THE ACTION OF DIAZOMETHANE UPON CYCLOHEXANDIONE-1,4*

JOHN R. VINCENT, A. F. THOMPSON, JR., † AND LEE IRVIN SMITH Received November 21, 1938

In 1910 Willstätter^{1,2} reported the synthesis of cyclooctatetraene. There exists a striking similarity in chemical and physical properties between Willstätter's compound and its derivatives and styrene and its derivatives. Because of this, it was decided to attempt a different synthesis of cyclooctatetraene. As an intermediate in the proposed synthesis cyclooctandione-1,5 was desired, and it was thought that this substance might be prepared by a ring enlargement, using a cyclic ketone and diazomethane. There are several examples of this type of reaction in the literature.^{3,4,5,6,7}

With this purpose in mind cyclohexandione-1,4 was treated with diazomethane in ether-methyl alcohol solution, and after repeated fractional distillation four compounds were separated from the reaction product.

I. A white crystalline solid; m.p. 106°-108°.

II. A colorless oil; b.p. 65°-66°/2 mm.; m.p. approx. 10°.

III. A colorless oil, which slowly becomes brown at room temperature, but which is stable indefinitely at 0°; b.p. $84^{\circ}-88^{\circ}/2$ mm., $107^{\circ}-111^{\circ}/10$ mm., and $133^{\circ}-139^{\circ}/26$ mm., with some decomposition.

IV. A rather viscous, colorless oil which becomes colored on standing; b.p. 105°-113°/3 mm.

Because of the complexity of the reaction product, the original purpose of the research was abandoned, and attention was turned to the nature of the compounds formed in the reaction between diazomethane and cyclohexandione-1,4.

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† Present address, Massachusetts Institute of Technology, Cambridge, Mass.

¹ WILLSTÄTTER AND WASER, Ber., 44, 3423 (1910).

² Willstätter and Heidelberger, *ibid.*, **46**, 517 (1913).

³ HELLER, *ibid.*, **52**, 741 (1919); **59**, 704 (1926).

⁴ HANTZSCH AND CZAPP, *ibid.*, **63**, 566 (1930).

⁵ MOSETTIG AND BURGER, J. Am. Chem. Soc., 52, 3456 (1930).

⁶ ROBINSON AND SMITH, J. Chem. Soc., 1937, 371.

⁷ GERAITIS AND BULLOCK, J. Am. Chem. Soc., 59, 951 (1937).

Compound I has the composition $C_8H_{12}O_2$, showing the introduction of two methylene groups into one molecule of the diketone. This compound on analysis in the Grignard machine[‡] shows no active hydrogen and no carbonyl groups. It combines, by addition, with two molecules of hydrogen chloride, two molecules of water and two molecules of piperidine. The piperidine addition product forms a dipicrate. Compound I does not form a semicarbazone, nor does it form a benzal derivative, and it gives no reaction with Fehling's solution or with decolorized fuchsin. After heating I with zinc chloride the fuchsin test is positive. The following chart in analogy with the chart of Arndt, Amende, and Ender,⁸ shows the compounds to be expected from the reaction of a carbonyl compound and diazomethane.



Of the above products which are theoretically possible from this reaction and which have the composition $C_8H_{12}O_2$, A, B, D, F, G, H and J all contain a methylene group alpha to a carbonyl group, which would be expected to condense with benzaldehyde. Of the other structures, only one, C, satisfactorily accounts for any of the properties of I, and all these properties together constitute proof that compound I is 1,4-dimethylenecyclohexane dioxide. (C)

[‡] We are indebted to Mr. W. W. Prichard for the Grignard analyses reported in this paper.

⁸ ARNDT, AMENDE, AND ENDER, Monatsh., 59, 202 (1932).

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The structure of compound II has not been determined. Carbonhydrogen analyses and molecular weight determinations indicate that its formation involves two molecules of cyclohexanedione and either one or two methylene groups. It forms a semicarbazone and a phenylhydrazone, and reacts with piperidine, forming an oily product. When boiled with very dilute hydrochloric acid II yields two products; one is an organic solid which does not melt below 325°, and the other is a viscous oil.

Compound III has the composition $C_{14}H_{20}O_2$. Attempts to prepare a semicarbazone of III yield the disemicarbazone of 1.4-cyclohexanedione. Further, a sample of this compound, which has been exposed to the air and then cooled with dry ice, precipitates cyclohexanedione. Two facts indicate that the diketone is not present in the oil as an impurity. First. assuming the cleavage of a compound of molecular weight 252, a 67 per cent yield of the semicarbazone of cyclohexanedione is obtained. It is hardly likely that this amount of diketone would be present in the oil as an impurity. Second, if a sample of III is exposed to the air for a short time, cyclohexanedione can be frozen out. After filtering, no more crystallization occurs until the sample has again been exposed to the atmosphere. This process may be repeated several times, until finally no more diketone can be obtained. After this, the remaining oil no longer yields a semicarbazone. From these facts it is concluded that compound III is easily cleaved by moisture, yielding as one of the cleavage products 1,4-cyclohexanedione.

Other properties of III are as follows:

1. Compound III was analysed in the Grignard machine, and showed 1.06 moles of carbonyl and 0.32 moles of active hydrogen per mole of compound, assuming a molecular weight of 252.

2. III reacts with phenylmagnesium bromide giving an oil. This oil is colorless immediately after distillation, but in the presence of air it goes through a very impressive series of color changes, which are repeated on redistillation.

3. III is oxidized by silver oxide or chromium trioxide and is reduced by hydrogen and Raney-nickel or aluminum isopropoxide, to give oily products.

4. III reacts with benzaldehyde in the presence of hydrogen chloride or sodium ethoxide, with malonic acid in the presence of pyridine, and with butyl nitrite in the presence of sodium ethoxide, but in each case the product is an oil.

5. With hydroxylamine and phenylhydrazine compound III reacts to give tarry products.

6. III reacts with bromine with the formation of hydrogen bromide.

7. With dry hydrogen chloride in absolute ether a tar is produced.

8. Attempts to hydrate III by dissolving it in water and heating, with or without acid catalysts, yielded only oils, from which no solid derivatives could be obtained.

9. With piperidine, III gives a solid dipiperidine addition product, without cleaving.

10. III reacts with phthalic anhydride, but the product is an oil.

11. III does not react with α -naphthyl isocyanate.

The only structure which seems at all reasonable for compound III is



While the reactions given cannot be considered as proof, this structure explains all the properties of III, even the fact that the glycol which would be expected as one of the hydrolysis products (1,4-dihydroxy-1,4-dihydroxymethylcyclohexane) and its derivatives do not crystallize, for this might be expected because of the number of possible stereoisomers.

Some time after this work was completed it was found that O. Pauli⁹ in an unpublished dissertation had reported on a study of the action of diazomethane on certain methoxyketones. He obtained two products from each ketone, one of which was the expected ethylene oxide and the other was an oil for which Pauli wrote the cyclic acetal structure, on the basis of the fact that these compounds gave the same glycols on hydrolysis as did the corresponding ethylene oxides. It is interesting that in Pauli's work he was able to isolate only the glycol while in the work described here the cleavage of a similar product led only to the ketone.

Pauli also studied the action of diazomethane on 1,4-cyclohexanedione and obtained compound I, for which he wrote the same structure as is written above, that is, 1,4-dimethylenecyclohexane dioxide, and an oil the structure of which he did not determine.

Compound IV was not investigated because it decomposes in a short time at room temperature.

EXPERIMENTAL

Preparation of 1,4-cyclohexanedione.—Ethyl succinate was prepared by the very useful method of Thielepape¹⁰, in 95% yields. Using the method of Liebermann¹¹

⁹ PAULI, Dissertation, Marburg, 1935.

¹⁰ THIELEPAPE, Ber., 66, 1454 (1933).

¹¹ LIEBERMANN, Ann., 404, 272 (1914).

this ester was condensed to ethyl succinosuccinate, in yields of 60-65%. The cyclohexanedione was obtained by heating ethyl succinosuccinate in a small hydrogenating bomb with an equal weight of water and a few small pieces of soft-glass tubing. The bomb was heated to $195^{\circ}-200^{\circ}$ for from 8 to 10 minutes and then cooled rapidly with running water. Several runs of 20-30 g, were always worked up together by distillation under approximately 20 mm. Cyclohexanedione, boiling at $132^{\circ}/20$ mm. and melting at $78^{\circ}-79.5^{\circ}$, was obtained in yields of 80% to 85%.

Reaction of cyclohexanedione with diazomethane.—To a cold solution of diazomethane (28.0 g.) in ether (1310 cc.), cyclohexanedione (55.4 g.) was added. A very slight evolution of gas began immediately. Then methyl alcohol (415 cc.) was added, and the mixture kept in an ice bath for 15 minutes and then allowed to stand at room temperature until the yellow color had completely disappeared (23.5 hours). After removal of the solvents the product was fractionated through a three-inch column packed with helices. The following fractions were collected:

1. 118-29°/25 mm. Bath temp. 155-60°. Consisted of an oil and a solid.

Filtration	yielded
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	(a) Solid	2.08 g	. (3.0%)
	(b) Oil	17.6 g.	(25.4%)
2.	76-95°/2 mm. Bath temp. 125-30°	6.2 g.	(8.9%)
	Mostly 94-95°		
3.	95-98°/2 mm. Bath temp. 130°	9.8 g.	(14.2%)
4.	98-05°/2 mm. Bath temp. 130-134°	5.9 g.	(8.5%)
5.	105-08°/2 mm. Bath temp. 134-140°	14.4 g.	(20.8%)
	Distillation was stopped at this point to change reacontinued.	ceivers	and then
6.	98-107°/2 mm. Bath temp. 140-65°	2.0 g.	(2.9%)
7.	Residue	4.0 g.	(5.8%)

61.98 g. (89.5%)

The yields are based on the assumption of two moles of diazomethane reacting with each molecule of diketone. The yield based on the diazomethane used was 95.8%. The material was fractionated nine more times, during which 0.85 g. of the solid (compound I) was obtained. The tenth distillation gave the following fractions:

1.	65-66°/2 mm. Bath temp. 89-90°	0.42 g.	(0.6%)
2.	66°/2 mm. Bath temp. 90-93°	2 .04 g.	(2.9%)
3.	81-84°/2 mm. Bath temp. 100-101°	0.90 g.	(1.3%)
4 .	84-85°/2 mm. Bath temp. 101-102°	1.69 g.	(2.4%)
5.	85-86°/2 mm. Bath temp. 102-102.5°	6.32 g.	(9.1%)
6.	86-87°/2 mm. Bath temp. 102.5-103°	3.93 g.	(5.7%)
7.	87-88°/2 mm. Bath temp. 103-104°	9.40 g.	(13.6%)
8.	88°/2 mm. Bath temp. 104-107°	1.61 g.	(2.3%)
9.	101-105°/3 mm. Bath temp. 131-133°	0.91 g.	(1.4%)
10.	105-109°/3 mm. Bath temp. 133-136°	1.80 g.	(2.6%)
11.	109-113°/3 mm. Bath temp. 136°	3.71 g.	(5.4%)
		32.73 g.	(47.3%)
In tl	his way four distinct compounds were obtained:		
I	, Solid	2.93 g.	(4.2%)
II	. Oil, b.p. 65–66°/2 mm	2.46 g.	(3.6%)
III	. Oil, b.p. 81-88°/2 mm	23.85 g.	(34.4%)
IV	. Oil, b.p. 101-113°/3 mm	6.42 g.	(9.3%)
		35.66 g.	(51.5%)

Properties of compound I

Compound I does not react with semicarbazide hydrochloride, Fehling's solution, or decolorized fuchsin.

Anal. Calc'd for C₈H₁₂O₂: C, 68.57; H, 8.57.

Found: C, 68.61; H, 8.91.

Addition of hydrogen chloride to I.—In an attempt to prepare a benzal derivative of I dry hydrogen chloride was passed for 6 hours through an absolute ether solution of 0.3 g. of I and 0.6 g. of benzaldehyde, at 0°. After removal of the ether the resulting product was recrystallized from benzene. It weighed 0.14 g. After two more recrystallizations from benzene it melted at $142.5-143^{\circ}$.

Anal. Calc'd for C₈H₁₄Cl₂O₂: C, 45.28; H, 6.66.

Found: C, 45.29, 45.44; H, 7.54, 7.36.

This analysis does not check at all for any of the possible benzal derivatives, but rather indicates the addition of two molecules of hydrogen chloride to I.

Addition of piperidine to I.—When 0.35 g. of piperidine was added to a solution of 0.20 g. of I dissolved in 2 cc. of water the mixture solidified in a few minutes. Two cubic centimeters more of water was added, and the solution was filtered. The white, crystalline solid melted at $124-130^{\circ}$ and weighed 0.41 g. After recrystallizing from alcohol, then petroleum ether, and then ether this product melted at $128.5-130^{\circ}$. Molecular weight, by the Rast method, gave 294 and 303.5.

Anal. Calc'd for C13H34N2O2: C, 69.68; H, 11.05, mol. wt., 310.

Found: C, 69.45; H, 11.16.

This amine forms a picrate melting with decomposition at 222-223.5°.

Anal. Calc'd for C₃₀H₄₀N₈O₁₆: C, 46.88; H, 5.21.

Found: C, 46.71; H, 5.23.

Addition of water to I.—A mixture of 0.20 g. of I, 0.5 cc. of water and 2 drops of a 2% solution of acetic acid was heated on the steam bath for 6 hours. The water was removed, leaving a viscous oil. After 10 days in the icebox, partially dissolved in ether-petroleum ether, it had deposited 0.05 g. of crystals of m.p. 190–194°. Approximately half of this solid was recrystallized from alcohol; m.p. 199.5–201.5°.

Anal. Calc'd for C₈H₁₆O₄: C, 54.55; H, 9.16.

Found: C, 53.76; H, 9.16.

Though not a first-class analysis, this indicates that two molecules of water have been added rather than one, since the calculated values for $C_{3}H_{14}O_{3}$ are C, 60.76; H, 8.86.

Other attempts to hydrate I yielded viscous oils which could not be crystallized.

A small amount of I was heated in a test-tube with freshly fused zinc chloride. A few drops of alcohol was added to extract any organic material. This alcohol solution gave a positive fuchs n test (a blank on the alcohol alone was negative), indicating that some of the aldehyde had been formed.

Properties of compound II

Molecular-weight determinations by the Rast method gave the values 242 and 250 for compound II.

Anal. Calc'd for C₁₃H₁₈O₂: C, 65.55; H, 7.62; mol. wt., 238.

Found: C, 65.42; H, 7.85.

Semicarbazone of II.—In the usual manner, 0.30 g. of II yielded 0.28 g. of a white solid, which melted with decomposition at 202° after having been twice recrystallized from alcohol.

Anal. Calc'd for C₁₆H₂₆N₆O₄: C, 52.46; H, 7.16. Found: C, 52.33; H, 7.24. Phenylhydrazone of II.—Compound II forms a phenylhydrazone in the usual manner. After two recrystallizations from alcohol it melts at 121-127°. This derivative is unstable, decomposing into a dark-brown liquid on standing over night.

Reaction of II with piperidine.—When piperidine is added to a water solution of II a colorless oil separates in a few minutes. This oil could not be crystallized. It forms a picrate which melts with decomposition at 200-205° after darkening at about 190°. This picrate is unstable, rapidly decomposing at room temperature.

Hydrolysis of II.—A mixture of 0.4 g. of II, 0.5 cc. of water and 1 drop of concentrated hydrochloric acid was heated for 7 hours on the steam bath, and then 20 cc. of alcohol was added. The mixture was filtered. The insoluble material was organic, but it did not melt below 325°. From the alcoholic solution a viscous oil was obtained, which did not react with semicarbazide or α -naphthyl isocyanate.

Properties of compound III

Molecular-weight determinations by the Rast method gave values of 236, 239, and 241 for compound III.

Anal. Calc'd for C₁₄H₂₀O₂: C, 66.67; H, 8.00; mol. wt., 252.

Found: C, 66.79; H, 8.21.

Compound III gives positive tests with both Fehling's solution and fuchsin reagent.

Addition of piperidine to III.—A few minutes after dissolving 0.2 g. of III and 0.11 g. of piperidine in 0.5 cc. of water, an oil separates. On standing this oil solidifies and after recrystallization from alcohol, petroleum ether, and finally from ether it melts at 100–101°. The yield was 61%. A molecular-weight determination by the Rast method gave the value 395.

Anal. Calc'd for C₂₄H₄₂N₂O₂: C, 68.25; H, 9.95; mol. wt., 422.

Found: C, 67.99; H, 10.58.

The picrate of this compound was obtained as a red oil.

Action of semicarbazide on III.—When III is treated with semicarbazide hydrochloride in the usual way, a 66.7% yield of the semicarbazone of cyclohexanedione is obtained. It melts with decomposition at 228.5° and shows no depression of melting point when mixed with an authentic sample of the disemicarbazone of 1,4-cyclohexanedione.

Anal. Calc'd for C₈H₁₄N₈O₂: C, 42.48; H, 6.19.

Found: C, 42.55; H, 6.18.

When the diazomethane from 5 g. of methyl nitroso urea was distilled into a solution of 2 g. of III in 16 cc. of ether and 16 cc. of methyl alcohol, and the solution was allowed to stand at room temperature, it became colorless in 19 hours. The solvents were removed, and the residue was distilled. A small forerun, containing a few crystals, was obtained, but the main fraction boiled at $135-140^{\circ}/33$ mm. This sample of III should contain no cyclohexanedione, but treatment with semicarbazide hydrochloride again yields the disemicarbazone of cyclohexanedione.

Hydrolysis of III by moist air.—A solution of 1 cc. of III in 2 cc. of ether was allowed to stand open to the air for a short time and then was cooled in a bath of carbon dioxide snow and chloroform. Filtration removed the white crystals which melted, after crystallization from petroleum ether, at $79-80^{\circ}$. No depression in melting point resulted when this solid was mixed with known cyclohexanedione. The filtrate was again cooled and filtered, and this was repeated until no crystallization took place. Then the solution was allowed to stand open to the air for 24 hours. The freezing process was repeated and more crystals of cyclohexanedione were obtained. This was repeated every day for 6 days, and then after standing

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for 2 days more, no crystals were obtained when the oil or its ether solution was cooled to -80° . Apparently hydrolysis was complete. The remaining oil gave no semicarbazone but it did give a 43% yield of the piperidine addition product of III.

Action of piperidine on 1,4-cyclohexanedione.—When 2.0 g. of cyclohexanedione, 5 g. of piperidine, and 10 cc. of water were allowed to stand in a tightly-stoppered flask, at room temperature, no change was observed after 2.5 hours. After 22 hours the mixture was slightly yellow and possessed a green fluorescence. A small sample poured onto a watch glass became red in a few seconds. After about half the water was removed under reduced pressure the solution was extracted with ether. During the extraction the water layer turned dark red. The ether layer had a green fluorescence. When the ether was removed the residue was a yellow liquid which turned red on contact with air and which possessed a strong ammonia-like odor. When this oil was added to water it solidified (white solid) and then rapidly turned to a red gummy material. The water layer from the extraction was further evaporated and then filtered. This gave a white solid (0.23 g.) that was stable in air, and which melted at 223.5-224° after recrystallization from alcohol.

SUMMARY

Four compounds have been isolated from the reaction between 1,4cyclohexanedione and diazomethane.

One of these is 1,4-dimethylenecyclohexane dioxide.

Another is probably the cyclic acetal of 1,4-cyclohexanedione and 1-hydroxy-1-hydroxymethyl-4-methylenecyclohexane oxide.

A third compound has been characterized, but its structure has not been determined.