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

EFFECT OF SODIUM ON MIXTURES OF MALONIC AND SUCCINIC ESTERS.

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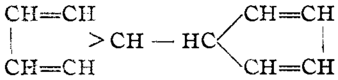
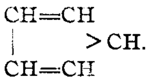
The following paper describes some work commenced by the authors which, owing to the outbreak of the war, has been indefinitely postponed. It is published with no idea of reserving the field in any way.

The original intention was to attempt the synthesis of

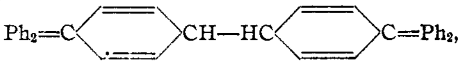


to see whether this compound showed any tendency to break up to give the radical cyclopentadienyl



$$\begin{array}{ll}CH{=}CH & \\ | & >CH.\\ CH{=}CH & \end{array}$$

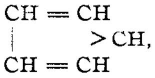
This was thought to be possible, as in accordance with Werner's theory the unsaturation of the doubly bound carbon atoms would satisfy some of the affinity of the others, and thereby weaken the junction between the two halves of the molecule. The analogy between this compound and hexaphenylethane may be readily seen if the latter be written in its quinoid form,



an analogy which can be carried over to a comparison between the colors of quinoid derivatives and those of the fulvenes.

The especial interest in the free radical, cyclopentadienyl, if it can be obtained, would be in its comparatively low molecular weight which might allow a study of its vapor and would throw light on the suggestion of G. N. Lewis[1] that the large mass of such a radical as triphenylmethyl plays an important part in the dissociation of hexaphenylethane. The existence of such small radicals might also refute the possibility that the phenomenon may be due to the size of the molecule preventing the radicals from uniting.

The five-membered ring was chosen so that should the molecule split, giving the radical



$$\begin{array}{ll}CH = CH & \\ | & >CH,\\ CH = CH & \end{array}$$

any rearrangement not involving the transfer of a hydrogen atom, since it would be essentially an α,γ shift of the unsatisfied valence, would pro-

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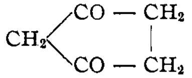
[1] Lewis, This Journal, 38, 762 (1916).

duce no change in the relative position of the trivalent carbon atom to the double bonds. A wandering of a hydrogen atom would be expected, as in the case of hexaphenylethane, to destroy the ability to give free radicals.

It was thought that by condensing malonic and succinic esters with sodium and then removing the carboxylic ester groups,



might be easily obtained and would serve as a good starting point for the type of compounds desired. This condensation did not turn out to be very promising, but following the motto "*ars brevis vita longa*" the reaction was studied somewhat more thoroughly than might be considered wise.

Experimental.

Experiment I.—0.13 mol of malonic ester was heated with 0.13 mol of succinic ester in the presence of 0.26 mol of sodium at a temperature of 100° for 3 hours. The reaction was carried out in a flask provided with a reflux condenser. Ice was added to the reddish mud obtained, which was then neutralized with hydrochloric acid and extracted with ether. The ethereal solution was washed and dried over calcium chloride; after evaporation over a water bath about 35 cc. of dark brown oil remained in which crystals appeared on cooling. The crystals were separated from the mother liquor by filtration, and were washed with ether; 2.1 g. were obtained. They were identified as succinosuccinic ester[1] by means of a mixed melting point (128°). The mother liquor consisted chiefly of unaffected esters.

Experiment II.—0.29 mol of malonic ester and 0.28 mol of succinic ester were treated in a flask provided with a reflux condenser with 0.52 mol of sodium for 45 min. in an oil bath between 110° and 142°. The resulting product was subjected to the treatment outlined in the first experiment, and from the solution, deprived of ether by distillation over a water bath, 11.5 g. of yellow crystals were obtained, the melting point of which was 124°. On recrystallizing from hot alcohol they were identified as succinosuccinic ester by a mixed melting point (128°). The mother liquor consisted chiefly of unchanged esters.

Experiment III.—The method of procedure was to dissolve 0.1 mol of sodium in 0.4 mol of malonic ester; to this 0.1 mol of succinic ester was added. The whole was heated in a flask provided with a steam reflux condenser for 4 hours in an oil bath at a temperature between 150° and 160°. At the end of the time 8.5 g. of liquid containing alcohol had distilled over. The greenish mass so obtained was treated with hot, dry benzene and filtered. After evaporating the benzene from the fil-

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[1] Vorländer, *Ann.*, **280**, 186 (1894).

trate a liquid remained which was distilled *in vacuo* when 40 g. of unchanged esters was collected. The residue, which was insoluble in benzene, was treated with 90 cc. of 1 *N* sulfuric acid in the presence of ice. After ether extraction, the ethereal layer was evaporated over a water bath. From the solution remaining 2.8 g. of white crystals separated out, the melting point of which lay between 99 and 101°. On recrystallizing they melted at 104°. The mother liquor was evaporated *in vacuo* and 3 g. of orange crystals was obtained. After purifying by recrystallization from hot alcohol several times they, together with the white crystals mentioned previously, were identified as phloroglucinol tricarboxylic ester[1] by a mixed melting point (105°).

The aqueous layer separated from the ethereal, was treated with excess of 1 *N* sulfuric acid, extracted with ether and distilled *in vacuo*. From the distillate orange crystals separated out. After two recrystallizations from hot alcohol their melting point was 120–121°. The yield was 0.065 g. after purification; and a red color was obtained with alcoholic ferric chloride.

The residue which remained after distillation *in vacuo* yielded crystals on standing several days, but when these were dissolved in hot alcohol an oil formed on cooling and this had to be treated with alcohol and ether to help it to crystallize. This gave a slightly colored powder which melted between 140–145° with decomposition. Only a trace of this substance was obtained.

Experiment IV.—0.088 mol of malonic ester and 0.044 mol of succinosuccinic ester were heated with between 0.01 and 0.02 mol of sodium in an oil bath at a temperature of 170° for about 4.5 hours. The flask was fitted with a condenser bent a few inches from the top of the flask so that the alcohol might be removed to some extent from the reaction mixture. Alcohol and some esters distilled over. The residue was treated as in Expt. I. After the ether had been distilled off, a red syrup was left from which some crystals came down after standing two days. The crystals were separated by filtration; they melted between 112 and 125°. After recrystallization from hot alcohol orange crystals, melting sharply at 132°, were obtained. The melting point was lowered to 120° by the addition of succinosuccinic ester. With alcoholic ferric chloride it gave a greenish color. Further traces of this body were obtained from the syrup from which it first crystallized by dissolving in alcohol, adding water, and allowing the oily precipitate to stand. The total yield of the crude product was small.

Experiment V.—0.044 mol of malonic ester, 0.022 mol of succinosuccinic ester and 0.03 mol of sodium were heated together in an oil bath at 170° for about 3 hours. The flask was fitted with a short reflux con-

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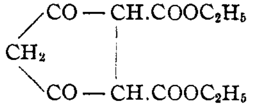
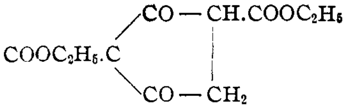
[1] Baeyer, *Ber.*, **18**, 3454 (1885); Willstätter, *Ibid.*, **32**, 1272 (1899).

denser through which steam was passed; above the jacket the tube was bent over and the distillate was collected, in all 1.6 g. It consisted chiefly of alcohol but also contained some esters. The residue was treated as in Expt. I. After removing the ether the colored syrup left behind partly crystallized. The mother liquor was separated off by filtration, and the solid purified by recrystallization from hot alcohol. 0.66 g. of a yellow substance was obtained. On dissolving the mother liquor in alcohol and precipitating with water a further crop of crystals appeared. The total yield of the crude product was nearly one gram.

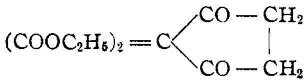
This body, after repeated purification, is a yellow crystalline solid, melting at 163°. It is soluble in ether, moderately soluble in cold alcohol and benzene, and insoluble in water. With alcoholic ferric chloride it gives an orange coloration.

An ultimate analysis corresponds to a dicarboxylic ester of diketocyclopentane, while the method of synthesis shows it to be





or



The last formula is not possible as a body of that constitution has been prepared[1] and melts at 68°.

Calc. for $C_{11}H_{14}O_6$: C, 54.5; H, 5.8; O, 39.7. Found: C, 54.1; H, 6.0; O, 39.9.

Experiment VI.—0.0058 mol of succinosuccinic ester and 0.0035 mol of phloroglucinol tricarboxylic ester were melted in a small flask fitted with an air condenser. To the mixture, which contained a trace of alcohol 0.0065 mol of sodium was added in small quantities. The flask was heated in an oil bath for 1.5 hr. at 160°.

The product was treated with hot, dry benzene and filtered. The filtrate was freed from benzene by evaporation and on standing crystals separated out. These were washed and purified: they melted at 129.5°. This is the same substance as that obtained in Expt. V as a mixture of the two melted at 131°.[2]

The residue consisting of undissolved sodium salts was neutralized with 5 to 6 cc. of 1 *N* sulfuric acid in the presence of ice, then extracted with ether, washed and dried as described in Expt. I.

The ethereal layer was then distilled and after the solvent had been re-

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[1] Scheiber, *Ber.*, **42**, 1321 (1909).

[2] Owing to an accident which happened during the combustion the compound melting at 132° was lost. The identity of the substance was not considered to be of sufficient importance to warrant any further expenditure of time on it.

moved a small quantity of a golden syrup remained which did not crystallize after standing several weeks.

The aqueous layer was further treated with 6 cc. of 1 *N* sulfuric acid and extracted with ether as before. After washing, drying and distilling a pale yellow oil was obtained which also showed reluctance to crystallize.

After the treatment recorded above a considerable quantity of a yellowish, amorphous body remained. Similar substances were found to a lesser extent in all the experiments. These amorphous products are soluble in alkali, giving a yellow solution. They are not readily soluble in organic solvents, and give strong violet color reactions with alcoholic or aqueous ferric chloride.

Discussion.

These results afford a strong confirmation of Dieckmann's[1] interpretation of the acetoacetic ester condensation in which he pointed out that the yield, owing to the reversibility of the reaction, depends largely upon the stability of the sodium salt of the resulting product.

The reaction may be written

$$3C_7H_{12}O_4 + Na^+ = \underset{\text{(solid)}}{C_{15}H_{17}O_9Na} + H^+ + 3C_2H_5OH$$

$$2C_8H_{14}O_4 + Na^+ = \underset{\text{(solid)}}{C_{12}H_{15}O_6Na} + H^+ + 2C_2H_5OH$$

and since they are reversible they are governed by the following equations:

$$\frac{(C_7H_{12}O_4)^3(Na^+)}{(C_2H_5OH)^3(H^+)} = K_1 \qquad \frac{(C_8H_{14}O_4)^2(Na^+)}{(C_2H_5OH)^2(H^+)} = K_2$$

It is obvious that in general one of these reactions will go to such an extent that the concentration of Na^+ will be too small and that of H^+ and alcohol too great for the precipitation of the other sodium salt, and that even if it had been formed before this condition was reached it would be decomposed. Also the formation of either salt will be favored by using an excess of its related ester.

This explains why in Expts. I and II in a mixture of succinic and malonic esters only the succinic ester condensed to a noticeable extent, while in Expt. III, where the malonic ester was in excess, phloroglucinol tricarboxylic ester was obtained, but no succinosuccinic ester, although the other conditions in these experiments were such that either of the esters would have condensed readily had they been pure.

The equilibrium in the liquid phase may, however, contain very different relative amounts of the various substances. Thus in Expt. IV, when very little sodium was used (this, therefore, may be considered as a homogeneous reaction) and in Expt. V, which was similar except that more sodium was present, different substances were obtained. In Expt. VI,

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[1] Dieckmann, *Ber.*, 33, 2670 (1900).

when the precipitated sodium salts were treated with benzene and filtered, the 132° body crystallized from the filtrate. This is to be expected since, just as in Expt. IV, this solution contains the products which are present in the liquid phase.

Further confirmation of the reversibility of the reaction was obtained in Expt. V, in which a succino-malonic ester was formed by replacing succinic ester by succinosuccinic ester. This reaction is probably represented by the equation

$$C_{12}H_{15}O_6Na + C_7H_{12}O_4 \rightleftarrows C_{11}H_{13}O_6Na + C_8H_{14}O_4.$$

In the earlier experiments the succinosuccinic ester was stable to this body in the presence of malonic ester owing to the higher concentration of succinic ester. It would appear that to obtain this body it would be best to use succinosuccinic ester and phloroglucinol tricarboxylic ester. However, it is likely that in these experiments the true equilibria were not reached, because the amorphous bodies obtained are more stable than any other. Too efficient conditions, therefore, are apt to form little else. So that it is not surprising that malonyl-succinic ester was not found among the sodium salts in Expt. VI.

The nature of the crystalline bodies obtained only give the major reaction which has taken place. Without doubt all the other possible substances are present in smaller amounts, at least in the liquid phase.

Owing to the lack of control in these experiments nothing definite can be said with regard to the effect of temperature on the equilibria.

Summary.

1. Equimolecular mixtures of malonic and succinic esters heated with odium give chiefly succinosuccinic ester.

2. When a large excess of malonic ester is used phloroglucinol tricarboxylic ester is found.

3. By using succinosuccinic and malonic esters malonyl-succinic ester is obtained.

4. These results are explained by Dieckmann's theory that the acetoacetic ester condensation is reversible.

[Contribution from the Richardson Chemical Laboratory of Tulane University.]

SALIVARY AMYLASE. I. A PRELIMINARY EXPERIMENTAL STUDY OF ITS STABILITY IN SALIVA.

By Rollin C. Myers and Leonard C. Scott.

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There appears to be a general view held among chemists that the enzymes as a class of substances are very prone to change, the change being marked by a slow or rapid decline of their power of degrading a given