Summary

Ethyl diphenylmalonate and ethyl di-(*p*-tolyl)malonate when subjected to the usual treatment with urea and sodium ethylate for condensation into a barbituric acid undergo decomposition with loss of a carboxyl group. When, however, the phenyl groups carry an hydroxyl group, as in ethyl di(*p*-hydroxyphenyl)malonate and ethyl di-(3-methyl-4-hydroxyphenyl)-malonate the condensation to a 5,5-diarylbarbituric acid is readily effected. Neither 5,5-di(*p*-hydroxyphenyl)barbituric acid nor its isomer, 5,5-diphenoxybarbituric acid, shows noticeable hypnotic properties. Attention is called to the fact that these derivatives differ from the great majority of synthetic hypnotics in that they are predominantly aromatic.

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THE UREA DEARRANGEMENT. II

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Just as urea dearranges into ammonia and isocyanic acid, so substituted ureas, thio-urea and guanidine, and their substitution products dearrange in similar fashion. When urea is heated with aniline, the isocyanic acid which is formed combines with the aniline to form phenylurea. This substance dearranges in two modes to form on the one hand aniline and isocyanic acid, on the other phenylisocyanate and ammonia; the phenylisocyanate and aniline combine to produce *sym*-diphenylurea which can dearrange in only one fashion to regenerate the substances from which it was produced. In the first paper[1] of this series, experiments were described which elucidate the mechanism of these reactions. By heating the dry materials together at about 160° we were able to prepare a number of derivatives of various aromatic primary amines.

In continuing the study we now find that the reactions take place in boiling aqueous solution. If urea and aniline hydrochloride are boiled together in water solution under a reflux condenser, phenylurea is formed and remains in solution in the hot liquid. After the clear solution has boiled for some time, diphenylurea begins to precipitate. Diphenylurea may be filtered from the hot liquid, and monophenylurea may be obtained by cooling the filtrate. By suitable modifications of the process, by repeating the boiling and filtration, it is possible to obtain either or both of the products in excellent yield. We find also that phenylurea refluxed in water solution yields *sym*-diphenylurea just as it does when heated at 160° in the dry state. When its aqueous solution is distilled, aniline passes over.

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[1] Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922).

In the aliphatic series, we have prepared *sym*-dimethylurea, diethylurea, di-*n*-butylurea, di-*n*-amyl-, di-*iso*-amyl-, benzyl- and dibenzylurea, by heating the amine hydrochloride with urea at 160–170° or by boiling the amine or its hydrochloride with urea in aqueous solution under a reflux condenser. When the amine hydrochloride was heated with urea, the amount of ammonium chloride which was produced indicated that the reaction had proceeded nearly to completion, but the aliphatic ureas are troublesome to manipulate and the yields of actual product, while considerable, were not as good as in the aromatic series.

When a solution of urea was refluxed with methylaniline hydrochloride and with ethylaniline hydrochloride, the corresponding unsymmetrical disubstituted ureas were produced. The yields were poor, but there was no evidence of tetrasubstituted urea, a fact which accords with our belief that the unsymmetrical disubstituted ureas dearrange in only one fashion: $RR'N{-}CO{-}NH_2 \rightleftarrows RR'NH + HNCO$. The poor yields may perhaps have been due to the hydrolytic action of the amine hydrochloride solution on the isocyanic acid leading to the formation of ammonia and carbon dioxide, a belief which is supported by the fact that an increasing amount of the free base precipitated out as the boiling was continued.

Striking evidence of the dearrangement of substituted ureas was found in the interaction of aniline with *sym*-diethylurea. Diethylurea dearranges in only one fashion: $C_2H_5NH{-}CO{-}NHC_2H_5 \rightleftarrows C_2H_5NCO + C_2H_5NH_2$. When it is heated with aniline, ethyl amine escapes and the ethyl isocyanate combines with the aniline to form *sym*-ethylphenylurea. This substance now dearranges in two modes: $C_2H_5NH_2 + C_6H_5NCO \rightleftarrows C_2H_5{-}NH{-}CO{-}NHC_6H_5 \rightleftarrows C_6H_5NH_2 + C_2H_5NCO$. When it is heated alone, the more volatile substances escape and the aniline and phenylisocyanate combine to form *sym*-diphenylurea. The same product is formed more quickly if *sym*-diethylurea or *sym*-ethylphenylurea is heated with an excess of aniline.

Discussion of Experiments

Phenylated Urea.—A solution of 190 g. of urea and 390 g. of aniline hydrochloride in a liter of water was boiled under a reflux condenser. At the end of an hour crystals of *sym*-diphenylurea suddenly separated from the liquid. The boiling was continued until the mixture bumped, the hot liquid was filtered at the pump, the diphenylurea was washed on the filter with hot water, and the filtrate on cooling deposited crystals of phenylurea. This material was separated, and the filtrate was again boiled under a reflux condenser until it bumped, again filtered hot, again cold, and again refluxed. After four such boilings the final filtrate was evaporated to half volume for another small crop of each of the products. The diphenylurea accumulated from the hot filtrations was practically pure, m. p., 235°, and weighed 80.3 g., a yield of 25.5%. It was obtained in splendid, colorless needles by recrystallization from alcohol, 1 liter of solvent for every 25 g. of the material. The phenylurea from the cold filtrates amounted to 218.5 g.; yield, 53.5%. It was freed from the small amount of diphenylurea which it contained by dissolving it in hot water, filtering, allowing to cool slightly until a flocculent precipitate of diphenylurea had appeared, and again filtering quickly without warming, and obtained as colorless needles or flakes; m. p., 147°.

A solution of 60 g. of urea and 300 g. of aniline hydrochloride in a liter of water was boiled under a reflux condenser for about 2 hours until the mixture bumped. The precipitated diphenylurea was filtered from the hot liquid and rinsed with a little hot water, the filtrate was returned at once to the flask and refluxed again until bumping recommenced, again filtered, etc. After four boilings the accumulated diphenylurea amounted to 192 g.; yield, 90%. The melting point indicated that the product was practically pure, but its appearance was improved greatly by recrystallization from alcohol with a little animal charcoal.

One experiment in which aniline itself was refluxed with a water solution of urea gave a good yield of the two products. One in which aniline and urea were refluxed in alcohol solution and the alcohol and excess aniline were removed by distillation with steam, gave a very poor yield, the reaction evidently not taking place to any great extent in alcohol and the products being probably formed during the distillation.

The reaction does not take place at ordinary temperatures. A solution of 30 g. of urea and 64.5 g. of aniline hydrochloride in 100 cc. of water was allowed to stand for 4 months in a stoppered flask. It was then extracted thoroughly with ether. The extract on evaporation yielded a residue too small in amount for a melting-point determination.

When a clear solution of 5 g. of phenylurea in 50 cc. of distilled water was boiled under a reflux condenser, it soon became turbid from the separation of small crystals. The crystals filtered from the hot liquid after 3 hours' boiling weighed 0.9 g. and were found to be pure diphenylurea; m. p., 235°. Further evidence of the dearrangement of phenylurea is found in the fact that its aqueous solution yields aniline on distillation. Six g. of phenylurea was dissolved in 250 cc. of water and the solution was distilled, more water being added, until a liter of distillate had been collected. An excess of bromine water was added to the distillate, and the mixture was extracted with chloroform. The chloroform on evaporation yielded 3.6 grams of residue which, recrystallized from chloroform, gave needles, m. p. 121°, identified as tribromo-aniline by mixed melting point with a known sample.

Methylated Urea.—A mixture of 13.5 g. of methylamine hydrochloride and 6 g. of urea was heated for 1 hour at 160–170°. The mass was extracted with boiling absolute alcohol and filtered for the removal of undissolved ammonium chloride. The alcohol solution was evaporated in a vacuum nearly to dryness. More ammonium chloride separated. This was removed by filtration and rinsed with ice cold absolute alcohol. Crystallization of the liquors yielded 6.9 g. of *sym*-dimethylurea, as colorless flakes, m. p., 99.5–100°; yield, 78.4%.

Ethylated Urea.—A mixture of 30 g. of ethylamine hydrochloride and 11.1 g. of urea was heated for 2 hours at 160–170°. Extraction of the product with absolute ether left a residue of 18.1 g. of ammonium chloride (90% yield) which indicated that the reaction had proceeded nearly to completion. The ether on evaporation yielded a pasty mass which, worked up from alcohol, gave 9.2 g. of *sym*-diethylurea as colorless needles; m. p., 112°; yield, 43%. The residue from the crystallization was a viscous, heavy, colorless sirup from which nothing further could be obtained.

Replacement of Ethyl by Phenyl.—A mixture of 4 g. of *sym*-diethylurea and 3.1 g. of aniline was heated at 160–170°. The material melted completely, ethylamine and ammonia were given off immediately, and after about 25 minutes needle crystals began to separate from the hot liquid. After an hour, the mixture was cooled and filtered with suction. The crystals, washed with alcohol and recrystallized from the same solvent, yielded *sym*-diphenylurea; m. p., 235°. The filtrate was kept in a vacuum until the aniline had evaporated. The residue, recrystallized from a mixture of water and alcohol, yielded 0.2 g. of fine white needles, m. p., 98–99°, identified as *sym*-ethylphenylurea by a mixed melting point with a sample prepared by the interaction of phenylisocyanate with ethylamine in toluene solution.

Two g. of *sym*-ethylphenylurea was heated for 1$^1/_2$ hours at 160–170°. Ethylamine was evolved. The residue taken up in hot alcohol yielded on cooling 1.3 g. of *sym*-phenylurea as needle crystals; yield, 80%.

Butylated Urea.—A solution of 8 g. of *n*-butylamine and 3.3 g. of urea in 50 cc. of water was refluxed for 2$^1/_2$ hours. The solution was evaporated to dryness, and the residue, dried in the steam oven and recrystallized from benzene, yielded 6.5 g. of *sym*-di-*n*-butylurea, as white flakes, sparingly soluble in water; m. p., 70.5–71.0°; yield, 70%.

Analysis. Calc. for $C_9H_{20}ON_2$: N, 16.28. Found: 16.15.

An experiment with the hydrochloride gave a similar result; 21 g. of *n*-butylamine was converted to the hydrochloride by treatment with hydrochloric acid and evaporated to dryness. When the resulting material was refluxed for 3 hours with 8.3 g. of urea in 150 cc. of water, the solution evaporated to dryness, and the residue extracted with ether for the separation of the product from ammonium chloride, the product recrystallized from benzene amounted to 17.3 g. of di-*n*-butylurea; yield, 71.7%.

Sym-di-*n*-butylurea heated with aniline at 160–170° yielded *sym*-diphenylurea, as expected. A small quantity of another substance was isolated as white flakes, m. p., 65°, which was possibly *sym*-*n*-butylphenylurea, but not enough was obtained for analysis.

We have not been able to prepare *unsym*-di-*n*-butylurea by boiling the secondary amine or its hydrochloride with a water solution of urea under a reflux condenser or by heating the hydrochloride with urea at 160–170°.

***n*-Amyl and *iso*-Amyl Urea.**—Three and three-tenths g. of *n*-amylamine, b. p., 99–108°, prepared by the reduction of *n*-butyl cyanide, was converted to the hydrochloride, and the resulting dry product was heated with 1.1 g. of urea for 2 hours at 160–170°. The product was broken up under hot alcohol and filtered. Water was added to the filtrate until a turbidity began to appear. The crystals collected from the cold liquid amounted to 0.8 g. of crude product; m. p., 84–85°. By recrystallization from hot water, pure *sym*-di-*n*-amylurea was obtained as white flakes; m. p., 92.8°.

Analysis. Calc. for $C_{11}H_{24}ON_2$: N, 13.99. Found: 13.93.

A mixture of 5 g. of *iso*-amylamine hydrochloride and 1.2 g. of urea was heated for 3 hours at 160–170°. When the melt was treated with water, a light yellow oil separated. This was extracted with ether, and the ether solution, dried with fused sodium sulfate and allowed to evaporate, deposited an oil. When this oil was distilled in a vacuum, the first portion had an odor of isonitrile and did not crystallize, while the later portion crystallized in part to a pasty mass. After this had been spread on a porous tile, it yielded a product which could be recrystallized from alcohol and gave transparent plates; m. p., 37.5°.

Benzylated Urea.—*Sym*-dibenzylurea, m. p. 167°, was obtained in 69.2% yield by heating 2 equivalents of benzylamine with 1 equivalent of urea for 2 hours at 160–170°, and working up the product from alcohol.

Monobenzylurea, m. p., 146.6°, was produced along with dibenzylurea when urea and benzylamine were heated at 160–170° in molecular proportions. Two g. of benzylurea heated at 160–170° for 3 hours gave off ammonia, and 0.6 g. of pure dibenzyl was obtained from the product.

When urea was refluxed with benzylamine in aqueous solution, benzylurea was formed (95.8% yield, calculated from urea), but no dibenzylurea was produced even when a large excess of the amine was present. Unlike phenylurea, benzylurea is not converted into dibenzylurea by boiling in water. Even long-continued boiling alone and in the presence of benzylamine and of dil. sulfuric acid were without effect, except that in the latter case an odor of isonitrile was noticed.

Reactions with Secondary Amines.—When urea was refluxed in aqueous solution with methylaniline, no ammonia was given off and no new substance was isolated from the mixture. No product was isolated from the mixture which resulted from the heating together of dibutylamine hydrochloride and urea. The 1,1-disubstituted ureas have been obtained (in poor yield) by boiling urea with aqueous solutions of the hydrochlorides of methylaniline and ethylaniline.

A mixture of 15.3 g. of ethylaniline hydrochloride and 6 g. of urea was refluxed in 50 cc. of water for 5 hours. Considerable oil separated. The material was extracted with ether and the extract was shaken with dil. hydrochloric acid for the removal of amine. Some of the substituted urea was also evidently removed, for the ether solution, dried and evaporated, yielded only about 0.1 g. of oil which crystallized after long standing. Recrystallized from ligroin this yielded pure *unsym*-ethylphenylurea, as white, lustrous, thin plates, m. p., 62°, identified by mixed melting point with a sample prepared from potassium cyanate and ethylaniline hydrochloride.

A mixture of 7.4 g. of methylaniline hydrochloride and 2 g. of urea in 20 cc. of water was refluxed for 9 hours. Considerable oil separated. The ether extract, when dried and allowed to evaporate, yielded about 1 g. of crystals, which when recrystallized from ligroin gave thin plates, m. p. 150°, that were identified as *unsym*-methylphenylurea by mixed melting point with a synthetic sample.

Summary

Urea may be used for the preparation of mono-substituted ureas from primary amines, by heating at 160° or by boiling in aqueous solution. The monosubstituted ureas, in the same way, are equivalent to the isocyanate for purposes of synthesis and yield *sym*-disubstituted ureas. The syntheses have been studied with the phenyl compounds and with a number of substances in the aliphatic series.

Certain secondary amines react with the nascent isocyanic acid from urea to form *unsym*-disubstituted ureas, but the yields are poor.

Unsymmetrical disubstituted ureas and symmetrical disubstituted ureas in which the groups are alike, dearrange in only one fashion. Symmetrical disubstituted ureas in which the substituent groups are different dearrange in two modes. Striking evidence is found in the fact that *unsym*-ethylphenylurea yields carbanilide when heated.

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