[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE REACTION BETWEEN CYANO-ACETIC ESTERS AND BENZALACETONE

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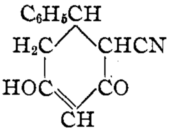
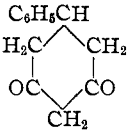
In a paper dealing with the mechanism of the reaction between ethyl cyano-acetate and ketones Haworth[1] used as one of his illustrations the condensation of this ester with benzalacetone. In this reaction he obtained an unsaturated acid for which he gives the melting point 188° and which he represents by Formula I. He hydrolyzed this first to an acid amide, II, and finally to an another monobasic acid melting at 190° to which he ascribes Formula III.

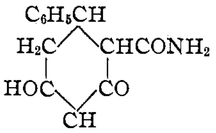
$$\underset{\text{I}}{C_6H_5CH:CHC(CH_3):C(CN)CO_2H}, \quad \underset{\text{II}}{C_6H_5CH:CHC(CH_3):C(CONH_2)CO_2H}$$

$$\underset{\text{III}}{C_6H_5CH:CHC(CH_3):CHCO_2H}$$

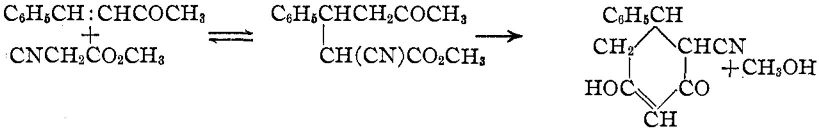
Vorländer,[2] 12 years earlier, had made a careful study of this same reaction. By almost exactly the same procedure that was used by Haworth, he obtained an unsaturated monobasic acid melting at 180°, which on complete hydrolysis gave another monobasic acid which melted at 187–188°. Vorländer showed pretty conclusively that these substances are the hydro-resorcinol derivatives represented by Formulas IV and V.


IV


V


VI

We have repeated this condensation following Haworth's procedure exactly, and obtained a product melting at 180°. Although there was no reasonable doubt that this is a hydro-resorcinol derivative, we, nevertheless, oxidized it with permanganate. The product was phenylsuccinic acid, which could not possibly be formed from the unsaturated compound represented by I, but would be the normal oxidation product of a substance represented by IV. Vorländer's conclusions are, therefore, confirmed in every respect, and Haworth's products are represented by IV, V and VI. The process by which the hydro-resorcinol derivative is formed may be represented as follows:



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[1] Haworth, *J. Chem. Soc.*, **95**, 480 (1909).

[2] Vorländer, *Ann.*, **294**, 253 (1897).

The first step constitutes Michael's reaction which, as was shown by Vorländer in the paper cited, is reversible. In the presence of the large amounts of sodium alcoholate used by Vorländer and by Haworth the concentration of the primary addition is always small but when the amount of condensing agent is reduced to a trace there is no difficulty in isolating the intermediate compound. The process is, therefore, exactly like that considered in the preceding paper, the conjugated system behaving, as usual, like an elongated carbonyl group.

Experimental Part

I. Condensation According to Vörlander and to Haworth

A suspension of sodium ethyl cyano-acetate in alcohol was made by adding 28 g. of ethyl cyano-acetate to a concentrated solution of sodium ethylate containing 5 g. of sodium. To this was added a solution of 36 g. of benzalacetone in just enough alcohol to liquefy it. When this mixture was heated it turned dark and gradually deposited a solid sodium compound. After this had been heated for an hour it was removed, washed thoroughly with absolute alcohol and ether until it became nearly white, dissolved in water, and acidified. The resulting solid, after repeated recrystallization from methyl alcohol, melted constantly at 180°; yield, 26.5%. Three more condensations carried out with variations in the conditions gave the same product.

Methyl Ether.—Dry hydrogen chloride was passed slowly into a methyl alcoholic solution of the condensation product for 15 minutes. The solution on evaporation deposited a solid which had the composition of a methyl ether, melted at 171–172°, and in every way answered Vorländer's description of the methyl ether of cyanophenyl-dihydro-resorcinol. There can, therefore, be no doubt that Haworth's product is identical with that previously obtained by Vorländer.

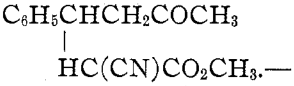
Oxidation.—A solution of 9.4 g. of the condensation product melting at 180–181° in sodium carbonate was treated with aqueous permanganate until the color no longer disappeared at the ordinary temperature; this required 33.5 g. All the organic products were collected in ether by suitable operations, and the acids were then extracted from the ether with sodium carbonate. From the carbonate solution hydrochloric acid precipitated a solid which melted at 165° and which gave a methyl ester that crystallized in tables and melted at 58°. The melting points of phenylsuccinic acid and of its methyl ester are given as 168° and 57°, respectively. As the observed melting points are slightly different from these, the ester was analyzed.

Analysis. Calc. for $C_{12}H_{14}O_4$: C, 64.8; H, 6.2. Found: C, 64.5; H, 6.4.

These results prove that the oxidation product is phenylsuccinic acid and that Vorländer's formula for the condensation product is right.

II. Condensation with a Small Quantity of Sodium Methylate

Methyl α-Cyano-β-phenyl-γ-acetyl Butyrate,



$C_6H_5\underset{\substack{|\\ HC(CN)CO_2CH_3}}{C}HCH_2COCH_3$.—

A 5% solution of sodium methylate was added drop by drop to a solution of 27.5 g. each of benzalacetone and methyl cyano-acetate until the mixture was alkaline to litmus. The solution was then boiled for about 12 hours, alkalinity being maintained meanwhile by addition of small quantities of the methylate solution as required. The resulting yellow liquid was freed from alcohol by distillation and from acids by solution in ether and extraction with sodium carbonate. The ether on evaporation left an oil. As this showed no tendency to crystallize, it was rectified under diminished pressure. The fractions collected below 190° contained unchanged ketone which was identified by its melting point and probably also unchanged cyano ester. The very pale yellow liquid distilling at about 196° at 7 mm. was analyzed; yield, 32.5 g., or 70.2%.

Analyses. Calc. for $C_{14}H_{15}O_3N$: C, 68.6; H, 6.2. Found: C, 68.7, 68.6; H, 6.2, 6.2.

The Ethyl Ester.—In the hope that the ethyl ester might solidify, ethyl cyano-acetate was substituted for the methyl ester in the condensation with benzalacetone; but it likewise was obtained only as a very viscous oil. It boils at 203° at 12 mm. The yield was 50%.

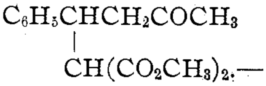
Analysis. Calc. for $C_{15}H_{17}O_3N$: C, 69.5; H, 6.5. Found: C, 69.2; H, 6.6.

Semicarbazone.—As all efforts to induce the esters to solidify were fruitless, the methyl ester was converted into a semicarbazone in order to get a solid compound for identification. To this end a strong solution containing semicarbazine and a large excess of potassium acetate was made by adding a saturated methyl alcoholic solution of potassium acetate to a concentrated solution of 4 g. of the hydrochloride in water, and removing the precipitated potassium chloride. The clear solution obtained in this way was mixed with a solution of 3 g. of the addition product in methyl alcohol and the mixture set aside. It soon began to deposit the semicarbazone in minute white needles that melted at 156–157°.

Analysis. Calc. for $C_{15}H_{18}O_3N_4$: C, 59.6; H, 6.0. Found: C, 59.3; H, 6.2.

Internal Condensation.—A concentrated methyl alcoholic solution of the methyl ester was boiled with the equivalent quantity of sodium methylate for an hour. The sodium salt which separated was washed with alcohol and ether, then dissolved in water. From the water solution acids precipitated cyano-phenyl-dihydro-resorcinol which melted at 181°.

Dimethyl β-Phenyl-γ-acetyl-ethylmalonate,



$C_6H_5\underset{\substack{|\\ CH(CO_2CH_3)_2}}{C}HCH_2COCH_3$.—

A solution of 3.5 g. of the cyano ester in methyl alcohol was saturated with hydrogen chloride and set aside. On slow evaporation it deposited a colorless solid which after recrystallization from methyl alcohol melted at 64°. The filtrate, on suitable treatment, yielded more of the same substance, the total yield being about 60%. It is much more easily obtained by direct addition of dimethyl malonate to benzalacetone. Thus a methyl alcoholic solution containing 2.4 g. of ketone and 3 g. of ester was allowed to stand at room temperature for several days during which it was kept alkaline by successive additions of a few drops of a dilute solution of sodium methylate. On evaporation it deposited a pale yellow solid, which became colorless on recrystallization. When the substance was heated alone or mixed with the product from the cyano ester the melting point was 64°.

Analysis. Calc. for $C_{16}H_{18}O_5$: C, 64.7; H, 6.5. Found: C, 64.4; H, 6.3.

The substance has neither the composition nor the properties of a dihydro-resorcinol derivative. As it does not reduce permanganate it cannot be an unsaturated compound such as would be formed by addition to the carbonyl group of the ketone. It must, therefore, have the structure assigned to it.

Summary

1. In the presence of a small quantity of sodium alcoholate, benzalacetone combines with cyano-acetic esters and malonic esters. The products are saturated compounds formed by addition to the double linkage of the ketone.

2. In more concentrated solutions of the alcoholate the addition products undergo further condensation to hydro-resorcinol derivatives. The reaction, therefore, takes place in the manner stated by Vorländer, and Haworth's interpretation is incorrect.

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

ASYMMETRIC DYES

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During the past 5 years, 35 asymmetric dyes have been synthesized in this Laboratory and studied with reference to the possibility of selective dyeing. We have held the opinion that selective absorption of an optically active form from a racemic mixture by silk, wool or living tissue would constitute evidence of chemical, rather than physical, union between the dye and the substance which it colors. Interest in this type of investigation has been stimulated by the observation that optically active forms of other types of asymmetric compounds show specific biochemical reactions.[1]

[1] Neuberg and Wohlgemuth, *Ber.*, **34**, 1745 (1901). Piutti, *Compt. rend.*, **103**, 134 (1886). Mayor, *Ber.*, **37**, 1225 (1904).