

alone and on admixture with the original 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 (m. p. 147-148°). The recovery of original material was 6.2 g. (88% by weight).

Summary

A new method of preparation of 2-alkylamino-

and 2-arylalkylaminoimidazolines and -tetrahydropyrimidines is described. The formation of cyclic ureas, e. g., 1,3-diazacyclohexanone-2, as by-products in this reaction is discussed.

KINGSTON, ONTARIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Acylation of Certain α -Alkoxy and α -Aryloxy Ketones and Esters¹

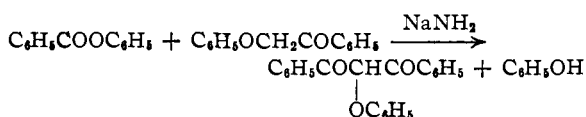
BY JON MUNCH-PETERSEN² AND CHARLES R. HAUSER

Although many acylations of ketones³ and esters⁴ have been described in the literature, relatively few successful acylations of α -alkoxy and α -aryloxy ketones and esters have been reported previously. The present paper describes some new contributions to this field. Various condensing agents have been employed.

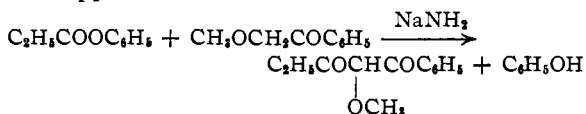
Acylation of α -Alkoxy and α -Aryloxy Ketones.—Apparently the only acylations of this type effected previously are those reported by Malkin and Robinson⁵ who acylated α -methoxy and α -4-dimethoxyacetophenone with ethyl formate using sodium ethoxide. The copper salts of the resulting β -ketoaldehydes (named as enols) were obtained in yields of 16 and 81%, respectively.⁶

We have found that, in contrast to acetophenone, α -methoxyacetophenone fails to be acylated with ethyl acetate, ethyl propionate, or ethyl benzoate, and α -phenoxyacetophenone fails to be acylated with ethyl acetate, employing sodium amide under the usual conditions.^{3a} Similarly α -methoxyacetophenone fails to be acylated with ethyl acetate employing potassium triphenylmethide⁷ in refluxing ether. In each of these cases, the methoxy or phenoxy ketone was largely recovered. However, both of these ketones may be acylated with phenyl benzoate or phenyl propionate by means of sodium amide. The benzoylations of α -methoxyacetophenone and α -

phenoxyacetophenone have been effected in yields of 26 and 59%, respectively.



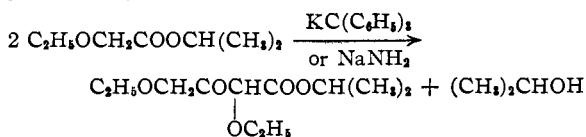
The benzoylation of α -methoxyacetophenone has also been effected with benzoyl chloride but the yield was only 11%. The propionylations of α -methoxyacetophenone and α -phenoxyacetophenone have been effected in yields of 25 and 50%, respectively; however, the latter yield is only for the copper salt.



Since some starting materials were recovered in these cases, the yields of acylation products could probably be improved.

The acylation of α -methoxyacetophenone with acetic anhydride has been effected in 10% yield by means of boron trifluoride.

Acylation of α -Alkoxy and α -Aryloxy Esters.—The self-condensation of ethyl ethoxyacetate was first reported by Conrad⁸ who used sodium, but no yield was given. Similarly, Pratt and Robinson⁹ effected the self-condensation of methyl and ethyl methoxyacetate in yields of 40-50% using sodium. Darzens and Meyer¹⁰ reported a 75% yield in the self-condensation of ethyl ethoxyacetate using sodium ethoxide. We have self-condensed isopropyl ethoxyacetate in 69% yield using potassium triphenylmethide and in 35% yield using sodium amide



The lower yield with the sodium amide may be accounted for on the basis that this reagent reacts

(8) Conrad, *Ber.*, **11**, 58 (1878).

(9) Pratt and Robinson, *J. Chem. Soc.*, 163 (1925).

(10) Darzens and Meyer, *Compt. rend.*, **198**, 478 (1934).

(1) Paper XLI on "Condensations"; paper XL, *THIS JOURNAL*, **69**, 2649 (1947).

(2) On leave of absence from the Department of Organic Chemistry, The Technical University of Denmark, Sølvgade 83, Copenhagen, Denmark.

(3) See especially (a) Adams and Hauser, *THIS JOURNAL*, **66**, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945); (c) Hauser and Adams, *ibid.*, **66**, 345 (1944); (d) Adams and Hauser, *ibid.*, **67**, 284 (1945).

(4) See especially Hauser and Hudson, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., Vol. I, pp. 266-302.

(5) Malkin and Robinson, *J. Chem. Soc.*, **127**, 1190 (1925).

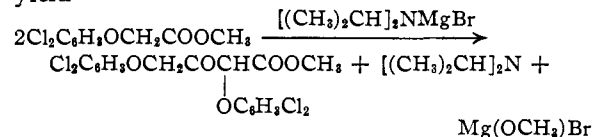
(6) We have verified this result with α -methoxyacetophenone, but the yield of the free β -ketoaldehyde was only 3%; most of the methoxy ketone was recovered. It should be pointed out that this reaction was carried out at 0° and that, when attempts were made to effect the formylation of the sodium derivative of α -methoxyacetophenone (prepared with sodium amide or potassium triphenylmethide) in refluxing ether, only the methoxy ketone was recovered.

(7) Levine, Baumgarten and Hauser, *THIS JOURNAL*, **66**, 1230 (1944).

not only with the α -hydrogen of the ester leading to condensation but also with the carbonyl carbon resulting in the formation of ethoxyacetamide which was isolated from the reaction mixture in 35% yield. Since sodium amide self-condenses isopropyl acetate in better yield (57%)¹¹ and apparently produces little if any acetamide,¹² the substitution of an α -hydrogen of this ester by the ethoxy group evidently activates the carbonyl carbon¹³ relative to the α -hydrogen toward sodium amide.¹⁴

The self-condensation of ethyl α -ethoxypropionate could not be effected satisfactorily. With potassium triphenylmethide or sodium hydride only a small amount of product was obtained even though the ester anion appeared to be formed readily.¹⁵ With di-isopropylmagnesium bromide a product was obtained but it was apparently contaminated with some of the di-isopropyl amide, giving a positive test for nitrogen. Since di-isopropylmagnesium bromide self-condenses ethyl *n*-butyrate and ethyl isobutyrate to form a nitrogen free β -ketoester,¹⁶ the formation of some amide with the ethyl α -ethoxypropionate lends further support to the view expressed above, that the α -ethoxy group activates the carbonyl carbon relatively more than the α -hydrogen.

Ethyl phenoxyacetate was first self-condensed by Johnson and Hill¹⁷ using sodium; the yield of the sodium derivative of the β -ketoester was good, but the free β -ketoester was not isolated. We have similarly obtained a good yield (76%) of the sodium derivative of the β -ketoester using di-isopropylmagnesium bromide. We also self-condensed methyl 2,4-dichlorophenoxyacetate; the free β -ketoester was obtained in a 65% yield



Ethyl α -phenoxypropionate and ethyl α -(2,4-dichlorophenoxy)-propionate apparently self-condensed in the presence of di-isopropylmagnesium

(11) Shivers, Dillon and Hauser, *THIS JOURNAL*, **69**, 120 (1947).

(12) Hauser, Levine and Kibler, *ibid.*, **68**, 26 (1946).

(13) That the carbonyl carbon is activated by the ethoxy group toward a basic anion is indicated by the six times larger rate of alkaline hydrolysis of methyl ethoxyacetate than methyl acetate. See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 212.

(14) In agreement with this, an attempt to carbonate isopropyl methoxyacetate after treatment with sodium amide failed; methoxyacetamide (m. p. 92–93°) was isolated in 70% yield. Under similar conditions isopropyl acetate gives the carbonation product (56%) and apparently none of the amide.¹³

(15) With potassium triphenylmethide, the color of the reagent was discharged immediately, see ref. 7. With sodium hydride the calculated amount of hydrogen was evolved when equivalent amounts of this reagent and the ester were refluxed in *n*-butyl ether (b. p. 140°). See Swamer and Hauser, *THIS JOURNAL*, **68**, 2647 (1946).

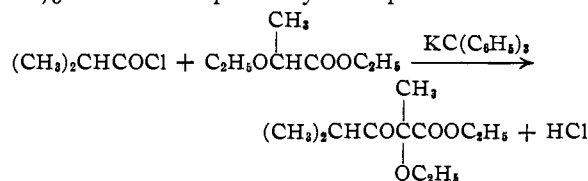
(16) Hauser and Frostick, unpublished work from this Laboratory.

(17) Johnson and Hill, *Am. Chem. J.*, **48**, 296 (1912); *THIS JOURNAL*, **35**, 1026 (1913).

bromide, but the pure products were not isolated.

Apparently an alkoxy ester has not previously been acylated with a different ester. In an attempt to acylate isopropyl ethoxyacetate with phenyl benzoate using sodium amide¹¹ or potassium triphenylmethide⁷ we have obtained the self-condensation product of the ethoxyacetate (35%) even though the addition of the ethoxyacetate to the reagent was followed immediately by the addition of the phenyl benzoate.¹⁸ Since isopropyl acetate has been benzoylated with phenyl benzoate by means of sodium amide under similar conditions,¹¹ either the anion of isopropyl ethoxyacetate is acylated more slowly by phenyl benzoate than the anion of isopropyl acetate or, more likely, isopropyl ethoxyacetate undergoes self-condensation more rapidly than isopropyl acetate. This again is an indication of the above-mentioned effect of the ethoxy group.

However, we have succeeded in acylating ethyl α -ethoxypropionate with isobutyryl chloride using potassium triphenylmethide. The yield was only 15% but it could probably be improved



Koelsch and Whitney¹⁹ have acylated ethyl phenoxyacetate with ethyl oxalate and ethyl formate using sodium ethoxide. We have benzoylated ethyl α -phenoxypropionate with phenyl benzoate using sodium amide but, rather surprisingly, the β -ketoacid (13%) instead of the β -ketoester was obtained. Most of the ethyl α -phenoxypropionate was recovered.

Acknowledgment.—One of the authors (J. Munch-Petersen) wants to express his gratitude to The Academy of Technical Sciences, Denmark, Laurits Andersens Fond, Otto Monsteds Fond, The American-Danish Foundation and the Duke University Research Council for financial support, without which his participation in this work would have been impossible.

Experimental²⁰

α -Methoxyacetophenone²¹ and α -phenoxyacetophenone²² were prepared as described in the literature.

(18) In these experiments isopropyl benzoate was obtained in yields of 67 and 50%, respectively. This ester was identified by its boiling point and by hydrolysis to benzoic acid and isopropyl alcohol. In the experiment with sodium amide a 35% yield of ethoxyacetamide (m. p. 80°) was obtained. The isopropyl benzoate was formed, presumably, by reaction of the phenyl benzoate with the isopropoxide ion which was produced as a by-product in the self-condensation of isopropyl ethoxyacetate and, in the experiment with sodium amide, also in the formation of ethoxyacetamide.

(19) Koelsch and Whitney, *THIS JOURNAL*, **63**, 1762 (1941).

(20) Boiling points and melting points are uncorrected; analyses are by Microchemical Laboratory, University of Pittsburgh, Pittsburgh, Pa.

(21) Moffett and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 21, 1941, p. 79.

(22) Mohlau, *Ber.*, **15**, 2498 (1882).

Isopropyl ethoxyacetate, b. p. 161°, was prepared according to the procedure for ethyl ethoxyacetate,²³ using isopropyl alcohol in the esterification of the ethoxyacetic acid.

Ethyl α -ethoxypropionate was prepared according to the same procedure,²³ using α -chloropropionic acid instead of chloroacetic acid; the ester boiled at 153–155° (reported b. p. 155°).²⁴ The over-all yield was 58%, the yield of α -ethoxypropionic acid, b. p. 89–93° at 10 mm., being 77%.

Ethyl phenoxyacetate, b. p. 247–249° (reported b. p. 250°)²⁵ and ethyl α -phenoxypropionate, b. p. 242–244°²⁶ and b. p. 96° at 4 mm., were obtained in 80% yields from the corresponding acids by the general method involving the saturation of an ethanolic solution of the acid with hydrogen chloride.

Ethyl α -(2,4-dichlorophenoxy)-propionate, b. p. 129–130° at 4 mm. (reported b. p. 173–176° at 12 mm.)²⁷ was prepared by esterification of α -(2,4-dichlorophenoxy)-propionic acid, m. p. 115–116° (reported m. p. 117–118°),²⁷ which was obtained in 31% yield following the procedure given by Pakorny²⁸ for 2,4-dichlorophenoxyacetic acid.

Acylation of α -Methoxy- and α -Phenoxyacetophenone by the Sodium Amide Method. Table I.—The general procedure described previously^{30,29} has been modified. To a stirred suspension of 0.2 mole of sodium amide was added an ether solution of 0.1 mole of the ketone. After ten minutes, an ether solution of the ester was added. The mixture was refluxed for two hours and then poured onto ice. The water layer, after washing with ether, was acidified and extracted with ether. The ether layer, after washing with saturated sodium bicarbonate solution and water, was dried and the solvent distilled. Treatment of the residue varied.

TABLE I

ACYLATIONS OF ROCH ₂ COC ₆ H ₅ USING SODIUM AMIDE			M. p., °C.	Yield, %
R	Acyating compound	β -Diketone		
CH ₃	PhBz	α -Methoxydibenzoyl-methane ^a	77–78	26
C ₆ H ₅	PhBz	α -Phenoxydibenzoyl-methane ^b	97–100	59
CH ₃	BzCl	α -Methoxydibenzoyl-methane	77–78	11
CH ₃	PhPr	α -Methoxy- α -propionyl acetophenone ^c	B. p. 129–130 at 6 mm.	25
C ₆ H ₅	PhPr	α -Phenoxy- α -propionyl acetophenone		50 ^d

^a Anal. Calcd. for C₁₆H₁₄O₃: C, 75.57; H, 5.55. Found: C, 75.78; H, 5.20. ^b Anal. Calcd. for C₂₁H₁₆O₃: C, 79.73; H, 5.10. Found: C, 79.91; H, 4.90. ^c Anal. Calcd. for C₁₂H₁₄O₃: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.65. ^d Obtained as the copper salt.

In the benzoylation of α -methoxyacetophenone with phenyl benzoate the β -diketone was isolated by the copper salt method²⁸ and recrystallized from methanol.

In the benzoylation of α -phenoxyacetophenone most of the phenol was distilled off *in vacuo*. The residue, which crystallized, was brought into solution in 2 *N* sodium hydroxide. By acidifying, the β -diketone was precipitated, filtered, washed with water and a little ice-cold ethanol and finally recrystallized from ethanol.

(23) Fuson and Wojcik, "Organic Syntheses," John Wiley and Sons, Inc., N. Y., Coll. Vol. II, 1943, p. 260.

(24) Schreiner, *Ann.*, **197**, 13 (1879); Purdie, *J. Chem. Soc.*, **73**, 863 (1898).

(25) Morel, *Bull. soc. chim.*, [3] **21**, 968 (1899).

(26) Saabach, *J. prakt. Chem.*, [2] **21**, 152 (1880).

(27) Bischoff, *Ber.*, **33**, 1604 (1900).

(28) Pakorny, *THIS JOURNAL*, **63**, 1768 (1941).

(29) Hauser, Ringler, Swamer and Thompson, *ibid.*, **69**, 2649 (1947).

In the benzoylation of α -methoxyacetophenone with benzoyl chloride equivalent amounts of sodium amide, the ketone and benzoyl chloride were used; before adding the ketone, the ether suspension of sodium amide was refluxed for several hours.

In the propionylation of α -methoxyacetophenone with phenyl propionate the β -diketone was separated from the phenol by fractional distillation *in vacuo*.

In the propionylation of the α -phenoxyacetophenone with phenyl propionate most of the phenol was removed by heating *in vacuo* (4 mm.) in an oil-bath kept at 20° for thirty minutes. The residue, which gave a strong red enol test with ferric chloride, was treated with a saturated copper acetate solution and the copper salt³⁰ of the β -diketone crystallized by standing overnight. After washing, the yield of the copper salt was 50%. From the copper salt, the β -diketone was recovered as a brown oil, the over-all yield being 37%, but it did not crystallize.

Acetylation of α -Methoxyacetophenone by the Boron Trifluoride Method.—The general procedure described previously³⁰ has been modified. The reaction mixture of 0.2 mole of the ketone and 0.4 mole of acetic anhydride, after saturation with boron trifluoride at temperatures between –10 and 0°, was kept at 0° for one hour and at room temperature (28–30°) for another hour. The mixture was refluxed with sodium acetate for thirty minutes and cooled. After neutralization of most of the acetic acid with sodium hydroxide, the mixture was extracted with ether and the ether solution washed with sodium bicarbonate solution and water. α -Methoxybenzoyl acetone, isolated by the copper salt method, was obtained as a yellow liquid, boiling at 110–111° at 4 mm.

Anal. Calcd. for C₁₁H₁₂O₃: C, 68.73; H, 6.29. Found: C, 68.78; H, 6.12.

None of the ketone was recovered and a considerable amount of tar was obtained.

When the reaction mixture was worked up within twenty minutes after saturation below 0° as described for other ketones,³⁰ no β -diketone was obtained and the ketone was largely recovered.

Self-condensation of α -Alkoxy and α -Aryloxy Esters. Table II.—The self-condensation of isopropyl ethoxyacetate with potassium triphenylmethide was carried out according to the general procedure,⁷ except that the reaction mixture was refluxed for three hours. The condensation was also effected by sodium amide¹¹; in this experiment ethoxyacetamide (m. p. 80°) was isolated.

Ethyl phenoxyacetate and methyl 2,4-dichlorophenoxyacetate (m. p. 39–40°)³⁰ were self-condensed by diisopropylmagnesium bromide by adaptation of the procedure for the condensation of certain esters using diethylmagnesium bromide.³¹ The reactions were generally carried out on a 0.1 or 0.2 mole scale.

To the stirred solution of ethylmagnesium bromide was added an ether solution of an equivalent of diisopropylamine, b. p. 83–84°,³² and after twenty minutes an ether solution of an equivalent of the ester was added. After spontaneous refluxing ceased, the mixture was refluxed on the steam-bath for one and one-half hours. After cooling in an ice-salt-bath, crushed ice and concentrated hydrochloric acid were added and the mixture stirred until no solid was left. The ether phase, after combining with an ether extract of the aqueous phase, was stirred with 2 *N* sodium hydroxide. The white precipitate of the sodium derivative of the β -ketoester was filtered off, washed with water and dried in the air.

In the experiment with ethyl phenoxyacetate the sodium derivative of the β -ketoester was a white powder, which melted under slight decomposition at 199°. It was converted into the free β -ketoester by shaking in a separatory funnel with ether and hydrochloric acid. The water layer was extracted with ether, the combined ether ex-

(30) We are indebted to J. T. Baker Chemical Company for a sample of this ester.

(31) Hauser and Walker, *THIS JOURNAL*, **69**, 295 (1947).

(32) We are indebted to the Shell Chemical Corporation for a sample of this amine.

TABLE II
 SELF-CONDENSATION OF ALKOXY- AND ARYLOXYESTERS

Ester	Condensing agent	β -Ketoester	B. p. °C.	Mm.	Yield %
Isopropyl ethoxyacetate	NaNH ₂	Isopropyl α, γ -diethoxyacetoacetate	107-108	5	35
Isopropyl ethoxyacetate	KC(C ₆ H ₅) ₃	Isopropyl α, γ -diethoxyacetoacetate ^a	103-104	4	69
Ethyl phenoxyacetate	(<i>i</i> -Pr) ₂ NMgBr	Ethyl α, γ -diphenoxyacetoacetate ^b			63 ^c
Methyl 2,4-dichlorophenoxyacetate	(<i>i</i> -Pr) ₂ MgBr	Methyl α, γ -di-(2,4-dichlorophenoxy)- acetoacetate ^{b, d}	102-104 (m. p.)		65

^a *Anal.* Calcd. for C₁₁H₂₀O₅: C, 56.88; H, 8.68. Found: C, 56.59; H, 8.82. ^b No nitrogen was found by the sodium fusion test. ^c The sodium derivative was obtained in 76% yield. ^d *Anal.* Calcd. for C₁₇H₁₈O₆Cl₄: C, 46.60; H, 2.76; Cl, 32.37. Found: C, 46.92; H, 2.78; Cl, 32.10.

tracts washed with a saturated sodium bicarbonate solution and water, and dried. After evaporation of the solvent, the β -ketoester was obtained as a yellow oil, which, however, did not crystallize. Attempts to distil the β -ketoester *in vacuo* (3 mm.) resulted in decomposition. Attempts to effect ketonic cleavage in acid³³ and slightly alkaline⁹ solution gave phenol and tar.

In the experiment with methyl 2,4-dichlorophenoxyacetate, the sodium derivative of the β -ketoester was similarly converted into the free keto ester, and this, after evaporation of the ether, crystallized, and was recrystallized from ethanol.

Acylation of Ethyl α -Ethoxypropionate with Isobutyryl Chloride.—To an ether suspension of 0.2 mole of potassium triphenylmethide (freed from ammonia by refluxing the mixture for four hours followed by purging the apparatus with nitrogen) was added 29.2 g. (0.2 mole) of ethyl α -ethoxypropionate. The red color disappeared immediately. After ten minutes, 21.2 g. (0.2 mole) of isobutyryl chloride was added. After refluxing on the steam-bath for three hours, the mixture was poured onto ice and 5 ml. of glacial acetic acid. The ether layer, after combining with an ethereal extract of the aqueous phase, was washed with saturated sodium bicarbonate solution, then with water, and dried. The solvent was distilled and the residue fractionated *in vacuo*, yielding 53% of the original ester and 10 g. of crude β -ketoester. Redistillation gave 6.5 g. (15%) of ethyl α -isobutyryl- α -ethoxypropionate, b. p. 75-76° at 4 mm.

Anal. Calcd. for C₁₁H₂₀O₄: C, 61.08; H, 9.32. Found: C, 61.31; H, 9.41.

Benzoylation of Ethyl α -Phenoxypropionate with Phenyl Benzoate.—To the stirred suspension of 0.1 mole of sodium amide was added an ether solution of 19.4 g. (0.1 mole) of ethyl α -phenoxypropionate. After fifteen minutes, an ether solution of 19.8 g. (0.1 mole) of phenyl benzoate was added. The mixture was refluxed on the steam-bath for one hour and then poured onto ice and hydrochloric acid. The water layer was extracted with ether. The combined ether phase was extracted with sodium hy-

droxide solution. From the ether phase there was recovered 70% of ethyl α -phenoxypropionate, b. p. 241-248° and 20% of the phenyl benzoate, m. p. 68°. Acidification of the alkaline extract yielded a precipitate from which, after fractional crystallization, there was obtained 0.3 g. of α -phenoxypropionic acid, m. p. 114-115° (reported m. p. 115-116°)³⁴ and 3.5 g. (13%) of α -benzoyl- α -phenoxypropionic acid, m. p. 136-137°, neutr. equiv.: Calcd. 270.3; found 270.3 and 270.8.

Anal. Calcd. for C₁₆H₁₄O₄: C, 71.10; H, 5.22. Found: C, 71.47; H, 5.35.

Summary

1. Although α -methoxy- and α -phenoxyacetophenone failed to be acylated with ethyl acetate, ethyl propionate, and ethyl benzoate by the sodium amide method, these ketones have been acylated with phenyl propionate and phenyl benzoate. α -Methoxyacetophenone has been acetylated by the boron trifluoride method.

2. Isopropyl ethoxyacetate has been self-condensed by potassium triphenylmethide and by sodium amide; ethyl phenoxyacetate and methyl 2,4-dichlorophenoxyacetate have been self-condensed by diisopropylaminomagnesium bromide.

3. Ethyl α -ethoxypropionate has been acylated with isobutyryl chloride by potassium triphenylmethide.

4. Certain related condensations have been studied. The effect of the α -ethoxy group on the relative reactivities of the carbonyl carbon and the α -hydrogen of esters has been considered.

DURHAM, N. C.

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(33) Hudson and Hauser, *THIS JOURNAL*, **63**, 3163 (1941).

(34) Bischoff, *Ber.*, **33**, 926 (1900).