[Contribution from the Chemical Laboratory of Harvard University]

STUDIES IN THE CYCLOPROPANE SERIES. XII. NITROCYCLOPROPANES

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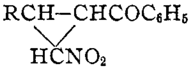
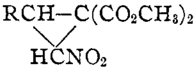
The manner in which bases convert derivatives of nitrocyclopropane into open-chained compounds is still obscure because each type of derivative that has been studied has ended in a different type of open chained compound, and it has not been possible to isolate intermediates in the process. In the hope of discovering such intermediates we have prepared still another type of derivative which is closely related to two that have been studied heretofore


A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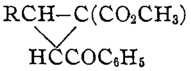
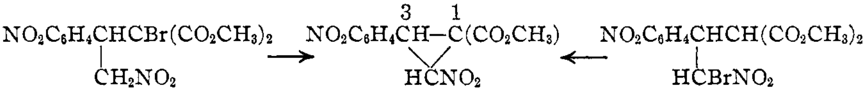

C

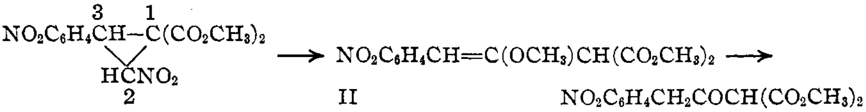
In order to keep as close as possible to known substances, we planned to prepare a nitrocyclopropane derivative of the type represented by B in which the hydrocarbon residue was to be a phenyl group; but owing to experimental difficulties, it became necessary to secure greater crystallizing power by resorting to substances in which the phenyl groups were substituted. Most of our experiments were carried out, therefore, with the *m*-nitrophenyl derivative.

The fact that our parent substance was obtained both from an α-bromo and from a γ-bromo compound is adequate proof that it is a cyclopropane derivative



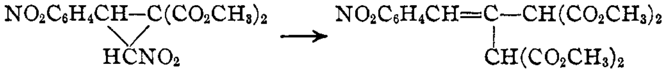
I

When this cyclopropane derivative is heated with methyl alcoholic potassium acetate—a very feeble base—it is slowly converted into a yellow methoxy compound. The structure of this yellow product was easily established. Its composition and molecular weight are represented by the formula $C_{14}H_{15}O_7N$. It is actively unsaturated, contains three methoxyl groups, is hydrolyzed to a β-ketonic ester, and yields *m*-nitrobenzaldehyde when ozonized. It is, therefore, an open-chained compound that has a methoxyl group in the β-position.



I II III

When the same cyclopropane derivative is allowed to react in the cold with a methyl alcoholic solution of sodium dimethyl malonate—a relatively strong base—it is rapidly and quantitatively converted into the sodium salt of an unsaturated compound which contains two malonic ester residues and likewise gives *m*-nitrobenzaldehyde when ozonized

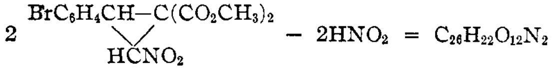


IV

From these two reactions it is clear that bases open the new cyclopropane derivative between the carbon atoms numbered 1 and 3. Since this is the same point at which they open the chain in the nitrocyclopropane derivative represented by A while that in C is opened between the atoms numbered 2 and 3, it is evident also that the presence or absence of hydrogen in the 1-position does not affect the process.

By using cold concentrated sodium methylate it was possible to secure a substance which appears to be an intermediate in the process by which the ring is opened. The cyclopropane derivative dissolved readily in the cold methylate, forming a dark red solution which by suitable manipulation could be made to yield a red crystalline sodium compound that still contained nitrogen and also had additional methoxyl. While this sodium compound appeared to be an addition product, it was not possible to establish this with certainty because the substance is extremely unstable and we found no way to purify it. Its remarkable red color is not due to the *m*-nitro group because unsubstituted nitrocyclopropanes of the same type likewise develop this color.

When this red sodium compound was added to a cold solution of hydrogen chloride in dry methyl alcohol it formed nitrous acid, sodium chloride, a yellow, and a colorless organic compound. The yellow product is the same unsaturated methoxyl compound (II) that is formed by the action of methyl alcoholic potassium acetate on the cyclopropane derivative. The colorless product is more interesting, because its composition and molecular weight show that it is formed from two molecules of the cyclopropane in accordance with the equation



The behavior of this colorless substance is peculiar. It is extremely sensitive to basic reagents. In the presence of sodium methylate it combines with two molecules of methyl alcohol and forms, quantitatively, two molecules of the yellow unsaturated methoxyl compound II. It likewise combines with sodium dimethyl malonate in the cold and forms—again quantitatively—the same unsaturated compound (III) that is obtained by the interaction of the malonate and the cyclopropane derivative. Even potassium permanganate, which does not attack the cyclopropane derivative, readily oxidizes this colorless product in the cold. All these basic reagents cleave the molecule symmetrically.

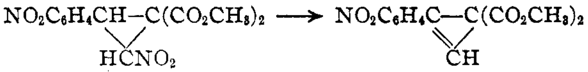
Toward acidic reagents the colorless substance is comparatively indifferent. Acids inhibit its reaction with permanganate. It does not combine with bromine. By prolonged heating with excess of bromine the two hydrogen atoms that are not located either in the phenyl or in the ester groups are replaced step by step but the carbon skeleton of the molecule remains intact. The skeleton even survives the action of concentrated sulfuric acid, which deprives the substance of two ester groups without causing cleavage. Acidic reagents in no circumstances bring about the symmetrical cleavage that invariably accompanies the action of bases.

The peculiar properties of this colorless product may be summed up in the statement that it behaves toward acidic reagents as if it were saturated and toward basic reagents as if it were an extremely sensitive unsaturated compound. Such peculiar properties must be due to an equally peculiar structure. Since the substance is cleaved symmetrically, it may be assumed that it is composed of two halves each of which has the skeleton that is present in all of its cleavage products, namely

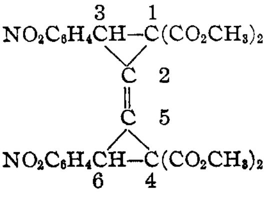
$$NO_2C_6H_4{-}C{-}C{-}C(CO_2CH_3)_2$$

For each of these skeletons but one hydrogen atom is available, and neither of these two hydrogen atoms is sufficiently active to be detected by the Zerewitinoff method; neither is, therefore, in the α-position to the ester groups. The substance is slowly attacked by ozone but it gives neither nitrobenzaldehyde nor nitrobenzoic acid when ozonized—therefore does not, like its cleavage products, have an outlying $NO_2C_6H_4CH{=}$group.

The formation of the substance is associated with the elimination of nitrous acid from the cyclopropane derivative. As far as is known the only way in which this can occur is that represented by the equation



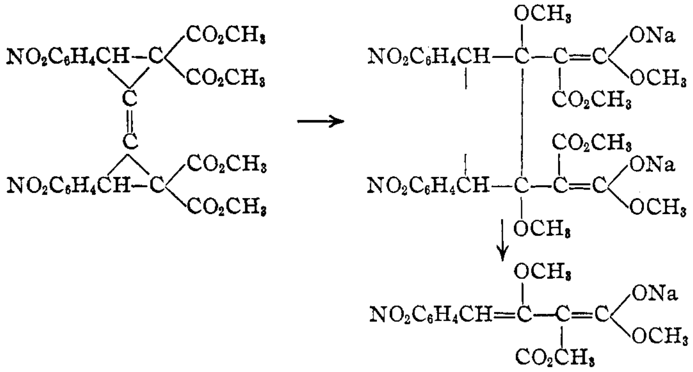
Polymerization of the resulting cyclopropene derivative in a manner that is common in ethylenic compounds would involve the usual shift of the hydrogen and of double linkages, and would lead to the formula indicated.



V

This peculiar formula, in our opinion, best expresses our present knowledge of the substance. It doubtless represents a structure with considerable internal strain, but it is not possible to construct a cyclic model that meets the requirements and has less. It manifestly accounts for the lack of active hydrogen atoms, the inability to add bromine, the sluggishness toward ozone, and the fact that ozonization does not result in nitrobenzaldehyde.

The formula also is consistent with and to a degree accounts for the cleavage of the dimer by bases. Addition of sodium methylate to a substance so constituted would, as is usual in the case of cyclopropane derivatives, lead to a 1,4-addition product, the sodium going to carbonyl, the methoxyl either to the 2- or 3-positions in the upper ring and to the corresponding positions in the lower ring. In the case of so novel a structure it would be reckless to choose between these alternatives; but if we assume that for adequate reasons the methoxyl groups seek the positions 2 and 5, then the necessary readjustments within the molecule will inevitably result in rupture of the rings between atoms 1 and 3 and between atoms 4 and 6, in cleavage between atoms 2 and 5, and in the formation of the cleavage product that is actually obtained



Experimental Part

The general scheme for securing our parent substance was the same that has been used for obtaining a number of cyclopropane derivatives—the preparation of the proper unsaturated compound, addition of nitromethane, bromination of the addition product, and elimination of hydrogen bromide from the bromo compound. In order to be able to select the most advantageous materials, we carried out these preliminary operations with a number of closely related substances.

Thus we prepared not only the methyl ester of benzalmalonic acid but also the methyl and ethyl esters of *p*-nitrobenzalmalonic and *m*-nitrobenzalmalonic acid. Except in solubility and melting point the nitrated members are, naturally, very similar to benzalmalonic esters, but we found that they combine much more readily with methyl alcohol and that the resulting addition products are sufficiently stable to survive bromination.

The unsaturated esters were prepared by the method of Knoevenagel.[1] The methyl alcohol addition products were formed by adding one equivalent of sodium methylate to methyl alcoholic solutions of the esters and, within a minute, acidifying with glacial acetic acid; the brominations

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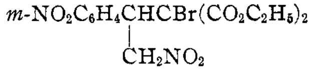
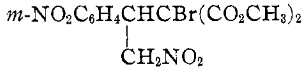
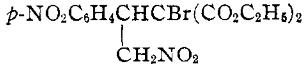
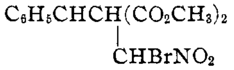
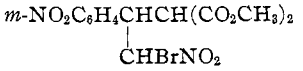
[1] Knoevenagel, *Ber.*, **31**, 2593 (1898).

were carried out in dry chloroform at the ordinary temperature. All yields were good. The properties of the new substances are given in the following table.

No.	Formula	M. p., °C.	Appearance	Analyses Calcd. C	Calcd. H	Calcd. OCH_3	Found C	Found H	Found OCH_3
VI	p-$NO_2C_6H_4CH{=}C$- $(COCH_3)_2$	133–134	Leaflets	54.3	4.1		53.9	4.2	
VII	m-$NO_2C_6H_4CH{=}C$- $(CO_2CH_3)_2$	98–99	Small prisms	54.3	4.1		54.1	4.1	
VIII	m-$NO_2C_6H_4CH{=}C(CN)$- CO_2CH_3	135–137	Fine needles	57.0	3.3		57.3	3.4	
IX	p-$NO_2C_6H_4CH(OCH_3)CH$- $(CO_2CH_3)_2$	116	Leaflets	52.5	5.1	31.3	52.5	5.0	30.7
X	m-$NO_2C_6H_4$—$CH(OCH_3)$- $CH(CO_2CH_3)_2$	66	Plates	52.5	3.1	31.3	52.3	5.1	30.0
XI	p-$NO_2C_6H_4CH(OCH_3)$- $CBr(CO_2CH_3)_2$	133	Diamond-shaped	41.5	3.8	24.7	40.7	3.8	24.9
XII	m-$NO_2C_6H_4CH(OCH_3)$- $CBr(CO_2CH_3)_2$	78–80	Plates	41.5	3.8	24.7	40.9	3.7	22.4

The Nitromethane Addition Products.—The method used for adding nitromethane to the unsaturated esters was essentially that given by Kohler and Engelbrecht.[2] For preparing the α-bromo compounds the addition products were treated with bromine in dry chloroform with the help of sunlight to start the reaction when this was necessary, and the bromo compounds were isolated by removing excess bromine and solvent under diminished pressure at the ordinary temperature. For bromination in the γ-position a solution of the addition product in sodium methylate was added to a solution of bromine in dry methyl alcohol. The mixture was evaporated to crystallization under diminished pressure, then diluted with water.

No.	Formula	M. p., °C.	Form	Analysis	Calcd.	Found
XIII	 $m\text{-}NO_2C_6H_4\underset{\substack{\mid\\ CH_2NO_2}}{C}HCBr(CO_2C_2H_5)_2$	85.5	Small rhombs	C H	41.6 3.9	41.3 4.1
XIV	 $m\text{-}NO_2C_6H_4\underset{\substack{\mid\\ CH_2NO_2}}{C}HCBr(CO_2CH_3)_2$	123	Needles or cubes	C H	38.5 3.2	39.1 3.4
XV	 $p\text{-}NO_2C_6H_4\underset{\substack{\mid\\ CH_2NO_2}}{C}HCBr(CO_2C_2H_5)_2$	88	Needles	C H	41.6 3.9	41.6 4.1
XVIa	 $C_6H_5CH\underset{\substack{\mid\\ CHBrNO_2}}{C}H(CO_2CH_3)_2$	81.5–83	Cubes	C H	43.3 3.9	43.4 4.0
XVIb	Isomer	107–109	Needles	C H	43.3 3.9	43.7 4.1
XVII	 $m\text{-}NO_2C_6H_4\underset{\substack{\mid\\ CHBrNO_2}}{C}HCH(CO_2CH_3)_2$	147–148	Prisms	C H	38.5 3.2	38.7 3.3

The Cyclopropane Derivative.—Of all the bromine compounds tabulated, the last (XVII) alone gave a satisfactory yield of a cyclopropane.

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[2] Kohler and Engelbrecht, THIS JOURNAL, **41**, 764 (1919).

Fortunately this gave a single substance in almost calculated quantity. The procedure was as follows.

Dimethyl 2-(3-Nitrophenyl)-3-nitrocyclopropane Dicarboxylate, I.—Equal weights of the γ-bromo compound XII and potassium acetate were added to sufficient dry methyl alcohol to dissolve all of the acetate at the boiling point. The suspension was boiled until all of the bromo compound had dissolved, then diluted with enough water to dissolve the precipitated potassium bromide. From the resulting clear light yellow solution, the cyclopropane crystallized in almost the theoretical quantity. It was purified by recrystallization from methyl alcohol.

Anal. Calcd. for $C_{13}H_{12}O_8N_2$: M, 324; C, 48.1; H, 3.7. Found: M, 322; C, 48.1; H, 3.8.

The substance is moderately soluble in most organic solvents. It crystallizes in small hexagonal plates and melts at 122–123.5°. It does not reduce a solution of potassium permanganate in acetone.

The same substance was obtained in a similar manner from the α-bromo compound IX. Since it is much easier to prepare this bromo compound than its isomer XVI, many efforts were made to find a satisfactory method for converting it into the cyclopropane derivative, but the yield was in all cases very small.

Reaction between the Cyclopropane Derivatives and Basic Reagents.—The cyclopropane derivative, like all the other nitrocyclopropanes, is very sensitive to bases. We studied the action of methyl alcoholic potassium acetate, aqueous alkalies, dilute and concentrated sodium methylate and the sodium derivative of dimethyl malonate. All of these reagents dissolve the substance and form brilliant red solutions, but the last alone forms a single product which is formed quantitatively and is readily isolated.

Reaction with Sodium Dimethylmalonate, Methyl Benzalpropanetetracarboxylate.—A solution of 0.8 g. of sodium in 35 cc. of dry methyl alcohol containing 7 g. of dimethyl malonate was cooled in ice water. To this solution was added 5 g. of the cyclopropane derivative. It dissolved promptly, forming a deep red solution which was boiled for a few minutes, then cooled again to 0° and poured into cold dilute hydrochloric acid. The pale yellow oil that precipitated soon solidified. By recrystallization from methyl alcohol the solid was obtained as small colorless prisms melting at 92–94°.

Anal. Calcd. for $C_{18}H_{19}O_{10}N$: C, 52.8; H, 4.6. Found: C, 52.9; H, 4.8.

The substance is very soluble in ether and boiling methyl alcohol. It neither combines with bromine nor reduces permanganate in acetone.

Ozonization.—A current of ozonized oxygen was passed through a solution of 1 g. of the substance in ethyl bromide. At the outset the absorption of the ozone was complete. After an hour, the solution was shaken with ice water and then freed from solvent in a current of air. It left an oil. This was dissolved in methyl alcohol and treated with semicarbazide. The methyl alcoholic solution soon began to deposit a crystalline semicarbazone which melted at 233–236°. The melting point remained the same when the substance was mixed with the semicarbazone of *m*-nitrobenzaldehyde.

Methyl Alcoholic Potassium Acetate.—A solution of 1 g. of the cyclopropane derivative and 3 g. of potassium acetate in 25 cc. of methyl alcohol was boiled for fifteen minutes, during which it turned to a bright red color. On concentrating and cooling, it deposited 0.4 g. of unchanged cyclopropane derivative. The mother liquors yielded, in addition to a small quantity of discolored oil, 0.3 g. of a substance that crystallized in yellow needles and melted at 104–105°. The same substance was obtained in larger amounts by the action of sodium methylate.

Aqueous Alkalies and Sodium Methylate.—The cyclopropane derivative is soluble in aqueous alkalies and in dilute sodium methylate but it is not possible to get solid products by acidifying the resulting red solutions. Solid products were finally obtained in the following manner. A solution of 10 g. of sodium in the smallest possible quantity of methyl alcohol was cooled in a freezing mixture to −5°. To this cooled solution was added, with constant shaking, 10 g. of the substance in the form of minute crystals or a fine powder. The solution at once became yellow and soon turned red. In order to hasten solution, the flask was removed from the freezing mixture and shaken until solution was complete and crystallization started. It was then returned to the freezing mixture to complete the crystallization.

The red crystalline product was collected on a suction filter, drained as completely as possible and finally washed thoroughly with anhydrous ether. Various preparations were analyzed but the results have no significance because no two preparations gave the same values. It is variable in composition, too sensitive for recrystallization, and it deteriorates at the ordinary temperature. It dissolves in water to a strongly alkaline red solution containing sodium nitrite. The yield was, uniformly, 7–7.5 g. from 10 g. of the cyclopropane derivative.

Action of Acids on the Red Sodium Compound.—When the sodium compound is acidified in the usual manner it yields only oily products. To get solids it is necessary to add the sodium compound to the acid. The best procedure was found to be as follows. The freshly prepared red material was ground and added gradually to an ice cold solution of hydrogen chloride gas in dry methyl alcohol. The red color disappeared and salt was precipitated. After dilution with water the solution was extracted with ether. The ethereal extract on evaporation deposited two products—one yellow and the other colorless. The mixture was separated by crystallization from a mixture of ether and petroleum ether. The relative amounts of these products varied with different samples of the red product, but the total yield was usually 4.5 g. from 7.5 g. of the red compound.

Dimethyl β-Methoxy-γ,β-nitrophenyl Vinyl Malonate, (II).—The yellow product, obtained as described in the preceding paragraph, is identical with the substance that was obtained by the action of methyl alcoholic potassium acetate on the cyclopropane derivative. It crystallizes from methyl alcohol in plates and from ether–petroleum ether in thin needles which melt at 104–105°.

Anal. Calcd. for $C_{14}H_{15}O_7N$: C, 54.4; H, 4.9; OCH_3, 30.1; M, 309. Found: C, 54.2; H, 5.0; OCH_3, 30.1; M, 301.

Ozonization.—A current of ozonized oxygen was passed through a solution of 0.45 g. of the yellow unsaturated compound in ethyl bromide for fifty minutes, after which the solvent was removed under diminished pressure and the residue shaken with ice water. The resulting colorless oil, when boiled with methyl alcoholic semicarbazide hydrochloride, formed the semicarbazone of *m*-nitrobenzaldehyde.

Hydrolysis to *m*-Nitrophenacyl Dimethyl Malonate.—A solution of 2 g. of the yellow unsaturated compound in aqueous methyl alcohol containing a little hydrochloric acid was boiled for an hour and a half, during which the color disappeared. The solution was then diluted with water and extracted with ether. After washing with sodium bicarbonate, the ethereal solution was shaken with saturated aqueous copper acetate, which precipitated a gray-green crystalline solid. The solid was recrystallized from benzene, from which it separated in fine needles melting, with decomposition, at 195–200°.

Anal. Calcd. for $(C_{13}H_{12}O_7N_2)Cu$: C, 48.0; H, 3.7; Cu, 9.8. Found: C, 47.8; H, 3.7; Cu, 9.6.

The free ketonic ester was obtained by shaking a suspension of the copper derivative in ether and methyl alcohol and with a little dilute aqueous hydrochloric acid. After several recrystallizations from ether–petroleum ether it was obtained in the form of fine needles melting at 64–66°.

Anal. Calcd. for $C_{13}H_{13}O_7N$: C, 52.9; H, 4.4. Found: C, 53.5; H, 4.8.

Reaction with Semicarbazide.—When the ketonic ester is allowed to react with semicarbazide in the usual manner, it gradually deposits a crystalline solid which melts at 177–179°. This is, doubtless, a cyclic compound because its composition corresponds to that of a substance formed from the semicarbazone by loss of water.

Anal. Calcd. for $C_{14}H_{14}O_6N_4$: C, 50.9; H, 4.2. Found: C, 50.8; H, 4.5.

The Dimeric Product, VI.—This colorless substance always constitutes the major portion of the mixture obtained by treating the cyclopropane derivative with bases and acidifying. It crystallizes in needles and melts at 115–116°.

Anal. Calcd. for $C_{26}H_{11}O_{12}N_2$: M, 555; C, 56.3; H, 4.0; OCH_3, 22.4. Found: M, 566; C, 56.1; H, 4.2; OCH_3, 22.9.

Oxidation.—A solution of the substance in acetone reduced a solution of permanganate in the same solvent as rapidly as it was added. The principal oxidation product was *m*-nitrobenzoic acid, which was identified by comparison with a sample on hand. In addition to this there was formed a minute quantity of a neutral oil which could not be identified. A current of ozonized oxygen containing about 6% ozone was passed through a solution of the substance in pure dry ethyl bromide. Ozone appeared in the effluent gas from the outset, and no ozonide appeared in the liquid. After one and one-half hours the solvent was removed and the residue decomposed in the usual manner; it yielded only oily neutral products. When these oils were collected in methyl alcohol and treated with semicarbazide they formed a minute quantity of the semicarbazone of *m*-nitrobenzaldehyde. Repeated ozonizations in chloroform and in glacial acetic acid likewise gave only oily products.

Bromination.—The colorless substance does not combine with bromine. A chloroform solution containing one equivalent of bromine was boiled for two hours, then allowed to stand overnight. After removing solvent and excess of bromine there remained a colorless oil that soon solidified. The solid crystallized from a mixture of methyl alcohol and benzene in fine silky needles melting at 154–155°.

Anal. Calcd. for $C_{26}H_{21}O_{11}N_2Br$: C, 49.6; H, 3.5. Found: C, 49.6; H, 3.6.

This substance is evidently a monobromo derivative of the cyclic compound. When it was boiled with excess of bromine in chloroform it very slowly lost hydrogen bromide but even after twenty hours some unchanged substance was recovered along with oily bromine compounds.

Action of Concentrated Sulfuric Acid.—Five grams of the finely powdered substance was added to 50 cc. of pure concentrated sulfuric acid. The substance dissolved to a clear colorless solution which gradually became yellow, acquired the odor of sulfur dioxide and evolved a small quantity of gas. After fifteen minutes the solution was stirred into chipped ice. A light yellow solid separated. It was collected on a filter, thoroughly washed with water and dissolved in ether. The dried ethereal solution on evaporation deposited a mixture of two substances, which was separated by laborious fractional crystallization from mixtures of chloroform, benzene and petroleum ether.

One of the substances crystallized from benzene and petroleum ether or chloroform and petroleum ether in colorless plates that melt with effervescence at 122°. The effervescence is due to water of crystallization. The same substance crystallizes from methyl alcohol in colorless needles which melt at 156–157°, which is also the melting point of the dehydrated form.

One of the substances has a tendency to extract amorphous coloring matter from the solution and separate in orange colored crystals, but if its solution in benzene is shaken with fuller's earth and then diluted with petroleum ether, it separates in stout canary-yellow needles that soften at 135° and melt at 140°.

Anal. Calcd. for $C_{22}H_{18}O_8N_2$: M, 438; C, 60.3; H, 4.1; OCH_3, 14.0. Found: M, 458; C, 60.0; H, 4.0; OCH_3, 12.7.

The substance is readily soluble in benzene and in chloroform, sparingly soluble in ether and in methyl alcohol. It reduces permanganate rapidly but *m*-nitrobenzoic acid was the only product that could be isolated.

The second substance that was formed by the action of concentrated sulfuric acid separated from benzene and petroleum ether in colorless plates which melted with effervescence at 122°. The effervescence is due to loss of water, which can be removed by heating it at 100° in a Fischer pistol. Since the molecular weight of the hydrated form in freezing benzene is only about half that of the anhydrous form, the loss is evidently due to water of crystallization. The anhydrous form crystallizes from methyl alcohol in colorless needles and melts at 157°.

Anal. Calcd. for $C_{24}H_{20}O_{11}N_2.H_2O$: H_2O, 3.4. Found: H_2O, 3.0.

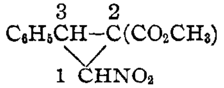
Anal. Calcd. for $C_{24}H_{20}O_{11}N_2$: M, 512; C, 56.2; H, 3.9; OCH_3, 12.1. Found: M, 528; C, 55.5; H, 4.1; OCH_3, 14.3.

This substance seems to be some sort of an anhydride of a dibasic acid formed by hydrolysis and reduction of the dimer. It is not an acid and it differs from all the other complex products in that it does not reduce permanganate in acetone.

Reaction with Basic Reagents, Sodium Methylate and Sodium Dimethyl Malonate.—A quarter of a gram of the "dimer" was dissolved in an excess of dilute sodium methylate at the ordinary temperature and the resulting red solution acidified with dilute acid. It deposited the unsaturated yellow methoxyl compound in the calculated quantity. The reaction with sodium dimethyl malonate was carried out in the same manner. The dimer behaved exactly like the cyclopropane derivative and gave an excellent yield of the same *m*-nitrobenzal derivative.

Summary

1. The action of bases on the cyclopropane derivative



$$\overset{3}{C_6H_5CH}-\overset{2}{C}(CO_2CH_3) \quad 1\ CHNO_2$$

results in ring cleavage between the carbon atoms in Positions 2 and 3.

2. By operating in a very particular manner it is possible to isolate a dimeric product which has a peculiar structure and which appears to be an intermediate between the cyclopropane derivative and the open-chained ethylenic cleavage products.

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