[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Further Observations on the Condensation of Benzene with Alloxan[1]

BY HARRY M. BARNES AND S. M. MCELVAIN

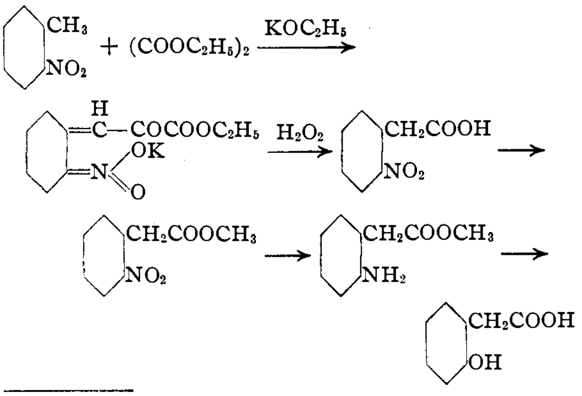
In an earlier paper[2] the preparation of 5,5-diphenylbarbituric acid (II) by the condensation of alloxan with benzene was reported. In this paper it was stated that "only relatively small amounts of pure diphenylbarbituric acid, m. p. 290–292°, are obtained from the products of this reaction. The main reaction product is a higher-melting (above 320°) acidic compound, the characterization of which has not been attempted as yet." The diphenylbarbituric acid was removed from this material by recrystallization from glacial acetic acid. Morsman,[3] in a later paper, reported the same synthesis of diphenylbarbituric acid. He removed the associated by-products by oxidation with potassium permanganate.

The present paper is the report of an investigation of the chemical nature of the products which are obtained along with the diphenylbarbituric acid from the condensation of alloxan with benzene. In this work fuming sulfuric acid was used as the condensing agent instead of concentrated sulfuric acid, because it was thought from the previous work that the former reagent would give more of the higher melting material.

When a more thorough study of the separation of the reaction products was made, it was found that a decided revision of the earlier report[2] of the ratio of these products was necessary. Instead of diphenylbarbituric acid being formed in the condensation in only relatively small amounts, it is now known to be the main reaction product. The method of separation which was devised utilized the difference in acidity of the various substances formed in the reaction, and briefly was as follows: the reaction product obtained by the dilution of the sulfuric acid reaction mixture was dissolved in sodium hydroxide solution. At this point, depending upon the time of contact with the strong alkali, a small amount of a neutral substance separated. It was removed and the alkaline solution then saturated with carbon dioxide, whereupon about 35–50% of the original reaction product precipitated as diphenylbarbituric acid. When this precipitate was filtered off and the filtrate concentrated, a relatively insoluble sodium salt separated. This salt yielded a free acid which melted at 351–353°, and amounted in weight to approximately 12% of the original reaction product. The filtrate, from which this sodium salt had separated, gave, upon evaporation, a mixture of salts which, upon acidification, yielded acids that amounted in weight to approximately 15–30% of the original reaction product. From this latter acid mixture was isolated a small amount of a sodium- and sulfur-containing acid.

The neutral product which separated from the alkaline solution proved to be diphenylacetylurea (III). It undoubtedly had resulted from the hydrolysis and decarboxylation of diphenylbarbituric acid in the alkaline solution since it was prepared readily from diphenylbarbituric acid by allowing this compound to stand overnight in alkaline solution. It also was obtained for comparison from diphenylacetic ester and urea by the procedure of Stendal.[4]

The acidic substance which melted at 351–353° was a sufficiently strong acid to be titrated against phenolphthalein. Analyses and molecular weight determinations indicated the formula $C_{10}H_6O_3N_2$. It was very resistant to hydrolysis, but could be broken up completely by refluxing for seventy hours in 10% sodium hydroxide solution. The hydrolysis products, ammonia, carbon dioxide and an acidic substance, $C_8H_8O_3$, were obtained in the molecular ratio of 2:2:1. This acid was shown to be *o*-hydroxyphenylacetic acid by its conversion into *o*-methoxybenzoic acid and by comparison with an authentic specimen prepared by the synthesis shown



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[1] This work was supported in part by a grant from the Wisconsin Alumni Research Foundation.

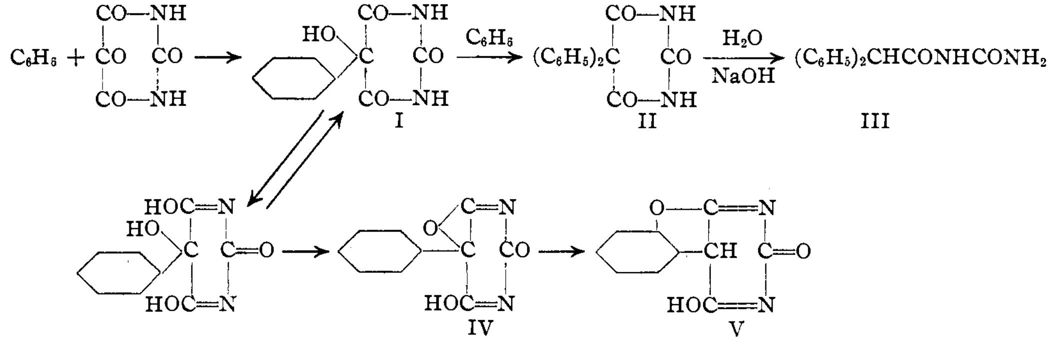
[2] McElvain, THIS JOURNAL, **57**, 1303 (1935).

[3] Morsman, *Helv. Chim. Acta*, **18**, 1254 (1935).

[4] Stendal, *Compt. rend.*, **196**, 810 (1933).

These data point to the conclusion that the 351–353° melting material is 4-hydroxybenzofuro-[2,3-*d*]-pyrimid-2(4*a*)-one[5] (V). This compound probably was produced from the enol of the intermediate 5-hydroxy-5-phenylbarbituric acid (I) through dehydration to (IV) followed by rearrangement to (V).

The formation of the products which have been isolated from the condensation of alloxan with benzene may be illustrated thus



The sodium- and sulfur-containing acid, which was isolated from the residual salt mixture, is believed to be a sodium diphenylbarbituric acid sulfonate. It was not obtained sufficiently pure for analysis but a quasi-quantitative hydrolysis showed that ammonia, carbon dioxide and an acid, which titration and analyses indicated to be sodium diphenylacetic acid sulfonate, were obtained from it in the molecular proportions of 2:2:1. Attempts to obtain diphenylacetic acid by removal of the sulfonic acid group from this hydrolysis product were unsuccessful.

Experimental

Alloxan Monohydrate.—This material was prepared by the chlorination of uric acid.[2] It was found that the addition of a small quantity of sulfur (0.2 g.) to the reaction mixture before the chlorination was started gave more easily reproducible results.

Reaction of Benzene with Alloxan.—One hundred and ten grams of fuming sulfuric acid (20% SO_3) was placed in a 500-cc. 3-necked flask and cooled in an ice-bath. Fifty grams of finely powdered alloxan monohydrate was added in small portions while the acid was well stirred. It did not all dissolve. A thermometer well, an efficient stirrer and a reflux condenser were attached to the flask. The flask was surrounded by an oil-bath, the stirrer started, and 150 cc. of benzene poured through the condenser. Reaction took place immediately and the heat of reaction was sufficient to raise the temperature to 50–60°. A succession of color changes, yellow to red to purple to black and finally to tan, took place. The oil-bath was heated to 75–80° and the reaction allowed to proceed for three hours. The stirring was sufficiently vigorous to emulsify the two phases of the reaction mixture. The flask was then cooled and as much of the benzene layer decanted as possible. The acid mixture was poured over crushed ice and the resultant precipitate filtered, washed twice in a separate beaker and dried in a vacuum desiccator. The product weighed 52 g.

This 52 g. of material was dissolved in a solution of 12 g. of sodium hydroxide in 200 cc. water at 90° and filtered. An insoluble residue (III), which varied from 0 to 3 g., remained. The filtrate was diluted to 1 liter, heated on the steam-bath to 80–90°, and carbon dioxide passed in. The diphenylbarbituric acid (II) precipitated and was filtered through a heated Büchner funnel. It amounted to 26 g. The filtrate was cooled to 0°, whereupon a sodium salt was precipitated. This salt was recrystallized twice from ten times its weight of hot water. Acid was added to a solution of this salt in hot water and an acid (V) was precipitated. The yield of this product amounted to 5.9 g. The filtrate from the precipitation of the sodium salt of (V) upon acidification yielded 7 g. of a sodium- and sulfur-containing acid. This acid still contained 1 to 2 g. of the acid (V) which was removed by dissolving it in the minimum quantity of hot, saturated sodium bicarbonate solution, chilling and filtering (see sodium diphenylbarbituric acid sulfonate below).

Diphenylacetylurea.—The insoluble residue (III) upon recrystallization from glacial acetic acid gave a crystalline material melting at 227–228°. It was hydrolyzed by refluxing 1.000 gram with 75 cc. of 15% sodium hydroxide in a nickel flask for twenty hours and the resulting ammonia distilled into standard acid; 0.122 g. (calcd. 0.134) was collected. The alkaline solution was transferred to a 3-necked flask equipped with an air inlet tube, a dropping funnel and a reflux condenser whose upper end was attached to a drying system and then an ascarite bulb. Acid was added through the dropping funnel and carbon dioxide-free air bubbled through the solution while it was heated on the steam-bath. The liberated carbon dioxide was absorbed and weighed in the ascarite. It weighed 0.143 g. (calcd. 0.173). Acidification precipitated diphenylacetic acid which, upon filtering and drying, weighed 0.782 g. (calcd. 0.835). This material melted at 145–146° and when mixed with known diphenylacetic acid it melted at 144–146°.

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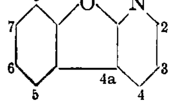
[5] This name was suggested by Professor Austin M. Patterson, Antioch College, Yellow Springs, Ohio. The basic ring system, benzofuro-[2,3-*d*]-pyrimidine, is,



Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 70.83; H, 5.55; N, 11.0. Found: C, 70.50; H, 5.67; N, 10.85.

The identity of this ureide was confirmed by its synthesis according to Stendal.[4] The synthetic product melted at 225–225.5° and when mixed with (III) the mixture melted at the same point.

The diphenylacetylurea was also prepared from diphenylbarbituric acid by dissolving 5 g. of the latter in twice the theoretical quantity of 3% sodium hydroxide solution and allowing it to stand overnight. After filtering and drying the precipitated ureide, it weighed 1.1 g. and melted at 225–226°. When it was mixed with (III) the melting point was unchanged.

4-Hydroxy-benzofuro-[2,3-d]-pyrimid-2(4a)-one.—The acid (V) melted at 351–353° and showed a neutral equivalent of 203 by titration with 0.1 *N* sodium hydroxide, using phenolphthalein as an indicator.

Anal. Calcd. for $C_{10}H_6O_3N_2$: C, 59.40; H, 2.97; N, 13.86. Found: C, 59.74; H, 3.15; N, 14.45.

A preliminary hydrolysis of (V) had shown that this compound hydrolyzed very slowly in 10% sodium hydroxide solution, seventy hours being necessary to completely remove all of the ammonia. This long hydrolysis time necessitated the use of a metal flask. A solution of 2.956 g. of the acid (V) was placed in a nickel flask and boiled under a reflux with 14 cc. of saturated, carbonate-free sodium hydroxide solution and 75 cc. of water for sixty-eight hours. The ammonia was distilled into excess standard acid and back-titrated; 0.495 g. (calcd. 0.497 g.) was found. The hydrolysis solution was then acidified and the carbon dioxide evolved, absorbed and weighed in ascarite as previously described; 1.206 g. of carbon dioxide (calcd. 1.288 g.) was obtained.

The solution was acidified to congo red with hydrochloric acid and evaporated to dryness. The residue was finely ground and extracted several times with ether. A yield of 1.56 g. (70%) of *o*-hydroxyphenylacetic acid was obtained; m. p. 148–149°; neutral equivalent, 152.

Anal. Calcd. for $C_8H_8O_3$: C, 63.16; H, 5.26. Found: C, 62.89; H, 5.32.

When this material was sublimed another compound appeared in the sublimate. It was a liquid which at first melted at about 20°, but on standing changed to a product which melted at 48°. This compound was shown to be the lactone of *o*-hydroxyphenylacetic acid.[6]

Anal. Calcd. for $C_8H_6O_2$: C, 71.64; H, 4.48. Found: C, 71.46; H, 4.61.

This lactone was converted readily into *o*-hydroxyphenylacetic acid by refluxing with water for two hours.

The *o*-hydroxyphenylacetic acid was further characterized by its conversion into *o*-methoxybenzoic acid by the following procedure: 0.2657 g. of the acid from the hydrolysis of (V) was placed in a 50-cc. glass-stoppered glass bottle with 4 cc. of *N* sodium hydroxide and 0.83 g. of dimethyl sulfate. The bottle was shaken for ten minutes and allowed to stand for one hour. The material was transferred to a flask with a reflux condenser and refluxed with 10 cc. of *N* sodium hydroxide for thirty minutes to destroy the excess dimethyl sulfate and to hydrolyze the ester. The solution was cooled, acidified and extracted with ether. The residue upon evaporation of the ether was placed in a flask with a solution of 1.3 g. of potassium permanganate in about 100 cc. of water and refluxed for one hour. The excess permanganate was removed by addition of a little alcohol. The resulting solution was cooled and 2 cc. of 10% sodium hydroxide added, after which it was filtered and the filtrate extracted with ether and the ether discarded. The aqueous solution was acidified and extracted with ether. The crystals left upon evaporation of the ether were sublimed twice at 140° and 3 mm., after which they melted at 95–99°. When mixed with *o*-methoxybenzoic acid (m. p. 100–102°) the melting point was 94–100°.

Synthesis of *o*-Hydroxyphenylacetic Acid.—*o*-Nitrotoluene was condensed with oxalic ester according to Wislicenus.[7] After drying, the yield of the potassium salt of *o*-nitrophenylpyruvic ester amounted to 82% of the theoretical.

Fifty grams of this salt was dissolved in 300 cc. of 3% sodium hydroxide solution and a 3% hydrogen peroxide solution was added in small portions until the solution was decolorized. The solution was extracted with ether to remove any *o*-nitrotoluene. Acidification gave a precipitate of crystalline *o*-nitrophenylacetic acid;[8] yield 19.6 g., 60% of theoretical. This material together with 5 g. of sodium hydroxide, 40 cc. of water and 13 g. of dimethyl sulfate was placed in a glass-stoppered bottle and shaken at intervals for one hour. The solution was then extracted with ether and the ether shaken vigorously with dilute sodium hydroxide solution. The ether solution was dried and after removal of the ether, the ester was distilled at 112–115° (2 mm.);[9] yield 11.5 g., 54% of theoretical.

Nineteen grams of this ester in 75 cc. of absolute alcohol was reduced with Adams platinum catalyst at 30–50 lb. (2–3 atm.) pressure of hydrogen. The reduction was so rapid that the temperature of the solution rose to 80–100°. Approximately 96% of the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the alcohol evaporated under reduced pressure. The residue was dissolved in ether and extracted with dilute hydrochloric acid. To the acid extract was added 50 cc. of 4 *N* hydrochloric acid and the solution cooled to 5° in ice. A cold solution of 3 g. of sodium nitrite in 50 cc. of water was then added with stirring. The resulting diazonium solution was allowed to come to room temperature and finally warmed on a steam-bath for one hour. After cooling, it was extracted with ether and the ether solution dried. After evaporation of the ether the residue was distilled under reduced pressure. Distillation was very slow and yielded only about 1 g. of product. This distillate was boiled with 5% sodium hydroxide solution, acidified and extracted with ether. The residue upon evaporation of the ether was three times sublimed, after which it melted at 146–147°. When mixed with some *o*-hydroxyphenylacetic acid from the hydrolysis of (V), which melted at 146–147°, there was no change in the melting point.

The acidic fraction containing sodium and sulfur was a mixture of several relatively strong acids, only one of

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[6] *Cf.* Stoermer, *Ann.*, **313**, 84 (1900).

[7] Wislicenus, *Ann.*, **436**, 42 (1924).

[8] *Cf.* Salkowski, *Ber.*, **17**, 507 (1884).

[9] *Cf.* Goldschmidt, *Chem. Z.*, **25**, 793 (1901).

which was characterized. It was separated by dissolving 10 g. of the fraction in 75 cc. of 5% sodium hydroxide solution at 100°, and cooling to 0°. This procedure precipitated out the sodium salt of (V) which upon acidification yielded 2.0 g. of the acid (V). The filtrate was saturated with carbon dioxide which precipitated a small amount of diphenylbarbituric acid (II). After filtering off (II) the solution was diluted to 400 cc., heated to boiling, acidified with hydrochloric acid and filtered hot. The material which was filtered off, when dried, weighed 3.0 g. It was a dark brown material, melting between 100–200° to a very tacky liquid. The filtrate upon cooling yielded a crystalline precipitate, which, when filtered and dried, weighed 2.1 g. This product was boiled with 100 cc. of glacial acetic acid. The insoluble portion, when filtered and dried, weighed about 1.3 g. Recrystallization of this material from water gave 1.0 g. of a crystalline substance which still contained sodium and did not melt below 380°. This compound is believed to be the sulfonated diphenylbarbituric acid. Titration showed the neutral equivalent of the substance to be about 370 (calcd., 382).

When 0.496 g. of this material was subjected to a quantitative hydrolysis as described above, the ammonia evolved amounted to 0.043 g. (calcd. 0.044) and the carbon dioxide amounted to 0.118 g. (calcd. 0.114). The acid precipitated upon acidification weighed 0.290 g. (calcd. for the sodium salt of the monosulfonate of diphenylacetic acid, 0.4082). Evaporation of the solution to dryness, and extraction of the finely ground salt with absolute alcohol yielded an additional 0.0843 g. of the acid. The material showed a neutral equivalent of 318 (calcd., 314).

Anal. Calcd. for $C_{14}H_{11}O_5SNa$: C, 53.50; H, 3.53. Found: C, 53.78; H, 4.09.

Attempts were made to remove the sulfonic acid group by boiling for six hours with 20% hydrochloric acid and by heating for five hours in a sealed tube at 190–200° with 20% hydrochloric acid. Neither of these procedures produced any diphenylacetic acid.

Summary

Further study of the condensation of alloxan with benzene has showed that diphenylbarbituric acid is the main reaction product. Diphenylacetylurea, 4-hydroxybenzofuro-[2,3-*d*]-pyrimid-2(4*a*)-one, and a sulfonated diphenylbarbituric acid have been found to be associated products.

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The Dehydrogenation of Hydroaromatic Hydrocarbons with an Alkyl Disulfide

BY JOHN J. RITTER AND EVA DOUGLASS SHARPE

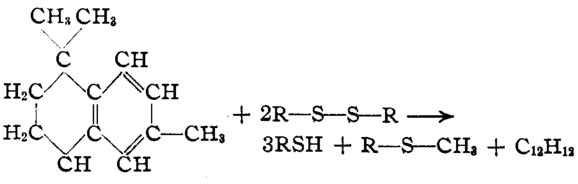
Previous chemical methods for the dehydrogenation of hydroaromatic substances have been limited principally to the well-known sulfur and selenium treatments of Vesterberg[1] and Diels.[2] Dehydrogenation with an alkyl(isoamyl) disulfide has now been accomplished in this Laboratory in the conversion of tetralin to naphthalene and of ionene (1,1,6-trimethyltetralin) to 1,6-dimethylnaphthalene. The general characteristics of the new method, as far as can be concluded from the data at hand, indicate that it is about as efficient as sulfur dehydrogenation in the case of tetralin and distinctly superior in the arylization of ionene. The yield of naphthalene from tetralin (70%) is equal to that resulting from sulfur dehydrogenation[3] while ionene yielded 32% of 1,6-dimethylnaphthalene as compared with the 10–12% reported in the literature.[3,4]

The action of the disulfide on tetralin proceeds as follows

$$C_{10}H_{12} + 2R{-}S{-}S{-}R \longrightarrow C_{10}H_8 + 4RSH$$

Tetralin which contains products of auto-oxidation reacts promptly and comparatively rapidly; after removal of these by distillation over sodium there is no evidence of reaction until three hours have elapsed. This suggests an accelerating effect of oxygen compounds which remains to be confirmed by the study of their dehydrogenation.

The case of ionene presents some interesting aspects. It dehydrogenates in a comparatively short time with formation of somewhat more isoamyl mercaptan than expected from the equation



$$+ 2R{-}S{-}S{-}R \longrightarrow 3RSH + R{-}S{-}CH_3 + C_{12}H_{12}$$

No methyl isoamyl thioether could be detected among the reaction products. It was found, however, that about one-half mole of neutral gases is evolved from one mole of ionene during the dehydrogenation. The gases consist in small

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(1) A. Vesterberg, *Ber.*, **36**, 4200 (1903).

(2) O. Diels, W. Gadke and P. Kording, *Ann.*, **459**, 1 (1927).

(3) L. Ruzicka and E. A. Rudolph, *Helv. Chim. Acta*, **10**, 915 (1927).

(4) M. T. Bogert and Victor G. Fourman, THIS JOURNAL, **55**, 4670 (1933).