

Summary

A study has been made of the gases formed during the preparation and in the hydrolysis of some alkylmagnesium halides. From the nature of these gases it appears that the free radicals that are probably formed prior to the formation of organomagnesium halides undergo disproportionation and coupling to varying degrees.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF MESOXALATES BY INTERACTION OF NITROGEN TETROXIDE WITH ESTERS OF MALONIC ACID¹

BY ELIZABETH GILMAN² AND TREAT B. JOHNSON

RECEIVED JULY 24, 1928

PUBLISHED DECEMBER 10, 1928

Only a few examples of organic compounds are known in which two hydroxyl groups appear to exist in stable union with a single carbon atom. What influence such linkages have on physiological activity is not well understood. Although the physiological action of chloral hydrate is not definitely linked with the property of hydrate formation, and while the effect of this drug is regarded as due to the organic radical containing chlorine, yet the prevalence of activity among hydrated constructions of the type which we are investigating (alloxan, for example) leads the writers to suppose that mesoxalates may be of pharmacological interest. As far as we have been able to ascertain, mesoxalates have never been investigated physiologically. They are admirably suited to intravenous injection. The diethyl ester is soluble in its own weight of water and it has been our experience that even the esters of higher molecular weight are surprisingly soluble in water. Diethyl mesoxalate is also a valuable reagent for synthetic work and any method that can be devised for preparing it more easily and cheaply will undoubtedly find important applications.

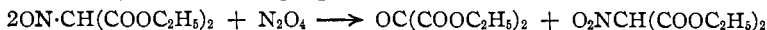
Bouveault and Wahl,³ in 1903, provided the basis for the present method of preparing mesoxalates when they succeeded in obtaining diethyl mesoxalate from diethyl isonitrosomalonnate by the action of oxides of nitrogen generated from sodium nitrate and nitrosyl-sulfuric acid. The principal oxide generated in this manner is nitrogen tetroxide (N_2O_4). They made their isonitrosomalonnate from diethyl malonnate in alcoholic sodium ethylate solution by interaction with methyl nitrite. Treatment with an ex-

¹ Constructed from a dissertation presented by Elizabeth Gilman in June, 1927, to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

² Holder of the Alice Freeman Palmer Fellowship of Wellesley College in 1926-27.

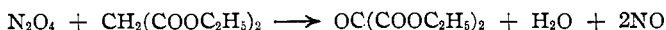
³ Bouveault and Wahl, *Compt. rend.*, **137**, 196 (1903).

cess of nitrogen tetroxide at 0° then led to the formation of the mesoxalates, as expressed by the following equation



These same investigators later prepared ethyl diketobutyrate from ethyl acetoacetate by action of nitrous oxide (N_2O_3) in acetic anhydride solution and mention the fact that either N_2O_3 or N_2O_4 will give the desired ketone.⁴ Schmidt⁵ applied this latter procedure for the preparation of diethyl mesoxalate, and later Curtiss⁶ utilized the Schmidt reaction, using no solvent, and reported a yield of 95% of the theoretical. Several investigators who have followed the directions of Curtiss for the preparation of diethyl mesoxalate have not been able to obtain the yield reported by him.⁷ The latest work on this preparation is that of Dox,⁸ who followed the Curtiss procedure with the exception that his nitrous oxide was dried over calcium chloride before being brought into reaction with diethyl malonate. He quotes yields of diethyl mesoxalate corresponding to 74–75% of the theoretical.

We are now able to report new data contributing to our knowledge of the methods applicable for the synthesis of mesoxalates. In the study of the reactivity of nitrogen tetroxide toward organic combinations, now in progress in this Laboratory,⁹ we have investigated the action of this oxide on diethyl malonate and find that the reaction can be so well controlled as to be productive of a nearly quantitative yield of the mesoxalate. A detailed account of the technique of our modified method of preparation is given in the Experimental Part of this paper. Empirically this reaction may be represented as below, but it was our experience that an excess of the oxide is necessary in order to obtain a maximum yield of the mesoxalate.



In order to ascertain whether the reaction between nitrogen tetroxide and diethyl malonate is a general one and applicable to other esters of malonic acid we selected the following three representatives for further research: di- β -chloro-ethyl malonate, di- β -bromo-ethyl malonate and di- β -diethylamino-ethyl malonate. Of these only the chlorine compound has hitherto been described in the literature, and indeed our knowledge of any malonic ester derivatives of this type is very limited.

⁴ Bouveault and Wahl, *Compt. rend.*, **138**, 1221 (1904).

⁵ Schmidt, *ibid.*, **140**, 1400 (1905).

⁶ Curtiss, *Am. Chem. J.*, **35**, 477 (1906); *THIS JOURNAL*, **33**, 962 (1911).

⁷ A. Meyer, *Bull. soc. chim.*, [4] **9**, 423 (1911); Lemaire, *Rec. trav. chim.*, **29**, 22 (1910).

⁸ Dox, "Organic Syntheses," John Wiley and Sons, New York City, **4**, 27 (1925).

⁹ In the development of a new synthetical method for the preparation of alkaloids of the ephedrine type, we have made a new application of the reactivity of N_2O_4 in preparing one of our intermediate products utilized in the process. This work will be described in a future publication (T. B. J.).

Theoretically these ester combinations would yield three new esters of mesoxalic acid of immediate pharmacological interest if found reactive toward nitrogen tetroxide in the same manner as diethyl malonate. This is particularly true of the amino ester $(C_2H_5)_2NCH_2CH_2OOCCH_2COOCH_2CH_2N(C_2H_5)_2$ and the corresponding mesoxalate, both of which contain part of the molecular structure functioning in the well-known local anesthetic, *novocaine*. In consequence of this structural relationship aliphatic combinations of this type should possess intrinsic interest pharmacologically.

When subjected to the action of nitrogen tetroxide these three malonic esters presented individual problems. Di- β -chloro-ethyl malonate behaved almost exactly like diethyl malonate and gave consistently a 90% yield of the corresponding mesoxalate. Di- β -bromo-ethyl malonate was more sluggish in its reactivity toward nitrogen tetroxide. This ester was likewise more unstable and could not be heated to its boiling point at atmospheric pressure without decomposition. Conditions were found, however, under which good yields of di- β -bromo-ethyl mesoxalate could be obtained. Di- β -diethylamino-ethyl malonate presented many difficulties when treated with nitrogen tetroxide, behaving individually when allowed to interact with the oxide, and thus far we have not succeeded in isolating the corresponding pure mesoxalate. The free ester and the hydrochloride react with the oxide giving unstable oils which cannot be purified by distillation. The free base decolorizes three equivalents of nitrogen tetroxide while the hydrochloride reacts with only one, so that the amino groups apparently do not interact when protected by hydrochloric acid. It seems probable that the insoluble and unstable oil obtained in the case of the hydrochloride represents an intermediate formed by interaction of nitrogen tetroxide with the methylene carbon atom.

Pharmacological Report

Pharmacological experiments of a preliminary nature have thus far been carried out on three of these compounds by Professor Henry G. Barbour of the University of Louisville, Louisville, Kentucky, and the effects thus far reported to us are recorded below.

Diethyl Mesoxalate.—This ester has no hypnotic action but shows marked stimulative effects on respiration and blood pressure which last about thirty and ten minutes, respectively, and can be repeated. It can be injected intravenously into dogs and the fatal dose for mice is 0.3 g. per kilo.

Di- β -chloro-ethyl Mesoxalate.—The same tendency to produce sympathetic stimulation of the circulation is shown by this chlorine derivative accompanied by other effects suggestive of choline or eserine, that is, salivation and tremors. It is far more toxic than the diethyl mesoxalate, and increases the percentage of blood sugar.

Di- β -diethylamino-ethyl Malonate.—This ester is especially interesting. It is much less toxic than the two preceding esters and has a very definite, long-continued effect on the total metabolism which is stimulating. Both heat and blood sugar outputs

are very noticeably increased for quite an extended period of time. It has little effect on blood pressure and respiration and does not show marked anesthetic properties.

The series of compounds under investigation is unusually interesting from a physiological standpoint, and offers many possibilities for future research. The effects thus far recorded were entirely unexpected, but are exceedingly interesting and somewhat extraordinary.

Experimental Part

Preparation of Diethyl Mesoxalate by the Action of Nitrogen Tetroxide on Diethyl Malonate.—Nitrogen tetroxide was supplied for our research in a large bomb, and an all-glass apparatus was constructed for drying the gas over phosphorus pentoxide, condensing it at 0° , and weighing the condensate. No attempt was made to purify the gas from traces of nitrogen trioxide since either oxide produces the desired reaction. Units of about 25 g. of purified diethyl malonate were used for most of the experiments, cooled to 0° , and the calculated quantities of nitrogen tetroxide added in the liquid state. All reagents were protected from moisture during the time of reaction. The yield was calculated in percentage of the theoretical weight of the crystalline hydrate of diethyl mesoxalate obtained, in accordance with the equation $\text{N}_2\text{O}_4 + \text{CH}_2(\text{COOC}_2\text{H}_5)_2 = 2\text{NO} + \text{H}_2\text{O} + \text{CO}(\text{COOC}_2\text{H}_5)_2$.

The reaction between nitrogen tetroxide and diethyl malonate was found to proceed slowly at low temperatures. Temperatures above the boiling point of nitrogen tetroxide did not prove beneficial, since much of the oxide was lost by evaporation, and a smaller amount of nitrogen tetroxide, if allowed to interact a longer time at low temperatures, accomplished quite as complete a reaction. Slightly more than the theoretical quantity of nitrogen tetroxide required by the above equation was found desirable, but no more than a quantity equal in weight to that of the malonic ester was used.

In applying reactions with nitrogen tetroxide, ether, acetic anhydride, and carbon tetrachloride were incorporated as solvents but the best results were obtained when the last solvent was used. It was found, however, that this was unnecessary and all solvents were finally abandoned except for the purpose of rinsing, when carbon tetrachloride was employed.

In one experiment phosphorus pentoxide was introduced into the reaction mixture in the hope that the presence of this dehydrating agent would facilitate the desired reaction. A most surprising result was obtained in the quantitative recovery of unaltered malonic ester. This result led us to search for an alkaline catalyst which could be introduced without producing side reactions, and metallic sodium was found to serve this purpose. A small piece of sodium introduced into a mixture of anhydrous malonic ester and liquid nitrogen tetroxide at 0° appeared to under-

go no reaction, and when withdrawn at the end of three hours had suffered practically no loss in weight. At the end of the reaction period, the precaution was taken of pouring the reaction mixture upon phosphorus pentoxide in order to insure removal of any trace of alkali. The use of sodium was found to increase the yield of mesoxalate quite appreciably and our adopted procedure for preparing the mesoxalate was as follows.

Twenty-five grams of diethyl malonate was mixed with an equal weight of liquid nitrogen tetroxide at -5° and a freshly cut piece of sodium weighing one gram was introduced. The mixture was maintained at -5° for three hours with frequent shaking and protecting, as usual, from moisture by a calcium chloride tube. The sodium, apparently, did not enter into reaction and when removed at the end of three hours still weighed one gram. The reaction mixture was allowed to stand for two days at room temperature and was then poured into a flask containing phosphorus pentoxide and heated gently to the boiling point of the carbon tetrachloride which had been added as rinsings. It was then decanted into a Claisen flask, the pentoxide residue well rinsed with carbon tetrachloride and the rinsings added to the main lot. Heat was applied at ordinary pressure, when the decomposition of the oil took place in steps. The main distillate boiled almost entirely between 103 and 105° at 19 mm. representing 85% of the theoretical amount of anhydrous mesoxalate expected. The calculated amount of water converted it quantitatively into its crystalline hydrate. The residue in the distilling flask contained crystals of the hydrated mesoxalate and no indication of any other reaction product was observed. The hydrate when recrystallized from chloroform melted at 57° . The total yield, including the mesoxalate isolated from both residue and water distillate, was 90% of the theoretical.

The nature of the gas evolved in the above reaction was also studied. During the first two hours of reaction at 30° all of the gas evolved was collected over a 10% solution of alkali, all the air in the system having been previously displaced by carbon dioxide. No brown color developed as usual over the solution and 600 cc. of a colorless gas was collected which was very soluble in ferrous sulfate solution and produced brown fumes when exposed to air. Thus, during the first stages of the reaction, the principal gas evolved was nitric oxide.

Preparation of Some Substituted Ethyl Malonates

Di- β -chloro-ethyl Malonate, $\text{CH}_2(\text{COOCH}_2\text{CH}_2\text{Cl})_2$.—This ester has been prepared according to another method by George Bennett,¹⁰ and its boiling point is given as 164° at 15 mm. We prepared it by esterifying malonic acid with ethylene chlorohydrin, using hydrogen chloride as a catalyst. Two hundred grams of ethylene chlorohydrin was added to 50 g. of diethyl malonate and 50 g. of sodium sulfate (anhydrous). Dry hydrogen chloride was passed into the suspension to saturation and the

¹⁰ G. M. Bennett, *J. Chem. Soc.*, **127**, 1277 (1925).

mixture heated at 60° for three hours. It was then cooled, filtered, and excess of hydrochloric acid and ethylene chlorohydrin removed by heating under diminished pressure. The heavy oil remaining behind was washed with sodium bicarbonate solution until neutral and finally with pure water. After drying over anhydrous sodium sulfate it was distilled at 24 mm. and 90 g. of a colorless oil boiling at 178–182° was obtained. This represented a yield of 82% of the theoretical. On redistillation the oil had a boiling point of 143–144° at 4 mm. The ester is a heavy oil, insoluble in water and soluble in the ordinary organic solvents.

Anal. Calcd. for $C_7H_{10}O_4Cl_2$: Cl, 30.96. Found: Cl, 30.90.

Di- β -bromo-ethyl Malonate, $CH_2(COOCH_2CH_2Br)_2$.—This ester was prepared in a manner exactly analogous to the procedure used for the di- β -chloro ester, using ethylene bromohydrin and malonic acid. The yield of crude di- β -bromo-ethyl malonate was 84% of the theoretical, but it was found to contain considerable quantities of ethylene bromohydrin, which is insoluble in water and cannot be removed by washing with water as in the case of the chloro ester. The pure ester was obtained by fractional distillation as a heavy, colorless oil boiling at 153° at 1 mm. It decomposes if low pressures are not employed in its distillation and tends to turn dark on standing for long periods. It is soluble in all organic solvents, especially carbon tetrachloride and chloroform, and is very insoluble in water.

Anal. Calcd. for $C_7H_{10}O_4Br_2$: Br, 50.28. Found: Br, 49.7.

Di- β -diethylamino-ethyl Malonate, $CH_2(COOCH_2CH_2N(C_2H_5)_2)_2$.—We first attempted to prepare this ester by the action of diethylamine on di- β -chloro-ethyl malonate. Experiments were conducted at atmospheric pressure under a reflux, in bomb tubes at 110°, and also at room temperature under pressure, but in all cases the reaction was incomplete and none of the desired ester was obtained.

The procedure applied successfully for the preparation of this ester was the reaction of malonyl chloride on diethylamino-ethyl alcohol, and we operated as follows.

Forty-eight grams of β -diethylamino-ethyl alcohol was dissolved in 500 cc. of dry chloroform and hydrogen chloride gas passed into the solution until it was just acid to methyl red. After cooling, 28 g. of malonyl chloride dissolved in an equal volume of chloroform was added slowly through a dropping funnel. The reaction mixture was refluxed for three hours. Dry potassium carbonate was then added to the boiling mixture until it showed a neutral reaction, when it was filtered. The excess of chloroform was distilled off and on cooling the solution became solid with crystalline material. Purification was accomplished by trituration with acetone, when 55 g. of the reaction product was obtained, melting between 120 and 140° with decomposition. Two recrystallizations from absolute alcohol and acetone yielded 25 g. of a pink powder melting at 152–154° with decomposition. This was identified as the hydrochloride of the desired ester.

The free base, $CH_2(COOCH_2CH_2N(C_2H_5)_2)_2$, was prepared from its hydrochloride by digesting the salt in anhydrous chloroform with dry sodium bicarbonate and sodium sulfate. Ten grams of di- β -diethylamino-ethyl malonate dihydrochloride (m. p. 153–154°) was dissolved in chloroform, an excess of sodium bicarbonate and sodium sulfate added and the mixture refluxed for ten to fifteen minutes. After standing for two days, it was filtered and the chloroform distilled off, giving an orange oil with a pungent odor. This was dissolved in anhydrous ether, filtered to free it from traces of hydrochloride and the oil distilled under diminished pressure. The product distilled at 163° (4.5 mm.), and yielded quantitatively the original hydrochloride when treated with hydrogen chloride gas. The ester is soluble in all common organic solvents and also appears to be completely soluble in water, producing a strongly basic solution.

The dihydrochloride of di- β -diethylamino-ethyl malonate is a colorless powder

soluble in alcohol and chloroform, insoluble in ether, and very difficultly soluble in acetone. It deposits in opaque clusters from absolute alcohol and will dissolve in its own weight of this solvent at the boiling point. It is extremely soluble in water, producing a neutral solution, and the amino ester cannot be recovered from water by adding alkali and extracting the free base without considerable hydrolysis. It takes up water whenever exposed to moist air for any considerable length of time. When pure it melts at 154° with decomposition.

Anal. Calcd. for $C_{15}H_{32}O_4N_2Cl_2$: Cl, 18.9; N, 7.47. Found: Cl, 18.93; N, 7.72.

Action of Nitrogen Tetroxide on the above Malonates

Preparation of Di- β -chloro-ethyl Mesoxalate, $CO(COOCH_2CH_2Cl)_2$.—Thirty grams of di- β -chloro-ethyl malonate was mixed with 44 g. of liquid nitrogen tetroxide at -5° and a small piece of sodium added. After removing the sodium at the end of three hours, the mixture was allowed to stand for two to three days at room temperature and was then poured upon phosphorus pentoxide, heated at atmospheric pressure and finally distilled. Twenty-nine grams of a yellow oil boiling at $155-160^{\circ}$ (6 mm.) was obtained, representing a yield of 90%. After redistillation this gave a fraction boiling at 148° at 3 mm. The ester is a greenish-yellow oil with a pungent odor similar to that of anhydrous diethyl mesoxalate. It is soluble in the common organic solvents and combines with a molecular equivalent of water with evolution of heat and almost complete decolorization. The hydrate formed is an oil and could not be induced to crystallize even when cooled to 25° . Further addition of water is accompanied by a yellow color which disappears again as the dilution is increased. The ester is apparently soluble in water in all proportions.

Anal. Calcd. for $C_7H_8O_5Cl_2$: Cl, 29.18. Found: Cl, 29.07.

Preparation of Di- β -bromo-ethyl Mesoxalate, $CO(COOCH_2CH_2Br)_2$.—Eight grams of di- β -bromo-ethyl malonate was mixed with 10 g. of liquid nitrogen tetroxide and a piece of metallic sodium added at -5° . The sodium was allowed to remain in the solution for twelve hours at 0° and then removed. After standing for two days at room temperature, the reaction mixture was dissolved in chloroform, phosphorus pentoxide added, and excess nitrogen tetroxide boiled off. The yellow solution was then heated to remove chloroform, whereupon decomposition set in with evolution of oxides of nitrogen. As soon as the oil assumed a yellow color, heating was discontinued and the product distilled at 1 mm. pressure. We obtained 6 g. of a yellow oil boiling at $158-159^{\circ}$. This ester interacted with water with evolution of heat and almost complete decolorization but did not crystallize on cooling to 0° . It is soluble in an excess of water. On redistillation after removing water with phosphorus pentoxide, the anhydrous oil had a boiling point of 155° at 0.8 mm.

Anal. Calcd. for $C_7H_8O_5Br_2$: Br, 48.17. Found: Br, 48.16.

Action of Nitrogen Tetroxide on Di- β -diethylamino-ethyl Malonate.—The reaction between nitrogen tetroxide and the above ester proved to be explosively violent. Liquid nitrogen tetroxide could not be introduced and gaseous nitrogen tetroxide could be passed in only slowly at low temperatures. Three equivalents of nitrogen tetroxide were completely decolorized before any green color was imparted to the solution and an orange oil insoluble in carbon tetrachloride collected on the surface of the solution. The dihydrochloride of the malonic ester in question produced a much less vigorous reaction with nitrogen tetroxide and only one equivalent was decolorized, but an insoluble orange oil collected as before on the surface. None of the desired mesoxalate was isolated from either reaction. The reaction product decomposed violently upon gentle heating. A great many factors combine to make this preparation difficult; the amino malonic ester employed is peculiarly sensitive to hydrolysis, the alkyl amino

groups are apparently attacked in anhydrous solution by nitrogen tetroxide, the avidity of the methylene carbon atom for nitrogen tetroxide is apparently increased and no satisfactory method of decomposing the intermediate to yield mesoxalate has thus far been discovered.

Summary

1. An improved method for preparing diethyl mesoxalate has been described. It involves the action of nitrogen tetroxide on diethyl malonate.
2. Two new mesoxalates prepared by application of this nitrogen tetroxide reaction are: di- β -chloro-ethyl mesoxalate and di- β -bromo-ethyl mesoxalate.
3. Di- β -diethylamino-ethyl malonate has been prepared for the first time.
4. The pharmacology of these new ester combinations is being investigated.

NEW HAVEN, CONNECTICUT

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

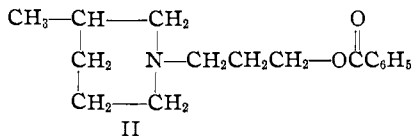
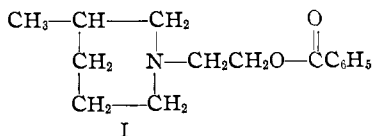
PIPERIDINE DERIVATIVES. VI. 3-METHYLPYPERIDINO-ALKYL BENZOATES¹

BY J. R. THAYER AND S. M. McELVAIN

RECEIVED AUGUST 3, 1928

PUBLISHED DECEMBER 10, 1928

In a previous communication² a number of substituted and unsubstituted piperidino-alkyl benzoates were described together with a brief report on their pharmacological behavior. Of these compounds it was noted that those containing an alkyl group substituted in the piperidine nucleus possessed the greatest local anesthetic efficiency. It seemed, therefore, advisable to ascertain the effect of variations in the alkylene group on the pharmacological properties of the type of compound represented by 3-methylpiperidino-ethyl and propyl benzoates (I and II).



In the previous work it was found that the number of carbon atoms in the alkylene group that joins the nitrogen to the oxygen was quite important. In I where there are two carbon atoms in this alkylene group,

¹ This paper is an abstract of a portion of the thesis submitted by J. R. Thayer to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

² McElvain, *THIS JOURNAL*, **49**, 2835 (1927).