[Contribution from the Chemical Laboratory of the University of Illinois].

THE ACTION OF HYDRAZINE ON ETHYL MESOXALATE.

By Richard Sydney Curtiss, Alfred R. Koch and E. J. Bartells.

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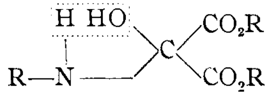
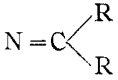
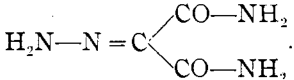
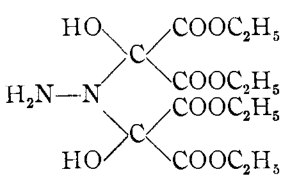
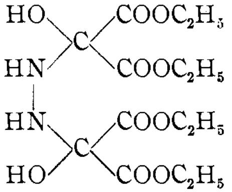
In previous papers,[1] the action of dry ammonia, and also hydrazine, on esters of the hydrated or the keto form of mesoxalic acid was described. It was shown that unstable addition compounds were formed, of the type  $R{-}N(H){-}C(OH)(CO_2R)_2$, which represents the hypothetical intermediate addition products in ketone reactions, where the oxime and hydrazone types of substances (R)  $N=C(R)_2$ are formed by loss of a molecule of water.

Ruheman and Orton[2] found that hydrazine and dibrommalonamide react to form a hydrazone of mesoxalamide,  $H_2N{-}N=C(CO{-}NH_2)_2$.

The general conditions for the reaction of hydrazine on dihydroxymalonates, as described in the above mentioned paper,[3] were first worked out on the ethyl ester. This study showed that the reaction of aqueous hydrazine solutions on ethyl mesoxalate may vary greatly, dependent on the conditions of temperature, solvent, concentration, and manner and rapidity of mixing. The chief reaction product may be represented by one of the isomeric forms:

(1)  or (2) 

Owing to the ease with which the addition product dissociates into hydrazine and mesoxalic ester when attempts were made to get acyl and other derivatives, it was impossible to decide between the two formulas.

Action of Hydrazine Hydrate on Ethyl Dihydroxymalonate.—These substances react vigorously. The best result was obtained by slowly adding 7.5 g. (2 mols) of the pure ester, m. 57°, to 10 cc. (1 mol) of an aqueous solution holding 6.5 per cent. of hydrazine. During the addition of the ester a colorless, heavy, oily product begins to separate out. The

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[1] Curtiss, *Amer. Chem.* J., **35**, 357. Curtiss and Tarnowski, This Journal, **30**, 1267.

[2] *J. Chem. Soc.*, 67, 1003.

[3] This Journal, **30**, 1267.

mixture was allowed to stand three minutes. When the supernatant liquid begins to turn pale yellow, indicating initial polymerization changes, the reaction is complete and it is chilled in a freezing mixture. The separated oil thickens, becomes doughy, and beautiful radiating clusters of crystals suddenly form and the mass solidifies. These crystals melt at —5° to —4°. Simultaneously with this crystallization phenomenon, other bits of the oil in the neck of the flask and near room temperature form a white crystalline mass where rubbed with a rod. This melts when pure at 57°–58°. When the mass below (m. —4°) is melted and rubbed with a rod on which are some of the crystals of the substance melting at 58°, the oil is completely converted into this product of higher melting point.

This interesting observation has been many times repeated on this pure substance—in aqueous suspension—and we hope to study it further.

The crystalline mass, after it was filtered and washed with ice-water, weighed 5.9 grams, and an additional gram was extracted from the aqueous filtrate with ether. The reaction is nearly quantitative. If the above conditions of preparation are not strictly adhered to, the whole product polymerizes to a thick red gum, or resinous mass, incapable of further purification. Very many experiments were carried out before this was avoided. Presence of alcohol hastens this polymerization at room temperatures.

The following method based on the use of a hydrazine carbonate solution gives a purer product, and eliminates the difficult preparation of hydrazine hydrate:

5.3 grams of sodium carbonate (anhydrous) were added to 6.5 grams of hydrazine sulphate in 30 cc. of water. This solution was slowly added to 19.2 grams of the ester in 10 cc. of water. The solution became turbid by the separation of a light oil, and carbon dioxide was evolved until about one-half of the hydrazine solution had been added. When the reaction was complete the oily product was crystallized by vigorous rubbing with a glass rod. If the crystallization is very fine the product can be easily purified by washing with cold water until perfectly white. It is but slightly soluble. The filtrate may be extracted with ether, and the yield somewhat increased. This product melted at 58°, was identical with that prepared from hydrazine hydrate, and corresponds by analysis to the same formula, $C_{14}H_{24}O_{10}N_2$.

An analysis was made of the product, which was recrystallized from equal parts of benzene and ligroin, and melted at 58°.

Calculated for $C_{14}H_{24}O_{10}N_2$: C, 44.17; H, 6.36, N, 7.38.
Found: C, 43.63; H, 6.04, N, 7.62, 7.98.

The substance, which we will call, provisionally, ethyl hydrazinobistartronate (Formula I), is colorless, and apparently rhombohedral.

It is easily soluble in hot water, ether, benzene, chloroform, methyl alcohol, ethyl alcohol, acetic ester and hot carbon bisulphide. It is fairly soluble in carbon tetrachloride and in cold water. It is slightly soluble in cold ligroin and carbon disulphide. The pure substance has a bitter taste and is stable in air. It apparently loses the elements of water, however, in a sulphuric acid desiccator, or when carefully heated, and forms a clear, colorless, or pale yellow oil. Either formula, 1 or 2, suggests this change.

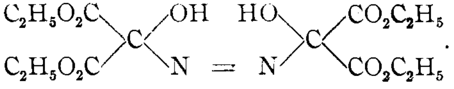
The following tests and experiments have been carried out on this substance with a view of determining its constitution.

It is oxidized by silver nitrate, liberating nitrogen and producing a silver mirror. Beautiful plates of platinum are likewise formed by its reducing action on a chlorplatinic acid solution. Ethyl nitrite acting on the substance in aqueous solution, in the presence of dilute sulphuric acid, forms nitrogen gas, ethyl dihydroxymalonate, and a small amount of a substance having a melting point of 253°. The same products were formed when absolute alcohol was used as a solvent. No evidence of a nitrosamine was found.

Phosphorus pentoxide appears to withdraw the elements of water from the substance, and a pale yellow syrup results, which, as it cannot be distilled or crystallized, was not analyzed. Syrups of the same appearance were produced when attempts were made to acylate the hydrazine radical with acetyl chloride and anhydride, or when the substance was dried over sulphuric acid for some days, or when the concentrated acid itself was poured over the crystals. Dehydration between the hydroxyl groups and hydrogen atoms of the hydrazine radical apparently occurs in all these cases.

Phosphorus pentachloride causes evolution of hydrochloric acid and proves the presence of hydroxyl groups.

To ascertain if an azotartronic ester

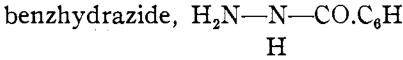


could be produced by removing the two remaining hydrazine hydrogen atoms the following oxidation experiment was made:

1.705 grams (one mol) of freshly prepared mercuric oxide were added to a solution of 3 grams of the hydrazine derivative in 12 cc. of benzene, and gently heated. The solution darkened, metallic mercury separated out, and nitrogen gas was evolved at 25°–30°. The temperature was raised to 60°, and at the end of an hour about three-fourths of the nitrogen present in the substance had been evolved. An additional 1.705 grams of mercuric oxide (one mol) increased the volume of gas in the azotometer about one-third. The apparatus having been freed of air at the start by passing carbon dioxide through it, the nitrogen was collected in an azotometer over a potash solution.

Calculated for $C_{14}H_{24}O_{10}N_2$: N, 7.36. Found, 6.86.

Mercuric oxide remained in excess. Ethyl dihydroxymalonate, m. p. 57.5°, was recovered from the filtrate. The hydrazine radical was therefore quantitatively oxidized to water and nitrogen, and mesoxalic ester regenerated.

This complete elimination of nitrogen suggests formula 1, as representing the structure of this substance. An azotartronic ester, which would be expected by oxidizing a substance of form 2, should be stable. Curtius[1] found that benzhydrazide,  $H_2N—\underset{H}{N}—CO.C_6H_5$, was oxidized to nitrogen, water, and dibenzoyl hydrazine by mercuric oxide.

Action of Benzaldehyde on the Hydrazine Derivative.—When these substances were mixed in the molecular ratios of 1 : 1 or 2 : 1 there was no apparent reaction in the cold. When in either case, however, absolute methyl alcohol was added, clusters of radiating crystals appeared in a few minutes. These crystals are yellow, melt at 93°, and are identical with benzalazine, $C_6H_5—CH = N—N = CHC_6H_5$, first made by Curtius.[2] Benzaldehyde therefore reacts with the hydrazine to form the azine compound. It is impossible to determine whether the dissociation of the hydrazine precedes the initial action of the benzaldehyde upon it or not.

Action of Benzoyl Chloride on the Hydrazine Derivative.—In order to show the exact hydrazine structure of this substance the following attempts were made to prepare the benzoyl derivatives:

Five grams of the substance were dissolved in 60 cc. of ether and to this solution were added 2.8 grams of anhydrous sodium carbonate dissolved in 15 cc. of water. 7.4 grams of benzoyl chloride were added, drop by drop, to the above mixture. A precipitation of crystals began after a minute or so. After standing several hours the white, curdy mass was washed with water in a separatory funnel. The crystals were then washed on a filter with ether, weighed 2.1 grams, and melted at 241°–241.5°, having been twice recrystallized from 95 per cent. alcohol.

We substituted pyridine, and sodium hydroxide, for the sodium carbonate in this reaction, but with like results. Neither did acetic anhydride with the pyridine materially affect the result. This product resembles fine asbestos fibre when wet and is chalky in appearance when dry and powdered. It is almost insoluble in cold water, chloroform, alcohol, and ether. It is fairly soluble in hot 95 per cent. alcohol, from which it is precipitated by cold water.

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[1] *J. prakt. Chem.* [2], **50**, 300.

[2] *Ibid.* [2], **39**, 44.

Calculated for $C_6H_5CO–NH–NH–COC_6H_5$: C, 70.0; H, 5.0; N, 11.66.
Found: C, 69.98, 69.92; H, 5.24, 5.22; N, 12.04, 12.07.

The product is a dibenzoyl hydrazine formed by hydrolysis, either of the original compound into hydrazine, and mesoxalic ester, or of its substituted dibenzoyl derivative.

Action of Benzoic Anhydride on the Hydrazine Derivative in Absolute Ether Solution.—The following test was made in order to find out if dibenzoyl hydrazine could be formed in the absence of water which might have acted as a hydrolyzing agent in the above reaction.

Two grams of the hydrazine derivative and 2.4 grams of benzoic anhydride (2 mols) were dissolved in absolute ether, freshly distilled over sodium, and the flask tightly closed. After standing two hours, white fibrous crystals began to separate out slowly. 0.5 gram was thus obtained after the mixture stood several days. This product appears identical with the one prepared from benzoyl chloride and the hydrazine derivative. In wet ether the action goes much faster but gives the same product.

Curtius[1] prepared the symmetrical dibenzoyl hydrazine,

$$C_6H_5CO — NH — NH — COC_6H_5,$$

by oxidizing benzoylhydrazide with iodine, which leaves no doubt of its symmetrical structure.

Our benzoyl derivative has the same characteristic appearance and relative solubilities as the substance thus formed by Curtius. It differs, however, in its melting point, which is 8° higher (241° cor.) than he found it. E. Mohr[2] gives the melting point of this substance as 237°–239°. G. Pellizzari[3] states that it melts at 238°.

A product identical with the one just described was prepared by Curtiss and Tarnowski by the action of benzoyl chloride on methyl hydrazotartronate.[4]

For purposes of comparison a dibenzoyl hydrazine was synthesized as follows: 11.24 grams of benzoyl chloride were dissolved in 45 cc. of ether, and to this was added slowly a solution of 4.24 grams of sodium carbonate and 5.2 grams of hydrazine sulphate in 40 cc. of water. Asbestos-like crystals appeared almost immediately after shaking and some heat was generated. 2.12 grams of sodium carbonate were added to neutralize the hydrochloric acid formed. The product, recrystallized from 95 per cent. alcohol, melted at 241°–242° and was identical in properties with the product formed by the action of benzoyl chloride on the hydrazine derivative of ethyl dihydroxymalonate. We have not

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[1] *J. prakt. Chem.* [2], **50**, 299. *Ber.*, **23**, 3029.

[2] *J. prakt. Chem.*, **70**, 281.

[3] *Chem. Centr.*, **1899**, I, 1240.

[4] THIS JOURNAL, **30**, 1268.

been able to find in the literature the asymmetric dibenzoylhydrazine described with certainty and until it is prepared it is impossible to say whether or not we have it in the above product.

The first experiments made in the study of the action of hydrazine on ethyl mesoxalate were in alcoholic solutions. The effect of this solvent was to increase the polymerization products. Under certain exact conditions, a crystalline product was obtained.

0.17 gram (1 mol) of ethyl dihydroxymalonate was dissolved in 1.5 cc. of alcohol. This was slowly poured, without mixing, down the side of a test tube into 1.9 cc. of alcohol containing 0.4 cc. (2 mols) of a 22 per cent. hydrazine hydrate solution. If the liquids are mixed, gummy products form which it is impossible to remove. A turbidity forms at the line of contact of the two solutions. After about one hour at 10°, colorless needles form between the solutions, and in twenty-four hours the lower half is filled with beautiful clusters of crystals. 0.11 gram was filtered off and washed with ether. As the substance was quickly decomposed in all attempts to recrystallize it an analysis was made of the crude substance:

Calculated for $C_4H_{13}N_2O_9$: C, 20.60; H, 5.58; N, 12.02.
Found: C, 20.92, 20.54; H, 5.67, 5.66; N, 12.01.

The substance decomposes at 125°–130°, evolves a gas, and leaves a yellow solid, which melts at 170°, giving off a gas. It is easily soluble in warm water and potassium hydroxide solution, slightly soluble in ether, methyl alcohol, acetone, benzene, carbon disulphide, and 25 per cent. acetic acid, insoluble in chloroform, carbon tetrachloride, ligroin, and nitrobenzene. Its aqueous solution turns red when warmed (polymerization gums). Alcohol hastens this change.

Glacial acetic acid gives a white product, but slightly soluble in most solvents and turned blood-red by potassium hydroxide solution.

We have made no further attempt to determine the structure of this substance.

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THE DETERMINATION OF UREA IN THE URINE.

BY CHARLES G. L. WOLF AND EMIL OSTERBERG.

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In the course of investigations in which one of us has been engaged for some years, dealing with the protein metabolism in normal and pathological conditions in man and animals,[1] it has been necessary to select a method

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[1] Marriott and Wolf, *Amer. J. Med. Sci.*, Feb., 1906; *Biochem. Z.*, 7, 213 (1907). Ewing and Wolf, *Amer. J. Med. Sci.*, **131**, 751 (1906): *Amer. J. Obstetrics.*, **55**, 1 (1907). Osterberg and Wolf, *J. Biol. Chem.*, **3**, 165 (1907); *Biochem. Z.*, **5**, 304 (1907). Wolf and Shaffer, *J. Biol. Chem.*, **4**, 439 (1908). Loewy and Wolf, *Biochem. Z.*, **8**, 132 (1908).