[A CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Michael Condensation. II. The Reactivity of the Addendum[1]

BY RALPH CONNOR AND DAVID B. ANDREWS

The fact that ethyl methylmalonate gave yields of 80% in the Michael condensation with benzalacetophenone[2] while ethyl phenylmalonate did not condense[3] brought to mind several questions concerning the influence of structure upon the ease with which the reaction occurs. In particular, for the bearing of these facts upon future work in this field, it seemed advisable to investigate (1) the modification in the reactivity of the addendum produced by the substitution of various alkyl groups, (2) the influence of the number of labilizing groups and (3) the possibility that the amount of enolization might bear some relationship to the reactivity.

In this and in forthcoming communications from this Laboratory references will be made to three types of products which have been reported as results of the Michael condensation. The *normal product* is the name given to that product which is formed, for example, in the reaction of ethyl methylmalonate with ethyl crotonate in the presence of a small amount of sodium ethoxide or with piperidine as a catalyst[4] (I). Under these conditions the fragments of the addendum which (in effect) add to the unsaturated system appear to be —H and $—C(CH_3)(COOC_2H_5)_2$.

$CH_3CH{=}CHCOOC_2H_5$ + $CH_3CH(COOC_2H_5)_2$ —(1/6 equivalent of $NaOC_2H_5$)→ $CH_3CHCH_2COOC_2H_5$ | $CH_3C(COOC_2H_5)_2$ I

Normal product

The *rearrangement product* is that obtained when an equivalent of sodium ethoxide is used as a catalyst[4] (II). In this product either a methyl[4] or a carbethoxyl[5] group of the addendum has migrated. In the cases where the products of

$CH_3CH{=}CHCOOC_2H_5$ + $CH_3CH(COOC_2H_5)_2$ —(1 equivalent of $NaOC_2H_5$)→ $CH_3CHCH(CH_3)COOC_2H_5$ | $CH(COOC_2H_5)_2$ II

Rearrangement product

the condensation are those which would be expected if the rearrangement product (obtained by the change in position of a carbethoxyl group through the intermediate formation of a cyclobutanone derivative according to the mechanism of Holden and Lapworth)[5] underwent the reversal of the Michael condensation, the cleavage products[6] are designated as *rearrangement–retrogression products* (III).

$C_6H_5CH{=}CHCOC_6H_5$ + $CH_3CH(COOC_2H_5)_2$ ⟶ $C_6H_5CHCH(COOC_2H_5)COC_6H_5$ | $CH_3CHCOOC_2H_5$ ↓ $C_6H_5CH{=}C(CH_3)COOC_2H_5$ + $C_6H_5COCH_2COOC_2H_5$

Rearrangement–retrogression products III

The Influence of Alkyl Groups.—The first column in Table I summarizes the results obtained by the reaction of various monosubstituted malonic and acetoacetic esters under conditions such that the normal product should be formed. It had previously been reported[7] that ethyl α-cyanopropionate did not react so readily as ethyl cyanoacetate and that in general the monosubstituted malonic esters were less reactive than the unsubstituted esters.[8] The present investigation has shown that the substitution of an alkyl group upon the active methylene group of malonic, acetoacetic or phenylacetic esters greatly diminishes the reactivity compared to the reactivity of the unsubstituted substance.

Although introduction of a methyl group upon the active methylene carbon decreases the reactivity of the system, an even greater influence is exerted when this methyl is replaced by a larger group. Thus, there is a great difference in the reactivity of ethyl methylmalonate and ethyl ethylmalonate under conditions suitable for the formation of the normal product. The same effect is also observed when the reaction is carried out under conditions that should give rise to

(1) A portion of the material in this paper was presented before the Division of Organic Chemistry at the Chicago meeting of the American Chemical Society, September 15, 1933.

(2) Michael and Ross, THIS JOURNAL, **55**, 1632 (1933).

(3) Connor, *ibid.*, **55**, 4597 (1933).

(4) Michael and Ross, *ibid.*, **52**, 4598 (1930).

(5) Holden and Lapworth, *J. Chem. Soc.*, 2368 (1931).

(6) Michael and Ross [THIS JOURNAL, **55**, 1632 (1933)] have advanced evidence to show that the formation of rearrangement–retrogression products need not be explained by assuming rearrangement followed by retrogression but may arise through the intermediate formation of trimolecular compounds.

(7) Thorpe, *J. Chem. Soc.*, **77**, 923 (1900).

(8) Kohler, THIS JOURNAL, **44**, 843 (1922).

TABLE I

ADDITION REACTIONS OF BENZALACETOPHENONE

Addendum	Normal product[a]	% Reaction Rearrangement–retrogression[m]	Normal product[r]	% of enolization[bb]
$C_6H_5COCH_3$	1[b]	...	82[s]	
$C_6H_5CH(C_2H_5)COOC_2H_5$	..	...	3[t]	
$C_6H_5CH_2COOC_2H_5$	0[c]	...	92[u]	
n-$C_4H_9CH(COOC_2H_5)_2$	0[d]	...	..	
$C_2H_5CH(COOC_2H_5)_2$	0[e]	15[n]	0[v]	Less than 0.006
$CH_3CH(COOC_2H_5)_2$	80[f]	42[o]	80[f]	
$C_6H_5CH_2CH(COOC_2H_5)_2$	0[g]	trace[p]	..	
$CH_2(COOC_2H_5)_2$	98[h]	...	93[h]	
$CH_3COCH(C_2H_5)COOC_2H_5$	0[i]	...	9[w]	3
$CH_3COCH_2COOC_2H_5$	(66)[j]	...	96[x]	7
$C_6H_5COCH_2COOC_2H_5$	93[k]	...	94[k]	22
$C_6H_5COCH_2COC_6H_5$	..	...	1[y]	100
$C_6H_5CH(COOC_2H_5)_2$	0[l]	0[q]	0[z]	..
$CNCH(COOC_2H_5)_2$	..	...	0[aa]	..

[a] Unless otherwise specified the reactions were carried out by the following general method. To 50 ml. of absolute ethanol was added 20.8 g. (0.1 mole) of benzalacetophenone, 0.1 mole of the compound to be used as addendum and 2.0 g. of piperidine. This solution was refluxed on the steam-bath for seventy-two hours and cooled. If crystals appeared they were removed by filtration, recrystallized, dried and weighed. The liquid (or the entire reaction mixture if no crystals had separated from the cold solution) was subjected to distillation to determine the amount of unreacted material. [b] In this reaction 0.46 mole of the reactants was dissolved in 450 ml. of benzene and refluxed for one hundred and twenty hours. There was obtained 1.4 g. of trimolecular compound[9] (m. p. 233° uncorr.). [c] Distillation gave 15.4 g. (94%) of ethyl phenylacetate, b. p. 115–120° (23 mm.). [d] Distillation gave 18.6 g. (86%) of unchanged ethyl n-butylmalonate, b. p. 94–96° (2 mm.). [e] After removal of the solvent the residue gave 8.4 g. of benzalacetophenone, m. p. 53–55°, when cooled in an ice-salt bath. Distillation gave 14.0 g. (75%) of unchanged ethyl ethylmalonate, b. p. 107–110° (23 mm.) and the residue gave 7.1 g. of benzalacetophenone, m. p. 53–55°. The total recovery of the ketone was 15.5 g. (75%). The recovery in this run was doubtless low because of the amount of manipulation involved. [f] This is reported by Michael and Ross.[2] [g] Distillation gave 23.5 g. (94%) of unchanged ethyl benzylmalonate, b. p. 141–150° (2 mm.). [h] Ethyl α-carbethoxyl-β-phenyl-γ-benzoylbutyrate, m. p. 70–71°.[2] [i] Distillation gave 13.2 g. (84%) of unchanged ethyl α-ethylacetoacetate, b. p. 93–97.5° (22 mm.). [j] The product isolated from this run was formed by intramolecular dehydration of ethyl α-acetyl-β-phenyl-γ-benzoylbutyrate. The compound obtained was 3,5-diphenyl-6-carbethoxylcyclohexene-2-one-1, m. p. 111–112.5°.[10] Previous investigators state[11] that the yield of dehydration product from the normal condensation product is not quantitative so that the 66% yield reported in this run may not be used in comparing the reactivity of ethyl acetoacetate with any compounds except those which undergo the same type of dehydration reaction. [k] Ethyl α,γ-dibenzoyl-β-phenylbutyrate, m. p. 135–135.5°. *Anal.* Calcd. for $C_{26}H_{24}O_4$: C, 77.96; H, 6.05. Found: C, 78.34; H, 6.18. [l] Distillation gave 21.2 g. (90%) of unreacted ethyl phenylmalonate, b. p. 144–148° (6 mm.). [m] These reactions were carried out between ethyl sodioalkylmalonate (prepared from powdered sodium in benzene and the ethyl alkylmalonate) and benzalacetophenone by the procedure of Holden and Lapworth.[5] [n] The reaction was carried out with 0.75 mole of the reactants in 95 ml. of benzene. After heating on the steam-bath for one hour the mixture was allowed to stand overnight. It was then added to 200 ml. of water containing 5 g. of acetic acid. The water layer was extracted with benzene, the combined benzene washings dried over magnesium sulfate, the solvent removed on the steam-bath and the residue distilled under reduced pressure. There was obtained 10.7 g. boiling at 105–119° (18 mm.) and 4 g. boiling at 120–160° (16 mm.). The distillation residue was very thick and tarry and could not be crystallized. Although the distillate gave a coloration with ferric chloride, no attempt was made to determine the ethyl benzoylacetate formed because of the possibility of loss due to alcoholysis (in the presence of the alcohol formed by the reaction of the sodium with the ester[3]) and due to formation of dehydrobenzoylacetic acid during distillation. The fraction boiling at 120–160° (16 mm.) was hydrolyzed with 25% KOH and 2.0 g. (15%) of α-ethylcinnamic acid obtained. It melted at 105–106° (reported m. p. 107°)[12] and had a neutral equivalent of 175.4 (calculated 176). The amide melted at 128° (reported m. p. 128°[13]). In another run in which the reactants were heated for thirteen hours there was isolated 2.6 g. (21%) of α-ethylcinnamic acid. [o] This is the result reported by Holden and Lapworth.[5] [p] In this reaction 0.1 mole of each of the reactants was used under the conditions described.[5] Upon adding the reaction mixture to aqueous acetic acid there was obtained 2.4 g. of material which did not melt below 250° (presumably trimolecular compound), 9.4 g. boiling at 100–130° (1 mm.), 5 g. boiling at 140–143° (1 mm.) and 8.5 g. boiling at 143–176° (1 mm.). The tarry residue weighed 13.4 g., would neither crystallize nor distil and was apparently polymerized chalcone. With ferric chloride solution all the distillates gave colors like that produced by a known sample of benzoylacetic ester. The boiling points of the products indicated that the ethyl benzylmalonate had undergone alcoholysis during the experiment. A trial run was therefore made

(9) Kostanecki and Rossbach, *Ber.*, **29**, 1493 (1896).
(10) Knoevenagel and Speyer, *ibid.*, **35**, 397 (1902).
(11) Kohler, *Am. Chem. J.*, **37**, 385 (1907).
(12) Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932).
(13) Perkin, *J. Chem. Soc.*, **31**, 394 (1877).

which confirmed these results. To 2.3 g. (0.1 mole) of sodium dissolved in 35 ml. of absolute ethanol was added 25 g. (0.1 mole) of ethyl benzylmalonate. The mixture was refluxed for sixteen hours, cooled, poured into 200 ml. of cold water containing 7 g. of acetic acid, extracted with ether, dried over magnesium sulfate and distilled. There were obtained 5.6 g. (34%) of ethyl β-phenylpropionate, b. p. 119–122° (12 mm.) and 12.1 g. (48%) of ethyl benzylmalonate, b. p. 165–167.5° (12 mm.). [q] This has been reported in a previous communication.[3] [r] These runs except where otherwise stated were made by the following general procedure, using as a catalyst a small amount of sodium ethoxide. To 5 ml. of absolute ethanol was added 0.75 g. (0.033 mole) of sodium, followed by 0.1 mole of the active methylene compound and 20.8 g. (0.1 mole) of benzalacetophenone in 250 ml. of dry ether. After standing for twenty-four hours at room temperature the mixture was added to 200 ml. of water containing 3 g. of acetic acid. The ether layer was separated, the aqueous layer extracted with ether, the combined ethereal washings dried over magnesium sulfate and the ether removed on the steam-bath. The residue was cooled and if a precipitate formed this was removed by filtration, recrystallized, dried and weighed. The liquid filtrate (or the entire reaction mixture if no crystals had separated upon cooling) was subjected to distillation to determine the amount of unreacted material. [s] In this run one-fifth of an equivalent of the catalyst and 0.21 mole of the reactants were used. When the first precipitate had been removed by filtration the filtrate was allowed to stand for a few days, after which another crop of crystals had formed. This process was repeated several times. There were obtained 32.1 g. (55.4%) of impure trimolecular compound, m. p. 187–189° (uncorr.) and 18.7 g. (26.8%) of the dimolecular compound, m. p. 80–83°[9] (uncorr.). [t] There was obtained 1.3 g. of trimolecular compound which did not melt below 240° and 16.1 g. (84%) of unchanged ethyl α-phenylbutyrate,[14] b. p. 113–115° (12 mm.). [u] Ethyl α,β-diphenyl-γ-benzoylbutyrate,[15] m. p. 152–154°. [v] In this run one-sixth of an equivalent of catalyst was used in order that this should be comparable to the result of Michael and Ross.[2] Distillation gave 16.4 g. (87%) of unchanged ethyl ethylmalonate, b. p. 108–111.5° (23 mm.). From the residue there was obtained 18.9 g. of benzalacetophenone (m. p. 53–56°) the identity of which was confirmed by a mixed melting point. [w] Distillation gave 8.6 g. (55%) of unchanged ethyl α-ethylacetoacetate and 13.4 g. (64%) of benzalacetophenone. After standing for three weeks the distillation residue gave 2.0 g. of material which after recrystallization from ethanol melted at 134–135°. The compound was synthesized by adding 4 g. (0.03 mole) of ethyl iodide and 6.36 g. (0.02 mole) of ethyl α-acetyl-β-phenyl-γ-benzoylbutyrate to a solution of 0.46 g. (0.02 mole) of sodium in 10 ml. of absolute alcohol. After refluxing for three hours the reaction mixture was added to 100 ml. of water, extracted with ether, dried over magnesium sulfate and the solvent removed on the steam-bath. The residue solidified and after recrystallization from ethanol melted at 135–135.5°. It showed no depression of the melting point when mixed with the product of the reaction of benzalacetophenone and ethyl α-ethylacetoacetate. Analysis indicated that in both cases intramolecular dehydration had occurred with the formation of 3,5-diphenyl-6-ethyl-6-carbethoxylcyclohexene-2-one-1. *Anal.* Calcd. for $C_{23}H_{26}O_4$: C, 75.41; H, 7.10. Calcd. for $C_{23}H_{24}O_3$: C, 79.31; H, 6.90. Found: C, 79.33; H, 6.87. [x] There was obtained 27.7 g. of the higher melting isomer,[11] m. p. 167–168°, and 4.8 g., m. p. 127–133°, of what was apparently a mixture of this isomer and the lower melting isomer (reported m. p. 121°) of ethyl α-acetyl-β-phenyl-γ-benzoylbutyrate. [y] The product gave 20.5 g. (82%) of the copper salt of dibenzoylmethane. From the extracts there was obtained 19.4 g. (93.5%) of benzalacetophenone and 0.2 g. of a white product melting at 149–150°. This presumably was the condensation product but not enough of it was obtained to permit of any detailed examination. [z] Distillation gave 41 g. (92%) of unreacted ethyl phenylmalonate, b. p. 130–135° (2 mm.) and benzalacetophenone, b. p. 168–170° (2 mm.). [aa] This is reported by Thorpe.[7] [bb] These values are those reported by von Auwers[16] and by Conant and Thompson.[17]

rearrangement–retrogression products (the second column in Table I). Furthermore, Michael and Ross[2] have previously reported that ethyl ethylmalonate and ethyl α-cyanobutyrate gave smaller yields of rearrangement products than did ethyl methylmalonate or ethyl α-cyanopropionate, respectively. Thus it seems that the decrease in reactivity is observed in any of the three types of reaction when a methyl group upon the active methylene of the addendum is replaced by an ethyl group. Another noteworthy point in this group of data is that ethyl phenylmalonate gives no rearrangement–retrogression product, although ethyl benzylmalonate does give a detectable amount.

The Influencing of Labilizing Groups.—It has been pointed out previously[3] that, in the case of ethyl phenylmalonate at least, the accumulation of labilizing groups does not cause an increase in reactivity. This statement is confirmed by the data in the third column of Table I. Thus, compounds with three activating groups (ethyl phenylmalonate and ethyl cyanomalonate) are unreactive under conditions that give quantitative yields with compounds containing two activating groups (ethyl malonate and ethyl phenylacetate) and with a compound with one activating group (acetophenone).[18] It cannot be concluded, moreover, that all compounds with the same number

(14) The authors are indebted to Dr. V. H. Wallingford of the Mallinckrodt Chemical Works for the ethyl α-phenylbutyrate used in this investigation.

(15) Avery and Jorgensen, THIS JOURNAL, **52**, 3628 (1930).

(16) Von Auwers, *Ber.*, **66B**, 955 (1933).

(17) Conant and Thompson, THIS JOURNAL, **54**, 4044 (1932).

(18) Reactivity similar to that of acetophenone is shown in varying degrees by other simple ketones, esters and nitriles but is usually complicated by the formation of both dimolecular and trimolecular compounds. A more detailed report of some of these studies will appear in a later communication.

of labilizing groups will possess the same degree of reactivity. This is demonstrated by the quantitative reaction of ethyl phenylacetate and ethyl malonate as compared to the lack of reactivity of dibenzoylmethane under similar conditions and by the fact (*cf.* the first column of Table I) that ethyl malonate reacts quantitatively with piperidine as a catalyst while ethyl phenylacetate does not react.

Comparison of Enolization with Reactivity.—The reactivity of a compound in the Michael condensation may be considered as a criterion of the activity of the methylene group involved. Still another method of classifying such groups may be in the order of enolization of the compounds. It therefore was of interest to ascertain whether or not the reactivity of active methylene groups as measured by these two methods bore any relationship. For this particular study it would have been more desirable to compare the reactivity in the Michael condensation with the amount of enolization under the conditions of the experiment. However, since there was no satisfactory way of ascertaining the latter value, the reactivity of the methylene compound as indicated by its tendency to enolize in the pure state seemed to be the next best basis for comparison.

The data in Table I indicate that there is no such relationship between these two methods of measuring the reactivities. This is shown by the fact that there is such a wide difference in reactivity among the first eight compounds listed, although they can differ only minutely in their tendency to enolize. Furthermore, ethyl acetoacetate is enolized to a greater extent than ethyl α-ethylacetoacetate and less than dibenzoylmethane but is more reactive than either of these compounds.

Summary

A study of the addition of various compounds containing an active methylene group to benzalacetophenone has indicated that no conclusion concerning the reactivity of the addendum may be drawn from the number of activating groups upon the carbon of the active methylene or from the amount of enolization. In any given structure, however, the reactivity is decreased by the introduction of substituents and the influence of methyl is much less than that of the higher alkyl groups.

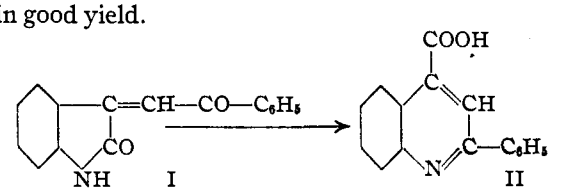
Ithaca, New York Received September 17, 1934

[Contribution from the Nichols Laboratory of New York University]

A Synthesis of 1,4-Dihydrocinchophens from 3-Phenacyloxindoles[1]

By R. N. DuPuis and H. G. Lindwall

It has been shown[2] that 3-phenacylideneoxindole (I) upon treatment with hydrochloric acid gives 2-phenylcinchoninic acid (cinchophen) (II) in good yield.



This reaction does not take place, evidently, when alkali is substituted for acid; an apparent mixture of products results and no recognizable amount of cinchophen is obtained.[3]

When 3-phenacyloxindole (III) (Chart I) is employed with hydrochloric acid as the reagent, a good yield of a (IV) chlorine-containing compound is obtained. By analogy to the case of 3-phenacylideneoxindole, and on the basis of its chemical behavior, the product was suspected of being a quinoline hydrochloride, and indeed it yielded a free base (V) upon treatment with alkali in the cold.

If the analogy to the case of the behavior of 3-phenacylideneoxindole is carried on to the extent of attempting to formulate a mechanism, such a sequence as that shown in Chart I may ensue.

It will be noted that an intermediate (not isolated) is indicated on the chart, having an hydroxyl at position 2 of the quinoline ring. Dimroth and Zoeppritz[4] were able to isolate such hydroxy derivatives in the course of the formation of a number of Schiff bases.

(1) Presented in part at the Cleveland meeting of the American Chemical Society, September, 1934.

(2) DuPuis and Lindwall, This Journal, **56**, 471 (1934).

(3) Lindwall and Maclennan, *ibid.*, **54**, 4739 (1932).

(4) Dimroth and Zoeppritz, *Ber.*, **35**, 984 (1902).