[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

The Interaction of Dimethylmalonyl Chloride with Malonic Ester. A New Synthesis of Filicinic Acid[1]

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The reaction of dimethylmalonyl chloride with two equivalents of methyl sodiomalonate is shown to form a crystalline substance of empirical formula $C_{15}H_{18}O_9$. Various possible structures for this compound are considered in the light of its chemical properties, and a decision is reached, based upon the transformation of the substance into filicinic acid, in favor of the structure 1,1-dimethyl-3,5,5-tricarbomethoxy-4-methoxy-3-cyclohexene-2,6-dione.

The literature describes the results of only a few investigations of the action of acid chlorides of dibasic acids upon sodiomalonic esters. Phthaloyl chloride was the first such acid chloride studied,[3] and it was concluded that prior to its reaction it was isomerized to the cyclic dichlorolactone form[4] so that the initial product of the reaction was postulated to be the malonylidene derivative I. More recently a study was reported of the action of succinyl chloride upon sodiomalonic ester.[5] On the basis of hydrogenation and degradative evidence Ruggli and Maeder concluded that the product of the interaction of *two equivalents* of sodiomalonic ester with *one equivalent* of succinyl chloride was also to be represented by an unsymmetrical malonylidene structure. It was agreed by both groups of workers, however, that additional sodiomalonic ester acted to open the lactone rings, forming as final products symmetrical diketodimalonates of structures analogous to II.

Our attention turned to the study of dimethylmalonyl chloride, since comparable reactions should lead to the dimethylmalonyl dimalonate II, a substance that was required in quantity. It was realized that the Thorpe-Ingold effect[6] might be sufficiently operative to overcome the strain involved in forming a four-membered ring,[7] and so permit the initial isomerization to the dichlorolactone form (as was the case with the other acid chlorides). However, if other structural factors were to prevent the operation of this effect, the direct formation of the desired diketodimalonate II *via* the action of *excess* sodiomalonic ester upon the acid chloride seemed eminently feasible.

As the result of protracted studies conditions were established for the formation of a crystalline substance by the action of dimethylmalonyl chloride upon methyl sodiomalonate.[8] This compound, however, possessed properties considerably at variance with those to be predicted for the expected product, $C_{15}H_{20}O_{10}$ (II), and it is with the structure of this substance, hereinafter referred to as compound A,[9] that this paper is mainly concerned.

Analytical data, methoxyl and molecular weight determinations established the empirical formula of compound A to be $C_{15}H_{18}O_9$. It will be apparent immediately that this product could have resulted from a spontaneous irreversible dehydration of the desired diketodimalonate. As the sequel will show, this is the case, and it should be mentioned that, despite considerable experimentation, it proved impossible to isolate any of the desired intermediate diketodimalonate. However, there are, in all, three possible reaction courses whereby compound A could be formed, any one of which was as valid, *prima facie*, as another. Thus it was possible that, as the result of isomerization to the dichlorolactone, the unsymmetrical malonylidene III might be the intermediate product. Further reaction of this with malonic ester *via* dehydration could lead to the dimalonylidene structure IV, which is empirically equal to compound A.

On the other hand, the normal acid chloride might react with one equivalent of malonate ion to form the cyclobutanedione malonate V. Such would be roughly analogous to the well-known Perkin cyclization.[10] Further action of malonic ester might lead, through elimination of water, to the malonylidenecyclobutanone malonate VI. In addition the possibility exists that the expected product did form but underwent immediate dehydration. There are two routes whereby this might occur which lead to two structures different from either IV or VI. In the sequence II → VIII hypothetical structure VII represents a formulation containing one normal enolization in the acetoacetic ester sense, and one abnormal carbomethoxy enolization in the malonic ester manner.[11] Dehydration of this di-enol could give the malonylidenemethoxydihydro-γ-pyrone (VIII), and this must be considered a possible structure for compound A. Alternatively, hypothetical structure IX in the sequence II → X represents an abnormal carbomethoxy mono-enol, dehydration of which through the enolic hydroxyl and malonic hydrogen would result in carbon alkylation, furnishing the methoxycyclohexenedione X, as the final possible structure.

All of these structures, IV, VI, VIII and X would accommodate the facts that compound A was a neutral substance immediately attacked by dilute potassium permanganate. However, a delayed enol test with ferric chloride solution (requiring about five minutes) would appear to eliminate structure VI, in view of the probability that the

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[1] Presented at the Organic Division of the National Meeting of The American Chemical Society, Atlantic City, N. J., September 19, 1952.

[2] From the doctoral dissertation of Thomas E. Gompf, The Johns Hopkins University, 1952.

[3] J. Wislicenus, *Ann.*, **242**, 23 (1887).

[4] E. Ott, *ibid.*, **392**, 245 (1912).

[5] P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **26**, 1476 (1943).

[6] C. K. Ingold, *J. Chem. Soc.*, **127**, 387 (1925).

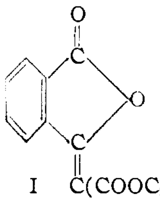
[7] Compare H. Staudinger, *Ber.*, **41**, 2208 (1908).

[8] The methyl ester was used after earlier work showed the difficulties involved in obtaining solid products from ethyl esters.

[9] Under slightly different experimental conditions (see Experimental part), an isomeric compound is formed. The structure of this substance has not been ascertained.

[10] W. H. Perkin, Jr., *Ber.*, **16**, 1793 (1883).

[11] Compare also the dehydration of symmetrical dialkylacetonedicarboxylic esters to form γ-pyrones; G. Schroeter, *ibid.*, **49**, 2697 (1916); E. B. Reid, THIS JOURNAL, **72**, 2853 (1950).



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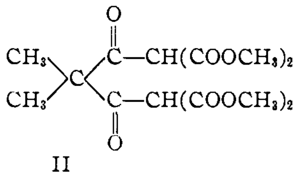

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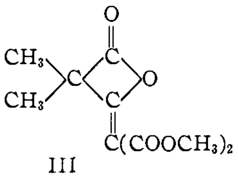

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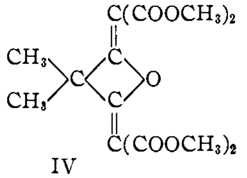

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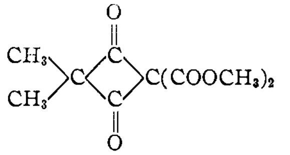

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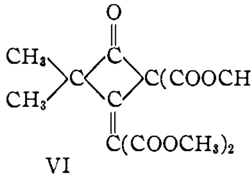

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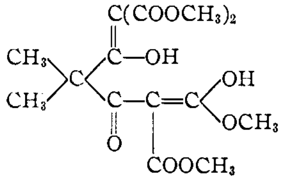

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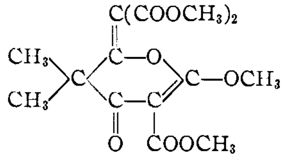

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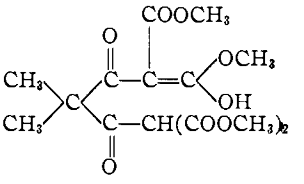

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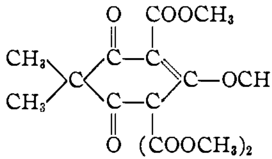

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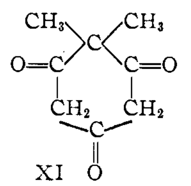

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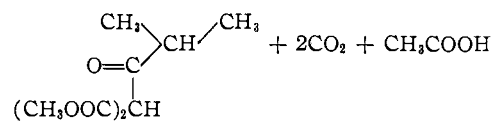

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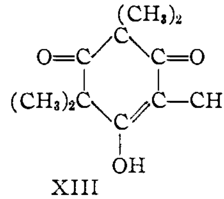

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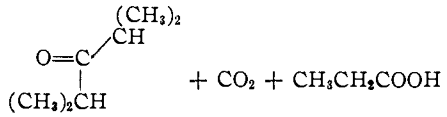

XIV

slow test resulted from preliminary hydrolysis of a β-methoxycrotonate structure. This test does not cast doubt on IV, since Ruggli and Maeder[5] found that their malonylidenesuccinyl lactone gave a delayed enol test with ferric chloride, but the fact that compound A readily absorbed one mole of hydrogen in the presence of 5% palladium, to yield a strongly enolic oil further attests to the probable presence in compound A, of a β-methoxycrotonate structure modified by attachment of a carbonyl group to the α-carbon of the ethylenic double bond. This structural requirement is afforded by VIII and X, and while it conceivably could be accommodated by IV, it renders VI exceedingly doubtful.

Chemical evidence was secured that compound A probably possessed a carbocyclic ring of six atoms. Thus, although strong base caused deep degradation, it was found that 1% sodium hydroxide at room temperature for five days effected smooth saponification. Acidification and decarboxylation resulted in the formation of filicinic acid (XI),[12] which was synthesized for comparison by the known procedure.[13] On the basis of this, together with the evidence described earlier, the conclusion is reached that compound must either be X, *i.e.* 1,1-dimethyl-3,5,5-tricarbomethoxy-4-methoxy-3-cyclohexene-2,6-dione, or a structure capable of being transformed into X by the action of mild base. For this latter alternative it may be noted that only two structures are pertinent, namely, IV and VIII, since either of these is theoretically capable of ring opening, through hydration, to yield the diketodimalonate II, which could then undergo cyclodehydration to form X.[14] To settle this point compound A was submitted to vigorous hydrolysis in hot dilute acid; under these conditions the compound yielded four moles of carbon dioxide with simultaneous formation of methyl isopropyl ketone and acetic acid. The well-known sensitivity of the vinyl system toward acid hydrolysis[15] requires that both IV and VIII should yield, with hot acid, 3,3-dimethyl-2,4-pentanedione,[16] a substance that was searched for in vain.

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[12] R. Boehm, *Ann.*, **302**, 171 (1898); **307**, 249 (1899); **318**, 230, 253 (1901); **329**, 289, 321 (1903).

[13] A. Robertson and W. F. Sandrock, *J. Chem. Soc.*, 1617 (1933).

[14] This basic hydrolysis eliminates structure VI, since under these conditions the cyclobutane ring would be cleaved. Compare the hydrolysis of ethyl 1,3-diketo-2,2,4,4-cyclobutanetetracarboxylate; H. Staudinger and H. Hirzel, *Ber.*, **50**, 1024 (1917).

[15] For example, the formation of acetaldehyde or a derivative thereof, on treatment of divinyl ether with hydroxylamine hydrochloride; A. Gulyaeva and T. Dauguleva, *Caoutchouc and Rubber* (*U.S.S.R.*), **1**, 49 (1937).

[16] A. Combes and C. Combes, *Bull. soc. chim.*, [3] **7**, 783 (1892); E. P. Kohler and J. L. E. Erickson, THIS JOURNAL, **53**, 2301 (1931); A. E. Favorskii and A. C. Onishenko, *J. Gen. Chem.*, (*U.S.S.R.*), **11**, 1111 (1941).

It occurred to us, in view of our failure to isolate 3,3-dimethyl-2,4-pentanedione from the above hydrolysis, that possibly the original dimethylmalonyl structure had been cleaved during its reaction with sodiomalonic ester. However, this was shown not to be the case, through vigorous oxidation of compound A with hot chromic acid. The isolation of dimethylmalonic acid from this oxidation clearly established the presence of either the original acyl skeleton or a structure that was oxidizable to this acyl unit. Further, since separate experiments demonstrated that filicinic acid itself was almost completely stable to hot acid under our hydrolysis conditions, we were forced to conclude that scission of carbon-to-carbon bonds occurred *prior* to ester group hydrolysis and decarboxylation. That this is definitely to be expected from structure X is apparent from consideration of the hydrolytic fission of pentamethylphloroglucinol by hot acid,[17] to yield diisopropyl ketone, carbon dioxide and propionic acid. This is shown in the sequence XIII → XIV, wherein it should be noted that the carbon dioxide is formed from either carbon 1 or 3, and the propionic acid from the remaining two ring carbon atoms, number 2 of which carries the methyl group. In an exactly analogous manner the sequence X → XII pictures the first phase of the hydrolysis of compound A to yield two moles of carbon dioxide and one of acetic acid; further action on XII would give methyl isopropyl ketone and two additional moles of carbon dioxide

Structure X is thus the only one that accommodates all the experimental evidence, and this structure is therefore proposed for compound A.

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Experimental

Compound A.—Sodium shot (10.9 g., 0.473 mole) was brought into reaction with dimethyl malonate (62.5 g., 0.473 mole) in an equal volume of dry benzene in a three-necked flask fitted with stirrer, dropping funnel and a reflux condenser carrying a drying tube. To the resulting paste was added dropwise and with rapid stirring dimethylmalonyl chloride (38.0 g., 0.225 mole) dissolved in an equal volume of dry benzene. The mixture became warm and less viscous and slowly turned yellow during the addition. After all the acid chloride was added the mixture was refluxed for one hour, cooled and cautiously acidified with 30 ml. of 50% hydrochloric acid. The organic layer was washed with sodium bicarbonate solution and water, and then dried over calcium chloride. After evaporation, the last traces of solvent together with some of the unreacted dimethyl malonate were removed from the residue by warming to about 50° under a vacuum of about 2 mm. for three hours. During this concentration solid slowly formed. Filtration of the thoroughly chilled residue gave 12.3 g. of crude white platelets (16% yield). Lesser yields were obtained by shortening or lengthening the time of refluxing, and by changing the proportions of reagents. If excess dimethyl malonate was used, no solid was obtained on concentration, but upon distillation at 2.0 mm., a small fraction of heavy yellow oil was isolated, boiling from 170–200°, which partly solidified to a white solid isomeric with compound A.

Recrystallization of crude compound A from ether–petroleum ether furnished flat needles about half an inch in length, m.p. 113–114°. The same product was obtained, though in poorer yield, if the concentration *in vacuo* was omitted.

Anal. Calcd. for $C_{15}H_{18}O_9$: C, 52.63; H, 5.30; OCH_3, 36.16; mol. wt., 342. Found: C, 52.58; H, 5.22; OCH_3, 36.02[18]; mol. wt. (micro-Rast),[19] 312.

Tests on Compound A.—Inert to sodium bicarbonate solution: rapidly attacked by neutral 2% potassium permanganate; inert to bromine in carbon tetrachloride solution; immediate negative test with dilute ferric chloride, but becoming positive on standing for five minutes or longer.

Reduction of Compound A.—Five grams (0.0146 mole) of compound A was shaken in 200 ml. of methanol containing 0.5 g. of 5% palladium-on-charcoal under hydrogen at 35 p.s.i. Just over 1 equivalent of hydrogen was absorbed within one hour, with no further reduction occurring on continued shaking. After removal of catalyst and solvent, a highly enolic oil remained. This oil would not form solid derivatives, and on attempted hydrolysis gave no recognizable products.

Oxidation of Compound A.—The procedure was based upon one previously used in this Laboratory.[20] One-half gram of compound A was dissolved in hot 25% sulfuric acid and to the hot solution was added slowly 4.0 g. of chromium trioxide dissolved in 20 ml. of water. After mixing, the solution was boiled for 15 minutes, cooled in ice, and extracted with ether. Concentration of the ether extracts and dilution with petroleum ether precipitated 20 mg. of dimethylmalonic acid, m.p. and mixed m.p. 189–190° (dec.).

Acid Hydrolysis of Compound A.—The apparatus used for the quantitative determination of carbon dioxide has been described.[20] A sample of 0.5732 g. of compound A was hydrolyzed with 50 ml. of 20% sulfuric acid at reflux temperature. After three hours the reaction was complete and 0.2933 g. of carbon dioxide had been evolved, corresponding to 3.98 moles per mole of compound A.

The residue smelled strongly of methyl isopropyl ketone, and this was isolated as the 2,4-dinitrophenylhydrazone, which failed to depress the m.p. of the authentic derivative.

The presence of acetic acid was proved by the formation of indigo with *o*-nitrobenzaldehyde[21] and a specimen of hydrolysate.

Basic Hydrolysis of Compound A.—To a mixture of 0.3 g. of compound A in 20 ml. of 1% aqueous sodium hydroxide was added 2 ml. of methanol. After two hours complete solution had been effected at room temperature. After five days at room temperature the solution was made acidic with hydrochloric acid and refluxed for four hours. The solution was then made basic and extracted several times with ether. The aqueous residue was again acidified and extracted eight times with ether. After drying, the ether was evaporated leaving several mg. of white crystalline material. Recrystallization from water gave an orange product, m.p. 208–211° (dec.). With ferric chloride solution the red-brown color typical of filicinic acid was produced. Pure white material was obtained by slow crystallization from a slightly diluted methanol solution at refrigerator temperature in a flask loosely covered with aluminum foil; this material had m.p. 214–215° (dec.).

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.01; H, 6.55.

Filicinic acid, prepared by the method of Robertson and Sandrock,[13] had m.p. 215–216° (dec.), not depressed on admixture with hydrolysis product, and forming the same color with ferric chloride solution. Final confirmation was obtained from ultraviolet absorption spectra, the spectrum of filicinic acid being superposable on that of the hydrolysis product.

It was found that filicinic acid can be obtained in somewhat better yield (10–15%) from the hydrolysis of compound A by the following modification. The five-day old basic hydrolysis solution, after extraction with ether, was evaporated to about one-tenth its original volume in a vacuum desiccator, then strongly acidified and refluxed. Chilling the acid solution caused precipitation of relatively pure though discolored product.

BALTIMORE 18, MD.

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[17] A. Spitzer, *Monatsh.*, **11**, 104 (1890)

[18] We are indebted to Dr. Bryant E. Harrell for this analysis.

[19] F. S. Schneider, "Qualitative Organic Microanalysis," John Wiley and Sons, Inc., New York, N. Y., 1946, p. 110.

[20] E. B. Reid, R. B. Fortenbaugh and H. R. Patterson, *J. Org. Chem.*, **15**, 572 (1950).

[21] F. Feigl, "Spot Tests," 2nd Edition, Nordemann Co., Inc., New York, N. Y., 1939, p. 331.