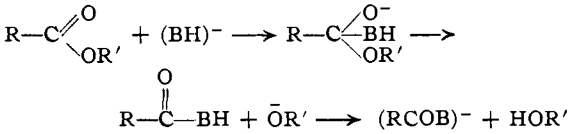
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

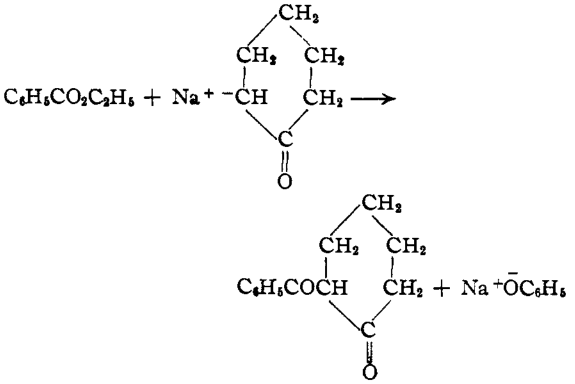
The Claisen Benzoylation of Certain Methylene Ketones with Phenyl Benzoate by the Sodium Amide Method[1]

BY CHARLES R. HAUSER, BETTY I. RINGLER, FREDERIC W. SWAMER AND DONALD F. THOMPSON

A survey of the literature has revealed that the relative reactivities of ethyl esters in the Claisen acylation of a ketone anion, which is the reactive intermediate in the condensation,[2] in general parallels the relative rates of alkaline hydrolysis of the esters.[3] For example, in both types of reaction ethyl oxalate and ethyl formate are especially reactive, ethyl acetate is more reactive than ethyl propionate or ethyl *n*-butyrate, and the latter are more reactive than ethyl isobutyrate or ethyl trimethylacetate.[4] This relationship arises presumably because the two types of reaction proceed by similar mechanisms which may be illustrated by the following general equation in which $(BH)^-$ represents hydroxyl ion or ketone anion.[5]



In the present investigation the relative rates of alkaline hydrolysis of the esters of benzoic acid have served as a guide in connection with the benzoylation of certain methylene ketones. Earlier workers have shown that only poor yields of β-diketones can be obtained with ethyl benzoate and the anions of cyclohexanone,[6] hydrindone,[7] propiophenone[8] or camphor.[9] In a further study of the reaction with ethyl benzoate and the anion of cyclohexanone, prepared by means of sodium amide, we have obtained evidence that most of the ketone self-condenses before much of its anion is benzoylated.[10] Hence a more reactive benzoylating agent appears to be required. However, benzoyl chloride is too reactive and produces mainly the O-benzoyl derivative of benzoylcyclohexanone.[6] Since phenyl benzoate undergoes alkaline hydrolysis almost thirteen times as rapidly as ethyl benzoate[3b] and yet does not usually effect dibenzoylation,[11] the phenyl ester promised to be suitable with the anions of cyclohexanone and certain other methylene ketones. This has been verified. The reaction may be illustrated as



Because part of the sodium amide or ketone anion is neutralized in converting the β-diketone to its anion,[2] there has been employed either two equivalents of sodium amide to one of ketone and one (or more) of ester (Method A),[2a] or two equivalents each of sodium amide and ketone to one of ester (Method B).[2b] Under the latter conditions half of the ketone would be recoverable. The isolation of the β-diketones was somewhat complicated by the presence of the by-product, phenol, except in the preparation of benzoylpropiophenone from which the phenol was readily extracted by alkali. In certain cases, the common copper salt method[2] was employed, but it was not entirely satisfactory, since the β-diketones were converted into, and regenerated from, their copper salts only with difficulty. In most cases, it was more convenient to isolate the β-diketones together with phenol as their sodium salts in aqueous solution and to remove the phenol from the regenerated β-diketones by distillation or by solution in water or in methanol.

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[1] Paper XL on "Condensations," reported at the Chicago Meeting of the American Chemical Society, September, 1946; paper XXXIX, THIS JOURNAL, **69**, 2325 (1947).

[2] See (a) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).

[3] For rate constants of a series of esters see (a) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 121, 211–212; (b) Eero Tommila, *et al.*, *Ann. Acad. Sci. Fennicae*, Ser. A59, No. 3, 3–34 (1942); *C. A.*, **38**, 6171 (1944).

[4] A more complete discussion will be given in the forthcoming chapter, "Acylations of Ketones to Form β-diketones," in "Organic Reactions."

[5] Since these two types of reaction may be affected differently by certain factors, no quantitative relationship should be expected. The larger ketone anion may invoke more "steric hindrance" than the hydroxyl ion. Moreover, in the Claisen condensation, the sodium ion of the sodium derivative of the ketone may coördinate to some extent with the carbonyl oxygen of the ester and permit an ephemeral ring mechanism to operate; this type of mechanism has been proposed for the corresponding magnesium derivative of the ketone (Hauser and Walker, THIS JOURNAL, **69**, 296 (1947)). It should be pointed out also that the Claisen condensation is more reversible than the alkaline hydrolysis of esters.

[6] Bauer, *Ann. chim. phys.*, **9** [1], 393 (1914).

[7] Robinson and Shah, *J. Chem. Soc.*, 610 (1933).

[8] (a) Smedley, *ibid.*, **97**, 1492 (1910); (b) Abell, *ibid.*, **101**, 989 (1912).

[9] (a) Tingle and Gorsline, *Am. Chem. J.*, **37**, 483 (1907); (b) **40**, 46 (1908).

[10] The best yield of benzoylcyclohexanone that could be isolated by employing the recently developed sodium amide methods (ref. 2) was about 10%. Benzoic acid and a mixture of high boiling products were mainly obtained. Apparently the ketone underwent aldol condensations with subsequent elimination of water which hydrolyzed the ester.

[11] In this connection see Abramovitch and Hauser, THIS JOURNAL, **64**, 2271 (1942).

TABLE I

BENZOYLATION OF METHYLENE KETONES WITH PHENYL BENZOATE

Ketone	Moles in Method A[a]	Moles in Method B[b]	β-Diketone	M. p., °C.	Method A[c] Yield %	Method B[d] Yield %	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
Cyclohexanone	0.15	0.30	α-Benzoylcyclohexanone[e]	88–89[f]	69	62 (58)[g]	77.20	77.49	6.97	7.15
Hydrindone-1	.075	.15	α-Benzoylhydrindone-1[h]	100–101[i]	80	64[g]	81.33	81.56	5.12	5.07
Tetralone-1	.13	.185	α-Benzoyltetralone-1[j]	75–77	46	33[g]	81.57	81.67	5.63	5.70
Propiophenone	.15	.15	Benzoylpropiophenone[k]	83.5–84[l]	53	46	...	...	..	..
Camphor	.10	.30	α-Benzoylcamphor[n]	87–88.5[m]	..[o]	11[g]	79.65	80.01	7.86	8.03

[a] Sodium amide, two equivalents; ester, one equivalent plus 5%. [b] Sodium amide, one equivalent; ester, one-half equivalent. [c] Yield based on ketone. [d] Yield based on ester. [e] Gave grayish-green copper salt, m. p. 193–195°, and purple enol test on standing. [f] Bauer (ref. 6) reported 92–93°. [g] The copper salt method of isolation was employed. [h] Gave green copper salt and brownish red enol test. [i] Robinson and Shah (ref. 7) reported 104°. [j] Gave brown copper salt and brown enol test. [k] Gave a copper salt with difficulty, but no enol test; on heating with 1% aqueous sodium hydroxide, the β-diketone was cleaved to benzoic acid and propiophenone. [l] Abell (ref. 4b) reported 83°. [m] Tingle and Gorsline (ref. 9b, p. 69) reported 91.5°; Malmgren, *Ber.*, **36**, 2629 (1903), reported 88°. [n] Gave green copper salt and violet (purple) enol test. [o] The main product, 5 g., white crystals, melted at 143–144°; this is the m. p. of the O-benzoyl derivative of benzoylcamphor reported by Foster, *J. Chem. Soc.*, **79**, 987 (1901).

It can be seen from Table I that the yields of β-diketones are satisfactory with cyclohexanone, hydrindone, tetralone and propiophenone; in these cases Method A is probably preferable to Method B. With camphor the yield of β-diketone was low by Method B, while, by Method A, the benzoyl derivative of the β-diketone was apparently obtained. Attempts to benzoylate *p*-methoxypropiophenone with phenyl benzoate or to acylate propiophenone with phenyl anisate have been unsatisfactory.

Since methyl benzoate undergoes alkaline hydrolysis almost three times as rapidly as ethyl benzoate, the methyl ester should be a somewhat better benzoylating agent than the ethyl ester. In agreement with this, cyclohexanone has been benzoylated with methyl benzoate in 47% yield by Method A (using an extra equivalent of the ester) and in 25% yield by Method B; under the latter conditions considerable of the ketone self-condensed.[12] However, like the ethyl ester, methyl benzoate has been unsatisfactory with hydrindone, tetralone or propiophenone.

With the considerable improvement in yields using phenyl benzoate, or even methyl benzoate with cyclohexanone, the direct benzoylation of cyclohexanone, hydrindone, propiophenone or tetralone becomes a very satisfactory method for the synthesis of the corresponding β-diketones. Bauer[6] has prepared benzoylcyclohexanone in good yield by the cyclization of ethyl ε-benzoylcaproate but this keto ester was not readily available. Abell[8b] has prepared benzoylpropiophenone in good yield by the methylation of dibenzoylmethane.

In an attempt to benzoylate cyclopentanone with methyl benzoate, self-condensation of the ketone occurred followed by benzoylation to form α-benzoyl-α′-cyclopentylidene-cyclopentanone. Earlier workers have observed that cyclopentanone self condenses exceptionally rapidly in the presence of sodium amide[13] or sodium ethoxide.[14]

Experimental[15]

Reactions with Phenyl Benzoate.—To a stirred ether suspension of sodium amide was added an ether solution of the ketone, followed, after five to ten minutes, by an ether solution of phenyl benzoate, and the mixture was refluxed for two hours essentially as described previously.[2] In general the reaction mixture was poured carefully onto 200 g. of crushed ice and water and the resulting mixture shaken in a separatory funnel until all the solid had dissolved; in the experiments with tetralone and hydrindone, more ice water (600 and 1300 ml., respectively) was added to effect solution. The cold aqueous phase containing the β-diketone, phenol and some benzoic acid (as sodium salts), after washing with a little ether, was acidified with ice-cold 10% hydrochloric acid and the resulting mixture extracted with ether. The combined ether extract was washed with 5% sodium bicarbonate solution, then with water, dried over Drierite, and the solvent distilled, leaving a residue of β-diketone and phenol. In the preparation of benzoylcyclohexanone, the residue was distilled in a small von Braun flask (having a short column) on the water-bath at about 5-mm. pressure until most of the phenol was removed, and the crude β-diketone, remaining in the flask, was recrystallized from dilute ethanol. With benzoylhydrindone, the residue was merely recrystallized from methanol, the phenol remaining in solution. With benzoyltetralone, the residue was ground with warm water in a mortar until most of the phenol was dissolved, and the crude β-diketone was filtered off and recrystallized from ligroin (60–90°).

In certain cases the reaction mixture was poured onto ice and hydrochloric acid and the β-diketone isolated by the copper salt method.[2] The copper salts usually oiled out and required cooling, sometimes for several days, to crystallize. The salts, which were collected on a Buchner funnel, required an unusually thorough washing with water and ligroin in order to obtain an essentially pure β-diketone on decomposition with acid; moreover, this decomposition took place only slowly. For example, in the preparation of benzoylcyclohexanone from 0.3 mole of phenyl benzoate and 0.15 mole each of cyclohexanone and sodium amide, the copper salt was washed with approximately 400 ml. each of water and ligroin, then alternately shaken and allowed to stand for eight hours with a mixture of ether and 10% sulfuric acid. The presence of petroleum ether (one part to three parts of ether) somewhat facilitated the decomposition. Before recovering the β-di-

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(12) The greater self condensation of the ketone by Method B is not surprising, since, although the ketone is first converted essentially to its anion even in this method, the free ketone, one of the components of the aldol condensation, is continually being regenerated. In Method A the concentration of free ketone is kept at a minimum throughout the reaction by the presence of the excess amide ion.

(13) Haller and Cornubert, *Compt. rend.*, **158**, 298, 1616 (1914).

(14) Wallach, *Ber.*, **29**, 2963 (1896).

(15) Analyses by Oakwold Laboratories, Alexandria, Va.

ketone, it is advisable to wash the ether solution with 5% sodium bicarbonate solution in order to remove benzoic acid formed during the condensation.

In the experiment with propiophenone, the reaction mixture was poured onto ice and hydrochloric acid and the mixture was extracted with ether. Since benzoylpropiophenone is insoluble in cold alkali, the ether phase was washed with cold 10% sodium hydroxide until free from phenol, then with water, dried over Drierite, and the solvent distilled. The β-diketone was isolated from the residue (containing a red oil) either by the addition of ligroin (30–60°) followed by recrystallization of the precipitated crystals from ethanol, or by direct recrystallization from ethanol. In the latter method the ethanol solution was decanted from the red oil and chilled.

The yields of β-diketones and other data, using Methods A and B are given in Table I. Aqueous-alcoholic ferric chloride was used for the enol tests.

Reactions with Methyl Benzoate.—The reaction of 0.2 mole of cyclohexanone with 0.4 mole each of methyl benzoate and sodium amide (Method A, in which excess ester is used)[2] was carried out in the usual manner and the reaction mixture worked up by the first procedure described above. The residue, obtained on distillation of the solvent from the dried ether solution, was recrystallized from dilute ethanol, yielding 18.7 g. (47%) of benzoylcyclohexanone, m. p. 88–89°. From the ether phase, obtained on decomposing the reaction mixture with water, there was recovered 24 g. (0.18 mole) of methyl benzoate, b. p. 94–97° (25 mm.), and 7.7 g. of material b. p. 90–180° (6 mm.), which was assumed to be a mixture of aldol condensation products. From the bicarbonate wash there was obtained on acidification 8.0 g. of benzoic acid, m. p. 120–121°. This corresponds to 15% of the methyl benzoate charged.

From the reaction of 0.5 mole each of cyclohexanone and sodium amide with 0.25 mole of methyl benzoate (Method B), there was isolated only a 22% yield of benzoylcyclohexanone, along with 12.0 g. (0.1 mole) of benzoic acid and 19.0 g. (0.1 mole calculated as the dimer) of a product, b. p. 100–210° (9 mm.), which apparently resulted from aldol condensations.

With cyclopentanone (0.15 mole), methyl benzoate (0.3 mole), and sodium amide (0.3 mole) there was obtained 8.3 g. (21%) of α-benzoyl-α′-cyclopentylidenecyclopentanone, yellow needles from ethanol, m. p. 99.5° (not benzoylcyclopentanone, m. p. 45°).[6]

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.31; H, 7.14. Found: C, 80.73; H, 7.39.

The product gave a light green copper salt and an immediate brown enol test. The diketone was cleaved by suspending it in cold sodium hydroxide, followed by rapid steam distillation. The distillate contained a small amount of α-cyclopentylidenecyclopentanone, which was extracted with ether and the extract dried over Drierite. After removal of the ether the remaining oil was converted to an oxime, m. p. 123–124°.[14] The residue from the steam distillation, on acidification, yielded benzoic acid, m. p. 120–121°, and a small amount of an unidentified acid.

Summary

1. The anions of cyclohexanone and certain other methylene ketones, prepared by means of sodium amide, are benzoylated in much better yields with phenyl benzoate than with ethyl benzoate.

2. The anion of cyclohexanone is benzoylated in better yield with methyl benzoate than with the ethyl ester. With cyclopentanone, self-condensation occurs followed by benzoylation.

3. The parallelism between the reactivities of esters in the Claisen acylation of a ketone anion and the rates of alkaline hydrolysis of the esters is pointed out.

DURHAM, N. C. RECEIVED JUNE 2, 1947

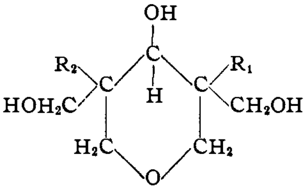
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, GENERAL MILLS, INC.]

The Condensation of Formaldehyde with Lower Aliphatic Ketones. Allylation as a Means of Structure Proof[1]

BY J. ROBERT ROACH, HAROLD WITTCOFF AND SIDNEY E. MILLER

The separation of pentaerythritol and dipentaerythritol in a technical mixture has been achieved in this Laboratory by distillation of their allyl ethers. The determination of the physical constants, in particular the iodine number, of the allyl ethers established a basis for the identification of the parent compounds, whereas the amount of each fraction in the distillate served as a roughly quantitative measure of the composition of the original mixture. These observations have led to a procedure for the separation of pure compounds from the sirupy reaction products resulting from the condensation of excess formaldehyde with lower aliphatic ketones. Thus allylation and subsequent distillation has made possible the establishment of the structures of the chief constituents, and the postulation of possible structures of the minor constituents.

Apel and Tollens[1a,b] reported that acetone condenses with excess formaldehyde to yield an "anhydroenneaheptitol," which Mannich and Brose[2] later identified as tetrahydro-3,3,5,5-*tetrakis*-(hydroxymethyl)-4-pyranol, Ia. Although these investigators employed long periods of reaction, the present work has shown that at slightly elevated temperatures the reaction proceeds in a few hours. The resulting sirupy reaction product was converted by the action of allyl bromide in the



Ia, $R_1 = R_2 = CH_2OH$
Ib, $R_1 = CH_2OH$, $R_2 = CH_3$
Ic, $R_1 = R_2 = CH_3$

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[1] Paper No. 78, Journal Series, Research Laboratories, General Mills, Inc. Presented at the 111th meeting of the American Chemical Society, Atlantic City, N. J., April 14–18, 1947.

(1a) M. Apel and B. Tollens, *Ber.*, **27**, 1087 (1894); (b) M. Apel and B. Tollens, *Ann.*, **289**, 46 (1895).

(2) C. Mannich and W. Brose, *Ber.*, **55**, 3155 (1922).