighed 2.5 g. (yield 40%), and gave the following analysis.

*Anal.* Calc'd for  $C_{15}H_{15}N_2O_2$ : C, 63.11; H, 5.33; N, 14.73.

Found: C, 63.00, 63.24; H, 5.41, 5.17; N, 14.83, 15.00.

*1-Ethyl-3-(4-nitrophenyl)-1-phenylurea. (4-Nitro-N'-ethylcarbanilide).* Since the reaction between 4-nitrophenyl isocyanate and N-ethylaniline took place readily, the compound was prepared by refluxing for 2 hrs. a solution of 4 g. of 4-nitrophenyl isocyanate (recrystallized Eastman Practical) and 3 g. of N-ethylaniline in 25 ml. of chloroform. The oil which remained after removal of the solvent under vacuum was crystallized by dissolving in a mixture of 75 ml. of methanol and 15 ml. of water and cooling. Recrystallization from a mixture of 75 ml. of isopropyl ether and 75 ml. of ethyl ether after treatment with Norit yielded 4.4 g. (64%) of large pale yellow prisms which melted at 79.5–80.5°.

*Anal.* Calc'd for  $C_{15}H_{15}N_2O_2$ : C, 63.11; H, 5.33; N, 14.73.

Found: C, 63.05; H, 5.31; N, 15.01.

#### SUMMARY

A number of new ethyl, phenyl, and nitrophenyl derivatives of urea and several intermediate compounds have been synthesized.

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