[Contribution from the Chemical Laboratory of Middlebury College]

THE MECHANISM UNDERLYING THE REACTION BETWEEN ALDEHYDES OR KETONES AND TAUTOMERIC SUBSTANCES OF THE KETO-ENOL TYPE

II. THE CONDENSATION OF OXOMALONIC ESTER WITH CYANO-ACETIC AND MALONIC ESTERS

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Various mechanisms have been proposed for the reaction between carbonyl compounds and substances containing active hydrogen. Among these is the suggestion that aldol condensation is preceded by and is dependent upon preliminary enolization of the carbonyl compound.[1]

On this basis, the well-known ease with which benzaldehyde (a substance incapable of enolization) condenses with cyano-acetic ester, malonic ester and other substances containing active hydrogen, has been explained[2] by a sort of pseudo-enolization resulting in a tautomeric form containing bivalent carbon, $C_6H_5—\overset{|}{\underset{|}{C}}—OH$.

The inability of benzophenone to condense has been advanced as an argument for this mechanism of preliminary enolization. It is true that benzophenone cannot enolize and that it does not undergo condensation reactions, but these two facts need not be related as cause and effect. If the mechanism of condensation between aldehydes or ketones and substances containing active hydrogen is assumed to be, first, 1–2 addition to the carbonyl group—equivalent to aldol condensation—and, second, elimination of water from the addition product, then the reactivity of a carbonyl compound in condensation would run parallel with its reactivity in other addition reactions and one would predict from the sluggishness of benzophenone toward addition reactions[3] in general that benzophenone would undergo condensation with great difficulty, if at all. Thus it would be a mere coincidence that benzophenone is at the same time unable to enolize and also to condense.

Inasmuch as there are carbonyl compounds that are incapable of enolization and yet undergo addition reactions readily, it is possible to determine definitely whether enolization is involved in these condensations or not. The two most promising substances for this purpose are the esters of benzoylformic and oxomalonic acids. In a previous paper[4] it was shown

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[1] (a) Rogerson and Thorpe, *J. Chem. Soc.*, **87**, 1685 (1905); (b) Harding, Haworth and Perkin, *ibid.*, **93**, 1943 (1908); (c) Haworth, *ibid.*, **95**, 480 (1909).

[2] Ingold, *ibid.*, **119**, 329 (1921).

[3] (a) Stewart, *ibid.*, **87**, 185 (1905); (b) Petrenko-Kritschenko, *Ann.*, **341**, 150 (1905).

[4] Kohler and Corson, This Journal, **45**, 1975 (1923).

that the esters of benzoylformic acid condense with cyano-acetic and malonic esters with extraordinary ease; this paper deals with the corresponding reactions of oxomalonic ester.

The condensation of oxomalonic ester with cyano-acetic ester has already been studied by Schmitt[5] but he did not succeed in establishing the structure of any of his products. We have repeated his experiments and have established the structure of his principal product. The reaction proceeds as he assumed.

$$CO(CO_2C_2H_5)_2 + 2CH_2(CN)CO_2CH_3 \longrightarrow \underset{\text{I}}{(CO_2C_2H_5)_2C[CH(CN)CO_2CH_3]_2}$$

By hydrolysis and subsequent loss of carbon dioxide the product was converted into tricarballylic acid.

$$\underset{\text{I}}{(CO_2C_2H_5)_2C[CH(CN)CO_2CH_3]_2} \longrightarrow \underset{\text{II}}{CH_2CO_2HCHCO_2HCH_2CO_2H}$$

Besides repeating Schmitt's experiments with cyano-acetic ester, we also condensed malonic ester with oxomalonic ester. This condensation is more significant because here we were able to isolate an intermediate compound which could be formed only by the addition of malonic ester to the carbonyl group of the oxo compound.

$$(CH_3O_2C)_2CO + CH_2(CO_2CH_3)_2 \longrightarrow \underset{\text{III}}{(CH_3O_2C)_2COHCH(CO_2CH_3)_2}$$

The elements of water were eliminated from the hydroxy compound to form an unsaturated ester.

$$\underset{\text{III}}{(CH_3O_2C)_2COHCH(CO_2CH_3)_2} \longrightarrow \underset{\text{IV}}{(CH_3O_2C)_2C\!:\!C(CO_2CH_3)_2} + H_2O$$

This unsaturated compound was also obtained as the direct condensation product of the two original esters.

The unsaturated compound was reduced to the saturated ester, which in turn was hydrolyzed to the corresponding tetrabasic acid. The resulting acid decomposed on heating and formed succinic acid.

$$\begin{tikzcd}
\underset{\text{V}}{(C_2H_5O_2C)_2C\!:\!C(CO_2C_2H_5)_2} \arrow[r] & (C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2 \;\text{VI} \arrow[d] \\
HO_2CCH_2CH_2CO_2H & \underset{\text{VII}}{(HO_2C)_2CHCH(CO_2H)_2} \arrow[l]
\end{tikzcd}$$

Our results show that a substance which is incapable of enolization undergoes condensation readily. Therefore, there is no reason for assuming that aldol (or ketol) condensation involves enolization of the carbonyl compound as a preliminary step.

Experimental Part

I. Condensation of Oxomalonic Ester with Cyano-acetic Ester

Tetramethyl 1,3-Dicyano-propane-1,2,2,3-tetracarboxylate, VIII.—Thirty-seven g. of dimethyl oxomalonate was added to 55 g. of methyl cyano-acetate and to the mixture

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[5] Schmitt, *Ann. chim.*, [8] **12**, 411 (1907).

were added, with shaking, 30 drops of piperidine. The mixture became warm and darkened. It was heated under a calcium chloride tube on a steam-bath for two hours. At the end of two hours[6] drops of water could be seen floating in the oil, thus showing that reaction had taken place. On cooling and filtering (sometimes it was necessary to add some alcohol in order to induce crystallization), 20 g. of the substance in question was obtained (25% of the theoretical amount). It was crystallized from methyl alcohol; it also crystallizes nicely from dilute acetic acid. It is very soluble in acetone; less soluble in alcohol, chloroform, benzene; sparingly soluble in ether; insoluble in toluene and petroleum ether. It melts at 118–120°.[7] Schmitt gave the melting point as 120°.

Anal. Calcd. for $C_{13}H_{14}O_8N_2$: N, 8.6. Found: N, 8.9.

Molecular Weight. Calcd. for $C_{13}H_{14}O_8N_2$: 326. Found, in freezing acetic acid: 324.

Dimethyldiethyl 1,3-Dicyano-propane-1,3,2,2-tetracarboxylate, I.—This substance was obtained by the same procedure. The yield was somewhat better—42% of the theoretical amount. It melts at 114–115°. Schmitt gave 103° as the melting point.

Anal. Calcd. for $C_{15}H_{18}O_8N_2$: C, 50.9; H, 5.1; N, 7.9. Found: C, 51.4, 51.2; H, 5.1, 5.1; N, 8.0.

Molecular Weight. Calcd. for $C_{15}H_{18}O_8N_2$: 354. Found, in freezing acetic acid: 333, 369.

Ineffectual Attempt to Obtain Triethylcyano-ethylenetricarboxylate, $(C_2H_5O_2C)_2$-C: $C(CN)CO_2C_2H_5$.[5]—At first we followed Schmitt's directions, using piperidine as catalyst, but we were unable to duplicate his results.

We next used a zinc chloride catalyst.[8] This catalyst gave good results in the condensation of malonic ester but it was not very successful with cyano-acetic ester. We did, however, obtain a small amount of liquid which distilled around 170° at 5 mm. and which solidified to a waxy solid after cooling for several hours. It gave figures for molecular weight which could be applied to the cyano-ester, but Kjeldahl analysis showed but 3% of nitrogen whereas the formula for triethylcyano-ethylenetricarboxylate calls for 5.2%. We did not investigate this product further but considered it a mixture of tetra-ethylethylenetetracarboxylate (V) and triethylcyano-ethylenetricarboxylate. In several of the runs we were able to isolate small amounts of tetra-ethylethylenetetracarboxylate. This product must have been due to an impurity of ethyl malonate in our ethyl cyano-acetate.

Finally, we tried the following procedure which had been found to give good results with malonic ester. We mixed oxomalonic ester with cyano-acetic ester and added piperidine. The mixture was allowed to stand for fifteen minutes at room temperature and finally for one hour in the ice-bath. We then poured the mixture into cold, concentrated sulfuric acid, allowed the solution to stand for thirty minutes and finally poured it into water. We tried this procedure on both the methyl and ethyl esters but the only product we could isolate was the tetra ester in very small yield.

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[6] Schmitt obtained this substance and the one described below, but only after allowing the reaction to run for three weeks or so.

[7] All melting points are corrected for exposed stem and were read from a thermometer which had been calibrated against a thermometer tested by the U. S. Bureau of Standards.

[8] This catalyst was prepared by adding 100 g. of anhydrous zinc chloride to 200 g. of acetic anhydride and shaking the mixture on a shaking machine for about four hours. The greater part of the zinc chloride dissolved. The solution should be used while fresh since it becomes viscous and dark on standing.

II. Proof of the Structure of Condensation Product I

We were unable to esterify the nitrile groups in the tetramethyl dicyano ester (I) to form the corresponding hexamethyl ester,[9] but the structure of the substance was finally established by its hydrolysis and decarboxylation to tricarballylic acid (II).

Hydrolysis and Decarboxylation with Hydrochloric Acid.—Twenty g. of the ester was gently refluxed for nine hours with 200 cc. of 20% hydrochloric acid in the apparatus described by Clarke[10] for the preparation of tricarballylic acid. The solution was then heated by means of a boiling water-bath and evaporated to dryness in a vacuum. Dry air was slowly aspirated through the flask to remove the last traces of hydrochloric acid. Finally, the mixture of ammonium chloride and tricarballylic acid was dissolved in water and the solution treated with Norit. After filtering, the solution was evaporated to dryness in a vacuum. The solid was thoroughly dried by the slow aspiration of dry air through the flask and was finally extracted with acetone. The solid obtained by evaporating the acetone was washed with ether. It weighed 6.5 g., which corresponds to a quantitative yield of tricarballylic acid. The solid melted at 153–157°.

Purification of the Tricarballylic Acid Obtained by Hydrolysis.—Tricarballylic acid is difficult to recrystallize in small amounts. We tried dry ether[10] without success. Eventually, we found a method which could be applied to our crude acid. The product was dissolved in 30 cc. of acetone and to the solution was added an equal volume of benzene. The solution was heated on a steam-bath and about half of the solvent was evaporated. On cooling, the product crystallized pure and in good yield. It melted at 159–160° and was completely identified by comparison with a specimen of tricarballylic acid.[10]

III. Condensation of Oxomalonic Ester with Malonic Ester

Tetramethyl 1-Hydroxy-ethane-1,1,2,2-tetracarboxylate, III.—This was the only addition product we were able to isolate. Nine g. of dimethyl oxomalonate was added to 6.5 g. of dimethyl malonate and to the mixture was added 20 drops of piperidine. The mixture darkened and became hot. On cooling in ice the liquid quickly solidified. The product weighed 7 g. (50% of the theoretical amount) after crystallizing from methyl alcohol. Usually aldols are so prone to reverse to the original components that it is advisable to acidify slightly the solvent used in crystallization with a few drops of acetic acid in order to neutralize any traces of the alkaline catalyst which might be present. However, this aldol seemed quite stable and was recovered in good yield on crystallization from ordinary methyl alcohol. It melts at 87.5–88.5°. It is very soluble in acetone; less soluble in methyl alcohol, ether, benzene and water; insoluble in petroleum ether. It crystallizes nicely from alcohol, ether or benzene.

Anal. Calcd. for $C_{10}H_{14}O_9$: C, 43.2; H, 5.0. Found: C, 43.1; H, 4.9.

Molecular Weight. Calcd. for $C_{10}H_{14}O_9$: 278. Found, in boiling acetone: 291.

Removal of Elements of Water from Aldol.—The first dehydrating agent tried was one which often gives good results with aldols,[4] namely, glacial acetic acid. For this purpose 1.3 g. of the hydroxy compound was warmed on a steam-bath for one hour with 5 cc. of acetic acid; the solution was then poured into water. No solid was deposited. However, a 40% yield resulted through the action of concentrated sulfuric acid. Two g. of aldol was dissolved in 10 cc. of cold, concentrated sulfuric acid and the solution allowed to stand for twenty-five minutes at room temperature. On pouring into 300 cc. of water, 0.7 g. of the unsaturated product quickly crystallized. Dilute

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[9] Bischoff, *Ber.*, **29**, 1279, 1746 (1896).

[10] Clarke and Murray, "Organic Syntheses," John Wiley and Sons, Inc., New York, **1925**, Vol. IV, p. 77.

sulfuric acid, corresponding to 10 cc. of concentrated acid in 300 cc. of water, did not bring about dehydration. Neither was the unsaturated product obtained by adding molecular equivalents of oxomalonic and malonic esters to concentrated sulfuric acid, allowing the solution to stand for twenty-five minutes and then pouring into 300 cc. of water. Therefore, the unsaturated product was formed by the dehydration of the hydroxy compound and not from the original components into which the aldol might have been reversed during contact with the concentrated sulfuric acid.

Dehydration did not take place when an alcoholic solution of the aldol was treated with piperidine and allowed to stand for several days at room temperature nor when the solution was refluxed for several hours. Sodium alcoholate hydrolyzed the ester groups and yielded a sodium salt which we did not investigate.

Tetra-ethyl 1-Hydroxy-ethane-1,1,2,2-tetracarboxylate, $(C_2H_5O_2C)_2COHCH(CO_2C_2H_5)_2$.—This substance could not be isolated in pure condition since it is a liquid which cannot be distilled. It was prepared in the same way as the tetramethyl ester (III). It was obtained as a yellow, viscous liquid which reversed to the original components when subjected to vacuum distillation. Molecular weight determination in boiling acetone gave figures which could be applied equally well to the hydroxy compound or to the unsaturated ester. However, it seemed that it must be the hydroxy compound since the unsaturated ester distils nicely in a vacuum. We were unable to acetylate this product but we did obtain from it good yields of the unsaturated ester by the dehydrating action of concentrated sulfuric acid.

Eleven g. of diethyl oxomalonate was mixed with 8 g. of diethyl malonate and to the mixture was added 20 drops of piperidine. The temperature of the mixture quickly rose to 90°.[11] After standing at room temperature for fifteen minutes it was cooled[12] in ice for an hour. The thick, yellow liquid was poured into 50 cc. of cold, concentrated sulfuric acid and the solution allowed to stand for thirty minutes at room temperature. This solution was then poured with stirring into 500 cc. of water. On standing for twelve hours, 8 g. of the unsaturated ester (V) was obtained (50% of the theoretical amount). It was also established that sulfuric acid under the conditions of the experiment did not bring about condensation between ethyl oxomalonate and ethyl malonate.

Tetra-ethyl Ethylenetetracarboxylate, V.—A mixture of 66 cc. of ethyl oxomalonate, 50 cc. of ethyl malonate and 145 cc. of zinc chloride-acetic anhydride catalyst was heated in a boiling water-bath for one hour under a reflux condenser protected by calcium chloride. The mixture was then poured into 500 cc. of water and allowed to stand for twelve hours with occasional stirring. A more or less dark solid was deposited. The mixture was extracted with three portions of ether. The ethereal solution was washed several times with water to remove zinc chloride, then with sodium carbonate solution to neutralize the acetic acid and finally with water. It was then warmed with Norit, filtered and dried with calcium chloride. After distilling the ether the solid was crystallized from ethyl alcohol. The yield was 79 g. or 80% of the theoretical amount. It melts at 54.5–56.5°.

Molecular Weight. Calcd. for $C_{14}H_{20}O_8$: 316. Found, in boiling acetone: 322, 290; in freezing acetic acid: 306.

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[11] This rise in temperature is no indication that condensation has taken place between the two esters since a heating effect is observed when piperidine is added to oxomalonic ester alone.

[12] Koelichen [*Z. physik. Chem.*, **33**, 129 (1900)], in his study of the kinetics of the condensation of acetone to diacetone alcohol, showed that low temperature forced equilibrium in the direction of the addition product. Low temperature has the same effect in this condensation and also in the reaction between methyl benzoylformate and methyl cyano-acetate.

It was identified as tetra-ethyl ethylenetetracarboxylate by mixed melting point comparison with a sample prepared according to the directions of Blank and Samson.[13]

Tetramethyl Ethylenetetracarboxylate, IV.—This substance was obtained by condensing dimethyl oxomalonate with dimethyl malonate in the presence of a solution of zinc chloride in acetic anhydride. In this condensation and in the one above an excess of oxomalonate is preferable to an excess of malonate since the former is removed during extraction due to its solubility in water. Since the tetramethyl ester is not very soluble in ether the greater part of the yield was obtained by filtering off the solid rather than by ether extraction. The yield was 51% of the theoretical amount. It melts at 119–120°. This substance was identical with the product obtained by removing the elements of water from hydroxy compound III.

Molecular Weight. Calcd. for $C_{10}H_{12}O_8$: 260. Found, in boiling acetone: 240, 265.

Its identity was proved by a mixed melting point comparison with a sample of tetramethyl ethylenetetracarboxylate.

IV. Proof of the Structure of the Condensation Products

Our formula for the addition product (III) is based on the method by which it is obtained and on its relation to the unsaturated ester (IV) which is formed from it by the elimination of water. Although the unsaturated condensation product proved identical with ethylenetetracarboxylate as prepared by the method of Blank and Samson, we thought it advisable to relate its structure directly to that of succinic acid, since bromomalonic ester is capable of yielding various products with only slight changes in manipulation. We therefore reduced it to the corresponding saturated ester (VI), hydrolyzed this and decomposed the resulting acid (VII). The product was succinic acid.

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Summary

1. In the presence of a small quantity of piperidine, oxomalonic ester condenses with malonic ester as follows.

$$(RO_2C)_2CO + CH_2(CO_2R)_2 \longrightarrow (RO_2C)_2COHCH(CO_2R)_2$$

2. With zinc chloride-acetic anhydride as catalyst, oxomalonic ester reacts with malonic ester to form the corresponding unsaturated ester, which can also be formed by eliminating water from the addition product.

3. With piperidine as catalyst, oxomalonic ester reacts with 2 equivalents of cyano-acetic ester to produce compounds of type $(CO_2R)_2C[CH(CN)CO_2R]_2$.

4. It seems certain that enolization of aldehydes or ketones is not involved in the reaction between aldehydes or ketones and substances containing active hydrogen.

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[13] Blank and Samson, *Ber.*, **32**, 860 (1899).