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Preparation of Ketones from γ -Diethylaminobutyronitrile and Aromatic Grignard Reagents and their Conversion to Diamines. Synthesis of Quinacrine Analogs^{1,2}

BY WILBERT J. HUMPHLETT, MARTIN J. WEISS³ AND CHARLES R. HAUSER

It has been shown recently⁴ that, contrary to the general impression, the reaction of propionitrile or a higher aliphatic nitrile with phenylmagnesium bromide gives a good yield of the ketone even when only a slight excess of the Grignard reagent is employed. In the present investigation this method has been adapted to the preparation of ketones of type (III) which may be used as intermediates in the synthesis of analogs of SN 7618 (I) or quinacrine (II).⁵



The nitrile used in this work has been γ -diethylaminobutyronitrile which was prepared in two steps from trimethylene chlorobromide.

$$CICH_{2}CH_{2}CH_{2}Br \xrightarrow{HN(C_{2}H_{5})_{2}} \rightarrow CICH_{2}CH_{2}CH_{2}N(C_{2}H_{5})_{2} \xrightarrow{KCN} NCCH_{2}CH_{2}CH_{2}N(C_{2}H_{5})_{2}$$

The nitrile was obtained in an over-all yield of 50% which is almost twice the yield reported for the more common procedure of introducing the cyanogen group first,⁶ followed by the diethylamino group.⁷

 γ -Diethylaminobutyronitrile has reacted with various aromatic Grignard reagents in which aryl is α -naphthyl, p-chlorophenyl, p-flurophenyl, mtrifluoromethylphenyl, α -thienyl, or p-phenoxyphenyl to form the corresponding ketones. The aryl halides used in the preparation of the Grignard reagents were obtained commercially with the exception of m-bromobenzotrifluoride which was made by the bromination of benzotrifluoride. The yields of ketones are given in Table I.

$$\begin{array}{r} \text{Aryl-MgBr} + \text{NCCH}_{2}\text{CH}_{2}\text{CH}_{2}\text{N}(\text{C}_{2}\text{H}_{5})_{2} \xrightarrow{+\text{HCl}} \\ + \text{HOH} \\ \text{Aryl-COCH}_{2}\text{CH}_{2}\text{CH}_{2}\text{N}(\text{C}_{2}\text{H}_{5})_{2} \end{array}$$

This method of synthesis of ketones of type (III) appears superior generally to the two methods

(1) This investigation was supported in part by a grant from the Duke University Research Council.

(2) Paper I on antitubercular drugs. Paper IX on antimalarials; for Paper VIII of this series see THIS JOURNAL, **70**, 437 (1948).

(3) Eli Lilly Fellow, 1947-1948.

- (4) Hauser, Humphlett and Weiss, THIS JOURNAL, 70, 426 (1948).
- (5) Breslow, Walker, Yost and Hauser, ibid., 67, 1472 (1945).

(6) Allen, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156.

(7) Untermohlen and Hamilton, THIS JOURNAL, 63, 156 (1941).

	ARYL	-COCH ₂ C	CH₂C	$CH_2N(C_2H_5)_2$		
Aryl	Vield, %	°C. 1	Mm.	Formula	equiva Calcd.	itral alentª Found
α -Naphthyl	62	168 - 170	1	$C_{18}H_{23}NO$	269	271
p-Chloro-						
phenyl	79	135 - 138	2	$C_{14}H_{20}NOC1$	254	255
p-Fluoro-						
phenyl	75	114-116	2	$C_{14}H_{20}NOF$	237	239
m-Trifluoro-						
methyl-						
phenyl	72	137 - 138	5	$C_{15}H_{20}NOF_3$	287	285
α -Thienyl	60	122 - 123	2	$C_{12}H_{19}NOS$	225	225
p -Phenoxy-						
nhenvl	65	196-199	1	Con Has NOo	311	308

TABLE I

^a Samples for analysis were taken from the products whose boiling points are given.

employed previously involving either the alkylation of the appropriate β -keto ester with β -diethylaminoethyl chloride followed by ketonic cleavage⁵ or the reaction of appropriate aromatic aldehydes with γ -diethylaminopropylmagnesium chloride followed by oxidation of the resulting carbinol.⁵ The present method has produced better yields and it has been more convenient to carry out.

The ketones (III) have been converted to the corresponding oximes which were reduced to the corresponding diamines. The yields are given in Tables II and III, respectively. The oxime of the ketone in which Aryl is *p*-phenoxyphenyl was not obtained pure. With the exception of the oxime in which Aryl is trifluoromethylphenyl, which was reduced with sodium in butanol, the oximes were reduced with zinc dust and acetic acid. This method appears not to affect the relatively sensitive naphthalene and thiophene nuclei; neither does it remove aromatic halogen which is removed, at least sometimes, by sodium in butanol.⁵ Unsuccessful attempts were made to convert the ketone in which aryl is thienyl⁸ directly to the diamine by the ammonium formate procedure⁹ and also to hydrogenate the corresponding oxime at high pressures with Raney nickel at room temperatures or at 70° by the usual procedure.¹⁰

The diamines were coupled with 2-methoxy-6,9dichloroacridine to form quinacrine analogs (II) which were isolated as their hydrochlorides. The yields are given in Table IV. Certain of the yields

⁽⁸⁾ This part of the work was carried out under a contract with the Office of Scientific Research and Development with the coöperation of Dr. David S. Breslow.

⁽⁹⁾ See Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 503.

⁽¹⁰⁾ See Breslow, Yost, Walker and Hauser, THIS JOURNAL, 66, 1921 (1944).

TABLE II Aryl-C(N==NOH)CH₂CH₂CH₂N(C₂H₅)₂

Aryl	$\stackrel{ ext{Vield},}{\%}$	°C.	Mm.	Formula	Neu equiv Calcd	itral alent ^a Found
α -Naphthyl	88	205-207	3	$C_{18}H_{24}N_2O$	284	286
p-Chloro-						
phenyl	92	166 - 168	1	$C_{14}H_{21}N_2OCl \\$	269	271
p-Fluoro-						
phenyl	91	156 - 157	2	$\mathrm{C_{14}H_{21}N_{2}OF}$	252	253
m-Trifluoro-						
methyl-						
phenyl	80	172 - 174	3	$C_{14}H_{21}N_2OF_3$	302	302
α-Thienyl	81	172 - 173	2	$C_{12}H_{20}N_2OS$	240	242
<i>p</i> -Phenoxy-						
phenvl		215-217	1	ConHosNoOo		

^a Samples for analysis were taken from the products whose boiling points are given. ^b Since the oxime appeared to decompose to a considerable extent during distillation, it was not further studied.

TABLE III

$A_{RYL}-CH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$

	Yield	. B. 1	D.,		М.р.,
Aryl	%	°C. `	́Мп	1. Derivative	°C.
α -Naphthyl	50^a	162 - 166	1	Picrolonate	144–145
p-Chloro-					
phenyl	52^a	133 - 135	1	Dipicrate ^d	228-229
¢-Fluoro-					
phenyl	42^a	110 - 112	2	Dipicrate	203 - 204
m-Trifluoro-					
methyl-					
phenyl	73^{b}	116 - 118	1	Picrate ⁷	202
α -Thienyl	40^{a}	100 - 102	1	Dipicrolonate ⁹	211
4 Tino in ac	her bid	nction	^b Sor	tium in hutanol	reduction.

^a Zine in acid reduction. ^o Sodium in butanol reduction. ^c Anal. Calcd. for C₂₈H₃₄N₆O₈: C, 62.9; H, 6.39. Found: C, 63.2; H, 5.76. ^d Anal. Calcd. for C₂₆H₂₉-N₈O₁₄Cl: C, 43.7; H, 4.10; N, 15.7. Found: C, 43.5; H, 4.13; N, 16.1. ^e Anal. Calcd. for C₂₆H₂₉N₈O₁₄F: N, 16.1. Found: 16.2. ^f Anal. Calcd. for C₂₁H₂₆N₅-O₇F₂: N, 16.1. Found: N, 16.2. ^e Anal. Calcd. for C₂₁H₂₆N₅-O₇F₃: N, 16.1. Found: N, 16.2. ^e Anal. Calcd. for C₃₂H₃₅N₁₀O₁₀S: N, 18.6; S, 4.21. Found: N, 18.5; S, 4.31.

Heating

ries of reactions starting with the known *m*-trifluo-romethylbenzonitrile.



It was found later that the ketones in which aryl is *m*-trifluoromethyl and α -thienyl could be prepared more satisfactorily by the Grignard method described above. It seems likely that the ketone in which aryl is α -furyl,¹¹ could also be made by this method. An unsuccessful attempt was made to hydrogenate with Raney nickel the oxime in which aryl is α -furyl⁸ according to the usual procedure¹⁰; however, it seems likely that the zinc dust-acetic acid method would be successful.

The compounds listed on Table IV were tested as potential anti-malarial and anti-tubercular drugs at the Lilly Research Laboratories of Eli Lilly and Company, Indianapolis, Indiana. The anti-malarial tests were carried out in ducks infected with *P. Lophurae*. The *m*-trifluoromethylphenyl and the *p*-fluorophenyl compounds showed quinine equivalents of 1.2. The other three compounds in the table were inactive (quinine equivalent = 0.16). The anti-tubercular tests were *in vitro* using avirulent human strain no. 599. All the compounds in Table IV showed a minimum active dosage of 0.2 mg. per 10 ml. of culture. As a comparison the compound in which aryl is phenyl showed a minimum active dosage of 1 mg. under the same conditions.

Experimental¹²

 γ -Diethylaminobutyronitrile.—1-Diethylamino-3chloropropane was prepared in 60% yield from trimethyl-

TABLE IV

QUINACRINE ANALOGS (II)

	period.	Yield.			N analyses, %	
Aryl	hr.	%	М . р., °С.	Formula	Calcd.	Found
α-Naphthyl	3	35	>360	$C_{32}H_{34}N_3OC1\cdot 2HC1\cdot H_2O^a$	6.97	7.15
p-Chlorophenyl	5.5^{b}	66°	218–219 cor.	$C_{28}H_{31}N_3OCl_2 \cdot 2HCl$	7.38	7.58
p-Fluorophenyl	4 ^b	71°	214 - 215	C ₂₈ H ₃₁ N ₃ OFCl·2HCl	7.60	7.57
<i>m</i> -Trifluoromethylphenyl	2.5^d	69	>36 0			
a-Thienvl	2	26	>360			

^a Anal. Caled.: C, 63.73; H, 6.35; Cl (total), 17.64. Found: C, 63.73; H, 5.93; Cl (total), 17.92. ^b In addition allowed to stand overnight at room temperature. ^c Based on yield of free base. ^d In addition allowed to stand for three hours at room temperature.

could probably be increased by increasing the reaction time. The coupled products from the diamines in which Aryl is α -thienyl and *m*-trifluoromethylphenyl failed to analyze satisfactorily.

In the earlier part of this investigation ketones of type (III) in which aryl is *m*-trifluoromethylphenyl, α -thienyl,⁸ and α -furyl⁸ were prepared from the appropriate β -keto esters. The first of these ketones was synthesized by the following seene chlorobromide¹³ and diethylamine as described previously.⁵

To a solution of 90 g. (1.38 mole) of potassium cyanide

(11) For the preparation of α -furylmagnesium iodide see Gilman, Mallory and Wright, THIS JOURNAL, **54**, 733 (1932).

(12) Microanalyses for compounds listed in Table III were by Oakwold Laboratories, Alexandria, Va.; all others were by the Microchemical Laboratory of the University of Pittsburgh.

(13) We are indebted to the Dow Chemical Company for a supply of trimethylene chlorobromide. (95%) in 300 ml. of water was added 650 ml. of 95% ethanol followed by 179 g. (1.21 mole) of 1-diethylamino-3chloropropane. The resulting solution was refluxed with stirring for twelve hours. To the cooled solution was added an excess of solid sodium carbonate or potassium carbonate. The mixture was extracted with ether and the ether phase was distilled until both ether and alcohol were removed. The residue was distilled through a 15 cm. Vigreux column yielding 142 g. (84%) of γ -diethylaminobutyronitrile, b. p. 92-93° at 14 mm. The over-all yield from trimethylene chlorobromide was 50%.

from trimethylene chlorobromide was 50%. Preparation of Ketones (III) from γ -Diethylaminobutyronitrile and Grignard Reagents.—The following bromides, which were obtained commercially, were purified by distillation or crystallization: α -bromonaphthalene (b. p. 146–149° at 16 mm.), p-bromofluorobenzene (b. p. 152–155°), p-bromophenoxybenzene (b. p. 167–168° at 15 mm.), α -bromothiophene¹⁴ (b. p. 149–151°), and pchlorobromobenzene (m. p. 63–65°). The m-bromobenzotrifluoride (b. p. 151–153°) was prepared by bromination of benzotrifluoride.¹⁵ These bromides were converted to Grignard reagents which were treated with γ -diethylaminobutyronitrile as illustrated by the following example.

In a 500-ml. three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and efficient reflux condenser protected by a drying tube were placed 6.6 g. (0.27 atom) of magnesium turnings, 32 ml. of dry ether and a crystal of iodine. Addition of $1 \text{ ml. of } \alpha$ -bromonaphthalene and gentle refluxing of the mixture started the reaction. With stirring the remainder of the α -bromonaphthalene (52 g., 0.25 mole) in 117 ml. of dry ether was added at a rate which maintained vigorous refluxing. After the addifor thirty minutes. Titration¹⁶ indicated a 95% yield of Grignard reagent. To the stirred refluxing Grignard solution was added 31.5 g. (0.225 mole) of γ -diethylaminobutyronitrile in 100 ml. of dry ether during a period of thirty minutes. Stirring and refluxing were continued for six hours. The cooled mixture was decomposed by the slow addition of a solution of 25 g. of ammonium chloride in 75 ml. of water. The ether was removed on a steambath under an ether still. After heating an hour longer to ensure hydrolysis of the ketimine, the ketone was extracted with four 100-ml. portions of ether. The combined ether solutions were extracted with three 100-ml. portions of cold 2 N hydrochloric acid. The combined acid solutions were made alkaline with excess potassium carbonate and the amino-ketone was extracted with ether. After drying over anhydrous potassium carbonate, the ether was distilled and the residue fractionated through a 10-cm. Vigreux column at 1 mm. yielding 4-diethylamino- $1-(\alpha-naphthyl)$ -butanone-1 as a pale yellow, non-viscous oil.

The results obtained with various Grignard reagents are summarized in Table I.

Preparation of Oximes.—The ketones were converted to oximes as described previously,¹⁰ the oximes being fractionated at reduced pressure through a 10-cm. Vigreux column yielding pale yellow, viscous oils. The results are summarized in Table II.

Preparation of Diamines.—The oxime of the *m*-trifluoromethylphenyl ketone was reduced with sodium in butanol according to the general procedure described previously.¹⁰ The oximes of the α -naphthyl, *p*-chlorophenyl, *p*-fluorophenyl and α -thienyl ketones were reduced by means of zinc dust and acetic acid. The method is illustrated by the following procedure for the reduction of the oxime of 4diethylamino-1-(α -naphthyl)-butanone-1.

To 42.4 g. (0.149 mole) of the oxime of 4-diethylamino-1- $(\alpha$ -naphthyl)-butanone-1 dissolved in 390 ml. of glacial acetic acid and 19 ml. of water was added 52 g. of zinc dust in small portions at a rate which maintained lively ebullition. Upon completion of the addition the mixture was

(14) We are indebted to the Michigan Chemical Corporation for a supply of α -bromothiophene.

(16) Gilman, Zoellner and Dickey, ibid., 51, 1576 (1929).

stirred and refluxed two hours longer. The well-cooled mixture was made alkaline by cautious addition of a concentrated solution of sodium hydroxide. The copious precipitate was dissolved by the addition of solid ammonium chloride. The mixture was extracted with ether several times. The ether phases were combined and dried over anhydrous potassium carbonate. The solvent was distilled and the residue was fractionated through a 10-cm. Vigreux column at reduced pressure yielding 4-diethyl-amino-1-(α -naphthyl)-butylamine-1.

The results obtained on the reduction of the various oximes are summarized in Table III.

Preparation of Quinacrine Analogs (II).—The diamines were coupled with 2-methoxy-6,9-dichloroacridine and the resulting products converted to their hydrochloride salts essentially as described previously.¹⁰

In general the hydrochloride salts were purified by dissolving them in a sufficient quantity of boiling 95% ethanol,¹⁷ filtering and evaporating the filtrate to a volume of about 75 ml. An equal volume of isopropyl ether was added, the mixture was chilled and suction-filtered. After washing with ether the product was dried *in vacuo*. Analytical samples were obtained after several recrystallizations from a mixture of 95% ethanol and isopropyl ether.

The α -thienyl hydrochloride salt, which was very insoluble, was refluxed with ten times its weight of 95% ethanol, the suspension chilled and suction filtered. An analytical sample was prepared by several recrystallizations from 95% ethanol.

Preparation of Ketones (III) by the β -Keto Ester Method.—*m*-Trifluoromethylbenzonitrile was obtained from benzotrifluoride¹⁸ by nitration, reduction and the Sandmeyer reaction.¹⁹

m-Trifluoromethylacetophenone (b. p. 198–200°) was prepared from 45 g. (0.263 mole) of *m*-trifluoromethylbenzonitrile and 0.298 mole of methylmagnesium iodide. The yield was 39 g. (79%). The semicarbazone, after recrystallization from ethanol and water melted at 205–206°.

Anal. Calcd. for $C_{10}H_{10}N_2OF_3$: C, 48.9; H, 4.11; N, 17.1. Found: C, 48.5; H, 4.29; N, 16.8.

Ethyl *m*-trifluoromethylbenzoylacetate (b. p. $125-126^{\circ}$ at 4 mm.) was synthesized by the carbethoxylation of 25 g. (0.133 mole) of *m*-trifluoromethylacetophenone with 31.7 g. (0.266 mole) of diethyl carbonate by the sodium amide method.²⁰ The yield was 22 g. (62%). The phenylpyrazolone, after recrystallization from ethanol and water, melted at 140°.

Anal. Calcd. for $C_{16}H_{11}N_2OF_3$: C, 63.2; H, 3.64. Found: C, 62.9; H, 3.36.

4-Diethylamino-1-(*m*-trifluoromethylphenyl)-butanone-1 (b. p. 128–135° at 3 mm.) was prepared from 30 g. (0.115 mole) of ethyl *m*-trifluoromethylbenzoylacetate and 15.6 g. (0.115 mole) of γ -diethylaminoethyl chloride by the general method described previously.¹⁰ The yield was 17 g. (50%).

17 g. (50%). 4-Diethylamino-1- $(\alpha$ -thienyl)-butanone-1 was synthesized in 41% yield from ethyl β -keto- β -(2-thienyl)-propionate²⁰ and γ -diethylaminoethylchloride.¹⁰

4-Diethylamino-1- $(\alpha$ -furyl)-butanone-1 (b. p. 126° at 5 mm.) was obtained in 32% yield from ethyl $(\alpha$ -furoyl)-acetate²¹ and γ -diethylaminoethyl chloride.¹⁰

Anal. Calcd. for $C_{12}H_{19}NO_2$: neut. eq., 209. Found: neut. equiv., 215.

The oxime (b. p. 159–160° at 2 mm.) was obtained in 82% yield.

(17) The beuzotrifluoride hydrochloride salt was especially in soluble, 1500 ml. of 95% ethanol being required to dissolve 12.5 g. of the salt.

(18) We are indebted to the Hooker Electrochemical Company for a supply of benzotrifluoride.

(19) Swarts, Bull. Acad. roy. Belg., 35, 375 (1898).

(20) Levine and Hauser, THIS JOURNAL, 66, 1768 (1944).

(21) This compound (b. p. $133-135^{\circ}$ at 9 mm.) was prepared in 64% yield from ethyl acetate and ethyl furoate using sodium by an adaptation of the method of Torrey and Zanetti, Am. Chem. J., 44, 405 (1910).

⁽¹⁵⁾ Simons and Ramler, THIS JOURNAL, 65, 389 (1943).

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Anal. Calcd. for $C_{12}H_{20}N_2O_2$: neut. equiv., 224. Found: neut. equiv., 225.

Summary

1. The recently developed method for the preparation of ketones from aliphatic nitriles and aromatic Grignard reagents has been adapted to the preparation of ketones which may be used as intermediates in the synthesis of potential antimalarial or antitubercular drugs.

2. The mild method of reduction employing zinc dust and acetic acid has been adapted to the reduction of certain oximes to diamines.

3. A number of new intermediates and certain new quinacrine analogs have been synthesized.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

Alkaline Cleavage of Unsymmetrical β -Diketones. Ring Opening of Acylcylohexanones to Form ϵ -Acyl Caproic Acids¹

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There is evidence^{2,3,4} that the cleavage of β -diketones by aqueous alkali to give carboxylic acids and ketones is concerned with the ketonic form (I) rather than with the enolic form (II) or with the anion (III) into which both (I) and (II) are first largely converted reversibly.



Perhaps the best evidence for the cleavage of (I)is that α, α -disubstituted β -diketones, which cannot be enolized or ionized, undergo alkaline cleavage much more rapidly than the unsubstituted compounds⁴ and that the relative yields of the two possible acids from the cleavage of p-chloro, pbromo and p-methoxydibenzoylmethanes are approximately the same as those from the corresponding mono-methylated β -diketones, the enolization of which appears to be almost completely suppressed.³ Since the cleavage amounts to a reverse Claisen condensation, it is presumably initiated by the attack of hydroxyl ion at the carbonyl carbon. The mechanism for the cleavage² and also that for the alkaline hydrolysis of esters,⁵ the relationship to which is considered below, may be illustrated by the following general equation in which B represents CH₂COR' or OR', respectively.6

(1) Reported at the Chicago Meetings of the American Chemical Society, September, 1946, and April, 1948.

(2) Bradley and Robinson, J. Chem. Soc., 129, 2356 (1926).

- (3) Bickel, THIS JOURNAL, 67, 2204 (1945).
- (4) Kutz and Adkins, ibid., 52, 4391 (1930).

(5) See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 354.

(6) It is possible that, with certain β -diketones which have fixed enolic structures, the enolic form or its anion is cleaved. See Fieser, THIS JOURNAL, **51**, 940 (1929). It is also possible that even with certain ordinary β -diketones the enolic form is cleaved, but, if so, the carbonyl group would presumably be involved (see Beckham and Adkins, *ibid.*, **56**, 1119 (1934)), the mechanism being represented by equation (1) in which B is CH=C(OH)R.

(1)
$$RC - B + OH^{-} \longrightarrow R - C - B \longrightarrow$$

 OH
 $RC OH$
 $B^{-} \rightarrow RC O^{-} + BH$

Since the relative yields of the two possible acids, RCOOH and R'COOH, from the cleavage of an unsymmetrical β -diketone (1) would depend on the relative rates of reaction of the two carbonyl groups with hydroxyl ion, a direct relationship might be expected between these

yields and the relative rates of alkaline hydrolysis of the corresponding ethyl esters, RCOOC_2H_5 and $\text{R'COOC}_2\text{H}_5$, respectively. Actually such a relationship can be deduced from the results obtained by earlier workers with certain substituted dibenzoylmethanes, such as *p*-methoxy,³ *p*-chloro^{2,3} and *p*-nitro² dibenzoylmethanes, and with benzoylacetone.⁷ In each case the acid whose ethyl ester undergoes alkaline hydrolysis the more readily is obtained in the greater yield.⁸ However, the relationship fails with *o*-chlorodibenzoylmethane,^{9,10}

A direct relationship might also be expected between the relative yields of the *p*-substituted benzoic acids produced on the cleavage of a series of *p*-substituted dibenzoylmethanes or of a series of *p*-substituted benzoylacetones and the relative rates of alkaline hydrolysis of the corresponding ethyl esters. In these cases the R group in both (I) and equation (1) is varied while the R' group

(7) Adkins and Kutz, *ibid.*, **52**, 4036 (1930).

(8) Bradley and Robinson (ref. 2) have pointed out that the relative yields of the two possible acids from substituted dibenzoylmethanes are in general related directly to the strengths of the acids. However, this relationship fails with benzoylacetone (see ref. 7).

(9) Bickel, This Journal, 68, 865 (1946).

(10) The failure of the relationship with the ortho substituted dibenzoylmethane is not surprising since steric factors should be especially operative in such cases and these factors might affect the rates of cleavage of β -diketones and of the alkaline hydrolysis of esters to considerably different degrees. Even with the para-substituted dibenzoylmethanes, the relationship is only qualitative; of course a quantitative relationship could hardly be expected as the two types of reactions have been carried out under different conditions.