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# CHAPTER 1

# THE CLEAVAGE OF NON-ENOLIZABLE KETONES WITH SODIUM AMIDE. THE HALLER-BAUER REACTION

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## CONTENTS

1

## INTRODUCTION

In this chapter the Haller-Bauer reaction is defined as the action of sodium amide on a non-enolizable ketone causing cleavage of a carbon to carbon bond and resulting in the formation of an amide and a hydrocarbon.

$$R\text{—}\underset{\underset{O}{\|}}{C}\text{—}R' \xrightarrow{\text{NaNH}_2} RCONH_2 + R'H$$

Textbook definitions of the Haller-Bauer reaction have limited it to the alkylation of ketones in which sodium amide acts as a condensing agent[1,2] or have considered it a combination of the alkylation and cleavage reactions.[3]

The cleavage of ketones by sodium amide was discovered in 1906 by Semmler[4] in connection with his investigations of the structure of fenchone. Suspecting that fenchone contained no α-hydrogen atoms, Semmler chose sodium amide as a reagent that might effect a cleavage without causing rearrangement of the molecule. As a result, the sodio derivative of fencholic acid amide was obtained. He did not explore the potentialities of the reaction. This was done by Haller and Bauer,[5] who in 1908 reported the isolation of benzamide after the treatment of benzophenone with sodium amide in boiling benzene or toluene and who followed this observation with an extended study of the reaction.

A modification of the Haller-Bauer reaction involving the use of a fused eutectic mixture of sodium and potassium amides[6] has been applied to certain alicyclic and bicyclic terpenoid ketones as well as to some amides. The carbonyl group was completely eliminated from these compounds. For example, fenchone was cleaved to 1-methyl-3-isopropylcyclopentane, and 1-benzoylpiperidine gave rise to benzene and piperidine.

<center>MECHANISM</center>

On the basis of their early experiments, Haller and Bauer proposed a mechanism for the reaction of sodium amide with benzophenone which involved a preliminary addition to the ketone.[5] The "sodium salt of

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[1] Cohen, *Organic Chemistry for Advanced Students*, I, 4th ed., p. 217, Longmans, Green and Co., New York, 1924.

[2] Degering, *An Outline of Organic Chemistry*, 4th ed., p. 321, Barnes and Noble, 1941.

[3] *The Merck Index*, 6th ed., p. 1055, Merck and Co., Rahway, N.J., 1952.

[4] Semmler, *Ber.*, **39**, 2577 (1906).

[5] Haller and Bauer, *Compt. rend.*, **147**, 824 (1908).

[6] Freidlin, Balandin, and Lebedeva, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, **1941**, 167 [*C. A.*, **37**, 3749 (1943)].

diphenylaminocarbinol" (I) thus formed could be isolated as a crystalline

$$C_6H_5COC_6H_5 + NaNH_2 \rightarrow C_6H_5\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}C_6H_5$$

I

$$C_6H_5\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}C_6H_5 + H_2O \rightarrow C_6H_5CONH_2 + C_6H_6 + NaOH$$

product. Upon treatment with water it gave rise to benzamide and benzene. In 1922 Haller published a review article and repeated his ideas on the mechanism of the reaction.[7]

Schönberg in 1924 and 1925 described his researches on the action of sodium amide on diaryl ketones.[8,9] His observations with benzophenone were in agreement with those of Haller and Bauer; his interpretation of the reaction, however, differed from theirs as far as the decomposition of the adduct I was concerned. It was Schönberg's view that the addition product I undergoes thermal cleavage in boiling benzene or toluene to furnish benzene and the sodio derivative of benzamide,[10] which can be isolated from the reaction mixture. Treatment with water hydrolyzes *this latter* sodio derivative to benzamide.

$$C_6H_5\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}C_6H_5 \xrightarrow{\text{Heat}} C_6H_6 + C_6H_5\overset{\overset{O}{\|}}{C}NHNa \text{ or } C_6H_5\overset{\overset{ONa}{|}}{C}{=}NH$$

I

$$C_6H_5CONHNa + H_2O \rightarrow C_6H_5CONH_2 + NaOH$$

Further evidence to support this mechanism was provided by the reaction of *p*-phenylbenzophenone with sodium amide. When these materials were heated under refluxing conditions in dry toluene and the solid so formed was removed by filtration, biphenyl was isolated from the filtrate. As both the hydrocarbon and the sodio derivative of the amide were formed in the absence of water it was evident that water was not necessary for the formation of the hydrocarbon. Lea and Robinson[11] have carried out additional experiments on the action of sodium amide

[7] Haller, *Bull. soc. chim. France*, [4] **31**, 1117 (1922).

[8] Schönberg, Abelsdorff, Kirchrath, Malchov, and Rosen, *Ann.*, **436**, 205 (1924).

[9] Schönberg, *Ber.*, **58**, 580 (1925).

[10] Curtius, *Ber.*, **23**, 3038 (1890).

[11] Lea and Robinson, *J. Chem. Soc.*, **1926**, 2351.

on unsymmetrical benzophenones. Their description of the reaction mechanism is in full agreement with that of Schönberg.

A modern interpretation of the reaction might be written as follows:

$$\text{RCOR}' + \text{N}\overset{-}{\text{H}}_2 \rightleftarrows \text{R}-\underset{\underset{\text{NH}_2}{|}}{\overset{\overset{\text{O}^-}{|}}{\text{C}}}-\text{R}' \rightleftarrows \text{R}\overset{-}{:} + \text{H}_2\text{NCOR}' \rightarrow \text{RH} + \overset{-}{(}\text{HNCOR}')$$

The direction of cleavage depends upon the relative electronegativities of R and R'. If R' in the ketone, RCOR', is more strongly electron repelling than R the primary product is R'CONH$_2$.

The mechanism suggested by Freidlin[6] for the modification of the Haller-Bauer reaction in which a fused eutectic mixture of sodium and potassium amides reacts with a ketone or an amide is given below. Cleavage occurs to eliminate the carbonyl group with the formation of metal cyanamides.

$$\text{RCOR}' \xrightarrow{\text{NaNH}_2} \text{RR}'\text{C(OH)NHNa} \rightarrow \text{R}'\text{H} + \text{RCONHNa}$$

$$\text{RCONHNa} \xrightarrow{\text{NaNH}_2} \text{RC(OH)(NHNa)}_2 \rightarrow \text{RH} + (\text{NaHN})_2\text{CO}$$

$$(\text{NaHN})_2\text{CO} \longrightarrow \text{Na}_2\text{CN}_2 + \text{H}_2\text{O}$$

### SCOPE AND LIMITATIONS

The Haller-Bauer reaction has been applied to many non-enolizable ketones[12] and with certain classes of these compounds has considerable synthetic utility. It is one of the few general methods for the synthesis of tertiary carboxamides, compounds which are useful as intermediates for tertiary carboxylic acids or tertiary carbinamines. By hydrolysis of the amides,[13] many tertiary carboxylic acids have been made available, and an even less accessible class of compounds, the tertiary carbinamines, can be formed by application of the Hofmann, Schmidt, and Curtius reactions to the amides or acids.[14]

$$\underset{\underset{\text{R}''}{|}}{\overset{\overset{\text{R}'\ \ \text{O}}{|\ \ \ ||}}{\text{R}-\text{C}-\text{C}}}-\text{R}''' \xrightarrow{\text{NaNH}_2} \underset{\underset{\text{R}''}{|}}{\overset{\overset{\text{R}'}{|}}{\text{R}-\text{C}}}-\text{CONH}_2 \longrightarrow \underset{\underset{\text{R}''}{|}}{\overset{\overset{\text{R}'}{|}}{\text{R}-\text{C}}}-\text{CO}_2\text{H}$$

$$\searrow \quad \underset{\underset{\text{R}''}{|}}{\overset{\overset{\text{R}'}{|}}{\text{R}-\text{C}}}-\text{NH}_2 \quad \swarrow$$

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[12] A few ketones having an α-hydrogen atom have been cleaved by sodium amide during attempted alkylation. Some of these cleavages are considered on pp. 8 and 12; all are cited in Table I.

[13] Sperber, Papa, and Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

[14] *Organic Reactions*, Vol. III, Chapters 7, 8, and 9, John Wiley & Sons, New York, 1946.

## The Cleavage of Aliphatic or Alicyclic Phenyl Ketones (Table I)

The most important application of the Haller-Bauer reaction is the cleavage of aliphatic or alicyclic phenyl ketones. Broadly, the cleavage occurs in such a way as to produce the tertiary carboxamides. For example, $\alpha,\alpha$-dimethylpropiophenone when heated in benzene under refluxing conditions with sodium amide affords a nearly quantitative yield of pivalamide. Similarly, 1-methylcyclohexyl phenyl ketone under the same conditions readily forms 1-methylcyclohexanecarboxamide in 88% yield. Since the starting ketones in general are rather easily obtained, the reaction has found considerable application.

When two of the substituents (for example, R and R') of a trialkylaceto-phenone II are methyl, the third (R'') may be increased in size to $C_{18}$ without interfering with the normal direction of the reaction. On the

$$
\begin{array}{c}
R \\
| \\
R'\!-\!\overset{|}{C}\!-\!\overset{\|}{\underset{\|}{C}}\!-\!C_6H_5 \\
| \quad \| \\
R'' \ O
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
R \\
| \\
R'\!-\!\overset{|}{C}\!-\!\overset{\|}{\underset{\|}{C}}\!-\!NH_2 \\
| \quad \| \\
R'' \ O
\end{array}
$$

II

other hand, as R and R' increase in size and complexity, the yields of trialkylacetamides fall off rapidly and the amount of benzamide increases. This effect was studied in detail by restricting one alkyl group to methyl or ethyl and progressively increasing in size the other two.[15] No difficulty was experienced in the preparation of variously branched amides containing up to ten carbon atoms. However, in II, where R, R', and R'' total eleven carbon atoms, certain irregularities became evident and more benzamide resulted. For example, $\alpha$-methyl-$\alpha$-$n$-butyl-$n$-hexamide and $\alpha$-ethyl-$\alpha$-$n$-propyl-$n$-hexamide were formed readily. On the other hand, $\alpha$-methyl-$\alpha$-ethyl-$n$-octamide was obtained in an impure state while $\alpha,\alpha$-diethylheptamide could not be isolated. With a total of twelve or more carbon atoms in the three substituent groups, the molecules exhibited even greater variation from the normal direction of cleavage. The investigators concluded that failure of the method might be expected with alkyl phenyl ketones of relatively low molecular weight where the three substituents are highly complex.

The results of these workers may be explained partly on the basis of steric hindrance: the more complex the branching about the carbonyl group, the less successful is the cleavage. Recovery of some starting ketone from the reaction mixture is possible with such compounds. However, the isolation of increasing amounts of benzamide indicates that some attack on the carbonyl group occurs.

[15] Carter and Slater, *J. Chem. Soc.*, **1946**, 130.

The application of Newman's "Rule of Six"[16] to account for the st effects of branching about the carbonyl group is only partly satisfact The results are neither strikingly in agreement nor strikingly in agreement with the rule.

The cleavage of alicyclic phenyl ketones by their reaction with sod amide[17-21] follows the direction reported for alkyl phenyl ketc Good yields of the expected 1-alkyl alicyclic carboxamides were obta with little evidence of benzamide where the alkyl substituent (R) methyl, ethyl, $n$-propyl, isopropyl, or $n$-butyl.

$$(CH_2)_nC \begin{cases} R \\ COC_6H_5 \end{cases}$$

Anomalous results were reported with 1-methylcyclopropyl ph ketone, which furnished benzamide and no 1-methylcyclopropanecarl amide.[17]　On the other hand, replacement of methyl by benzyl chan the direction of cleavage and 1-benzylcyclopropanecarboxamide obtained readily.　This cleavage of 1-benzylcyclopropyl phenyl keton the expected manner was confirmed by the hydrolysis of the amide identification of the 1-benzylcyclopropanecarboxylic acid.[20]

Diketones of type III provide an excellent source of $\alpha,\alpha,\alpha',\alpha'$-te alkyldiamides.　The diketones, where R is methyl and $n$ has been va from 3 to 14, have been converted to diamides.[22-24]

$$C_6H_5C \underset{\underset{O}{\|} \underset{R}{|}}{\overset{\overset{R}{|}}{-}} C(CH_2)_n \underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}} \underset{\underset{O}{\|}}{-} CC_6H_5 \xrightarrow{\ NaNH_2\ } H_2NC \underset{\underset{R}{|}}{\overset{\overset{O}{\|}\ \overset{R}{|}}{-}} C(CH_2)_n \underset{\underset{R}{|}}{\overset{\overset{R}{|}\ \overset{O}{\|}}{C}} - CNH_2$$

III

The reaction also proceeds in the expected manner with diketones s as IV, synthesized by use of a dihalide containing a benzene nucleus. corresponding *ortho* and *meta* derivatives were also prepared.[25]

[16] Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).

[17] Haller and Benoist, *Ann. chim. Paris*, [9] **17**, 25 (1921).

[18] Wash, Shive, and Lochte, *J. Am. Chem. Soc.*, **63**, 2975 (1941).

[19] Hamlin and Freifelder, *J. Am. Chem. Soc.*, **75**, 369 (1953).

[20] Piehl and Brown, *J. Am. Chem. Soc.*, **75**, 5023 (1953).

[21] Hamlin and Biermacher, *J. Am. Chem. Soc.*, **77**, 6376 (1955).

[22] Haller and Bauer, *Compt. rend.*, **152**, 1638 (1911).

[23] Adams and Anderson, *J. Am. Chem. Soc.*, **73**, 136 (1951).

[24] Leonard and Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).

[25] Dumesnil, *Ann. chim. Paris*, [9] **8**, 70 (1917).

$$C_6H_5C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{\overset{\|}{C}}}-CH_2-\langle\text{benzene}\rangle-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}C_6H_5 \xrightarrow{\text{NaNH}_2}$$

IV

$$H_2N\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_2-\langle\text{benzene}\rangle-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}NH_2$$

An interesting secondary reaction is encountered in a series of 1,1-dialkyl-3-butenyl phenyl ketones (V). These ketones on treatment with sodium amide yield unsaturated amides which cyclize to the corresponding pyrrolidones (VI). Brown and van Gulick[26] conclusively proved that for

$$CH_2{=}CHCH_2-\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-\overset{\overset{\displaystyle}{\underset{\underset{\displaystyle O}{\|}}{C}}}C_6H_5 \rightarrow \underset{\displaystyle\underset{\displaystyle\underset{H}{N}}{}}{\overset{\displaystyle CH_2-CR_2}{\underset{\displaystyle H_3CCH\quad C{=}O}{|\qquad\quad|}}}$$

V                                         VI

3,3,5-trimethyl-2-pyrrolidone the reaction takes the course proposed by Haller and Bauer,[27] viz., the 2,2-dimethyl-4-pentenamide arising from the sodium amide cleavage of 1,1-dimethyl-3-butenyl phenyl ketc̀ cyclize under basic conditions.

$$CH_2{=}CHCH_2C(CH_3)_2COC_6H_5 \xrightarrow{\text{NaNH}_2}$$

$$[CH_2{=}CHCH_2C(CH_3)_2CONH_2] \rightarrow \underset{\displaystyle\underset{\displaystyle\underset{H}{N}}{}}{\overset{\displaystyle CH_2-C(CH_3)_2}{\underset{\displaystyle H_3CCH\quad C{=}O}{|\qquad\quad|}}}$$

Several 5-methyl-3,3-dialkyl-2-pyrrolidones have been prepared by this method, and the reaction is considered to be general.[28]

Most aralkyl and heterocyclic-alkyl phenyl ketones on treatment with sodium amide give the expected substituted alkylacetamides (Table I). However, α,α-dimethyl-γ,δ-epoxybutyl phenyl ketone is not attacked.[29]

The synthetic utility of the Haller-Bauer reaction is limited by the unavailability of the starting ketones. The simpler ketones are readily obtained by the alkylation of various acetophenones by conventional

[26] Brown and van Gulick, *J. Am. Chem. Soc.*, **77**, 1092 (1955).

[27] Haller and Bauer, *Compt. rend.*, **158**, 1086 (1914).

[28] Haller and Bauer, *Compt. rend.*, **160**, 541 (1915).

[29] Ramart-Lucas and Haller, *Compt. rend.*, **158**, 1302 (1914).

methods. The introduction of the third group into ketones of high molecular weight is restricted by steric effects. Such alkylations become progressively more difficult as the size of the entering group becomes larger; this is a major drawback to the use of the method for synthesis of acids containing a quaternary carbon atom.[30] Thus, it is impossible to methylate $\omega,\omega$-di-$n$-decylacetophenone. This barrier to the synthesis of trialkylacetophenones in which two substituents are long chain can be obviated by introducing the small group first into a higher homolog of acetophenone and then replacing the tertiary hydrogen by a long-chain alkyl group.[15]

Attempts to introduce an alkyl group in the tertiary position of an alicyclic phenyl ketone sometimes gave anomalous results. Alkylation of 2-methylcyclopentyl phenyl ketone was usually normal, but if the ketone was allowed to react with sodium amide in boiling xylene and then treated with isopropyl iodide a mixture of 2-methylcyclopentanecarboxamide, N-isopropyl-2-methylcyclopentanecarboxamide, and the isopropyl ether of the enol form of the parent ketone resulted.[18,19] Cleavage of this



ketone, containing an $\alpha$-hydrogen atom, was occurring in place of alkylation. The cleavage of cyclohexyl phenyl ketone by sodium amide resulted in a 1% yield of cyclohexanecarboxamide.[19] Similarly cyclopropyl phenyl ketone with sodium amide in boiling benzene gave a 42% yield of cyclopropanecarboxamide as well as a small amount (2%) of benzamide. These results could not be repeated and do not coincide with those previously reported that, with sodium amide in moist benzene, benzamide was the only product isolated.[17]

## The Cleavage of Aliphatic Ketones (Table II)

Symmetrically substituted acetones react with sodium amide to form the predicted tertiary carboxamide and trialkylated methane.[31] Thus hexamethylacetone gives an excellent yield of pivalamide by this method.

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[30] Birch and Robinson, *J. Chem. Soc.*, **1942**, 488.

[31] Haller and Bauer, *Compt. rend.*, **150**, 664 (1910).

On the other hand, a mixture of the four possible products (two amides and two hydrocarbons) is obtained from 2,2,4,4-tetramethyl-3-hexanone (VII).

$$
\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{CH_3-C}}-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH_2CH_3
\qquad
\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{CH_3-C}}-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH_2C_6H_5
$$
$$
\text{VII} \qquad\qquad\qquad\qquad \text{VIII}
$$

$$
\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{CH_3-C}}-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle C_2H_5}{|}}{\overset{\overset{\displaystyle C_2H_5}{|}}{C}}-CH_2CH_3
\qquad
(CH_3)_2CH-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH(CH_3)_2
$$
$$
\text{IX} \qquad\qquad\qquad\qquad \text{X}
$$

Although substituted acetones may furnish a mixture of two possible amides and two hydrocarbons, one direction of cleavage may predominate. 2,2,4,4-Tetramethyl-5-phenyl-3-pentanone (VIII) cleaves exclusively to pivalamide and isobutylbenzene;[32] 4,4-diethyl-2,2-dimethyl-3-hexanone (IX) when treated with sodium amide at the boiling point of xylene forms pivalamide and α,α,α-triethylacetamide in a 5-to-1 ratio.[31]

An additional limitation to the practical use of the reaction with aliphatic ketones is encountered when the substituents are highly branched. For instance, the ketone X is inert to the action of sodium amide under vigorous conditions.[32]    Since in such cases the starting ketone is recovered, the failure of the reaction is possibly attributable to steric hindrance about the carbonyl group.

### The Cleavage of Diaryl Ketones (Table III)

Diaryl ketones are readily attacked by sodium amide.    If symmetrically substituted they can yield only one amide and one hydrocarbon.    Unsymmetrical diaryl ketones in which the substituents cause one aromatic nucleus to be much more strongly electron donating than the other give predominantly one amide and one hydrocarbon.

From the large number of diaryl ketones falling between these two extremes, four possible products, two amides and two hydrocarbons, are formed in varying amounts.    Only the first two types of diaryl ketones are useful for the preparation of amides.

Schönberg[8,9] and Lea and Robinson[11] cleaved a variety of unsymmetrical diaryl ketones and determined the comparative yields of the various

[32] Haller and Bauer, *Ann. chim. Paris*, [9] 1, 5 (1914).

benzamides or benzoic acids. They and, later, de Ceuster[33] drew the conclusion illustrated below that the presence of an electron-supplying group favors cleavage to produce the substituted benzamide. The same substituent in an *ortho* position results in almost complete cleavage to yield the unsubstituted benzamide; e.g., 2-methoxybenzophenone furnishes benzamide almost exclusively.

$$Cl\text{—}C_6H_4\text{—}CO\text{—}C_6H_5 \rightarrow Cl\text{—}C_6H_4\text{—}CONH_2 + C_6H_5CONH_2$$
24%      76%

$$CH_3O\text{—}C_6H_4\text{—}CO\text{—}C_6H_5 \rightarrow CH_3O\text{—}C_6H_4\text{—}CONH_2 + C_6H_5CONH_2$$
72%      28%

$$CH_3O\text{—}C_6H_4\text{—}CO\text{—}C_6H_4\text{—}OCH_3 \rightarrow CH_3O\text{—}C_6H_4\text{—}CONH_2 + CH_3O\text{—}C_6H_4\text{—}CONH_2$$
86%      14%

The effect of conditions upon the Haller-Bauer reaction may be illustrated by the action of sodium amide on α-naphthyl phenyl ketone.[34] On heating in benzene under refluxing conditions, only traces of benzamide were found and nearly all the original ketone was recovered. When the ketone and amide were heated under refluxing conditions in toluene for five hours, considerable benzamide was found along with ketone. When the ketone and sodium amide were heated with benzene in a sealed tube for twelve hours, the major product was benzamide accompanied by traces of naphthalene. In contrast, the isomeric β-naphthyl phenyl ketone on treatment with sodium amide in benzene cleaved readily to afford β-naphthamide as the main product along with small amounts of benzamide.[9,34]

Examples of the action of sodium amide on cyclized aromatic ketones are few. Fluorenone has been shown to yield o-phenylbenzamide in the expected manner.[35,36] However, anthraquinone was recovered unchanged after treatment with sodium amide.[29]

[33] De Ceuster, *Natuurw. Tijdschr. Belg.*, **14**, No. 3–6, 188 (1932) [*C. A.*, **26**, 4323 (1932) *Chem. Zentr.*, **1932**, II, 1296].

[34] Lucas, *Ann. chim. et phys.*, [8] **17**, 127 (1909).

[35] Haller and Bauer, *Compt. rend.*, **147**, 824 (1908).

[36] Haller and Bauer, *Ann. chim. et phys.*, [8] **16**, 145 (1909).

## The Cleavage of Alicyclic Ketones (Table IV)

Following the first use of the Haller-Bauer reaction on fenchone, sodium amide cleavage was used in elucidation of the structure of certain terpenes related to camphor.[4]   Several dialkylcamphors were cleaved by sodium amide to the corresponding dialkylcampholamides.[37,38]   Each ketone cleaved in one direction and gave good yields of 1,2,2-trimethyl-3-alkylcyclopentanecarboxamide.

Symmetrically substituted cyclic ketones react with opening of the ring and give rise to one product only, an aliphatic carboxamide.   Thus, with 2,2,5,5-tetramethylcyclopentanone[39] (XI) cleavage proceeds as



XI

indicated.   Unsymmetrically substituted cyclopentanones, however, give a mixture of two aliphatic carboxamides, thereby limiting the usefulness of the reaction.   Cyclohexanones are reported[7] to be very resistant to the action of sodium amide.

## The Action of Sodium Amide upon Miscellaneous Carbonyl Compounds (Table V)

Other types of carbonyl compounds have been treated with sodium amide under similar conditions.   Aromatic aldehydes undergo the Cannizzaro reaction to yield the corresponding alcohol and acid.[40,41]   Benzil and substituted benzils give a typical benzilic acid rearrangement.[41,42] An interesting exception is the reaction of acenaphthadione, which cleaves to oxamide and naphthalene.   α-Phenylbenzoin reacts with sodium amide;   both the expected products, benzilamide and benzamide, are formed, although the latter predominates.[8]

$$C_6H_5COC(OH)(C_6H_5)_2 \xrightarrow{\text{NaNH}_2} (C_6H_5)_2C(OH)CONH_2 + C_6H_5CONH_2$$

Certain diketones undergo an intramolecular Claisen condensation under the influence of sodium amide.   Thus, 1,6-diphenylhexane-1,6-dione

[37] Haller and Bauer, *Compt. rend.*, **148**, 1643 (1909).

[38] Haller and Louvrier, *Ann. chim. Paris*, [9] **9**, 189 (1918).

[39] Haller and Cornubert, *Compt. rend.*, **158**, 298 (1914).

[40] Haller and Bauer, *Ann. chim. et phys.*, [8] **16**, 145 (1909).

[41] Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 66 (1926) [*C. A.*, **20**, 2491 (1926)].

[42] Oliverio, *Boll. sedute accad. Gioenia sci. nat. Catania*, [3] **5**, 37 (1937) [*C. A.*, **34**, 7886 (1940)].

$$C_6H_5\underset{\underset{O}{\|}}{C}(CH_2)_4\underset{\underset{O}{\|}}{C}C_6H_5 \quad \xrightarrow[\text{Benzene}]{\text{NaNH}_2}$$



reacts in the following manner.[43]   The mixture of isomers was separated and each isomer was treated with sodium amide.   The lower-melting isomer undergoes the Haller-Bauer reaction and hence was assigned structure XII.[43,44]   The higher-melting isomer that has an α-hydrogen does not undergo cleavage with sodium amide and hence could be designated by structure XIII or by an analogous structure in which the double bond is in another position in the ring.   A parallel reaction sequence has been established for 1,7-diphenylheptane-1,7-dione.[45]

2,4-Dimethyl-1,3,5-triphenylpentane-1,5-dione (XIV), which contains α-hydrogen atoms, was cleaved with sodium amide in what appears to be a reverse Michael reaction.[46]



### RELATED SYNTHETIC PROCESSES

Synthesis of Tertiary Carboxylic Acids.   The principal alternative methods for synthesis of tertiary carboxylic acids (trisubstituted acetic acids) are briefly surveyed here.   Most of the literature resulted from efforts to synthesize phthioic acid (ethyl-$n$-decyl-$n$-dodecylacetic acid) and similar structures.[30,47,48]

The aliphatic nitriles may be alkylated to the corresponding trialkyl-acetonitriles,[49] which may be hydrolyzed first to the amides with 80% sulfuric acid and finally to the acids.   Although the difficulty of hydrolysis

[43] Bauer and Haller, *Compt. rend.*, **156**, 1470 (1913).
[44] Bauer and Haller, *Compt. rend.*, **156**, 1684 (1913).
[45] Bauer, *Ann. chim. Paris*, **1**, 343 (1914).
[46] Bauer and Haller, *Compt. rend.*, **158**, 1680 (1914).
[47] Polgar and Robinson, *J. Chem. Soc.*, **1943**, 615.
[48] Hook and Robinson, *J. Chem. Soc.*, **1944**, 152.
[49] Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

of the nitriles is a serious limitation of the method, a series of trialkyl-acetonitriles in which the alkyl groups contain as many as seven carbon atoms has been successfully hydrolyzed.[13]

Trialkylacetic acids have also been prepared by the carbonation of $t$-alkylmagnesium chlorides.[50] This method suffers from many disadvantages, principally the difficulty of forming Grignard reagents from tertiary alkyl halides of high molecular weight.

$\alpha$-Alkylation of esters can be effected by means of sodium triphenyl-methyl and an alkyl halide.[51] However, the separation of unreacted disubstituted acetic acids or esters necessitates a tedious purification.

To a limited degree, the Favorski rearrangement of $\alpha$-halogenated ketones can be used in the synthesis of tertiary carboxylic acids.[52–54] However, wherever the R groups become large or complex only metathesis occurs in the first step.

$$\underset{\substack{| \\ Br \ O}}{\overset{\substack{R'' \\ |}}{R'-C-CR'''}} \xrightarrow{\text{NaOR}} \underset{\substack{| \ | \\ Br \ ONa}}{\overset{\substack{R'' \ OR \\ | \ |}}{R'-C-C-R'''}} \rightarrow \underset{\substack{O}}{\overset{\substack{R'' \ OR \\ | \ |}}{R'C----CR'''}} \rightarrow \underset{\substack{| \\ R'''}}{\overset{\substack{R'' \\ |}}{R'-C-CO_2R}}$$

**Synthesis of Tertiary Carbinamines.** Synthesis of amines in which the amino group is attached to a tertiary carbon atom has been reported in only isolated instances, and in most of them the simplest member of the series, $t$-butylamine, was the material prepared.

A group of tertiary carbinamines has been synthesized by reaction of certain nitriles with a Grignard reagent.[55] In this fashion, alkoxyalkyl, aralkyl, or alkenyl cyanides on treatment with allylmagnesium bromide formed tertiary carbinamines in which two of the substituent groups were allyl. Hydrogenation yielded the corresponding propyl compounds.

Tertiary nitriles, prepared by alkylation of primary nitriles,[49] can be hydrolyzed to the corresponding amides. After conversion to the isocyanates by the Hofmann method, tertiary carbinamines can be obtained by hydrolysis.

The most important innovation in synthetic methods for the preparation of such amines is that developed by Ritter and co-workers,[56,57] in which treatment of an alkene with a nitrile in the presence of concentrated sulfuric acid produces excellent yields of amides of $t$-carbinamines.

[50] Whitmore and Badertscher, *J. Am. Chem. Soc.*, **55**, 1559 (1933).

[51] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).

[52] Marker and Wagner, *J. Am. Chem. Soc.*, **64**, 216 (1942).

[53] Aston, Clarke, Burgess, and Greenburg, *J. Am. Chem. Soc.*, **64**, 300 (1942).

[54] Plattner, Heusser, and Boyce, *Helv. Chim. Acta*, **31**, 603 (1948).

[55] Henze, Allen, and Leslie, *J. Am. Chem. Soc.*, **65**, 87 (1943).

[56] Ritter and Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).

[57] Ritter and Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

When sodium cyanide is used as the nitrile, the N-alkylformamides formed can be hydrolyzed readily to the desired amines. A tertiary alcohol can be substituted for the alkene.

$$
\begin{array}{c}
R \\
\phantom{R}\diagdown \\
\phantom{RR}\diagup C = CHR'' \\
R' \\
\end{array}
\xrightarrow{\;H_2SO_4\;}
\begin{array}{c}
R \\
\phantom{R}\diagdown \\
R' \!-\! C \!-\! OSO_3H \\
R''CH_2 \diagup \\
\end{array}
$$

$$\downarrow R'''CN$$

$$
\begin{array}{c}
R \\
\phantom{R}\diagdown \\
R' \!-\! C \!-\! NHCOR''' \\
R''CH_2 \diagup \\
\end{array}
\longleftarrow
\begin{array}{c}
R \\
\phantom{R}\diagdown \\
R' \!-\! C \!-\! N = CR''' \\
R''CH_2 \diagup \quad | \\
\phantom{R''CH_2 \diagup}\; OSO_3H \\
\end{array}
$$

$t$-Butylamine has been prepared in 73% yield by the reaction of $t$-butylmagnesium chloride with methoxyamine.[58]

### EXPERIMENTAL CONDITIONS

The Haller-Bauer reaction is carried out by heating a non-enolizable ketone in an inert solvent in the presence of sodium amide. Benzene, toluene, and xylene have been used successfully. In certain instances where reaction has failed in benzene or toluene under refluxing conditions, the higher boiling temperature of xylene has led to success.

Although the quantities of sodium amide employed by various workers have varied, the use of two moles of this reagent for each carbonyl group to be cleaved is customary. Sodium amide now may be purchased, but usually it is freshly prepared in the vessel in which the reaction is to be carried out. Suitable directions for the preparation of sodium amide are found in *Organic Syntheses*.[59,60]

### EXPERIMENTAL PROCEDURES

α,α,α′,α′-Tetramethylsebacic Acid from Isobutyrophenone.[23] Sodium amide[59] is prepared in a 2-l. flask from 12.0 g. (0.52 mole) of sodium in 400 ml. of dry liquid ammonia using 0.15 g. of ferric nitrate hexahydrate as a catalyst. After the disappearance of the blue color and the formation of solid sodium amide, the residual ammonia is r ʾnoved by permitting the mixture to warm gradually. During this period of evaporation, 400 ml. of anhydrous toluene is added.

After evaporation of the ammonia, 74.0 g. (0.5 mole) of isobutyrophenone is added to the suspension. The resulting mixture is heated under reflux with stirring for an hour. Then 61 g. (0.25 mole) of hexamethylene dibromide is added dropwise over a period of one to two hours. Heating

[58] Sheverdina and Kocheshkov, *J. Gen. Chem. U.S.S.R.*, **8**, 1825 (1938) [*C. A.*, **33**, 5804 (1939)].

[59] *Organic Syntheses*, **25**, 25 (1945).

[60] *Organic Syntheses*, **30**, 72 (1950).

is continued for eight hours, and the mixture is washed with water and distilled. 2,2,9,9-Tetramethyl-1,10-diphenyldecane-1,10-dione distils at 200–265°/4–8 mm. (partial decomposition); yield 70.9 g. (75%).

A suspension of 29.25 g. (0.75 mole) of sodium amide in 600 ml. of anhydrous toluene is prepared in a 2-l. flask equipped with a stirrer, a dropping funnel, and a condenser carrying a drying tube. To the toluene-sodium amide suspension is added 70.9 g. (0.19 mole) of 2,2,9,9-tetra-methyl-1,10-diphenyldecane-1,10-dione. The mixture is heated under refluxing conditions with vigorous stirring for four hours and then cooled. After the gradual addition of 500 ml. of water, the mixture is filtered as rapidly as possible. The solid diamide thus obtained is washed with water, and the wash water is added to the filtrate. After the toluene is separated from the filtrate, the aqueous solution is concentrated. Upon acidification, this aqueous fraction yields a small additional amount of diamide. The total yield of crude $\alpha,\alpha,\alpha',\alpha'$-tetramethylsebacamide is 42 g. (87.5%). Recrystallization from ethanol results in a product melting at 210–213°.

A solution of 42 g. of crude diamide in 320 g. of concentrated sulfuric acid is cooled to 0–5° and treated with 45 g. of sodium nitrite in the minimal amount of water. The mixture is next heated to 50°, and water is added gradually with stirring. The solid acid that separates is removed by filtration, washed with water, and dissolved in aqueous sodium carbonate. The solution is decolorized with carbon, and the acid is repre-cipitated with hydrochloric acid; yield 29.4 g (70%). Purification is effected by recrystallization from ethyl acetate; pure $\alpha,\alpha,\alpha',\alpha'$-tetra-methylsebacic acid melts at 117–118°.

**1-Methylcyclohexylamine Hydrochloride from Cyclohexyl Phenyl Ketone.**[19] A suspension of 10 g. (0.25 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared in a 500-ml. flask equipped with a stirrer, a dropping funnel, and a condenser carrying a drying tube. To this is added dropwise 47 g. (0.25 mole) of cyclohexyl phenyl ketone. The mixture is stirred and boiled for one hour. It is stirred and cooled in an ice bath while 71 g. (0.5 mole) of methyl iodide is added in one portion. A sudden surge of heat after five minutes causes rapid boiling of the mixture. Stirring at room temperature is continued for twenty-four hours, after which the mixture is washed with water and distilled. The 1-methylcyclohexyl phenyl ketone distils at 134–140°/5 mm., $n_D^{25}$ 1.5316; yield 42 g. (80%).

A suspension of 15.6 (0.4 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared as outlined above. The toluene suspension is stirred while 42 g. (0.2 mole) of 1-methylcyclohexyl phenyl ketone is gradually added. Stirring is continued, and the mixture is heated under refluxing

conditions for six hours. After the reaction mixture is washed with water, the toluene layer is separated and distilled. 1-Methylcyclohexane-carboxamide distils at 151–154°/15 mm. and crystallizes on cooling. The amide is further purified by crystallization from pentane, m.p. 65°; yield 25 g. (88%).

A solution of 28.8 g. (0.18 mole) of bromine in 485 ml. of 20% aqueous potassium hydroxide is stirred and cooled in an ice bath while 25 g. (0.18 mole) of 1-methylcyclohexanecarboxamide is added as a fine powder. After the mixture has been stirred for an additional one-half hour, the resulting isocyanate is extracted with ether. The ethereal extract is added dropwise with stirring to 200 ml. of boiling concentrated hydrochloric acid. After the liberation of carbon dioxide ceases, the hydrochloric acid solution is concentrated in vacuum. The crystalline residue is recrystallized from a mixture of absolute ethanol and ether. A yield of 21 g. (80%) of 1-methylcyclohexylamine hydrochloride, m.p. 285° dec., is obtained.

**α,α-Dimethyl-β-phenylpropionamide from Isobutyrophenone.**[61] A suspension of 15.6 g. (0.4 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared in a 500-ml. flask equipped with a stirrer, a dropping funnel, and a condenser protected by a drying tube. A solution of 60 g. (0.4 mole) of isobutyrophenone and 68.5 g. (0.4 mole) of benzyl bromide in 100 ml. of anhydrous toluene is added dropwise with stirring. The reaction mixture is heated on a steam bath for forty-eight hours and then is washed with water. The toluene solution is distilled. 2,2-Dimethyl-1,3-diphenylpropan-1-one is obtained in a 75% yield (71.4 g.), distilling at 142–143°/3 mm.; $n_D^{20}$ 1.5652.

A suspension of 13 g. (0.33 mole) of sodium amide in 250 ml. of anhydrous toluene is prepared in a 1-l. flask as above. The mixture is stirred and heated to 60°. A solution of 71.4 g. (0.3 mole) of 2,2-dimethyl-1,3-diphenylpropan-1-one in 150 ml. of toluene is added, and the mixture is stirred and heated on a steam bath for five hours. The toluene suspension is cooled and washed with water, and the toluene is removed by distillation. There remains 36.5 g. (69%) of crystalline α,α-dimethyl-β-phenyl-propionamide. The product melts at 62° after recrystallization from benzene-petroleum ether.

**α-n-Butyl-α-methylcaprylic Acid from n-Heptyl Phenyl Ketone.**[15] A suspension of 6 g. (0.075 mole) of sodium amide in 50 ml. of anhydrous benzene is prepared in a 200-ml. flask equipped with a mechanical stirrer, a dropping funnel, and a condenser protected by a drying tube. The suspension is heated to boiling, and a solution of 15 g. (0.073 mole) of n-heptyl phenyl ketone in 50 ml. of anhydrous benzene is added dropwise.

[61] Abell, Bruce, and Seifter, U.S. pat. 2,590,079 [C. A., **46,** 10200 (1952)].

The mixture is heated and stirred for an additional hour and then cooled to room temperature, after which 21 g. (0.075 mole) of methyl iodide is added dropwise. Stirring at room temperature is continued for fifteen hours, and the benzene solution is washed with water and dried.

The dried benzene solution thus obtained is added to 6 g. (0.075 mole) of a sodium amide suspension as outlined above. The resulting sodio derivative of α-methyl-*n*-heptyl phenyl ketone is heated in benzene under refluxing conditions, and 37 g. (0.075 mole) of *n*-butyl iodide is added dropwise. This mixture is heated and stirred for an additional four hours. It is cooled, washed with water, dried, and distilled. A yield of 11 g. (55%) of α-*n*-butyl-α-methyl-*n*-heptyl phenyl ketone, b.p. 175–183°/ 17 mm., is obtained.

This ketone (0.04 mole) is added to a suspension of 1.6 g. (0.04 mole) of sodium amide in anhydrous benzene. The suspension is stirred and boiled for four hours and is then washed with water and distilled. A yield of 9 g. (quantitative) of α-*n*-butyl-α-methylcaprylamide is distilled at 167–169°/18 mm.

Without further purification, the amide so obtained is dissolved in 75 g. of concentrated sulfuric acid, and the resulting solution is cooled in a freezing mixture while an excess of a cold, saturated solution of sodium nitrite is stirred in. The mixture is warmed to about 50°, diluted with water, and extracted with ether. The ethereal extract is in turn extracted with dilute sodium hydroxide solution, and the combined alkaline extracts are acidified. The α-*n*-butyl-α-methylcaprylic acid distils at 160–162°/ 18 mm.; yield 2.4 g. (28%).

### TABULAR SURVEY OF CLEAVAGES OF NON-ENOLIZABLE KETONES WITH SODIUM AMIDE

In the following survey, the compounds have been arranged in the tables according to the type of ketone involved. Table I is concerned with the cleavage of aliphatic and alicyclic phenyl ketones. Since a single tertiary carboxamide is the normal product, the molecular formula of the expected amide is given. The compounds are listed by increasing molecular weight for ease of reference. Table IV, Alicyclic Ketones, is similarly arranged.

Tables II, III, and V involve the cleavage of ketones from which the isolation of a single product is the exception. For this reason, the molecular formula of the ketone is listed and the products are then given in order of increasing molecular weight.

The survey covers the literature available to the authors up to July 1, 1955.

When more than one reference is given for an entry, the yield reported is taken from the first reference.

## TABLE I

### A. CLEAVAGE OF ALKYL, ARALKYL, OR CYCLOALKYL PHENYL KETONES

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield,% | References |
|---|---|---|---|
| $(CH_3)_3C-$ | $C_5H_{11}NO$ | Quant. | 62, 32, 63 |
| $C_2H_5C(CH_3)_2-$ | $C_6H_{13}NO$ | Quant. | 62, 32, 15 |
| $CH_2=CHCH_2C(CH_3)_2-$ | $(CH_3)_2C\!-\!CH_2$, $O=C\!-\!N(H)\!-\!CHCH_3$ (lactam ring) | — | 26, 27 |
| $n\text{-}C_3H_7C(CH_3)_2-$ | $C_7H_{15}NO$ | Quant. | 62, 32, 15 |
| $C_2H_5C(CH_3)(C_2H_5)-$ | $C_7H_{15}NO$ | — | 15, 32, 62 |
| $i\text{-}C_3H_7C(CH_3)_2-$ | $C_7H_{15}NO$ | — | 32, 64 |
| $CH_2=CHCH_2C(CH_3)(C_2H_5)-$ | $H_3CC(C_2H_5)\!-\!CH_2$, $O=C\!-\!N(H)\!-\!CHCH_3$ (lactam ring) | — | 28 |
| $(C_2H_5)_3C-$ | $C_8H_{17}NO$ | — | 15, 32, 62 |
| $n\text{-}C_3H_7C(CH_3)(C_2H_5)-$ | $C_8H_{17}NO$ | — | 15, 32, 62 |
| $n\text{-}C_4H_9C(CH_3)_2-$ | $C_8H_{17}NO$ | 56 | 15 |
| [cyclopentyl]$C(CH_3)_2-$ | $\big[$cyclopentane-fused lactam$\ C(CH_3)_2,\ C=O,\ N(H)\big]$ | — | 86 |
| $CH_2=CHCH_2C(C_2H_5)_2-$ | $(C_2H_5)_2C\!-\!CH_2$, $O=C\!-\!N(H)\!-\!CHCH_3$ (lactam ring) | — | 28 |
| $n\text{-}C_5H_{11}C(CH_3)_2-$ | $C_9H_{19}NO$ | 80 | 19,15 |
| $n\text{-}C_3H_7C(C_2H_5)_2-$ | $C_9H_{19}NO$ | 42* | 15 |
| $CH_3C(C_3H_7\text{-}n)_2-$ | $C_9H_{19}NO$ | — | 15 |
| $CH_3CH(CH_3)CH_2CH_2C(CH_3)_2-$ | $C_9H_{19}NO$ | — | 39 |
| $n\text{-}C_4H_9C(CH_3)(C_2H_5)-$ | $C_9H_{19}NO$ | 97 | 15 |
| [cyclopentyl]$C(CH_3)(C_2H_5)-$ | $\big[$cyclopentane-fused lactam$\ C(CH_3)(C_2H_5),\ C=O,\ N(H)\big]$ | — | 86 |
| [cyclohexenyl]$C(CH_3)_2-$ | $\big[$cyclohexane-fused lactam$\ C(CH_3)_2,\ C=O,\ N(H)\big]$ | — | 86 |
| $n\text{-}C_6H_{13}C(CH_3)_2-$ | $C_{10}H_{21}NO$ | 91, 85 | 66, 15 |
| $n\text{-}C_4H_9C(CH_3)(C_3H_7\text{-}n)-$ | $C_{10}H_{21}NO$ | 94* | 15 |
| $n\text{-}C_4H_9C(C_2H_5)_2-$ | $C_{10}H_{21}NO\dagger$ | 52* | 15 |
| $n\text{-}C_5H_{11}C(CH_3)(C_2H_5)-$ | $C_{10}H_{21}NO\dagger$ | 78* | 15 |
| $C_2H_5C(C_3H_7\text{-}n)_2-$ | $C_{10}H_{21}NO$ | 47* | 15 |
| $C_6H_5CH_2C(CH_3)_2-$ | $C_{11}H_{15}NO$ | 62 | 61, 32, 64 |
| $C_6H_{11}CH_2C(CH_3)_2-$ | $C_{11}H_{21}NO$ | 80, 90 | 84, 70, 72 |
| $C_6H_5COC(CH_3)_2(CH_2)_3C(CH_3)_2-$ | $C(CH_3)_2CONH_2$, $(CH_2)_3$, $C(CH_3)_2CONH_2$ | 68* | 23, 22, 24 |

*Note:* References 62–96 are listed on p. 36.
\* This was the yield of crude product.
† Benzamide was also isolated.

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield, % | References |
|---|---|---|---|
| $n\text{-}C_7H_{15}C(CH_3)_2$— | $C_{11}H_{23}NO$ | — | 63 |
| $CH_3C(C_4H_9\text{-}n)_2$— | $C_{11}H_{23}NO$ | 58* | 15 |
| $n\text{-}C_4H_9C(C_2H_5)(C_3H_7\text{-}n)$— | $C_{11}H_{23}NO$ | 83* | 15 |
| $n\text{-}C_5H_{11}C(C_2H_5)_2$— | $C_{11}H_{23}NO\ddagger$ | — | 15 |
| $n\text{-}C_6H_{13}C(CH_3)(C_2H_5)$— | $C_{11}H_{23}NO\dagger$ | Quant.* | 15 |
| $C_6H_5(CH_2)_2C(CH_3)_2$— | $C_{12}H_{17}NO$ | Good | 69, 72 |
| $o\text{-}CH_3C_6H_4CH_2C(CH_3)_2$— | $C_{12}H_{17}NO$ | — | 32, 75 |
| $m\text{-}CH_3C_6H_4CH_2C(CH_3)_2$— | $C_{12}H_{17}NO$ | — | 32, 75 |
| $p\text{-}CH_3C_6H_4CH_2C(CH_3)_2$— | $C_{12}H_{17}NO$ | — | 32, 75 |
| $C_6H_5CH_2C(CH_3)(C_2H_5)$— | $C_{12}H_{17}NO\S$ | ca. 40 | 70, 25, 71, 72 |
| $p\text{-}CH_3OC_6H_4CH_2C(CH_3)_2$— | $C_{12}H_{17}NO_2$ | 90, 83 | 70, 72, 32, 75 |
| $C_6H_5O(CH_2)_2C(CH_3)_2$— | $C_{12}H_{17}NO_2$ | ca. 90 | 70 |
| $m\text{-}CH_3C_6H_{10}CH_2C(CH_3)_2$— | $C_{12}H_{23}NO$ | — | 83 |
| $p\text{-}CH_3C_6H_{10}CH_2C(CH_3)_2$— | $C_{12}H_{23}NO$ | — | 83 |
| $C_6H_{11}(CH_2)_2C(CH_3)_2$— | $C_{12}H_{23}NO$ | — | 83 |
| $C_6H_5COC(CH_3)_2(CH_2)_4C(CH_3)_2$— | $\diagup C(CH_3)_2CONH_2$ $(CH_2)_4$ $\diagdown C(CH_3)_2CONH_2$ | 78* | 23, 24 |
| $n\text{-}C_5H_{11}C(C_2H_5)(C_3H_7\text{-}n)$— | $C_{12}H_{25}NO\ddagger$ | — | 15 |
| $n\text{-}C_6H_{13}C(C_2H_5)_2$— | $C_{12}H_{25}NO\dagger$ | — | 15 |
| $n\text{-}C_6H_{13}C(CH_3)(C_4H_9\text{-}n)$— | $C_{12}H_{25}NO$ | Quant. | 15 |
| $n\text{-}C_4H_9CH(C_2H_5)CH_2C(CH_3)_2$— | $C_{12}H_{25}NO$ | — | 68 |
| $n\text{-}C_8H_{17}C(CH_3)_2$— | $C_{12}H_{25}NO$ | — | 15, 65, 66 |

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield, % | References |
|---|---|---|---|
| (benzothiophene)$CH_2C(CH_3)_2$— | $C_{13}H_{15}NOS$ | — | 80 |
| $C_6H_5(CH_2)_3C(CH_3)_2$— | $C_{13}H_{19}NO$ | — | 69 |
| $C_6H_5CH_2C(C_2H_5)_2$— | $C_{13}H_{19}NO$ | ca. 40 | 70, 72, 73, 74 |
| $C_6H_5CH_2C(CH_3)(C_3H_7\text{-}n)$— | $C_{13}H_{19}NO\S$ | — | 25 |
| $C_6H_5CH(C_2H_5)C(CH_3)_2$— | $C_{13}H_{19}NO\dagger\S$ | — | 77 |
| $p\text{-}CH_3OC_6H_4(CH_2)_2C(CH_3)_2$— | $C_{13}H_{19}NO_2$ | 76 | 78 |
| $m\text{-}CH_3C_6H_{10}(CH_2)_2C(CH_3)_2$— | $C_{13}H_{25}NO$ | — | 83 |
| $C_6H_5COC(CH_3)_2(CH_2)_5C(CH_3)_2$— | $\diagup C(CH_3)_2CONH_2$ $(CH_2)_5$ $\diagdown C(CH_3)_2CONH_2$ | 87* | 23 |
| $n\text{-}C_5H_{11}C(C_2H_5)(C_4H_9\text{-}n)$— | $C_{13}H_{27}NO\ddagger$ | — | 15 |
| $n\text{-}C_6H_{13}C(C_2H_5)(C_3H_7\text{-}n)$— | $C_{13}H_{27}NO\ddagger$ | — | 15 |
| $n\text{-}C_7H_{15}C(C_2H_5)_2$— | $C_{13}H_{27}NO$ | 97* | 15 |
| $n\text{-}C_9H_{19}C(CH_3)_2$— | $C_{13}H_{27}NO$ | 71 | 66 |
| (benzothiophene)$(CH_2)_2C(CH_3)_2$— | $C_{14}H_{17}NOS$ | — | 80 |
| (indane)$CH_2C(CH_3)_2$— | $C_{14}H_{19}NO$ | — | 79 |
| $C_6H_5CH_2C(C_2H_5)(C_3H_7\text{-}n)$— | $C_{14}H_{21}NO\S$ | — | 25, 71 |
| $CH_2{=}C(CH_3)(CH_2)_3CH(CH_3)(CH_2)_2C(CH_3)_2$— | $C_{14}H_{27}NO$ | — | 66, 67 |

*Note:* References 62–96 are listed on p. 36.
\* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.

| Ketone RCOC$_6$H$_5$<br>R | Product RCONH$_2$<br>Formula | Yield,% | References |
|---|---|---|---|
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_6$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$<br>(CH$_2$)$_6$<br>C(CH$_3$)$_2$CONH$_2$ | 87 | 23 |
| $n$-C$_6$H$_{13}$C(C$_2$H$_5$)(C$_4$H$_9$·$n$)— | C$_{14}$H$_{29}$NO‡ | — | 15 |
| $n$-C$_{10}$H$_{21}$C(CH$_3$)$_2$— | C$_{14}$H$_{29}$NO | 48* | 30, 32, 64, 65 |
| $\alpha$-C$_{10}$H$_7$CH$_2$C(CH$_3$)$_2$— | C$_{15}$H$_{17}$NO | — | 82 |
| $\beta$-C$_{10}$H$_7$CH$_2$C(CH$_3$)$_2$— | C$_{15}$H$_{17}$NO | — | 85 |
| C(CH$_3$)(C$_6$H$_5$CH$_2$)— | —C(CH$_3$)CH$_2$C$_6$H$_5$§<br>CO<br>N<br>H | — | 86 |
| C$_6$H$_5$CH(C$_2$H$_5$)C(C$_2$H$_5$)$_2$— | C$_{15}$H$_{23}$NO†§ | — | 76, 77 |
| $p$-(CH$_3$)$_3$CC$_6$H$_4$CH$_2$C(CH$_3$)$_2$— | C$_{15}$H$_{23}$NO | ca. 90 | 70, 72 |
| CH$_2$=CH(CH$_2$)$_9$C(CH$_3$)$_2$— | C$_{15}$H$_{29}$NO | 59 | 66, 67 |
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_7$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$<br>(CH$_2$)$_7$<br>C(CH$_3$)$_2$CONH$_2$ | 39* | 23 |
| $n$-C$_6$H$_{13}$C(C$_2$H$_5$)(C$_5$H$_{11}$·$n$)— | C$_{15}$H$_{31}$NO‡ | — | 15 |
| $n$-C$_7$H$_{15}$C(C$_2$H$_5$)(C$_4$H$_9$·$n$)— | C$_{15}$H$_{31}$NO† | Low‖ | 15 |
| $n$-C$_{10}$H$_{21}$C(CH$_3$)(C$_2$H$_5$)— | C$_{15}$H$_{31}$NO | — | 65 |
| $n$-C$_{11}$H$_{23}$C(CH$_3$)$_2$— | C$_{15}$H$_{31}$NO | — | 65 |
| $\alpha$-C$_{10}$H$_7$CH$_2$(CH$_3$)(C$_2$H$_5$)— | C$_{16}$H$_{19}$NO | — | 82 |
| $\beta$-C$_{10}$H$_7$CH$_2$C(CH$_3$)(C$_2$H$_5$)— | C$_{16}$H$_{19}$NO | — | 85 |
| CH$_2$C(CH$_3$)$_2$—<br>CH$_3$ | C$_{16}$H$_{19}$NO | 50 | 85 |
| $\alpha$-C$_{10}$H$_7$(CH$_2$)$_2$C(CH$_3$)$_2$— | C$_{16}$H$_{19}$NO | 80 | 81, 82 |
| $o$-C$_6$H$_5$COC(CH$_3$)$_2$CH$_2$C$_6$H$_4$CH$_2$C(CH$_3$)$_2$— | CH$_2$C(CH$_3$)$_2$CONH$_2$<br>$o$-C$_6$H$_4$<br>CH$_2$C(CH$_3$)$_2$CONH$_2$ | — | 25 |
| $m$-C$_6$H$_5$COC(CH$_3$)$_2$CH$_2$C$_6$H$_4$CH$_2$C(CH$_3$)$_2$— | CH$_2$C(CH$_3$)$_2$CONH$_2$<br>$m$-C$_6$H$_4$<br>CH$_2$C(CH$_3$)$_2$CONH$_2$ | — | 25 |
| $p$-C$_6$H$_5$COC(CH$_3$)$_2$CH$_2$C$_6$H$_4$CH$_2$C(CH$_3$)$_2$— | CH$_2$C(CH$_3$)$_2$CONH$_2$<br>$p$-C$_6$H$_4$<br>CH$_2$C(CH$_3$)$_2$CONH$_2$ | — | 25 |
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_8$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$<br>(CH$_2$)$_8$<br>C(CH$_3$)$_2$CONH$_2$ | 55* | 23 |
| $n$-C$_8$H$_{17}$C(C$_2$H$_5$)(C$_4$H$_9$·$n$)— | C$_{16}$H$_{33}$NO | Low | 15 |

*Note:* References 62–96 are listed on p. **36**.
* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.
‖ The product was isolated as the acid.

| Ketone RCOC$_6$H$_5$ R | Product RCONH$_2$ Formula | Yield,% | References |
|---|---|---|---|
| n-C$_{12}$H$_{25}$C(CH$_3$)$_2$— | C$_{16}$H$_{33}$NO | — | 65, 68 |
| (C$_6$H$_5$)$_2$CHC(CH$_3$)$_2$— | C$_{17}$H$_{19}$NO†§ | — | 76, 77 |
| (C$_6$H$_5$)$_2$CHCH(C$_2$H$_5$)— | C$_{17}$H$_{19}$NO§ | — | 77 |
| (C$_6$H$_5$CH$_2$)$_2$C(CH$_3$)— | C$_{17}$H$_{19}$NO | — | 32, 64 |
| CH$_2$C(CH$_3$)(C$_2$H$_5$)— (naphthalene, CH$_3$) | C$_{17}$H$_{21}$NO | 31 | 85 |
| CH$_2$C(CH$_3$)(C$_2$H$_5$)— (naphthalene, CH$_3$) | C$_{17}$H$_{21}$NO | — | 82 |
| α-C$_{10}$H$_7$(CH$_2$)$_2$C(CH$_3$)(C$_2$H$_5$)— | C$_{17}$H$_{21}$NO | — | 82 |
| C$_6$H$_5$CH$_2$C(CH$_3$)(C$_7$H$_{15}$-n)— | C$_{17}$H$_{27}$NO | Low | 70 |
| (CH$_3$)$_3$C—(benzene, CH$_3$, CH$_3$)—CH$_2$C(CH$_3$)$_2$— | C$_{17}$H$_{27}$NO | ca. 90 | 70, 72 |
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_9$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$ (CH$_2$)$_9$ C(CH$_3$)$_2$CONH$_2$ | 58* | 23 |
| n-C$_{10}$H$_{21}$C(CH$_3$)(C$_4$H$_9$-n)— | C$_{17}$H$_{35}$NO‡ | — | 15 |
| n-C$_8$H$_{17}$C(C$_2$H$_5$)(C$_5$H$_{11}$-n)— | C$_{17}$H$_{35}$NO‡ | — | 15 |
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_{10}$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$ (CH$_2$)$_{10}$ C(CH$_3$)$_2$CONH$_2$ | 86* | 23 |
| n-C$_{10}$H$_{21}$C(C$_2$H$_5$)(C$_4$H$_9$-n)— | C$_{18}$H$_{37}$NO‡ | — | 15 |
| n-C$_{14}$H$_{29}$C(CH$_3$)$_2$— | C$_{18}$H$_{37}$NO | Quant. | 68 |
| CH$_2$C(CH$_3$)(C$_2$H$_5$)— C(CH$_3$)$_3$ (naphthalene) | C$_{20}$H$_{27}$NO | — | 82 |
| (cyclopentane)(CH$_2$)$_{11}$C(CH$_3$)$_2$— | C$_{20}$H$_{37}$NO | Quant. | 87 |
| n-C$_{16}$H$_{33}$C(CH$_3$)$_2$— | C$_{20}$H$_{41}$NO | — | 30, 68 |
| (cyclopentane)(CH$_2$)$_{13}$C(CH$_3$)$_2$— | C$_{21}$H$_{39}$NO | — | 68 |
| CH$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_8$C(CH$_3$)$_2$— | C$_{22}$H$_{43}$NO | — | 68 |
| C$_6$H$_5$COC(CH$_3$)$_2$(CH$_2$)$_{14}$C(CH$_3$)$_2$— | C(CH$_3$)$_2$CONH$_2$ (CH$_2$)$_{14}$ C(CH$_3$)$_2$CONH$_2$ | — | 24 |
| n-C$_{18}$H$_{37}$C(CH$_3$)$_2$— | C$_{22}$H$_{45}$NO | — | 65 |
| n-C$_{12}$H$_{25}$C(C$_2$H$_5$)(C$_{10}$H$_{21}$-n)— | C$_{26}$H$_{53}$NO† | Low‖ | 15 |
| CH$_2$·CHCH$_2$C(CH$_3$)$_2$— (O) | No reaction | — | 29 |

*Note:* References 62–96 are listed on p. 36.
\* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.
‖ The product was isolated as the acid.

## TABLE I

### B. Cleavage of Alicyclic Phenyl Ketones

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield, % | Reference |
|---|---|---|---|
| CH₂\ CH— / CH₂ | $C_4H_7NO$* | 42 | 20, 17 |
| CH₂\ /CH₃ C / \ CH₂ | $C_5H_9NO$* | — | 17 |
| CH₂—C—CH₃ / CH₂—CH₂ | $C_6H_{11}NO$ | 50 | 21 |
| CH₂—C—C₂H₅ / CH₂—CH₂ | $C_7H_{13}NO$ | 60 | 21 |
| CH₂—CHCH₃ CH— / CH₂—CH₂ | $C_7H_{13}NO$ | 8 | 19, 18 |
| CH₂—CH₂ CH₂ CH— CH₂—CH₂ | $C_7H_{13}NO$ | 1 | 19 |
| CH₂—CHCH₃ CH₃ C CH₂—CH₂ | $C_8H_{15}NO$ | 71, 12 | 19, 18 |
| CH₂—CH₂ CH₃ CH₂ C CH₂—CH₂ | $C_8H_{15}NO$ | 88 | 19 |
| CH₂—CHCH₃ C₂H₅ C CH₂—CH₂ | $C_9H_{17}NO$ | 29 | 18 |

*Note:* References 62–96 are listed on p. 36.
* Benzamide was also isolated.

TABLE I (Part B)—*Continued*

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield, % | Reference |
|---|---|---|---|
| $CH_2$—$CH_2$, $C_2H_5$ / $CH_2$ $C$ / $CH_2$—$CH_2$ | $C_9H_{17}NO$ | 65 | 19 |
| $CH_2$—$CHCH_3$ $C_3H_7$-$n$ / $C$ / $CH_2$—$CH_2$ | $C_{10}H_{19}NO$ | — | 18 |
| $CH_2$—$CH_2$ $CH_3$ / $C$ / $CH$—$CH_2$ / $C_3H_7$-$i$ | $C_{10}H_{19}NO$ | — | 89 |
| $(H_3C)_2C$——$CHCH_3$ $CH_3$ / $C$ / $CH_2$—$CH_2$ | $C_{10}H_{19}NO$ | 68 | 90 |
| $CH_2$—$CH_2$ $C_3H_7$-$n$ / $CH_2$ $C$ / $CH_2$—$CH_2$ | $C_{10}H_{19}NO$ | 65 | 19 |
| $CH_2$ $CH_2C_6H_5$ / $C$ / $CH_2$ | $C_{11}H_{13}NO$ | 56 | 20, 17 |
| $CH_2$—$CH_2$ $C_4H_9$-$n$ / $CH_2$ $C$ / $CH_2$—$CH_2$ | $C_{11}H_{21}NO$ | 66 | 19 |
| $C_6H_5$ / $C$ / $CH_2$ $C$— / $CH_2$—$CH_2$ | $C_{12}H_{13}NO$*† | — | 44 |

*Note:* References 62–96 are listed on p. 36.

\* Benzamide was also isolated.

† The hydrocarbon RH corresponding to the R group in the ketone was also isolated.

## TABLE I (Part B)—*Continued*

| Ketone $RCOC_6H_5$ R | Product $RCONH_2$ Formula | Yield, % | Reference |
|---|---|---|---|
|  | $C_{13}H_{15}NO$*† | — | 43 |
|  | $C_{13}H_{15}NO$*† | — | 45 |
|  | No reaction | | 43 |
|  | No reaction | | 45 |

*Note:* References 62–96 are listed on p. 36.

\* Benzamide was also isolated.

† The hydrocarbon RH corresponding to the R group in the ketone was also isolated.

## TABLE II

### CLEAVAGE OF ALIPHATIC KETONES

| Ketone RCOR′ | | | | |
|---|---|---|---|---|
| R | R′ | Formula | Products | References |
| $(CH_3)_3C-$ | $(CH_3)_3C-$ | $C_9H_{18}O$ | $(CH_3)_3CCONH_2$, $(CH_3)_3CH$ | 91 |
| $(CH_3)_3C-$ | $C_2H_5C(CH_3)_2-$ | $C_{10}H_{20}O$ | $(CH_3)_3CCONH_2$, $C_2H_5C(CH_3)_2CONH_2$ $(CH_3)_3CH$, $C_2H_5CH(CH_3)_2$ | 32, 91 |
| $C_2H_5C(CH_3)_2-$ | $C_2H_5C(CH_3)_2-$ | $C_{11}H_{22}O$ | $C_2H_5C(CH_3)_2CONH_2$, $C_2H_5CH(CH_3)_2$ | 32, 91 |
| $(CH_3)_3C-$ | $(C_2H_5)_3C-$ | $C_{12}H_{24}O$ | $(CH_3)_3CCONH_2$, $(C_2H_5)_3CCONH_2$ (ratio 5 : 1); $(CH_3)_3CH$, $(C_2H_5)_3CH$ | 32, 91 |
| $(CH_3)_2CHC(CH_3)_2-$ | $(CH_3)_2CHC(CH_3)_2-$ | $C_{13}H_{26}O$ | No reaction | 32 |
| $(CH_3)_3C-$ | $C_6H_5CH_2C(CH_3)_2-$ | $C_{15}H_{22}O$ | $(CH_3)_3CCONH_2$, $C_6H_5CH_2CH(CH_3)_2$ | 32 |
| $(CH_3)_3C-$ | $C_6H_5CH_2C(C_2H_5)_2-$ | $C_{17}H_{26}O$ | $(CH_3)_3CCONH_2$, $C_6H_5CH_2C(C_2H_5)_2CONH_2$ (trace) $C_6H_5CH_2CH(C_2H_5)_2$ | 32 |
| $C_6H_5C(CH_3)_2-$ | $C_6H_5C(CH_3)_2-$ | $C_{21}H_{26}O$ | $C_6H_5C(CH_3)_2CONH_2$, $C_6H_5CH(CH_3)_2$ | 32 |

*Note:* References 62–96 are listed on p. 36.

# TABLE III

## CLEAVAGE OF AROMATIC KETONES

Ketone ArCOAr'

| Ar | Ar' | Formula | Products | References |
|---|---|---|---|---|
| $C_6H_5$— | 2-$C_4H_3$S— | $C_{11}H_8OS$ | $C_6H_5CONH_2$, 2-$C_4H_3SCONH_2$ (ratio 2.5 : 1 as acids) | 9 |
| $C_6H_5$— | 3-$BrC_6H_4$— | $C_{13}H_9BrO$ | $C_6H_5CONH_2$, 3-$BrC_6H_4CONH_2$ (ratio 5.5 : 1 as acids) | 8 |
| $C_6H_5$— | 4-$BrC_6H_4$— | $C_{13}H_9BrO$ | $C_6H_5CONH_2$, 4-$BrC_6H_4CONH_2$ (ratio 2.5 : 1 as acids) | 8 |
| $C_6H_5$— | 3-$ClC_6H_4$— | $C_{13}H_9ClO$ | $C_6H_5CONH_2$, 3-$ClC_6H_4CONH_2$ (ratio 11 : 1 as acids) | 8 |
| $C_6H_5$— | 4-$ClC_6H_4$— | $C_{13}H_9ClO$ | $C_6H_5CONH_2$, 4-$ClC_6H_4CONH_2$ (ratio 3.2 : 1 as acids) | 8 |
| $C_6H_5$— | $C_6H_5$— | $C_{13}H_{10}O$ | $C_6H_5CONH_2$ | 5, 8, 36 |
| $C_6H_5$— | 4-$CNC_6H_4$— | $C_{14}H_9NO$ | No cleavage* | 11 |
| $C_6H_5$— | 4-$CH_3C_6H_4$— | $C_{14}H_{12}O$ | 4-$CH_3C_6H_4CONH_2$, $C_6H_5CONH_2$ (slightly more of former) | 5, 36 |
| $C_6H_5$— | 4-$CH_3SC_6H_4$— | $C_{14}H_{12}OS$ | $C_6H_5CONH_2$, 4-$CH_3SC_6H_4CONH_2$ | 8, 9, 11 |
| $C_6H_5$— | 2-$CH_3OC_6H_4$— | $C_{14}H_{12}O_2$ | $C_6H_5CONH_2$ (poor yield) | 11 |
| $C_6H_5$— | 3-$CH_3OC_6H_4$— | $C_{14}H_{12}O_2$ | $C_6H_5CONH_2$, 3-$CH_3OC_6H_4CONH_2$ (ratio 3.6 : 1 as acids) | 11 |
| $C_6H_5$— | 4-$CH_3OC_6H_4$— | $C_{14}H_{12}O_2$ | 4-$CH_3OC_6H_4CONH_2$, $C_6H_5CONH_2$ (ratio 2.5 : 1 as acids) | 11, 5, 8, 36 |
| $C_6H_5$— | 2,4-$(CH_3)_2C_6H_3$— | $C_{15}H_{14}O$ | 2,4-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (mainly the latter) | 34 |
| $C_6H_5$— | 2,5-$(CH_3)_2C_6H_3$— | $C_{15}H_{14}O$ | 2,5-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (mainly the latter)† | 34 |
| $C_6H_5$— | 3,4-$(CH_3)_2C_6H_3$— | $C_{15}H_{14}O$ | 3,4-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (equal amounts) | 34 |
| 4-$CH_3OC_6H_4$— | 3-$CH_3OC_6H_4$— | $C_{15}H_{14}O_3$ | 4-$CH_3OC_6H_4CONH_2$, 3-$CH_3OC_6H_4CONH_2$ (ratio 6.3 : 1 as acids) | 11 |
| $C_6H_5$— | 2,4-$(CH_3O)_2C_6H_3$— | $C_{15}H_{14}O_3$ | $C_6H_5CONH_2$ (poor yield) | 11 |
| $C_6H_5$— | 2,5-$(CH_3O)_2C_6H_3$— | $C_{15}H_{14}O_3$ | $C_6H_5CONH_2$ (poor yield) | 11 |
| $C_6H_5$— | 3,4-$(CH_3O)_2C_6H_3$— | $C_{15}H_{14}O_3$ | $C_6H_5CONH_2$, 3,4-$(CH_3O)_2C_6H_3CONH_2$ (ratio 1.2 : 1 as acids) | 11 |
| $C_6H_5$— | 4-$(CH_3)_2NC_6H_4$— | $C_{15}H_{15}NO$ | $C_6H_5CONH_2$, 4-$(CH_3)_2NC_6H_4CONH_2$ | 8 |
| 3-$CH_3OC_6H_4$— | 3,4-$(CH_3O)_2C_6H_3$— | $C_{16}H_{16}O_4$ | 3,4-$(CH_3O)_2C_6H_3CONH_2$, 3-$CH_3OC_6H_4CONH_2$ | 11 |
| 4-$CH_3OC_6H_4$— | 3,4-$(CH_3O)_2C_6H_3$— | $C_{16}H_{16}O_4$ | 3,4-$(CH_3O)_2C_6H_3CONH_2$, 4-$CH_3OC_6H_4CONH_2$ | 11 |
| $C_6H_5$— | 1-$C_{10}H_7$— | $C_{17}H_{12}O$ | $C_6H_5CONH_2$, $C_{10}H_8$ (trace) | 34 |
| $C_6H_5$— | 2-$C_{10}H_7$— | $C_{17}H_{12}O$ | 2-$C_{10}H_7CONH_2$, $C_6H_5CONH_2$ (ratio 6 : 1); (ratio 2 : 1 as acids) | 9, 34 |
| 4-$ClC_6H_4$— | 4-$C_6H_5C_6H_4$— | $C_{19}H_{13}ClO$ | 4-$C_6H_5C_6H_4CONH_2$, 4-$ClC_6H_4CONH_2$ (ratio 2.3 : 1 as acids) | 33 |
| $C_6H_5$— | 4-$C_6H_5C_6H_4$— | $C_{19}H_{14}O$ | $C_6H_5CONH_2$, 4-$C_6H_5C_6H_4CONH_2$ (ratio 3 : 1 as acids) | 9, 33 |
| 4-$CH_3C_6H_4$— | 4-$C_6H_5C_6H_4$— | $C_{20}H_{16}O$ | 4-$C_6H_5C_6H_4CONH_2$, 4-$CH_3C_6H_4CONH_2$ (ratio 1.08 : 1 as acids) | 33 |
| 4-$CH_3OC_6H_4$— | 4-$C_6H_5C_6H_4$— | $C_{20}H_{16}O_2$ | 4-$C_6H_5C_6H_4CONH_2$, 4-$CH_3OC_6H_4CONH_2$ (ratio 1.45 : 1 as acids) | 33 |
| 1-$C_{10}H_7$— | 4-$C_6H_5C_6H_4$— | $C_{23}H_{16}O$ | 4-$C_6H_5C_6H_4CONH_2$, $C_{10}H_8$ (10% of mixture) | 33 |
| 2-$C_{10}H_7$ | 4-$C_6H_5C_6H_4$— | $C_{23}H_{16}O$ | 4-$C_6H_5C_6H_4CONH_2$, 2-$C_{10}H_7CONH_2$ (ratio 1.24 : 1 as acids) | 33 |
| $C_6H_5$— | $(C_6H_5)_3C$— | $C_{26}H_{20}O$ | No reaction | 8 |
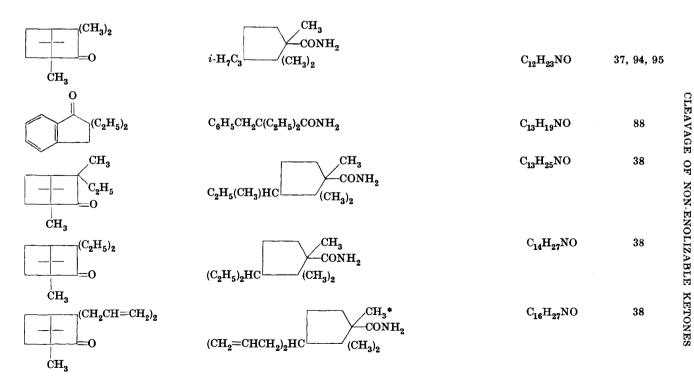
Note: References 62–96 are listed on p. 36.

* In this experiment the cyano group was hydrolyzed and the product was $p$-$C_6H_5COC_6H_4CO_2H$

† Catalytic quantities of mercury were added in a second experiment; 2,5-dimethylbenzamide and benzamide were obtained in a ratio of 1 : 3.5.

# TABLE IV

## Cleavage of Alicyclic Ketones

| Ketone | Products | Formula | References |
|---|---|---|---|
| [cyclopentane ring with (CH₃)₂, CH₂, =O] | i-H₇C₃ [cyclopentane] CONH₂ | $C_9H_{17}NO$ | 92 |
| [cyclopentanone, O, (CH₃)₂ and (CH₃)₂] | (CH₃)₂CH(CH₂)₂C(CH₃)₂CONH₂ | $C_9H_{19}NO$ | 39 |
| [cyclopentane ring with (CH₃)₂, CH₂, =O, CH₃] | i-H₇C₃ [cyclopentane] CH₃ / CONH₂ | $C_{10}H_{19}NO$ | 4 |
| [cyclopentanone, O, (CH₃)₂, (CH₃)₂, CH₃] | (CH₃)₂CHCH(CH₃)CH₂C(CH₃)₂CONH₂ and (CH₃)₂CHCH₂CH(CH₃)C(CH₃)₂CONH₂ | $C_{10}H_{21}NO$ | 96 |
| [indanone with (CH₃)₂] | C₆H₅CH₂C(CH₃)₂CONH₂ | $C_{11}H_{15}NO$ | 73, 74, 88 |

| Ketone | Products | Formula | References |
|---|---|---|---|
| [bicyclic ring with (CH₃)₂, =O, CH₃] | i-H₇C₃ [cyclopentane] CH₃ / CONH₂ / (CH₃)₂ | $C_{12}H_{23}NO$ | 37, 94, 95 |
| [indanone with (C₂H₅)₂] | C₆H₅CH₂C(C₂H₅)₂CONH₂ | $C_{13}H_{19}NO$ | 88 |
| [bicyclic ring with CH₃, C₂H₅, =O, CH₃] | C₂H₅(CH₃)HC [cyclopentane] CH₃ / CONH₂ / (CH₃)₂ | $C_{13}H_{25}NO$ | 38 |
| [bicyclic ring with (C₂H₅)₂, =O, CH₃] | (C₂H₅)₂HC [cyclopentane] CH₃ / CONH₂ / (CH₃)₂ | $C_{14}H_{27}NO$ | 38 |
| [bicyclic ring with (CH₂CH=CH₂)₂, =O, CH₃] | (CH₂=CHCH₂)₂HC [cyclopentane] CH₃* / CONH₂ / (CH₃)₂ | $C_{16}H_{27}NO$ | 38 |

*Note:* References 62–96 are listed on p. 36.

\* The structure of this product was not established. The investigators suggested cyclization to the pyrrolidone as an alternative possibility.

TABLE IV (*Continued*)

CLEAVAGE OF ALICYCLIC KETONES

| Ketone | Products | Formula | Reference |
|---|---|---|---|
|  | $C_3H_7CH(CH_3)CH_2CH(CH_3)C(C_3H_7)_2CONH_2$ and $(C_3H_7)_2CHCH(CH_3)CH_2C(CH_3)(C_3H_7)CONH_2$ | $C_{16}H_{33}NO$ | 93 |
|  | $C_6H_5CH_2(C_2H_5)HC$  | $C_{19}H_{29}NO$ | 38 |
|  | $C_6H_5CH(CH_3)CH_2CH(CH_3)C(CH_3)(CH_2C_6H_5)CONH_2$ and $C_6H_5CH(CH_3)CH(CH_3)CH_2C(CH_3)(CH_2C_6H_5)CONH_2$ | $C_{21}H_{29}NO$ | 93 |
|  | $(C_6H_5CH_2)_2HC$  | $C_{24}H_{31}NO$ | 38 |
|  | No reaction | | 92 |

## TABLE V

SODIUM AMIDE AND MISCELLANEOUS CARBONYL COMPOUNDS

| Carbonyl Compound | Formula | Products | References |
|---|---|---|---|
| Furfural | $C_5H_4O_2$ | Furfuryl alcohol, furoic acid | 41 |
| $C_6H_5CHO$ | $C_7H_6O$ | $C_6H_5CONH_2$, $C_6H_5CH_2OH$ (80% of mixture), and $C_6H_5CO_2H$ | 36 |
| $p$-$CH_3OC_6H_4CHO$ | $C_8H_8O_2$ | $p$-$CH_3OC_6H_4CONH_2$, $p$-$CH_3OC_6H_4CH_2OH$, and $p$-$CH_3OC_6H_4CO_2H$ | 36 |
| O=C—C=O  | $C_{12}H_6O_2$ | $(CONH_2)_2$, $C_{10}H_8$ | 41 |
| Fluorenone | $C_{13}H_8O$ | $o$-$C_6H_5C_6H_4CONH_2$ | 5, 36 |
| Anthraquinone | $C_{14}H_8O_2$ | No reaction | 5 |
| $(C_6H_5CO)_2$ | $C_{14}H_{10}O_2$ | $(C_6H_5)_2C(OH)CO_2H$ (good yield) | 41 |
| $(3,4$-$CH_2O_2C_6H_3CO)_2$ | $C_{16}H_{10}O_6$ | $3,4$-$CH_2O_2C_6H_3CO_2H$ (29%), $(3,4$-$CH_2O_2C_6H_3)_2CO$ (44%) | 42 |
| $(p$-$CH_3OC_6H_4CO)_2$ | $C_{16}H_{14}O_4$ | $(p$-$CH_3OC_6H_4)_2C(OH)CO_2H$ (87%) | 42 |
| $(C_6H_5COCH_2CH_2)_2$ | $C_{18}H_{18}O_2$ |  | 43 |
| $[3,4$-$(CH_3O)_2C_6H_3CO]_2$ | $C_{18}H_{18}O_6$ | $3,4$-$(CH_3O)_2C_6H_3CO_2H$ (quant.), and $[3,4$-$(CH_3O)_2C_6H_3]_2CO$ (27%) | 42 |
| $(C_6H_5COCH_2CH_2)_2CH_2$ | $C_{19}H_{20}O_2$ |  | 45 |
| $(C_6H_5)_2C(OH)COC_6H_5$ | $C_{20}H_{16}O_2$ | $C_6H_5C(OH)CONH_2$, $C_6H_5CONH_2$ (mainly the latter) | 8 |
| $[C_6H_5COCH(CH_3)]_2CHC_6H_5$ | $C_{25}H_{24}O_2$ | $C_6H_5COC_2H_5$, $C_6H_5COC(CH_3)=CHC_6H_5$ | 46 |

*Note*: References 62–96 are listed on p. 36.
* See Table I for the cleavage of these ketones.

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[65] Mentzer, Buu-Hoi, and Cagniant, *Bull. soc. chim. France*, [5] **10**, 141 (1943).

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[70] Mentzer, Buu-Hoi, and Cagniant, *Bull. soc. chim. France*, [5] **9**, 813 (1942).

[71] Haller and Dumesnil, *Compt. rend.*, **153**, 111 (1911).

[72] Laboratoires français de chimiothérapie, Brit. pat. 613,111 [*C. A.*, **43**, 5800 (1949)].

[73] Haller and Bauer, *Compt. rend.*, **150**, 1472 (1910).

[74] Haller and Bauer, *Ann. chim. Paris*, [9] **16**, 340 (1921).

[75] Haller and Bauer, *Compt. rend.*, **153**, 21 (1911).

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[80] Cagniant, *Bull. soc. chim. France*, **1949**, 382 (5–6).

[81] Laboratoires français de chimiothérapie, Swiss pat. 238,798 (1945).

[82] Cagniant, Mentzer, and Buu-Hoi, *Bull. soc. chim. France*, [5] **10**, 145 (1943).

[83] Mentzer and Chopin, *Bull. soc. chim. France*, [5] **15**, 586 (1948).

[84] Mentzer, Buu-Hoi, and Cagniant, Swiss pat. 237,879 (1945).

[85] Cagniant and Buu-Hoi, *Bull. soc. chim. France*, [5] **10**, 349 (1943).

[86] Buu-Hoi and Cagniant, *Compt. rend.*, **217**, 26 (1943).

[87] Buu-Hoi and Cagniant, *Bull. soc. chim. France*, [5] **9**, 355 (1942).

[88] Rothstein and Saville, *J. Chem. Soc.*, **1949**, 1946.

[89] Bouveault and Levallois, *Bull. soc. chim. France*, [4] **8**, 968 (1910).

[90] Shive, Horeczy, and Lochte, *J. Am. Chem. Soc.*, **62**, 2744 (1940).

[91] Haller and Bauer, *Compt. rend.*, **150**, 664 (1910).

[92] Nametkin and Kagan, *J. Gen. Chem. U.S.S.R.*, **16**, 885 (1946) [*C. A.*, **41**, 2019 (1947)].

[93] Haller and Cornubert, *Compt. rend.*, **158**, 1739 (1914).

[94] Haller and Ramart-Lueas, *Compt. rend.*, **173**, 682 (1921).

[95] Haller and Bauer, *Ann. chim. Paris*, [9] **8**, 117 (1917).

[96] Haller and Cornubert, *Compt. rend.*, **158**, 1616 (1914).

# CHAPTER 2

# THE GATTERMANN SYNTHESIS OF ALDEHYDES

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## CONTENTS

## INTRODUCTION

Gattermann developed two methods for introducing the aldehyde group into aromatic compounds. The first of these, known as the Gattermann-Koch reaction,[1] uses a mixture of carbon monoxide and hydrogen chloride in the presence of a mixture of anhydrous aluminum chloride and cuprous chloride. It is not adaptable to the preparation of aldehydes

$$\text{ArH} + \text{CO} + \text{HCl} \xrightarrow[\text{Cu}_2\text{Cl}_2]{\text{AlCl}_3} \text{ArCHO} + \text{HCl}$$

from phenols or phenolic ethers, however. The second method employs a mixture of hydrogen cyanide and hydrogen chloride with or without a catalyst, and permits the introduction of an aldehyde group into phenols, naphthols, and their ethers, and, under special conditions, into aromatic hydrocarbons and related compounds.[2] This chapter is concerned with the second method.

$$\text{ArH} + \text{HCN} + \text{HCl} \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) AlCl}_3 \text{ or ZnCl}_2} \text{ArCHO} + \text{NH}_4\text{Cl}$$

Aluminum chloride must be used as a catalyst with certain phenols and phenolic ethers;[3] with others, zinc chloride may replace aluminum chloride.[4] A modification of this method, which was described by Adams and his co-workers,[5,6] employs zinc cyanide as both a convenient source of anhydrous hydrogen cyanide and as a catalyst. When hydrogen chloride is introduced into the reaction mixture, hydrogen cyanide and zinc chloride are formed *in situ*. In those reactions that require anhydrous aluminum chloride as a catalyst, it may be introduced with the zinc cyanide.[6] Polyhydric phenols such as resorcinol and phloroglucinol in which the hydroxyl groups are *meta* to each other do not require a catalyst.[3]

More vigorous conditions are required to introduce the aldehyde group into aromatic hydrocarbons; e.g., the temperature must be raised.[7,8]

[1] Crounse, *Organic Reactions*, **5**, 290, John Wiley & Sons, 1949.
[2] Gattermann, *Ber.*, **31**, 1149 (1898).
[3] Gattermann, *Ann.*, **357**, 313 (1907).
[4] Gattermann and von Horlacher, *Ber.*, **32**, 284 (1899).
[5] Adams and Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).
[6] Adams and Montgomery, *J. Am. Chem. Soc.*, **46**, 1518 (1924).
[7] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1936**, 339.
[8] Hinkel, Ayling, and Morgan, *J. Chem. Soc.*, **1932**, 2793.

The choice of solvent and the proportion of aluminum chloride and hydrogen cyanide relative to the amount of hydrocarbon present affect the yields obtained. Zinc cyanide or sodium cyanide may be used in place of hydrogen cyanide.[8,9]

## MECHANISM

The mechanism of the reaction appears to be complex and has not been fully elucidated. Hinkel and his co-workers have presented evidence indicating that the mechanism may vary with the nature of the compound into which the aldehyde group is being introduced and with the conditions of reaction.[8,10–14] A study has been made of the products of the reaction of hydrogen cyanide, hydrogen chloride, and aluminum chloride with each other in the absence of an aromatic nucleus in order to find one or more species which might be serving as the agent of aromatic substitution. Thus, hydrogen cyanide reacts with aluminum chloride to give a complex with the structure I,[13] and with hydrogen chloride to give the "sesquichloride" II.[15,16] In turn, II gives chloromethyleneformamidine (III) when heated to 100°,[12] and iminoformylcarbylamine (IV) when heated with quinoline.[17] Aluminum chloride complexes of these latter substances

$$AlCl_3 \cdot HN{=}CHNC$$
I

$$NH{=}CHNHCHCl_2 \cdot HCl$$
II

$$ClCH{=}NCH{=}NH$$
III

$$\overset{..}{C}{\equiv}\overset{+}{N}{-}CH{=}NH$$
IV

were also prepared.[10,12,13] Since modern spectral methods were unavailable at the time this work was carried out, and in view of the experimental difficulties involved in characterizing such compounds, further investigation is desirable before the structures assigned can be considered as definitely established.

Although one or more of the substances mentioned or ions derived from them may serve as intermediates in the Gattermann reaction, it should be noted that yields of aldehydes in excess of 50% based on the hydrogen cyanide employed are often obtained. It follows then that, if an intermediate such as I, II, III, or IV is effective as the aromatic substituting

[9] Niedzielski and Nord, *J. Am. Chem. Soc.*, **63**, 1462 (1941).

[10] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1935**, 674.

[11] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1936**, 184.

[12] Hinkel and Dunn, *J. Chem. Soc.*, **1930**, 1834.

[13] Hinkel and Dunn, *J. Chem. Soc.*, **1931**, 3343.

[14] Hinkel and Watkins, *J. Chem. Soc.*, **1944**, 647.

[15] Dains, *Ber.*, **35**, 2496 (1902).

[16] Gattermann and Schnitzspahn, *Ber.*, **31**, 1770 (1898).

[17] Neff, *Ann.*, **287**, 337 (1895).

reagent in these reactions, it must be able to utilize both its carbon atoms for the formation of aldehyde.

In any event the reaction apparently proceeds by the formation of the conjugate acid of hydrogen cyanide (V) or of one of a number of other possible ions, which, with the aid of aluminum chloride, can serve as a

$$HC{\equiv}NH^+ \qquad\qquad ArCH{=}NH_2^+ \qquad\qquad ArCH{=}NH \cdot AlCl_3$$

$$V \qquad\qquad\qquad VI \qquad\qquad\qquad\qquad VII$$

substituting agent in a reaction which is presumably analogous to Friedel-Crafts acylation. Certain reactions, however, proceed without the aid of aluminum chloride or other catalyst. Apparently the product from the Gattermann reaction is the conjugate acid VI or aluminum chloride complex VII of the aldimine or a more complex derivative of it. Generally the nitrogen-containing substance is not isolated but is hydrolyzed directly to the aldehyde.

A detailed discussion of the mechanisms must await a thorough study of the kinetics of the reactions.

## SCOPE AND LIMITATIONS

### Ethers of Monohydric Phenols

A methylene formamidine adduct is formed by treating a mixture of a phenol ether, anhydrous aluminum chloride, and anhydrous hydrogen cyanide with anhydrous hydrogen chloride at approximately 40°.[2] This adduct is readily hydrolyzed to the corresponding aldehyde. The following list illustrates those phenol ethers into which the aldehyde group has been introduced in yields of 80 to 100%:[2,3,8] anisole, phenetole, o- and m-chloroanisole, m-chlorophenetole, the methyl and ethyl ethers of o- and m-cresol, and the methyl ether of 1-naphthol. The aldehyde group enters the position para to the ether linkage unless the para position is occupied, when it enters the position ortho to the alkoxyl group. For example, p-cresyl methyl ether yields 2-methoxy-5-methylbenzaldehyde (80%).[2,3] However, the preference of para substitution to ortho or occasional meta substitution is very strong both in the reactions with phenols and in the reactions with phenol ethers. The introduction of an aldehyde group into 2,4,6-trimethylanisole results in the formation of 3-hydroxy-2,4,6-trimethylbenzaldehyde (VIII) in only 5–10% yield along with small amounts of an unidentified hydroxydimethylbenzaldehyde.[18] Demethylation of the ether takes place concomitantly with the introduction of the aldehyde group. Other examples of demethylation of methyl ethers are given in the tables.

[18] von Auwers and Mauss, Ber., **61,** 1495 (1928).

With certain activated nuclei, hydrogen cyanide and hydrogen chloride may be used without a catalyst as in the preparation of the dialdehyde IX from the trimethylene ether of $\beta$-naphthol.[3]  Occasionally, zinc chloride

CHO
H₃C — CH₃
OH
CH₃
VIII

CHO — O(CH₂)₃O — CHO
IX (50%)

OR
H₃C — CH₃
X

may be used to replace aluminum chloride advantageously, for example, with the methyl and ethyl ethers of 3,5-dimethylphenol (X).[3]  However, with few exceptions, aldehydes of monohydric phenol ethers can be prepared only with the use of aluminum chloride as a catalyst.

Attempts have been made to avoid the direct use of anhydrous hydrogen cyanide because of the hazard involved therein.  Adams and his co-workers supplied a method whereby the phenol ether is treated in dry benzene with 2 equivalents of zinc cyanide.[5,6]  After dry hydrogen chloride is passed through the solution to its saturation point, $1\frac{1}{2}$ equivalents of anhydrous aluminum chloride are added and dry hydrogen chloride is again introduced at a temperature of approximately 40–45°.  By the above procedure, excellent yields of anisaldehyde, 2-methoxy-5-methyl-benzaldehyde, and 2-methoxy-1-naphthaldehyde have been reported; diphenyl ether gave $p$-phenoxybenzaldehyde in 50% yield.

Replacement of zinc cyanide by sodium or potassium cyanide or replacement of benzene by other solvents generally reduces the yields of aldehydes.[6,9]  Zirconium cyanide in the presence of zirconium chloride in dry benzene gave only a poor yield of anisaldehyde from anisole under the conditions used.[18a]

### Monohydric Phenols

The procedure just described for introducing an aldehyde group into a phenol ether must usually be modified when introducing an aldehyde group into a monohydric phenol.[3]  The phenol is treated with hydrogen cyanide in benzene, and the mixture is cooled with a salt-ice bath.  Powdered aluminum chloride is slowly added, and the temperature is brought to 40° while anhydrous hydrogen chloride is introduced.  The yields appear to vary with the structure of the phenol:[3,19]  phenol (30%),

[18a] Krishnamurti, *J. Madras Univ.*, (1928) [*C. A.*, **23**, 2164 (1929)].
[19] Gattermann and Berchelmann, *Ber.*, **31**, 1765 (1898).

*o*-cresol (35–40%), *m*-cresol (45–50%), 2,3-dimethylphenol (60%), 2,5-dimethylphenol (80%), 3,5-dimethylphenol (quantitative), carvacrol (30%), *m*-chlorophenol (50%), *m*-bromophenol (10%), *p*-cresol (5%). Only one aldehyde group is introduced, and it always enters *para* to the hydroxyl group if that position is unoccupied. If the *para* position is blocked, the reaction may not proceed at all or it may lead in poor yield to a product in which the aldehyde group is *ortho* to the hydroxyl group. 2-Naphthol is an exception in that an excellent yield of 2-hydroxy-1-naphthaldehyde is obtained.[3] 2,3-Dimethylphenol yields 4-hydroxy-2,3-dimethylbenzaldehyde (XI) in 60% yield with only a trace of the compound in which the aldehyde group has entered *ortho* to the hydroxyl group.[3,18] 2,3,4-Trimethylphenol (XII), however, also yields 4-hydroxy-2,3-dimethylbenzaldehyde (XI) as the chief product with only a trace of 2-hydroxy-3,4,5-trimethylbenzaldehyde (XIII), showing that the driving force towards *para* substitution is so strong that replacement of an alkyl group by an aldehyde group is preferred to *ortho* substitution. Several other examples of ring dealkylation are given in the tables.



XI     XII     XIII

Zinc chloride or the Adams modification may be substituted for aluminum chloride in the reactions with monohydric 2-naphthols that are unsubstituted in the 1-position and with 1-naphthols that are unsubstituted in the 4-position; the products containing the aldehyde group in the 1- and 4-position, respectively, are formed in almost quantitative yields.[3,4] In general, however, monohydric phenols fail to react unless aluminum chloride is added as a catalyst.[6] Using the Adams modification with aluminum chloride, the following phenolic aldehydes were prepared: 4-hydroxy-3-methylbenzaldehyde (38%),[6] 4-hydroxy-5-isopropyl-2-methylbenzaldehyde (quantitative),[6,20,21] *p*-carvacrolaldehyde (good),[20,21] and 4-hydroxy-2-methylbenzaldehyde (30%).[22]

## Polyhydric Phenols

The standard procedure for introducing an aldehyde group using hydrogen cyanide, hydrogen chloride, and aluminum chloride has given excellent results with a number of polyhydric phenols which includes resorcinol,

[20] Bell and Henry, *J. Chem. Soc.*, **1928**, 2215.
[21] Henry and Sharp, *J. Chem. Soc.*, **1926**, 2432.
[22] Love, *J. Roy. Tech. Coll.*, **3**, 385 (1935) [*C. A.*, **29**, 3995 (1935)].

phloroglucinol, and the 1,2-, 1,3-, and 2,7-naphthalenediols.[3,8,19,23-25] Resorcinol and its derivatives react with especial ease; an aldehyde group may even be introduced into resorcinols containing *m*-directing groups in the 4 position either by the standard procedure[24,25] or by use of the Adams modification with added aluminum chloride.[26-34]   The orientation of the aldehyde group in such molecules depends on the character of the substituents present.   For example, under Gattermann's conditions the aldehyde group enters almost exclusively in the 5 position of 2,4-di-hydroxytoluene,[3] but under the same conditions enters the 3 position (sometimes called the $\gamma$ position) of 2,4-dihydroxyacetophenone.[25]



This is explained by Shah and Shah as being due to chelation of the acetyl group with the hydroxyl group *ortho* to it, thereby increasing the



relative importance of the second resonance form pictured herewith.[25]

[23] Morgan and Vining, *J. Chem. Soc.*, **1921**, 177.

[24] Shah and Laiwalla, *Current Sci. India*, **5,** 197 (1936) [*C. A.*, **31,** 6219 (1937)].

[25] Shah and Shah, *Nature*, **142,** 163 (1938).

[26] Chandrashekhar and Shah, *Proc. Indian Acad. Sci.*, **29A,** 227 (1949) [*C. A.* **43,** 7925 (1949)].

[27] Gruber and Hoyos, *Monatsh.*, **80,** 303 (1949).

[28] Gruber and Traub, *Monatsh.*, **77,** 414 (1947).

[29] Shah and Laiwalla, *J. Chem. Soc.*, **1938,** 1828.

[30] Shah and Shah, *J. Chem. Soc.*, **1939,** 132.

[31] Shah and Shah, *J. Chem. Soc.*, **1939,** 300.

[32] Shah and Shah, *J. Chem. Soc.*, **1939,** 949.

[33] Shah and Shah, *J. Chem. Soc.*, **1940,** 245.

[34] Whalley, *J. Chem. Soc.*, **1949,** 3278.

This explanation is supported by the fact that neither gallacetophenone (XIV) nor isopaeonol (XV) yields a $\gamma$-substitution product when treated with zinc cyanide, hydrogen chloride, and aluminum chloride.[32,35]    When



XIV                                      XV

$\gamma$ substitution does occur yields are frequently excellent, e.g., 3-acetyl-2-hydroxy-4,6-dimethoxybenzaldehyde (84%),[28] 3,5-dicarbethoxy-2,4,6-tri-hydroxybenzaldehyde (85%),[28] 2,6-dihydroxy-3-propionylbenzaldehyde (64%),[33] 3-carbomethoxy-2,6-dihydroxybenzaldehyde (65%),[29] 3-carb-alkoxy-2,6-dihydroxy-4-methylbenzaldehydes (quantitative).[34]

The Adams modification using zinc cyanide and hydrogen chloride in the absence of aluminum chloride has also been successful in the preparation of aldehydes of polyhydric phenols having no nuclear deactivating substituents.[5,36–40]    Representative compounds prepared by this procedure follow:    $\beta$-resorcylaldehyde    (95%),[5]    2,4-dihydroxy-6-methyl-benzaldehyde (85%),[5] 3-ethyl-2,4-dihydroxybenzaldehyde (74–80%),[37] and 2,4-dihydroxy-3-methoxybenzaldehyde (93%).[37]    The formation of dialdehydes in low yields has been observed with phloroglucinol and its alkyl-substituted derivatives;[38]    phloroglucinol-3,5-dicarboxaldehyde is isolated from phloroglucinol in 1.5% yield.    The yield of dialdehyde is increased to 6.6% with methylphloroglucinol and to 24% with ethyl-phloroglucinol.

Zinc chloride has been successfully substituted for aluminum chloride in a number of instances.[3,23,41,42]    Its use with dihydric naphthols has been shown to result in the entrance of the aldehyde group into a free 1- or 4-position in the molecule in preference to a free 2-position.[23]    Thus, 1,8-dihydroxynaphthalene when treated with hydrogen cyanide, hydrogen chloride, and zinc chloride gives 4,5-dihydroxy-1-naphthaldehyde (24%) with only a very small amount of 1,8-dihydroxy-2-naphthaldehyde (0.8%). On the other hand, substitution in the 2-position is apparently favored

[35] Head and Robertson, J. Chem. Soc., **1930,** 2434.
[36] Baxter, Ramage, and Timson, J. Chem. Soc., **1949,** S30.
[37] Geissman, Schlatter, Webb, and Roberts, J. Org. Chem., **11,** 741 (1946).
[38] Gruber, Ber., **75,** 29 (1942).
[39] Shah and Mehta, J. Indian Chem. Soc., **13,** 361 (1936).
[40] Späth and Schmid, Ber., **74,** 193 (1941).
[41] Gattermann and Köbner, Ber., **32,** 278 (1899).
[42] Karrer, Rudlinger, Glattfelder, and Waitz, Helv. Chim. Acta, **4,** 724 (1921).

over substitution in an unsubstituted ring. For example, 1,4-dihydroxy-naphthalene reacts to give 1,4-dihydroxy-2-naphthaldehyde (13%) while no product is obtained which contains the aldehyde group in the unsubstituted ring of this molecule. In 1,6-dihydroxynaphthalene there are two most probable positions of attack. Substitution, however, occurs more extensively in the 4-position than in the 5-position,[23] the product consisting of 2,5-dihydroxy-1-naphthaldehyde (12–20%) and 4,7-dihydroxy-1-naphthaldehyde (64%). This last reaction was carried out with aluminum chloride instead of zinc chloride as the catalyst.

The use of hydrogen cyanide and hydrogen chloride in the absence of a catalyst has proved to be a satisfactory procedure with those polyhydric phenols having highly activated nuclei.[3,11,38,41,43–47] The yields, however, are considerably influenced by the conditions such as solvent and concentration.[43] For instance, if hydrogen cyanide is added rapidly at low temperature to a concentrated solution of the polyhydric phenol in ethyl acetate containing excess hydrogen chloride, the formation of the by-product imino methyl ethers, which occurs at higher dilutions, is minimized. The presence of two or more hydroxyl groups *meta* to each other as in resorcinol, phloroglucinol, or orcinol appears to be necessary for the introduction of an aldehyde group under the conditions described; compounds such as catechol and hydroquinone yield no aldehyde derivatives. These conditions have also been applied to the introduction of two aldehyde groups into 2-methyl- and 2-ethyl-phloroglucinol; 2-methylphloroglucinol-4,6-dicarboxaldehyde (6.6%) and 2-ethylphloroglucinol-4,6-dicarboxaldehyde (24%) are obtained.

Cyanogen bromide has been substituted for hydrogen cyanide in the preparation of $\beta$-resorcylaldehyde and phloroglucylaldehyde, but the yields obtained were not specified.[48] Although cyanogen bromide is more conveniently handled than hydrogen cyanide, nevertheless it is also extremely toxic.[49] The evidence is insufficient to indicate whether this procedure is preferable to the other methods.

The use of formamide and phosphorus oxychloride as a source of formimino chloride in the Gattermann reaction has been described;[50] e.g., $\beta$-resorcylaldehyde was prepared by this method in unspecified yield. The method has not found general application.

[43] Hinkel and Hullin, *J. Chem. Soc.*, **1949**, 1593.

[44] Johnson and Lane, *J. Am. Chem. Soc.*, **43**, 354 (1921).

[45] Robertson and Subramanian, *J. Chem. Soc.*, **1937**, 288.

[46] Robinson and R. Shah, *J. Chem. Soc.*, **1934**, 1497.

[47] Späth and Gruber, *Ber.*, **74**, 1492 (1941).

[48] Karrer, *Helv. Chim. Acta*, **2**, 89 (1919).

[49] Hartman and Dreger, *Org. Syntheses, Coll. Vol. 2*, 2nd ed., p. 150, John Wiley & Sons, 1941.

[50] Nenitzescu and Isacescu, *Bul.Soc.Chim. România*, **11**, 135 (1930) [*C. A.*, **24**, 2442 (1930)].

## Monoalkyl Ethers of Dihydric Phenols

In the monoalkyl ethers of resorcinol the aldehyde group usually enters *para* to the hydroxyl group rather than *para* to the alkoxyl group. For example, employment of Gattermann's procedure with aluminum chloride on the monomethyl ether of resorcinol results in a 75–80% yield of 4-hydroxy-2-methoxy-benzaldehyde.[3,19] In several instances, zinc chloride has been substituted for aluminum chloride, as in the preparation of 6-hydroxy-3-methyl-2,3-dihydrobenzofuran-5-carboxaldehyde.[51] In this latter synthesis, the position *para* to the hydroxyl group is occupied and substitution occurs in the position *para* to the ether linkage.

## Polyalkoxy Derivatives of Benzene

The Gattermann procedure with aluminum chloride is effective for the introduction of the aldehyde group into polyalkoxybenzenes.[2,3,52] As with polyhydric phenols, the aldehyde group always enters *para* to an alkoxyl group if this position is available; resorcinol dimethyl ether is converted to 2,4-dimethoxybenzaldehyde in 80% yield by the Adams modification with added aluminum chloride.[6] Substitution may occur *ortho* to the alkoxyl group when the *para* position is blocked; e.g., the dimethyl and diethyl ethers of hydroquinone are reported to give 2,5-dialkoxybenzaldehydes in unspecified yields.[3]

When mixed ethers are subjected to the Gattermann reaction, a mixture of the possible isomeric aldehydes is formed.[53,54] Determination of the relative amounts of each has demonstrated the following order of influence by the alkoxyl group in directing the aldehyde group to the *para* position:[53]

$$CH_2=CHCH_2O— > C_2H_5O— > CH_3CH_2CH_2O—, \; CH_3O—$$

## Molecules with Two Non-Fused Aromatic Nuclei

With molecules having two aromatic nuclei, each of which contains an ether linkage, it is possible to introduce an aldehyde group into each ring. The reaction has been applied to dimethylene and trimethylene ethers of phenol, *o*-cresol, *m*-cresol, 2,5-dimethylphenol, and 1- and 2-naphthol. The yields of dialdehydes vary from 30% to 75%.[3]



[51] Karrer, Glattfelder, and Widmer, *Helv. Chim. Acta*, **3**, 548 (1920).
[52] Gattermann and Eggers, *Ber.*, **32**, 289 (1899).
[53] Sonn and Patschke, *Ber.*, **58**, 1698 (1925).
[54] Ungnade and Orwall, *J. Am. Chem. Soc.*, **65**, 1736 (1943).

Similarly, 2,2'-dimethoxy- and 2,2'-diethoxy-biphenyl react to give the 5,5'-dialdehydes.[3]   The corresponding 2,2'-dihydroxybiphenyl, however, is converted to dibenzofuran by the aluminum chloride, and only one aldehyde group is introduced.[55]



## Aromatic Hydrocarbons

Gattermann was unable to introduce the aldehyde group into aromatic hydrocarbons under the conditions he used.   Tetralin was an exception, since it formed 3,4-tetramethylenebenzaldehyde in 33% yield.   In fact, Gattermann often used benzene and other hydrocarbons as solvents in his reactions.   It was later discovered, however, that an aldehyde group could be introduced into benzene provided that the conditions were modified so that free aluminum chloride was present.[8]   At 40°, in benzene, the complex of aluminum chloride with chloromethylene formamidine is not dissociated and reaction does not occur.   If the temperature is raised to 80° or above, the complex appears to dissociate to some extent, yielding free aluminum chloride, and reaction does occur.   If excess aluminum chloride is added, the yield of benzaldehyde is increased from 14% to 75%.[8]   It is advantageous to employ a mole-per-mole ratio of aluminum chloride to hydrogen cyanide when the aromatic compound is not very susceptible to polymerization; otherwise, the amount of aluminum chloride must be reduced and the time of reaction increased.   The yields of aldehydes reported by Hinkel and his co-workers are based on the amount of hydrogen cyanide used instead of on the amount of aromatic compound as reported by Gattermann.   On the assumption that 2 moles of hydrogen cyanide are required for every mole of aromatic compound converted to the aldehyde, the yields (which formerly were calculated to be only 50% based on the aromatic compound) actually correspond to yields of nearly 100% when a 1 : 1 molar ratio of reactants was employed. It is certain, however, that 2 moles of hydrogen cyanide are not necessary for introduction of an aldehyde group into phenols and phenol ethers under all conditions.

[55] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1937**, 778.

Just as the yield of benzaldehyde is markedly increased as the temperature is raised from that of the room to 100°,[7] so the yield of aldehydes from other aromatic hydrocarbons is also increased. Unfortunately, the increase in temperature also increases the tendency for aluminum chloride to induce polymerization of the hydrocarbon. Hinkel and his co-workers recommend approximately 70° as the optimum temperature for most reactions.[7]

Aldehydes can be prepared from liquid aromatic hydrocarbons by using excess hydrocarbon as the solvent; but, when the hydrocarbons are not liquid, are not easily procurable, or are unstable in the presence of aluminum chloride, the reaction must be modified by employment of inert solvents. Tetrachloroethane, o-dichlorobenzene, and chlorobenzene are suitable reaction media since they are good solvents for the hydrocarbons, hydrogen cyanide, and the final products, and since their high boiling points permit their use over a wide temperature range.[7] Tetrachloroethane appears to promote the aldehyde synthesis, but it also increases the tendency of the aluminum chloride to cause polymerization of the hydrocarbons. Indene is so readily polymerized that introduction of the aldehyde group has not been achieved.

Polymerization can usually be reduced by employing a solvent with a lower chlorine content and by using but a slight excess of aluminum chloride, with a subsequent increase in the time of reaction. The effect of solvent is quite pronounced with biphenyl, which yields a monoaldehyde in chlorobenzene or o-dichlorobenzene, and a dialdehyde when the solvent medium is tetrachloroethane. Pertinent to the mechanism of the latter reaction is the fact that the monoaldehyde cannot be converted to the dialdehyde under the same conditions.[7] A solvent effect has also been observed in the preparation of tolualdehydes from toluene; with excess toluene as solvent both m- and p-tolualdehyde are obtained, but with chlorobenzene as solvent only p-tolualdehyde is obtained.[56]

A few of the aldehydes formed in good yields from the representative hydrocarbons as described by Hinkel and his co-workers are: benzaldehyde (75%), p-tolualdehyde (91%), 3,4-dimethylbenzaldehyde (85%), 2,4,6-trimethylbenzaldehyde (67–83%), 4-phenylbenzaldehyde (75%), fluorene-2-carboxaldehyde (76%), and acenaphthene-5-carboxaldehyde (70–90%).[7,8,10,57]

The Adams modification of the Gattermann reaction using zinc cyanide in the presence of aluminum chloride was employed by Fuson and his co-workers for the preparation of some polyalkylated benzaldehydes.[58,59]

[56] Niedzielski and Nord, J. Org. Chem., **8**, 147 (1943).

[57] Hinkel, Brit. pat. 397,124 (1933) [C. A., **28**, 778 (1934)].

[58] Fuson, Horning, Rowland, and Ward, Org. Syntheses, Coll. Vol. III, 549 (1955).

[59] Fuson, Horning, Ward, Rowland, and Marsh, J. Am. Chem. Soc., **84**, 31 (1942).

Using tetrachloroethane as the solvent and a reaction temperature of 70°, 1,3,5-trialkylbenzenes are converted to 2,4,6-trialkylbenzaldehydes in 38–83% yield.

Complications that may be encountered with aromatic hydrocarbons are alkylation and alkyl migration; from ethylbenzene both mono- and di-ethylbenzaldehyde can be isolated.[56]

Sodium cyanide and hydrogen chloride with aluminum chloride have also been used.[9,56,60] This combination is generally applicable to aromatic hydrocarbons other than benzene. Aluminum chloride in excess of that required to form a 1 : 1 complex with chloromethylene-formamidine is necessary.[9] The yields of the corresponding aldehydes obtained from toluene and the isomeric xylenes appear to coincide with the polarity of the hydrocarbon reactants. Under these conditions, extensive migration and alkylation are observed so that some 2,4-dimethyl-benzaldehyde is obtained from all three xylenes. The yields of this compound, however, vary with the xylene used: from. $o$-xylene 75%, from $m$-xylene 26%, and from $p$-xylene 17%. In the reaction mixtures from $m$-xylene and $p$-xylene, 2,4,5-trimethylbenzaldehyde may be isolated in 13% and 21% yield, respectively; no trimethylbenzaldehyde is obtained from $o$-xylene.[56]

## Aromatic Amines

The Gattermann reaction generally cannot be applied to aromatic amines. The preparation of $p$-aminobenzaldehyde by the reaction of hydrogen cyanide and hydrogen chloride on aniline in ether solution has been reported but not confirmed.[61] Hinkel and his co-workers have obtained merely complex condensation products instead of aldehydes from aniline, dimethylaniline, and diphenylamine.[55]

## Pyrroles and Indoles

The aldehyde group is introduced with great ease into certain pyrroles and indoles. This reaction proceeds so readily that frequently no catalyst is required.[62-65] Both diethyl ether and chloroform have been employed as solvents. The yields often vary with the solvent and have been considerably better in chloroform than in ether.[63] An outstanding example

[60] Mistritta and Nord, *Nature*, **145**, 387 (1940).

[61] Wu, *J. Am. Chem. Soc.*, **66**, 1421 (1944).

[62] Fischer and Ammann, *Ber.*, **56**, 2319 (1923).

[63] Fischer and Zerweck, *Ber.*, **56**, 519 (1923).

[64] Reichstein, *Helv. Chim. Acta*, **13**, 349 (1930).

[65] Seka, *Ber.*, **56**, 2058 (1923).

is 2,3,5-trimethylpyrrole, which is converted in 67% yield to 2,4,5-trimethylpyrrole-3-carboxaldehyde in chloroform solution but which apparently gives no product in diethyl ether.

Aldehyde groups have not been introduced into unsubstituted pyrrole or indole.[64,66] This failure has been explained as the result of the reaction of the intermediate aldimine hydrochloride with the pyrrole or indole to give complex, colored condensation products.[66] No difficulty is encountered in introducing the aldehyde group into 1-alkylpyrroles such as 1-methylpyrrole, 1-n-butylpyrrole, 1-i-amylpyrrole, and 1-furfurylpyrrole.[66] The aldehyde group enters the 2- or 5-position if one is free, but if both these positions are occupied, it may readily enter the 3- or 4-position. Another noteworthy fact is that the carbethoxy group and various acyl groups apparently do not prevent the reaction; many of the best yields of pyrrole aldehydes have been from pyrroles containing such substituents which are normally nuclear deactivating. In the absence of an open position, a carbethoxy group may be replaced by an aldehyde group.[67] The aldehydes from a selected list of pyrroles are given below with the yields obtained.



$C_2H_5O_2C$ / $CH_3$ / $H_3C$ / CHO / N / H
(95%)[68]

$C_2H_5O_2C$ / CHO / $H_3C$ / $CH_3$ / N / H
(77%)[68]

$H_3C$ / CHO / $C_2H_5O_2C$ / $CH_3$ / N / H
(85%)[69]

$CH_3C$ (O) / $CH_3$ / $H_3C$ / CHO / N / H
(65%)[62]

$C_2H_5O_2C$ / CHO / $H_3C$ / $CH_3$ / N / $CH_3$
(90%)[70]

$C_2H_5O_2C$ / CHO / $H_3C$ / $CH_3$ / N / $C_6H_5$
(80-90%)[70]

$C_2H_5O_2C$ / CHO / $H_3C$ / $CH_3$ / N / $C_6H_4CH_3$-$p$
(80-90%)[70]

[66] Fischer and Pistor, *Ber.*, **56**, 2313 (1923).

[67] Fischer and Ernst, *Ann.*, **447**, 139 (1926).

[68] Fischer and Zerweck, *Ber.*, **55**, 1942, (1922).

[69] Fischer, Weiss, and Schubert, *Ber.*, **56**, 1194 (1923).

[70] Fischer and Smeykal, *Ber.*, **56**, 2368 (1923).

In one study, zinc chloride was used as the catalyst in the pyrrole series;[71] however, better yields were obtained in the absence of any catalyst. The Adams modification of the Gattermann synthesis has been successfully applied in the preparation of 5-phenylpyrrole-2-carboxalde-hyde,[72] 2-carbethoxyindole-3-carboxaldehyde (83%),[73] and 2-methyl-indole-3-carboxaldehyde (19%).[73] The best yields in these syntheses resulted when a deactivating nuclear substituent was present.

Formamide and phosphorus oxychloride in diethyl ether have been reported to yield pyrrole aldehydes in unspecified yields.[50] As with other reagents, the aldehyde group enters the 2- or 5-position if one is free; otherwise, the 3- or 4-position.

## Furans and Benzofurans

Furan undergoes the Gattermann reaction with anhydrous hydrogen cyanide and hydrogen chloride in the absence of a catalyst to give furfural (35%).[74] The furan nucleus is less susceptible to side reactions than the pyrrole nucleus, but it is also less reactive, as shown by the fact that, when both the 2- and 5-positions in a furan are occupied, no substitution occurs.[74] A carbethoxy group in the furan deactivates the nucleus so that no aldehyde group enters.[74]

Benzofuran fails to yield an aldehyde by the Gattermann method;[74] but benzofurans having activating substituents in the benzene nucleus do react, the aldehyde group entering the benzene and not the furan ring. A 9% yield of 4,6-dimethoxybenzofuran-7-carboxaldehyde is obtained from 4,6-dimethoxybenzofuran using hydrogen cyanide and hydrogen chloride without a catalyst.[75] However, the yield of aldehyde is increased to 72% by blocking the 2-position with a carbethoxy group and employing zinc chloride as a catalyst. 2-Carbethoxy-4,6-dimethoxybenzofuran-7-carboxaldehyde was obtained in 90% yield by Foster and Robertson using aluminum chloride as the catalyst.[75] These workers believed that, in the absence of the blocking group in the 2-position, the yield is low because of extensive resinification.[75] However, Karrer and his co-workers have prepared aldehydes in unspecified yields by the zinc chloride catalyzed reaction on benzofurans in which the 2-position was not blocked.[42,51]

The aldehyde group could not be introduced into 2-carbomethoxy-4,7-dimethoxy-6-hydroxybenzofuran by the Adams modification.[36]

[71] Barger and Ewins, *Biochem. J.*, **11**, 58 (1917).

[72] Plancher, Rossi, and Ghigi, *Gazz. chim. ital.*, **59**, 352 (1929).

[73] Boyd and Robson, *Biochem. J.*, **29**, 555 (1935).

[74] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).

[75] Foster and Robertson, *J. Chem. Soc.*, **1939**, 921.

## Thiophenes and Thiazoles

Few applications of the Gattermann reaction in the thiophene series have been made. Thiophene is less reactive than furan and pyrrole, and the aldehyde group may be introduced (in poor yield) only in the presence of aluminum chloride.[64] Undoubtedly, the tendency of thiophene to polymerize under acidic conditions is the chief obstacle to the application of the Gattermann reaction in this series.

2-Hydroxy-4-methylthiazole-5-carboxaldehyde (25%) is prepared by the use of hydrogen cyanide and hydrogen chloride in the absence of a catalyst, but 4-methylthiazole fails to react.[76]

## Enols

Ethyl acetoacetate dissolved in benzene is converted by hydrogen cyanide and hydrogen chloride in the presence of aluminum chloride into ethyl α-formiminoacetoacetate hydrochloride.[77]

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow[C_6H_6]{HCN, HCl, AlCl_3,} CH_3COCHCO_2C_2H_5$$
$$\underset{\displaystyle CH{=}NH \cdot HCl}{|}$$

Analogous results are obtained with acetylacetone, and, presumably, other active methylene compounds would act similarly. Simple olefins, however, do not yield the corresponding aldehydes under the conditions of the Gattermann reaction.[78]

### ALTERNATIVE METHODS FOR DIRECT INTRODUCTION OF AN ALDEHYDE GROUP

Several alternative methods for the direct introduction of aldehyde groups into aromatic compounds are available. The Gattermann-Koch reaction employing carbon monoxide, hydrogen chloride, and aluminum chloride, often with a cuprous chloride carrier, is used chiefly for the preparation of benzaldehyde and the mono- and poly-alkylbenzaldehydes.[1] It is unsuccessful with phenols, phenol ethers, and heterocyclic compounds.[1,2]

A second method employs N-methylformanilide and phosphorus oxychloride. It is limited to certain activated compounds such as ethers of the aromatic series,[79] secondary and tertiary aromatic amines,[80] and

[76] Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939).

[77] Wieland and Dorrer, *Ber.*, **58**, 818 (1925).

[78] Wieland and Dorrer, *Ber.*, **63**, 404 (1930).

[79] Kalischer, Scheyer, and Keller, German pats. 514,415 (1931), and 519,444 (1931) [*Chem. Zentr.*, **102**, II, 3394 (1931).]

[80] Vilsmeier and Haack, *Ber.*, **60**, 119 (1927).

highly reactive aromatic hydrocarbons such as anthracene and pyrene.[79,81-83] It is an excellent method for the preparation of thiophene-2-carboxaldehyde (71-74%)[83a] and pyrrole-2-carboxaldehyde (89%).[83b] An aldehyde group is also introduced into tertiary aromatic amines by means of dimethylformamide and phosphorus oxychloride.[84,85]



(77-84%)[84]

The Reimer-Tiemann reaction is limited to phenols,[86-90] halophenols,[91-94] certain heterocyclic compounds such as indoles[95] and hydroxyquinolines,[96] coumarones,[96] and hydroxyanthraquinones.[96] It gives predominantly *ortho* derivatives, although *para* derivatives are also formed as by-products. It is not applicable to phenol ethers or hydrocarbons. The yields of the resulting hydroxyaldehydes are rarely greater than 50%. A theoretical discussion of this reaction has been presented by Armstrong and Richardson.[91]

### EXPERIMENTAL CONDITIONS

Catalysts. Commercial anhydrous aluminum chloride, finely powdered, is satisfactory in the Gattermann aldehyde synthesis. Anhydrous zinc chloride is freshly fused before use. Zinc cyanide, which with hydrogen chloride gives zinc chloride and the required hydrogen cyanide, is prepared by treating aqueous sodium cyanide with magnesium chloride, filtering, and then adding an equivalent amount of zinc chloride in ethanol. The magnesium chloride removes sodium hydroxide. The resulting product is about 90% pure. It is claimed that pure zinc cyanide is ineffective, but when contaminated with potassium chloride or sodium

[81] Fieser and Jones, *J. Am. Chem. Soc.*, **64**, 1666 (1942).
[82] Fieser, Hartwell, and Jones, *Org. Syntheses*, Coll. Vol. III, 98 (1955).
[83] Wood and Bost, *J. Am. Chem. Soc.*, **59**, 1721 (1937).
[83a] Weston and Michaels, Jr., *Org. Synthesis*, **31**, 108 (1951).
[83b] Silverstein, Ryskiewicz, Willard, and Koehler, *J. Org. Chem.*, **20**, 668 (1955).
[84] Wilson, U.S. pat. 2,437,370 (1948) [*C. A.*, **42**, 5924 (1948)].
[85] Wilson, U.S. pat. 2,558,285 (1951) [*C. A.*, **46**, 1041 (1952)].
[86] Arnold, Zaugg, and Sprung, *J. Am. Chem. Soc.*, **63**, 1314 (1941).
[87] Reimer, *Ber.*, **9**, 423, 1285 (1876); **11**, 793 (1878).
[88] Tiemann and Muller, *Ber.*, **14**, 1985 (1881).
[89] Tiemann and Parrisius, *Ber.*, **13**, 2354 (1880).
[90] Tiemann and Schotten, *Ber.*, **11**, 767 (1878).
[91] Armstrong and Richardson, *J. Chem. Soc.*, **1933**, 496.
[92] Hodgson and Jenkinson, *J. Chem. Soc.*, **1927**, 1740, 3041; **1929**, 469, 1639.
[93] Hodgson and Nixon, *J. Chem. Soc.*, **1929**, 1632.
[94] Reimer and Tiemann, *Ber.*, **9**, 824, 1268 (1876).
[95] Blume and Lindwall, *J. Org. Chem.*, **10**, 255 (1945).
[96] Sen and Ray, *J. Indian Chem. Soc.*, **9**, 173 (1932).

chloride it reacts as desired.[97]   Zinc cyanide that has been washed
thoroughly with water and dried does not react, but after addition of
sodium chloride or potassium chloride it does react.   The amount of
catalyst usually used is slightly more than that needed for formation of the
hydrogen cyanide adduct.

Solvents.   Benzene is frequently used as a solvent particularly where
aluminum chloride and a comparatively low reaction temperature are
employed.   With zinc chloride or in the absence of any catalyst, ether is a
desirable solvent in view of its greater solvent action on polyhydric
phenols.   Furthermore, with ether as a solvent, the primary reaction
product, the pure crystalline imine salt, may separate from solution and
thus permit isolation before hydrolysis.[11]   Chloroform is preferable to
ether for the reaction with certain substituted pyrroles.[63]   The success of
and the orientation obtained in the Gattermann reaction are frequently
affected by the nature of the solvent.[56]   Tetrachloroethane has been used
frequently, as have o-dichlorobenzene and chlorobenzene since they
dissolve hydrocarbons, hydrogen cyanide, and final products alike and
have high boiling points.

Hydrogen Cyanide.   Cylinders of anhydrous hydrogen cyanide can
be purchased.   The acid can also be prepared readily by treating sodium
cyanide with sulfuric acid,[98] or by treating potassium ferrocyanide with
sulfuric acid followed by drying by passage over calcium chloride.[99]
Detailed directions for the preparation of hydrogen cyanide from sodium
cyanide and sulfuric acid are given in *Organic Syntheses.*[100]   Cyanogen
bromide as a substitute for hydrogen cyanide appears to have little if any
advantage.[48]

### EXPERIMENTAL PROCEDURES

Mesitaldehyde (hydrogen chloride, zinc cyanide, aluminum chloride,
tetrachloroethane as solvent).   Detailed directions for the preparation
of mesitaldehyde in 75–81% yield from mesitylene are given in *Organic
Syntheses.*[58]

4-Methoxy-3-methylbenzaldehyde (hydrogen cyanide, hydrogen
chloride, aluminum chloride).[2]   *Hydrogen cyanide is extremely poisonous
and should be handled with great care.   All connections should be thoroughly
tested for leaks, and the entire apparatus should be placed in a hood which is
in good working order.   Rubber gloves should be worn.   Adequate ventilation
should be maintained at all times.   Any vapors escaping from the system*

[97] Arnold and Sprung, *J. Am. Chem. Soc.*, **60**, 1699 (1938).

[98] Ziegler, *Ber.*, **54**, 110 (1921).

[99] Houben, *Ber.*, **59**, 2878 (1926).

[100] Ziegler, *Org. Syntheses, Coll. Vol.* 1, 2nd ed., p. 314, John Wiley & Sons, 1941.

*should not be allowed to escape freely, but should be destroyed by passage through solutions of potassium permanganate or hydrogen peroxide. Before handling hydrogen cyanide, one should consult textbooks on the handling of dangerous materials and the treatment and first aid of hydrogen cyanide poisoning.*

Gaseous hydrogen chloride is passed for one-half hour through a mixture of 25 g. (0.93 mole) of anhydrous hydrogen cyanide and 30 g. (0.25 mole) of *o*-cresyl methyl ether cooled in an ice bath. Aluminum chloride, 30 g. (0.22 mole), is added gradually. While slowly adding more hydrogen chloride, the temperature is raised to 45° and ‑kept there for four to five hours. The reaction mixture is poured over ice and hydrochloric acid. The resulting copious precipitate is heated under reflux with hydrochloric acid. The aldehyde is steam-distilled and then treated with sodium bisulfite solution. The bisulfite addition product is filtered and decomposed with aqueous sodium carbonate. The yield of colorless oil, b.p. 251°, is 30–37 g. (80–100%).

**4-Hydroxy-2,6-dimethylbenzaldehyde** (hydrogen chloride, hydrogen cyanide, aluminum chloride, benzene as solvent).[3]  To an ice-cooled solution of 20 g. (0.16 mole) of 3,5-dimethylphenol in 80 ml. of benzene is added 13.8 g. (0.51 mole) of dry hydrogen cyanide. This is followed by 30 g. (0.22 mole) of aluminum chloride. After hydrogen chloride has been passed through the mixture for four hours at a temperature of 35°, it is poured into a mixture of hydrochloric acid and ice.  Benzene is removed by steam distillation, and the residue is extracted with ether. The resulting ethereal solution is extracted with sodium bisulfite solution. After the aqueous layer has been washed with ether, it is acidified with dilute sulfuric acid.  The precipitated aldehyde is crystallized from ethanol in the form of long yellow needles, m.p. 189–190°, in an almost quantitative yield.

**2-Hydroxy-1-naphthaldehyde** (hydrogen chloride, hydrogen cyanide, zinc chloride, anhydrous ethyl ether as solvent).[4]  To a well-cooled mixture of 15 g. (0.10 mole) of 2-naphthol, 45 ml. of ether, and 6.9 g. (10 ml., 0.26 mole) of dry hydrogen cyanide is added 15 g. (0.11 mole) of anhydrous zinc chloride. Anhydrous hydrogen chloride is passed through this mixture at room temperature for two and one half hours. During this time a dark oil settles to the bottom and eventually solidifies. The solid is washed thoroughly with ether and then heated for a short time with water. The oily material, which crystallizes in almost quantitative yield on cooling, melts at 81° after crystallization from dilute ethanol.

**2,4-Dihydroxybenzaldehyde** (hydrogen chloride, hydrogen cyanide from potassium ferrocyanide and sulfuric acid, anhydrous ethyl ether as solvent).[44]  Potassium ferrocyanide (200 g.) is heated in a flask with a

mixture of 160 g. of concentrated sulfuric acid and 280 ml. of water. The evolved hydrogen cyanide is led from the flask by means of an air condenser and passed through a calcium chloride drying train kept at 35–40° (hydrogen cyanide liquefies at 26°), and into a flask kept at −5° that contains 1 part of resorcinol dissolved in 3 parts of anhydrous ether. When the increase in weight indicates a 50% excess of hydrogen cyanide, hydrogen chloride is led slowly through the same drying train until it ceases to be absorbed by the ether solution. The semisolid reaction mixture is allowed to stand for several hours, after which it is decomposed with boiling water. The resulting mixture is filtered, and, on cooling, crystals of the aldehyde separate in good yield.

**2,4-Dihydroxy-6-methylbenzaldehyde** (hydrogen chloride, zinc cyanide, anhydrous ethyl ether as solvent).[5]  A 500-ml. three-necked round-bottomed flask is fitted with a stirrer, a reflux condenser, and an inlet tube having a wide mouth to prevent clogging and extending nearly to the bottom of the flask. A safety bottle is placed in series with this tube and a dry hydrogen chloride generator. The top of the condenser connects to a tube leading into a wash bottle containing sulfuric acid, then to a safety bottle, and finally to the surface of aqueous sodium hydroxide. To the reaction flask, containing 20 g. (0.16 mole) of thoroughly dried orcinol (freed of water of crystallization) and 200 ml. of dry ether, is added 28.1 g. (0.24 mole) of dry zinc cyanide. The mechanical stirrer is started, and dry hydrogen chloride is passed in rapidly. A pink color develops, and the condensation product begins to separate as a thick oil. After about one and one half hours, the ether becomes saturated with hydrogen chloride; the hydrogen chloride is then passed in more slowly for an additional half hour. After the ether is decanted, the solid residue is boiled for two to three minutes with about 100 ml. of water. The hot solution is filtered and cooled to yield a crystalline product (85%) which, after crystallization from water, melts at 178–180°.

*p*-**Anisaldehyde** (hydrogen chloride, zinc cyanide, aluminum chloride, benzene as solvent).[6]  The same type of apparatus may be employed for this preparation as was used above for the preparation of 2,4-dihydroxy-6-methylbenzaldehyde. To a mixture of 30 g. (30.1 ml., 0.28 mole) of anisole and 75 ml. of dry benzene is added 52 g. (0.44 mole) of dry zinc cyanide. Dry hydrogen chloride is added rapidly to the cooled and continuously stirred mixture for thirty to sixty minutes. Anhydrous aluminum chloride (49 g., 0.34 mole) is added slowly and with further cooling and stirring. This is followed by a slow stream of hydrogen chloride which is added while the mixture is heated at 40–45° for three to four hours. The contents of the flask are added to an excess of 10% hydrochloric acid, which generally causes a heavy precipitate to separate.

The resulting mixture is heated under reflux for one-half hour, and the aldehyde is steam-distilled. The steam distillate is extracted with benzene, and the benzene is subsequently removed by distillation. The residue is shaken with sodium bisulfite solution, and the anisole is extracted with ether. The aldehyde is released from the bisulfite addition product by warming with aqueous sodium carbonate. The yield of aldehyde, boiling at 246–248°, is 94%.

*p*-Tolualdehyde (hydrogen chloride, hydrogen cyanide, aluminum chloride, toluene as solvent).[8] To a mixture of 52 g. (0.39 mole) of aluminum chloride and 50 ml. of toluene cooled in ice is added with shaking 10.3 g. (15 ml., 0.38 mole) of dry hydrogen cyanide during a period of fifteen minutes. After being kept at room temperature for five minutes, the mixture is heated to about 60° and a slow current of hydrogen chloride is passed through. A vigorous reaction occurs, and the mixture is maintained at 100° for two hours while hydrogen chloride is introduced and an additional three hours at 100° after the flow of hydrogen chloride is stopped. The reaction mixture is kept at room temperature overnight. After the viscous mixture is poured over a mixture of ice and concentrated hydrochloric acid, the resulting organic layer is steam-distilled. From the dried ethereal extract of the distillate, the aldehyde is obtained in quantitative yield by fractional distillation; b.p. 200–204°.

**3,5-Dimethylpyrrole-2-carboxaldehyde** (hydrogen chloride, hydrogen cyanide, chloroform as solvent).[63] To a solution of 4 g. (0.03 mole) of 2,4-dimethylpyrrole in 40 ml. of chloroform that has been previously dried with phosphorus pentoxide is added 5.5 g. (0.2 mole) of dry hydrogen cyanide. The mixture is cooled with an ice bath, and dry hydrogen chloride is introduced for one hour. Without ,attempting to filter the crystals, the solvent is removed under reduced pressure at room temperature, and the residue is dissolved in cold water. Sodium hydroxide is added, ammonia is evolved, and the aldehyde separates as dark yellow crystals of melting point 89°; yield, 92%.

### TABULAR SURVEY OF ALDEHYDES PREPARED BY THE GATTERMANN REACTION

In the following tables an attempt has been made to cover the syntheses of aromatic aldehydes by the Gattermann reaction reported in the literature to January 1, 1954. The first column in the tables lists the aldehydes formed, the second column the reagents and solvents, without parentheses. Also in the second column is listed in parentheses the starting material wherever it is not obvious.

Table I lists compounds obtained from aromatic hydrocarbons, chlorobenzene, and aniline. Usually the substituted benzaldehyde formed is

indicated merely by the substituent groups.   Table II gives the aldehydes derived from phenols and phenol ethers; Table III lists the aldehydes obtained from naphthols, naphthol ethers, and phenanthrol.   Heterocyclic aldehydes are listed in Table IV;  and compounds that did not yield aldehydes are shown in Table V.

The reagents are listed as A, B, C, D, E, and F as defined below:

A:   HCl, HCN.
B:   HCl, HCN, $ZnCl_2$.
C:   HCl, HCN, $AlCl_3$.
D:   HCl, NaCN, $AlCl_3$.
E:   HCl, $Zn(CN)_2$, $AlCl_3$.
F:   HCl, $Zn(CN)_2$.

## TABLE I

### ALDEHYDES PREPARED FROM AROMATIC HYDROCARBONS

| Substituent(s) in Benzaldehyde or Complete Name of Aldehyde | Reagents | Yield, % | Reference |
|---|---|---|---|
| Benzaldehyde | D | 11 | 60 |
| | C | — | 57 |
| | | 16–39 | 8 |
| | C, $CHCl_2CHCl_2$ | 75 | 7 |
| 4-Amino- | A, ether (aniline) | — | 61 |
| 4-Chloro- | C | 8 | 7 |
| 4-Methyl- | D | 39 | 9 |
| | | 20 | 60 |
| | C | — | 57 |
| | | 14–91 | 10 |
| | | 14–quant. | 8 |
| 4-Ethyl- | D | 27 | 9 |
| | | 38 | 60 |
| | C | 30 | 56 |
| | C, $C_6H_5Cl$ | 22 | 7 |
| | C, $CHCl_2CHCl_2$ | 5 | 7 |
| 4-Isopropyl- | D | 24 | 60 |
| 4-s-Butyl | D | 4 | 60 |
| 4-t-Amyl- | D | 8 | 60 |
| 4-Phenyl- | C, $CHCl_2CHCl_2$ | 75 | 7 |
| 2,4-Dimethyl- | C | — | 57 |
| | | 97 | 8 |
| | D | 26 | 56 |
| | D, (o-xylene) | 75 | 56 |
| | D, (p-xylene) | 17 | 56 |
| 2,5-Dimethyl- | C | 85 | 8 |
| 3,4-Dimethyl- | C | 85 | 8 |
| | D | 42 | 9 |
| Diethyl- | D, (ethylbenzene) | 13 | 56 |
| | C, (ethylbenzene) | 25 | 56 |
| 2-Isopropyl-5-methyl- | D | 25 | 56 |
| Isopropyl-methyl- | D, (p-cymene) | 5–17 | 56 |
| Diisopropyl- | D, (isopropylbenzene) | 12–18 | 9, 56 |
| | D, (m-diisopropylbenzene) | 17–39 | 56 |
| | D, (p-cymene) | 13 | 56 |
| 3,4-Trimethylene- | C, $CHCl_2CHCl_2$ (hydrindene) | 45–60 | 7 |

## TABLE I—*Continued*

### ALDEHYDES PREPARED FROM AROMATIC HYDROCARBONS

| Substituent(s) in Benzaldehyde or Complete Name of Aldehyde | Reagents | Yield, % | Reference |
|---|---|---|---|
| 3,4-Tetramethylene- | C, $CHCl_2CHCl_2$ (tetralin) | 4 | 7 |
| | C, $C_6H_6$ (tetralin) | 33 | 3 |
| 2,3,5-Trimethyl- | D, (mesitylene) | 13 | 56 |
| 2,4,5-Trimethyl- | D | 7 | 56 |
| | D, (*m*-xylene) | 13 | 56 |
| | D, (*p*-xylene) | 21 | 56 |
| 2,4,6-Trimethyl- | C, $CHCl_2CHCl_2$ | 67–83 | 7 |
| | E, $CHCl_2CHCl_2$ | 75–81 | 58, 59 |
| | D, (1,2,4-trimethylbenzene) | 7 | 56 |
| 2,4,6-Triethyl- | E, $CHCl_2CHCl_2$ | 69 | 58, 59 |
| Triethyl- | D, (ethylbenzene) | 5 | 56 |
| Diisopropyl-methyl- | D, (*p*-cymene) | 10–16 | 56 |
| 2,4,6-Triisopropyl- | E, $CHCl_2CHCl_2$ | 65 | 58, 59 |
| Triisopropyl- | D, (*m*-diisopropylbenzene) | 5–16 | 56 |
| 2-Fluorenecarbox- aldehyde | C, $CHCl_2CHCl_2$ | 52–70 | 7 |
| | C, $C_6H_5Cl$ | 76 | 7 |
| | C, $o$-$C_6H_4Cl_2$ | 62 | 7 |
| 1-Naphthaldehyde | C, $C_6H_5Cl$ | 31–60 | 7 |
| | C, $CHCl_2CHCl_2$ | 66 | 7 |
| 4-Methyl-1-naphth- aldehyde | C, $o$-$C_6H_4Cl_2$ | 51 | 7 |
| 2,3-Dimethyl-1- naphthaldehyde | E, $CHCl_2CHCl_2$ | 38 | 59 |
| 2,6-Dimethyl-1- naphthaldehyde | C, $C_6H_5Cl$ | 60 | 7 |
| 4,7-Dimethyl-1- naphthaldehyde | C, $C_6H_5Cl$ | 58 | 7 |
| 5-Acenaphthenecarbox- aldehyde | C, $CHCl_2CHCl_2$ | 70–90 | 7 |
| 9-Anthracenecarbox- aldehyde | C, $CHCl_2CHCl_2$ | 50 | 7 |
| | C, $C_6H_5Cl$ | 60 | 7 |
| 9-Phenanthrenecarbox- aldehyde | C, $C_6H_5Cl$ | 44 | 7 |

## TABLE II

### ALDEHYDES PREPARED FROM PHENOLS AND THEIR ETHERS

*A. Aldehydes Prepared from Monohydric Phenols or Their Ethers*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 4-Hydroxy- | C, $C_6H_6$ | 30 | 3, 19 |
| 4-Methoxy- | D | 43 | 9 |
| | C | 45–89 | 2, 3, 8 |
| | $Zr(CN)_2$, $ZrCl_4$, $C_6H_6$ | Poor | 18 |
| | E, $C_6H_6$ | 94 | 6 |
| 4-Ethoxy- | C | 80 | 2, 3 |
| 4-($\beta$-Bromoethoxy)- | C, $C_6H_6$ | 50 | 3 |
| 4-Phenoxy- | C or E, $C_6H_6$ | 50–80 | 3, 6, 101 |
| $(-CH_2OC_6H_4CHO\text{-}p)_2$ | C, $C_6H_6$ | — | 3 |
| $CH_2(-CH_2OC_6H_4CHO\text{-}p)_2$ | C, $C_6H_6$ | 30 | 3 |
| 4-(4'-Methoxyphenoxy)- | C, $C_6H_6$ | 6 | 54 |
| 2-Bromo-4-hydroxy- | C, $C_6H_6$ | 10 | 3 |
| 2-Bromo-4-ethoxy- | C, $C_6H_6$ | — | 3 |
| 2-Chloro-4-hydroxy- | C, $C_6H_6$ | 50 | 3 |
| 2-Chloro-4-methoxy- | C, $C_6H_6$ | — | 3 |
| 2-Chloro-4-ethoxy- | C, $C_6H_6$ | 80 | 3 |
| 3-Chloro-4-methoxy- | C | ca. 80 | 2 |
| | C, $C_6H_6$ | — | 3 |
| 2-Hydroxy-4-methyl- | E, $C_6H_6$ | Small | 22 |
| 2-Hydroxy-5-methyl- | C, $C_6H_6$ | 5 | 3 |
| 2-Methoxy-5-methyl- | E, $C_6H_6$ | 80 | 6 |
| | C, with or without benzene | ca. 80 | 2, 3 |
| 2-Ethoxy-5-methyl- | C, $C_6H_6$ | 80 | 3 |
| 4-Hydroxy-2-methyl- | E, $C_6H_6$ | 30 | 22 |
| | C, $C_6H_6$ | 45–50 | 3, 19 |
| | E, $C_6H_6$ (2-isopropyl-5-methylphenol) | Small | 20 |
| 4-Methoxy-2-methyl- | C | ca. 80 | 2, 3 |
| 4-Ethoxy-2-methyl- | C | 90 | 3 |
|  | C, $C_6H_6$ | 33 | 3 |

## TABLE II—*Continued*

### *A. Aldehydes Prepared from Monohydric Phenols or Their Ethers—Continued*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 4-Hydroxy-3-methyl- | C or E, $C_6H_6$ | 35–40 | 3, 6, 19 |
| | E, $C_6H_6$ (2-methyl-5-isopropylphenol) | Small | 20 |
| 4-Hydroxy-3-ethyl- | C, $C_6H_6$ | 65 | 3 |
| 4-Methoxy-3-ethyl- | C | 90 | 2, 3 |
| 4-Ethoxy-3-ethyl- | C | 80 | 2, 3 |
| 4-($\beta$-Bromoethoxy)-3-ethyl- | C, $C_6H_6$ | 50 | 3 |
| O—(CH$_2$)$_2$—O bis(phenyl-CH$_3$, CHO) | C, $C_6H_6$ | Almost quant. | 3 |
| O—(CH$_2$)$_3$—O bis(phenyl-CH$_3$, CHO) | C, $C_6H_6$ | ca. 33 | 3 |
| 2-Hydroxy-3,4-dimethyl- | C | Small | 18 |
| 2-Hydroxy-4,5-dimethyl- | C, $C_6H_6$ | — | 3 |
| 2-Hydroxy-6-isopropyl-3-methyl- | E, $C_6H_6$ | Small | 20 |
| 2-Hydroxy-3-isopropyl-6-methyl- | E, $C_6H_6$ | Small | 20 |
| 4-Hydroxy-2,3-dimethyl- | C, $C_6H_6$ | 60 | 3 |
| | C | — | 18 |
| | C, (2,3,4-trimethylphenol) | 52 | 18 |
| 4-Hydroxy-2,5-dimethyl- | C, $C_6H_6$ | 80 | 3 |
| 4-Hydroxy-5-isopropyl-2-methyl- | C or E, $C_6H_6$ | Almost quant. | 3, 6, 19, 20, 21 |
| 4-Hydroxy-2-isopropyl-5-methyl- | C, $C_6H_6$ | 30 | 3 |
| | E, $C_6H_6$ | Good | 20, 21 |
| O—(CH$_2$)$_2$—O bis(H$_3$C-phenyl-CH$_3$, CHO) | C, $C_6H_6$ | 66 | 3 |
| 4-Hydroxy-2,6-dimethyl- | C, $C_6H_6$ | Almost quant. | 3 |

TABLE II—*Continued*

*A.   Aldehydes Prepared from Monohydric Phenols or Their Ethers—Continued*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 4-Methoxy-2,6-dimethyl- | B, ether | — | 3 |
| 4-Ethoxy-2,6-dimethyl- | B, ether | Almost quant. | 3 |
| 4-Hydroxy-3,5-dimethyl- | C, $C_6H_6$ | — | 3 |
| | C, (2,6-dimethylanisole) | Main product | 3 |
| | C, $C_6H_6$ (2,4,6-trimethylanisole) | — | 18 |
| 4-Methoxy-3,5-dimethyl- | C | Poor* | 3 |
| 4-Ethoxy-3,5-dimethyl- | C | Moderate* | 3 |
| 2-Hydroxy-3,4,5-trimethyl- | C | Small | 18 |
| 3-Hydroxy-2,4,6-trimethyl- | C, (mesityl methyl ether) | — | 18 |

* This reaction involved some cleavage of the ether group.

## TABLE II—*Continued*

### B. *Aldehydes Prepared from Dihydric Phenols or Their Ethers*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 2,4-Dihydroxy- | A or F, ether | 56–97 | 3, 5, 11, 41, 43, 44 |
| | HCONH$_2$, POCl$_3$, ether | — | 50 |
| | C | Almost quant. | 19 |
| | | 69–82 | 8 |
| | BrCN, HCl, ZnCl$_2$, ether | — | 48 |
| 4-Hydroxy-2-methoxy- | C, C$_6$H$_6$ | 75 | 3 |
| | C | 80 | 19 |
| 2,4-Dimethoxy- | C or E, C$_6$H$_6$ | 80–almost quant. | 3, 6 |
| | C | ca. 80 | 2 |
| 2-Ethoxy-4-methoxy- and 4-ethoxy-2-methoxy- | B, ether | 26 and 32, resp. | 53 |
| 2-Methoxy-4-n-propoxy- and 4-methoxy-2-n-propoxy- | B, ether | 26 and 26, resp. | 53 |
| 4-Allyloxy-2-methoxy- and 2-allyloxy-4-methoxy- | B, ether | 32 and 16, resp. | 53 |
| 4-Benzyloxy-2-methoxy- and 2-benzyloxy-4-methoxy- | B, ether | Total yield, 40 | 53 |
| 4-Methoxy-2-phenoxy- and 2-methoxy-4-phenoxy- | C, C$_6$H$_6$ | Total yield, 40–45 | 54 |
| 2,5-Dimethoxy- | C, C$_6$H$_6$ | — | 3 |
| 2,5-Diethoxy- | C, C$_6$H$_6$ | — | 3 |
| 3,4-Dimethoxy- | C | ca. 80 | 2 |
| | C, C$_6$H$_6$ | 60 | 3 |
| 3,4-Diethoxy- | C, C$_6$H$_6$ | 75 | 3 |
|  | C, C$_6$H$_6$ | — | 3 |
| 4-Methoxy-3-phenoxy- and 4-(2'-methoxyphenoxy)- | C, C$_6$H$_6$ | 40–45 | 54 |

TABLE II—*Continued*

B.  *Aldehydes Prepared from Dihydric Phenols or Their Ethers—Continued*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 2,4-Dihydroxy-3-ethyl- | F | — | 37 |
| | A, ether | — | 46 |
| 2,4-Dihydroxy-3-formyl- | E, ether (2,4-dihydroxy-benzaldehyde) | 10 | 28 |
| 2,4-Dihydroxy-3-nitro- | E, ether | — | 26 |
| 3-Acetyl-2,4-dimethoxy- | C, ether | — | 25 |
| | E, ether | 80 | 32 |
| 2,4-Dihydroxy-5-methyl- | C, $C_6H_6$ | 90 | 3 |
| 2,4-Dihydroxy-5-ethyl- | C, $C_6H_6$ | Almost quant. | 3 |
| 5-Carbomethoxy-2,4-dihydroxy- | F, ether | 53 | 102 |
|  | B, ether | — | 51 |
| 2,4-Dimethoxy-5-methyl- | C, $C_6H_6$ | Almost quant. | 3 |
| 2,4-Dihydroxy-6-methyl- | A, ether | 93 | 3, 41 |
| | C | Quant. | 2 |
| | F, ether | 85 | 5 |
| 4-Hydroxy-2-methoxy-6-methyl- | C, $C_6H_6$ | — | 3 |
| 2,4-Dimethoxy-6-methyl- | C, $C_6H_6$ | 63 | 3 |
| 3-Acetyl-2,6-dihydroxy- | C, ether | — | 25 |
| | E, ether | 45 | 30 |
| 2,6-Dihydroxy-3-propionyl- | E, KCl, $CH_3CO_2C_2H_5$, ether | 64 | 33 |
| 3-*n*-Butyryl-2,6-dihydroxy- | E, KCl, $CH_3CO_2C_2H_5$, ether | 26 | 33 |
| 3-Benzoyl-2,6-dihydroxy- | E, KCl, $CH_3CO_2C_2H_5$, ether | 36 | 33 |
| | C, ether | — | 25 |
| 3-Carbomethoxy-2,6-dihydroxy- | C, ether | ca. 30 | 24 |
| | E, ether | 65 | 29 |
| 2,6-Dihydroxy-3-nitro- | E, ether | — | 26 |

## TABLE II—*Continued*

### B. *Aldehydes Prepared from Dihydric Phenols or Their Ethers—Continued*

| Substituent(s) in Benzaldehyde or Complete Structural Formula | Reagents | Yield, % | Reference |
|---|---|---|---|
| 4,5-Dimethoxy-2-methyl- | C, $C_6H_6$ | Almost quant. | 3 |
| 5-Ethoxy-4-methoxy-2-methyl- | C, $C_6H_6$ | — | 3 |
| Chloro-dihydroxy- | C, $C_6H_6$ | Almost quant. | 3 |
| 2,6-Dihydroxy-3,5-dimethyl- | F, ether | — | 39 |
| Acetyl-2,6-dihydroxy-3-phenyl- | E, KCl, $CH_3CO_2H_5$, ether | 51 | 33 |
| 3-Acetyl-5-ethyl-2,6-dihydroxy- | E, ether | 38 | 32 |
| 3-Carbomethoxy-5-ethyl-2,6-dihydroxy- | E, ether | 57 | 31 |
| 3-Formyl-2,6-dihydroxy-4-methyl- or 3-formyl-2,4-dihydroxy-6-methyl- | E, ether (2,4-dihydroxy-6-methylbenzaldehyde) | — | 27 |
| | E, KCl, ether (2,4-dihydroxy-6-methyl-benzaldehyde) | 11 | 28 |
| 3-Acetyl-2,6-dihydroxy-4-methyl- | C, ether | — | 25 |
| | E, ether | 26 | 32 |
| 3-Carbomethoxy-2,6-dihydroxy-4-methyl- or carbethoxy- analog | E, ether | Almost quant. | 34 |
| 3-Ethyl-4,6-dihydroxy-2-methyl- | F, ether | 51 | 39 |
| 2,5-Dihydroxy-3,4,6-trimethyl- | E, $C_6H_6$ | 47 | 103 |
| 3,5-Diethyl-2,6-dihydroxy-4-methyl- | F, ether | 52 | 39 |
| 5-Carbethoxy-2,4-dihydroxy-3,6-dimethyl- | E, ether | 62 | 34 |
|  | C, $C_6H_6$ | — | 3 |
|  | C, $C_6H_6$ | 50 | 3 |

TABLE II—*Continued*

*C. Aldehydes Prepared from Trihydric and Tetrahydric Phenols or Their Ethers*

| Substituent(s) in Benzaldehyde | Reagents | Yield, % | Reference |
|---|---|---|---|
| 2,3,4-Trihydroxy- | C, $C_6H_6$ | — | 19 |
| | B, ether | 50 | 3, 41 |
| | F, ether | 45 | 5 |
| 2,4-Dihydroxy-3-methoxy- | F, ether | 93 | 40 |
| 2,4,5-Trihydroxy- | B, ether | Almost quant. | 3, 41 |
| 2,5-Dihydroxy-4-methoxy- | A, $Zn(CN)_2$, ether | 39 | 35 |
| 2-Hydroxy-4,5-dimethoxy- | A, $Zn(CN)_2$, ether | 85 | 35 |
| 4-Ethoxy-2-hydroxy-5-methoxy- | A, $Zn(CN)_2$, ether | 86 | 35 |
| 5-Ethoxy-2-hydroxy-4-methoxy- | A, $Zn(CN)_2$, ether | 71 | 35 |
| 2,4,5-Trimethoxy- | C, $C_6H_6$ | Very good | 52 |
| 2,4,6-Trihydroxy- | A, ether | Good | 3, 41 |
| | BrCN, HCl, $ZnCl_2$, ether | — | 48 |
| 2,4-Dihydroxy-6-methoxy- or 2,6-dihydroxy-4-methoxy- | B, ether | — | 42 |
| 6-Ethoxy-2,4-dihydroxy- | A, ether | 97 | 45 |
| 3-Ethyl-2,4,6-trihydroxy- | A, ether | 78 | 47 |
| 3-Formyl-2,4,6-trihydroxy- | F, ether (phloroglucinol) | 2 | 38 |
| 3-Acetyl-2,4,6-trihydroxy- | E, ether | 32 | 28 |
| | | 51 | 32 |
| | C, ether | — | 25 |
| 2,6-Dihydroxy-4-methoxy-3-methyl- | E, ether | 72 | 28 |
| 4-Ethoxy-2,6-dihydroxy-3-methyl- | A, ether | 71 | 45 |
| 3-Formyl-2,4-dihydroxy-6-methoxy- | E, ether (2,4-dihydroxy-6-methoxybenzaldehyde) | 13 | 28 |
| 6-Hydroxy-2,4-dimethoxy-3-methyl- | A | 56 | 45 |
| 3-Formyl-2-hydroxy-4,6-dimethoxy- | E, ether (2-hydroxy-4,6-dimethoxybenzaldehyde) | 21 crude | 28 |
| 3-Acetyl-2-hydroxy-4,6-dimethoxy- | E, ether | 84 crude | 28 |

TABLE II—*Continued*

*C.  Aldehydes Prepared from Trihydric and Tetrahydric Phenols
or Their Ethers—Continued*

| Substituent(s) in Benzaldehyde | Reagents | Yield, % | Reference |
|---|---|---|---|
| 3-Formyl-2,4,6-trihydroxy-5-methyl- | A, ether (methylphloro-glucinol) | 7 | 38 |
| 5-Ethyl-3-formyl-2,4,6-trihydroxy- | A, ether (ethylphloro-glucinol) | 24 | 38 |
| 5-*i*-Amyl-3-formyl-2,4,6-trihydroxy- | A, ether (*i*-amylphloro-glucinol) | 15 | 38 |
| 3,5-Dicarbethoxy-2,4,6-trihydroxy- | E, KCl, ether | 85 crude | 28 |
| 2,4-Dihydroxy-3,6-dimethoxy- | F, ether (1,4-dimethoxy-2,6-dibenzoxybenzene) | — | 36 |
|  |  | 79 | 36 |

## TABLE III

### ALDEHYDES PREPARED FROM NAPHTHOLS AND THEIR ETHERS

| Product | Reagents | Yield, % | Reference |
|---|---|---|---|
| 2-Hydroxy-1-naphthaldehyde | B, ether | Quant. | 3, 4 |
|  | F, ether | 85 | 5 |
| 2-Methoxy-1-naphthaldehyde | E, $C_6H_6$ | Quant. | 6 |
|  | C, $C_6H_6$ | — | 3 |
| 2-Ethoxy-1-naphthaldehyde | C, $C_6H_6$ | — | 3 |
|  | A | 50 | 3 |
| 4-Hydroxy-1-naphthaldehyde | C, $C_6H_6$ | 34 | 3 |
|  | B, ether | Almost quant. | 4 |
|  | C | 90 | 19 |
|  | F, ether | 72 | 5 |
|  | F, KCl, ether | Good | 97 |
| 4-Ethoxy-1-naphthaldehyde | C, $C_6H_6$ | Almost quant. | 3 |
|  | C, $C_6H_6$ | ca. 75 | 3 |
| 2,3-Dihydroxy-1-naphthaldehyde | B, ether | 62 | 23 |
| 2,4-Dihydroxy-1-naphthaldehyde | B, ether | 42 | 23 |
| 2,5-Dihydroxy-1-naphthaldehyde | C, ether | 12–20 | 23 |
| 2,6-Dihydroxy-1-naphthaldehyde | B, ether | — | 3, 23 |
| 2,7-Dihydroxy-1-naphthaldehyde | B, ether | Almost quant. | 3 |
|  |  | 70 | 23 |
| 2,8-Dihydroxy-1-naphthaldehyde | B, ether | 38 | 23 |
| 3,4-Dihydroxy-1-naphthaldehyde | B, ether | 21 | 23 |
| 4,5-Dihydroxy-1-naphthaldehyde | B, ether | 24 | 23 |
| 4,6-Dihydroxy-1-naphthaldehyde | B, ether | 44 | 23 |
| 4,7-Dihydroxy-1-naphthaldehyde | C, ether | 64 | 23 |
| 4,8-Dihydroxy-1-naphthaldehyde | B, ether | — | 3, 23 |
| 1,4-Dihydroxy-2-naphthaldehyde | B, ether | 13 | 23 |
| 1,8-Dihydroxy-2-naphthaldehyde | B, ether | 1 | 23 |
| 3-Hydroxy-4-phenanthraldehyde | C, $C_6H_6$ | 70 | 104 |
|  | B, $C_6H_6$ | 10 | 104 |

## TABLE IV

### Aldehydes Prepared from Heterocyclic Compounds

| Product | Reagents | Yield, % | Reference |
|---|---|---|---|
| 2-Furfural | A, ether | 35 | 74 |
| 3-Methyl-2-furfural | A, ether | 56 | 105 |
| 5-Methyl-2-furfural | A, ether | 60 | 74 |
| 5-Ethyl-2-furfural | A, ether | 53 | 74 |
| 3,5-Dimethyl-2-furfural | A, ether | 12 | 105 |
|  | A, ether | Poor | 74 |
| 6-Hydroxybenzofuran-5-carboxaldehyde | B, ether | — | 51 |
| 6-Hydroxy-3-methylbenzofuran-5-carboxaldehyde | B, ether | — | 51 |
| 6-Hydroxy-3,4-dimethyl-benzofuran-5-carboxaldehyde | B, ether | — | 42 |
| 4,6-Dimethoxybenzofuran-7-carboxaldehyde | A, ether | 9 | 75 |
| 2-Carbethoxy-4,6-dimethoxy-benzofuran-7-carboxaldehyde | C, ether | 90 | 75 |
| | B, ether | 72 | 75 |
| Dibenzofuran-3-carboxaldehyde | C, CHCl₂CHCl₂ (o,o′-dihydroxy-biphenyl) | 81 | 55 |
| 2-Thiophenecarboxaldehyde | C | 8 | 64 |
| 1-Methylpyrrole-2-carbox-aldehyde | A, ether, CHCl₃ | 31 | 64 |
| 1-n-Butylpyrrole-2-carbox-aldehyde | A, ether | 61 | 64 |
| 1-i-Amylpyrrole-2-carbox-aldehyde | A, ether | 62 | 64 |
| 1-(2′-Furfuryl)-pyrrole-2-carboxaldehyde | A, ether | 16 | 64 |
| 5-Phenylpyrrole-2-carbox-aldehyde | F, ether | — | 72 |
| 5-Carbethoxypyrrole-2-carboxaldehyde | A, CHCl₃, ether | 28 | 64 |
| 3,4-Dimethylpyrrole-2-carboxaldehyde | A, ether | — | 106 |

TABLE IV—*Continued*

ALDEHYDES PREPARED FROM HETEROCYCLIC COMPOUNDS

| Product | Reagents | Yield, % | Reference |
| --- | --- | --- | --- |
| 3,5-Dimethylpyrrole-2-carboxaldehyde | A, CHCl$_3$ | 92 | 63 |
| | A, ether | Moderate | 63 |
| | HCONH$_2$, POCl$_3$ | — | 50 |
| 4-Bromo-3,5-dimethylpyrrole-2-carboxaldehyde | A, ether | 22 | 67 |
| 4-Ethyl-3,5-dimethylpyrrole-2-carboxaldehyde | A, CHCl$_3$ | 8 | 107 |
| 3-Carbethoxy-4,5-dimethyl-pyrrole-2-carboxaldehyde | A, ether | — | 109 |
| 4-Carbethoxy-3,5-dimethyl-pyrrole-2-carboxaldehyde | A, ether | 95 | 68 |
| 4-Acetyl-3,5-dimethylpyrrole-2-carboxaldehyde | A, ether or CHCl$_3$ | 65 | 62 |
| 5-Ethyl-3-methyl-4-propionyl-pyrrole-2-carboxaldehyde | A, ether | — | 109 |
| $\begin{array}{c} \text{H}_3\text{C} \quad\quad \text{CH}_3 \\ \text{OHC} \diagdown_\text{N}\diagup \text{CH=\!\!C(CN)CO}_2\text{CH}_3 \\ \text{H} \end{array}$ | A, CHCl$_3$, ether | 35 | 106 |
| 2,4,5-Trimethylpyrrole-3-carboxaldehyde | A, CHCl$_3$ | 67 | 63 |
| 5-Ethyl-2,4-dimethylpyrrole-3-carboxaldehyde | A, H$_2$O | 77 | 108 |
| 5-Carbethoxy-2,4-dimethyl-pyrrole-3-carboxaldehyde | A, ether | 85 | 69 |
| | HCONH$_2$, POCl$_3$, ether | — | 50 |
| 4-Carbethoxy-2,5-dimethyl-pyrrole-3-carboxaldehyde | A, ether | 77 | 68 |
| | HCONH$_2$, POCl$_3$, ether | — | 50 |
| 4-Carbethoxy-1,2,5-trimethyl-pyrrole-3-carboxaldehyde | A, ether | ca. 90 | 70 |
| 4-Carbethoxy-2,5-dimethyl-1-*p*-tolylpyrrole-3-carbox-aldehyde | A, ether | 80–90 | 70 |

TABLE IV—*Continued*

ALDEHYDES PREPARED FROM HETEROCYCLIC COMPOUNDS

| Product | Reagents | Yield, % | Reference |
|---|---|---|---|
| 4-Carbethoxy-1-phenyl-2,5-dimethylpyrrole-3-carbox-aldehyde | A, ether | 80–90 | 70 |
| 2-Methylindole-3-carbox-aldehyde | B, ether | 75 | 71 |
|  | F, ether | 19 | 73 |
|  | A, $CHCl_3$ | 90 | 66 |
|  | A, ether | 87 | 65 |
| 2-Carbethoxyindole-3-carboxaldehyde | A, $CHCl_3$ | — | 66 |
|  | F, ether | 83 | 73 |
| 2-Carbethoxy-7-methylindole-3-carboxaldehyde | F, ether | Good | 73 |
| 2-Hydroxy-4-methylthiazole-4-carboxaldehyde | A, ether, $CHCl_2CHCl_2$ | 25 | 76 |

## TABLE V

### Compounds That Did Not Yield Aldehydes

| Starting Material | Reference | Starting Material | Reference |
|---|---|---|---|
| Indene* | 7 | o-Methoxybiphenyl† | 55 |
| Nitrobenzene† | 55 | Pyrrole* | 64 |
| 2-Nitrophenol† | 55 | 2-Carboxypyrrole* | 64 |
| Benzoic Acid† | 55 | 2-Acetylpyrrole‡ | 64 |
| Cinnamic Acid† | 55 | Indole | 66 |
| Aniline† | 55 | Furfuryl methyl ether* | 74 |
| Diphenylamine† | 55 | Difurfuryl ether* | 74 |
| N,N-Dimethylaniline† | 55 | 2-Carbomethoxy-4,7-di- | |
| Azobenzene† | 55 | methoxy-6-hydroxy- | |
| Benzophenone† | 55 | benzofuran | 36 |
| Anthraquinone† | 55 | 4-Methylthiazole‡ | 76 |
| 1,5-Dihydroxyanthra- | | Benzofuran‡ | 74 |
| quinone† | 55 | Ethyl 2-furoate‡ | 74 |
| o-Hydroxybiphenyl† | 55 | 2-Acetylfuran‡ | 74 |

\* A polymeric solid was formed.

† The starting material was recovered or a polymeric solid was formed.

‡ The starting material was recovered.

# CHAPTER 3

# THE BAEYER-VILLIGER OXIDATION OF ALDEHYDES AND KETONES

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## CONTENTS

## INTRODUCTION

In 1899, Baeyer and Villiger[1] showed that the oxidation of the alicyclic ketones menthone, tetrahydrocarvone (I), and camphor with permonosulfuric acid led to the formation of lactones.



Further studies, using a variety of ketones or aldehydes and hydrogen peroxide or peracids in various media, have established that the oxidation represented by the following equation is of wide applicability.



This oxidation, the Baeyer-Villiger reaction, is the subject of this review. As the oxidation normally employs mild conditions, gives reasonable yields, and shows a high degree of selectivity, it has proved useful in a variety of both synthetic and degradative studies. Recent investigations have led to a better definition of favorable experimental conditions and have extended appreciably the scope of the reaction.

## MECHANISM OF THE REACTION

It is now generally agreed that the Baeyer-Villiger reaction is ionic in character. The favored reaction pattern was first outlined by Criegee in 1948.[2] It assumes that in the first instance addition of the peroxide to the carbonyl group yields a hydroxyperoxide (A). This dissociates to give an electron-deficient ion (B), which rearranges to C with cleavage of a carbon-carbon bond. The postulated carbonium ion C decomposes to the ester D in a normal way.

This mechanism has recently been the subject of detailed discussion by a number of authors.[3-9] The scheme accounts for the observation that in the oxidation of substituted acetophenones with perbenzoic acid the

[1] Baeyer and Villiger, Ber., 32, 3625 (1899).
[2] Criegee, Ann., 560, 127 (1948).

$$
\begin{array}{c}
R-\overset{\displaystyle \parallel}{\underset{O}{C}}-R' \\
+ \\
R''O_2H
\end{array}
\rightarrow
\left[
\begin{array}{ccc}
\underset{\text{HO}}{R-C-R'}\underset{\text{OOR}''}{} & \rightarrow & \underset{\text{HO}}{R-C-R'}\underset{O^+}{} \\
A & & B
\end{array}
\quad + \quad R''O^-
\right]
$$

$$
\downarrow
$$

$$
\begin{array}{ccc}
R-\overset{\displaystyle \parallel}{\underset{O}{C}}-OR' & \leftarrow &
\left[
R-\overset{+}{C}-OR' \ ,\ O-H
\right] \\
+ \ H^+ & & \\
D & & C
\end{array}
$$

rate-determining step is the acid-catalyzed addition of perbenzoic acid to the carbonyl group.[10] It recognizes that in certain cases hydroxyhydroperoxides have been isolated and converted to rearrangement products by heating alone.[11] It explains the fact that the migratory aptitude of aryl groups R, R' is normally proportional to their capacity for electron release.[4] There is a general similarity of the mechanism to those postulated, inter alia, for the Beckmann, pinacol-pinacolone, Hofmann,[12] Curtius,[12] Wagner-Meerwein, and acid-catalyzed hydroperoxide rearrangements.[13]

There is, however, no explicit evidence for an intermediate ion having six electrons and a positive charge on oxygen. The reaction sequence illustrated could take place without the occurrence of B as an intermediate if the steps from A to B and B to C were concerted.

In their discussion of the reaction Baeyer and Villiger[1] suggested that the simple "oxoxide" II participated as an intermediate in the oxidation of menthone to the lactone III. Until recently it appeared that this was

II                III

[3] Doering and Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).
[4] Doering and Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).
[5] Friess, *J. Am. Chem. Soc.*, **71**, 2571 (1949).
[6] Leffler, *J. Org. Chem.*, **16**, 1785 (1951).
[7] Turner, *J. Am. Chem. Soc.*, **72**, 879 (1950).
[8] Karrer and Haab, *Helv. Chim. Acta*, **32**, 950 (1949).
[9] Robertson and Waters, *J. Chem. Soc.*, **1948**, 1574.
[10] Friess and Soloway, *J. Am. Chem. Soc.*, **73**, 3968 (1951).
[11] Späth, Pailer, and Schmid, *Ber.*, **74**, 1552 (1941).
[12] Wallis and Lane, *Org. Reactions*, **3**, 267-306 (1946).
[13] Bartlett and Cotman, *J. Am. Chem. Soc.*, **72**, 3095 (1950).

supported by the observation that fluorenone peroxide, formulated as IV, rearranged to the lactone V on heating.[14] There is now evidence that fluorenone peroxide is a molecular complex of fluorenone and fluorenone hydroperoxide.[15] There is no evidence for the existence of stable "oxoxides."



IV                          V

It has been postulated that hydroxyl radicals may participate in the oxidation by interacting with the enolic form of the ketone.[16] It is unlikely that such a step is involved in the Baeyer-Villiger reaction, as many ketones that are not capable of enolization undergo the reaction. Also, in cases where it is established that attack on enols takes place, hydroxylation and not Baeyer-Villiger oxidation occurs.[17] It has been shown that unsaturated ketones may undergo Baeyer-Villiger oxidation without the olefinic bonds being attacked.[18] This would not be expected if free hydroxyl radicals were involved.[19]

### SCOPE OF THE REACTION

**Saturated Aliphatic Ketones.** There is only one example of the Baeyer-Villiger oxidation of a simple ketone of the type $RCH_2COCH_2R'$ to an ester. Methyl $n$-hexyl ketone gives $n$-hexyl acetate (VI) and its hydrolysis products on treatment with hydrogen peroxide in hydrofluoric acid.[20]

$$CH_3(CH_2)_5COCH_3 \xrightarrow[\text{HF}]{\text{H}_2\text{O}_2} CH_3(CH_2)_5OCOCH_3 + CH_3CO_2H + CH_3(CH_2)_5OH$$
$$\text{VI}$$

It has been shown that hydrogen peroxide in the presence of sulfuric acid may oxidize such ketones to ketone peroxides and $\alpha$-ketols.[21] Perbenzoic acid is said to have no significant action.[22] However, as peracids have not yet been used under the most favorable conditions there is no decisive evidence that they will not react with these simple ketones.

[14] Wittig and Pieper, *Ber.*, **73**, 295 (1940).
[15] Criegee, Schnorrenberg, and Becke, *Ann.*, **565**, 7 (1949).
[16] Böeseken, *Proc. Acad. Sci. Amsterdam*, **33**, 134 (1930) [*C. A.*, **24**, 3806 (1930)].
[17] Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).
[18] Karrer and Schneider, *Helv. Chim. Acta*, **30**, 859 (1947).
[19] Baxendale, Evans, and Park, *Trans. Faraday Soc.*, **42**, 155 (1946).
[20] Hudlecky, *Chem. Listy*, **45**, 380 (1952) [*C. A.*, **47**, 8012 (1953)].
[21] Pastureau, *Compt. rend.*, **140**, 1592 (1905); *Bull. soc. chim. France*, [4] **5**, 227 (1909).
[22] Baeyer and Villiger, *Ber.*, **33**, 1569 (1900).

When ketones with the carbonyl group attached to at least one secondary carbon atom are treated with peracids, esters are formed. The secondary grouping rearranges in preference to a primary one. In the series of alicyclic methyl ketones from methyl cyclobutyl ketone to methyl cycloheptyl ketone, oxidation with perbenzoic acid gives yields of acetates ranging from 58 to 78%.[23]



Steroid alcohols with the hydroxyl group attached to C–17 may be prepared conveniently by the Baeyer-Villiger oxidation of 20-keto steroids, such as pregnan-3α,12α-diol-20-one diacetate (VII).



This method was first applied using persulfuric acid,[24] but low yields were sometimes obtained,[25] and alternative procedures for the preparation of C–17 alcohols appeared preferable.[26]   However, it has been found that perbenzoic acid and monoperphthalic acid give higher yields, particularly when acid catalysts are present.[27, 28]   Also, unlike the alternative procedures, which involve ozonization or nitrosation, the reaction may be applied to unsaturated ketones such as pregnenolone.
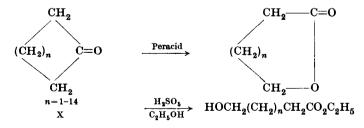
The oxidation has been used as the key step in a degradation of sarsapogenin (VIII) to pregnan-3,16,20-triol (IX).[29]

[23] Friess and Pinson, J. Am. Chem. Soc., 74, 1302 (1952).

[24] Marker and co-workers, J. Am. Chem. Soc., 62, 650, 2543, 2621, 3003 (1940).

[25] Koechlin and Reichstein, Helv. Chim. Acta, 27, 549 (1944).

[26] Fieser and Fieser, Natural Products Related to Phenanthrene, 3rd ed., p. 400, Reinhold Publishing Corp., 1949.

[27] Sarett, J. Am. Chem. Soc., 69, 2899 (1947).

[28] Wieland and Miescher, Helv. Chim. Acta, 32, 1768 (1949).

[29] Marker, Rohrmann, Crooks, Whittle, Jones, and Turner, J. Am. Chem. Soc., 62, 525 (1940).

$$CH_3$$
$$CHC(CH_2)_2CH(CH_3)CH_2OH$$

VIII

$$\begin{matrix} K_2S_2O_8 \\ CH_3CO_3H \\ H_2SO_4 \end{matrix}$$

CHOHCH₃ ... CHOCO(CH₂)₂CH(CH₃)CH₂OH

IX

The value of the Baeyer-Villiger reaction in this series is enhanced by decisive evidence that rearrangement occurs with retention of configuration.[7, 30, 31] This fact has been utilized in the preparation of 2-decalols and C-17 hydroxy steroids of definite configuration.[32]

**Alicyclic Ketones.** Alicyclic ketones ranging from cyclobutanone to cycloheptadecanone (X, $n = 14$)[5, 33, 34] have been oxidized under Baeyer-Villiger conditions. The reaction provides a convenient method for determining structure and for preparing relatively inaccessible lactones and hydroxy acids. When persulfuric acid or hydrogen peroxide-hydrofluoric acid[20] is used for the oxidation, polyesters of the hydroxy acids are obtained. The ethyl esters of the simple hydroxy acids are formed when ethanol is present.[35] Organic peracids give excellent yields of lactones.



$$\xrightarrow{\text{Peracid}}$$

$$n = 1-14$$

X

$$\xrightarrow[C_2H_5OH]{H_2SO_5} HOCH_2(CH_2)_nCH_2CO_2C_2H_5$$

[30] Mislow and Brenner, *J. Am. Chem. Soc.*, **75**, 2319 (1953).

[31] Gallagher and Kritschevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).

[32] Dauben and Hoerger, *J. Am. Chem. Soc.*, **73**, 1505 (1951).

[33] Friess and Frankenburg, *J. Am. Chem. Soc.*, **74**, 2679 (1952).

[34] Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

[35] Robinson and Smith, *J. Chem. Soc.*, **1937**, 371.

The oxidation has also been carried out under alkaline conditions but the yields recorded are low.[36-38]

In the steroid series the procedure has been applied to compounds having carbonyl groups at C-3,[28, 39-43] C-7,[44] and C-17.[45, 46] It has been demonstrated that conditions suitable for the oxidation of such compounds do not lead to any action on C-11[27] or C-12[40] carbonyl groups, although oxidation at C-12 does occur when a large excess of peracid is used. There is evidence that oxidation of the C-3 carbonyl group of cholestan-3-one and coprostan-3-one with persulfuric acid is inhibited by the presence of bromine in the 2- or 4-positions,[47] but that is not the case when excess perbenzoic acid is employed.[28] The oxidation of androstan-3-one (XI) gives the lactone XII.[43] 7-Ketocholestan-3β-ol (XIII) is oxidized to the lactone XIV.[44]



In the oxidation of 17-keto steroids there is some doubt as to which bond adjacent to the carbonyl group is broken, but the evidence available favors the formulation XV for the lactone.[46]

[36] Westerfield, J. Biol. Chem., **143**, 177 (1942).
[37] Fling, Minard, and Fox, J. Am. Chem. Soc., **69**, 2467 (1947).
[38] Heine and Jones, J. Am. Chem. Soc., **73**, 1361 (1951).
[39] Gardner and Godden, Biochem. J., **7**, 588 (1913).
[40] Burckhardt and Reichstein, Helv. Chim. Acta, **25**, 1434 (1942).
[41] Ruzicka, Prelog, and Meister, Helv. Chim. Acta, **28**, 1651 (1945).
[42] Salamon, Z. physiol. Chem., **272**, 61 (1941).
[43] Prelog, Ruzicka, Meister, and Wieland, Helv. Chim. Acta, **28**, 618, 1651 (1945).
[44] Heusser, Segrè, and Plattner, Helv. Chim. Acta, **31**, 1183 (1948).
[45] Jacobsen, J. Biol. Chem., **171**, 61 (1947).
[46] Picha, J. Am. Chem. Soc., **74**, 703 (1952).
[47] Marker, J. Am. Chem. Soc., **62**, 2543 (1940).

**Aromatic Ketones.** The oxidation of diaryl ketones with peracids regularly leads to the formation of esters or their hydrolysis products. Although this reaction is of little value as a preparative procedure, it does provide a convenient means of establishing the structures of polysubstituted benzophenones and alkyl aryl ketones.[48] The method is less drastic and more specific than the degradation procedures involving alkali fusion[49] or acid hydrolysis[50] that have been applied to natural products.

In the cleavage of unsymmetrical ketones the migrating group is normally the more electron-releasing one. Substituents in the aromatic nuclei influence the course of reaction in a manner similar to that observed in normal nucleophilic aromatic substitution. Thus treatment of p-methoxybenzophenone with peracetic acid gives benzoic acid and hydroquinone monomethyl ether, while cleavage of p-nitrobenzophenone gives p-nitrobenzoic acid and phenol exclusively.[4]



Insufficient information is available to make it possible to predict the course of reaction of alkyl aryl ketones with certainty. Treatment with peracids and hydrogen peroxide in acid or neutral solution may lead to the migration of either the aromatic or the aliphatic group.[10] Thus, with peracetic acid, acetophenone gives a mixture of esters,[4] and cyclohexyl phenyl ketone gives esters XVI and XVII in the approximate proportion of 5 : 1.[51]

$$C_6H_5COC_6H_{11} \rightarrow C_6H_5CO_2C_6H_{11} + C_6H_{11}CO_2C_6H_5$$
$$\qquad\qquad\qquad\quad \text{XVI} \qquad\qquad \text{XVII}$$

[48] Ballio and Almirante, *Ann. chim. Rome*, **41**, 421 (1951) [*C. A.*, **46**, 2518 (1952)].

[49] Kostanecki, *Ber.*, **39**, 4014 (1906).

[50] Graebe and Eichengrun, *Ann.*, **269**, 320 (1892).

[51] Friess and Farnham, *J. Am. Chem. Soc.*, **72**, 5518 (1950).

However, in one study of the oxidation of *meta-* and *para-*substituted acetophenones with perbenzoic acid, acetates alone were obtained in good yields.[10]

Alkyl aryl ketones containing hydroxyl groups in the *ortho* or *para* position are converted to polyhydric phenols by hydrogen peroxide in alkaline solution. The yields are poor.[52]

α,β-Unsaturated Ketones. The application of the Baeyer-Villiger reaction to this group of compounds should lead to reaction according to either A or B. Another possibility is preferential attack at the olefinic linkage leading to an α,β-epoxyketone (C).

$$RCH{=}CHOCOR'\quad A\quad \text{(cleavage toward C=C)}$$

$$RCH{=}CHCOR' \longrightarrow RCH{=}CHCO_2R'\quad B\quad \text{(cleavage away from C=C)}$$

$$\underset{RCH-CHCOR'}{\overset{O}{\diagup\ \diagdown}}\quad C$$

Although only a limited number of cases have been studied, examples of the formation of all three types of compound are available. The oxidation of benzalacetone (XVIII) with peracetic acid leads exclusively to the ester XIX.[53]

$$C_6H_5CH{=}CHCOCH_3 \rightarrow C_6H_5CH{=}CHOCOCH_3$$
$$\quad\quad\text{XVIII}\quad\quad\quad\quad\quad\quad\quad\text{XIX}$$

An α-phenyl-α,β-unsaturated ketone (XX) gives a mixture of epoxyketone and the ester XXI.[54]

$$RCH{=}C(C_6H_5)COCH_3 \rightarrow RCH{=}C(C_6H_5)CO_2CH_3 + \underset{RCH-C(C_6H_5)COCH_3}{\overset{O}{\diagup\ \diagdown}}$$
$$\quad\text{XX}\quad\quad\quad\quad\quad\text{XXI}$$

Oxidation of Δ16-20-ketosteroids with perbenzoic acid leads to preferential attack at the olefinic linkage. Pregna-5,6-dien-3β-ol-20-one acetate has been converted in this way to 16,17-epoxypregna-5-en-3β-ol-20-one acetate, a useful intermediate in the preparation of 17α-hydroxyprogesterone.[55]

When α,β-unsaturated ketones are treated with hydrogen peroxide in alkaline solution, epoxyketones are formed.[56-58] There is no evidence of the Baeyer-Villiger reaction occurring under these conditions.

[52] Dakin, *Am. Chem. J.*, **42**, 474 (1909).
[53] Böeseken and Soesman, *Rec. trav. chim.*, **52**, 874 (1933).
[54] Wenkert and Rubin, *Nature*, **170**, 708 (1952).
[55] Julian, Meyer, and Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).
[56] Kohler, Richtmeyer, and Hester, *J. Am. Chem. Soc.*, **53**, 213 (1931).
[57] Fieser and co-workers, *J. Am. Chem. Soc.*, **61**, 3216 (1939); **62**, 2866 (1940).
[58] Barkley, Farrar, Knowles, and Raffelson, *J. Am. Chem. Soc.*, **75**, 4110 (1953).

**Polycarbonyl Compounds.** $\alpha$-Diketones and $\alpha$-keto acids react readily with Baeyer-Villiger reagents.[59-64] In inert solvents anhydrides are formed,[65-67] while in alkaline or acidic media simple carboxylic acids are generally produced in good yields. It would appear from some comparisons of conditions that higher yields are obtained when the oxidations are conducted in alkaline solution.[68]

The oxidation has been used in establishing structure and in the preparation of relatively inaccessible carboxylic acids. As typical examples, 9,10-diketostearic acid is converted quantitatively to azelaic and pelargonic acid,[61]

$$CH_3(CH_2)_7COCO(CH_2)_7CO_2H + CH_3CO_3H \rightarrow$$
$$CH_3(CH_2)_7CO_2H + HO_2C(CH_2)_7CO_2H$$

and phenanthraquinone forms diphenic acid.[69, 70]

Unsaturated $\alpha$-diketones react in a similar manner. Treatment of 4-methyl-*o*-benzoquinone (XXII) with monoperphthalic acid gives $\beta$-methylmuconic anhydride XXIII.[65]



XXII                                    XXIII

Dicinnamylidenebiacetyl (XXIV) is oxidized to the anhydride XXV,[65]

$$\underset{\text{XXIV}}{C_6H_5(CH=CH)_2COCO(CH=CH)_2C_6H_5} \rightarrow$$

$$\underset{\text{XXV}}{C_6H_5(CH=CH)_2CO_2CO(CH=CH)_2C_6H_5}$$

[59] French and Sears, *J. Am. Chem. Soc.*, **70**, 1279 (1948).

[60] Holleman, *Rec. trav. chim.*, **23**, 170 (1904).

[61] Böeseken and Sloof, *Rec. trav. chim.*, **49**, 91 (1930).

[62] Reissert, *Ber.*, **30**, 1041 (1897).

[63] Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

[64] Bjorklund and Hatcher, *Trans. Roy. Soc. Can.*, (III), **44**, 25 (1950) [*C. A.*, **45**, 7951 (1951)].

[65] Karrer, Schwyzer, and Neuwirth, *Helv. Chim. Acta*, **31**, 1210 (1948).

[66] Karrer, Cochand, and Neuss, *Helv. Chim. Acta*, **29**, 1836 (1946).

[67] Karrer and Hohl, *Helv. Chim. Acta*, **32**, 1932 (1949).

[68] Meyer, *Helv. Chim. Acta*, **30**, 1976 (1947).

[69] Linstead and Walpole, *J. Chem. Soc.*, **1939**, 855.

[70] Perkin, *Proc. Chem. Soc.*, **23**, 166 (1907).

and puberulic acid (XXVI), presumably reacting through the keto form, is oxidized to aconitic acid (XXVII),[71]



$$OH \quad O$$
$$HO$$
$$OH$$
$$CO_2H$$

XXVI

$$CO_2H \quad CO_2H$$
$$CH \quad CH_2$$
$$C$$
$$CO_2H$$

XXVII

The oxidation of α-diketones normally involves cleavage between the carbonyl groups. However, it has been shown that the reaction of 2,2′,4,4′-tetranitrobenzil with alkaline hydrogen peroxide gives 2,4-dinitrophenol and not 2,4-dinitrobenzoic acid which is formed in an acidic medium.[72]

The oxidation of 1,3-diketones and β-keto acids with peracids does not follow the normal pattern of the Baeyer-Villiger reaction. Treatment of dibenzoylmethane derivatives with perbenzoic acid leads to the formation of the corresponding dibenzoylcarbinols.[73-76]

$$C_6H_5COCH_2COC_6H_5 \rightarrow C_6H_5COCH(OH)COC_6H_5$$

In an earlier study[77] it was found that an equimolecular amount of peracetic acid oxidized 1,3-diketones or β-keto acids to an acid and an alcohol. With excess peracetic acid a mixture of acids is formed. The first reaction was interpreted as involving migration of the group R′ lying between the carbonyl groups.

$$RCOCH(R')COR'' + CH_3CO_3H \rightarrow RR'CHOH + R''COCO_2H$$

$$R=CH_3, C_2H_5, C_5H_{11}; \quad R'=H, CH_3, C_6H_5CH_2; \quad R''=CH_3, OC_2H_5$$

When β-triketones such as 2-acetylindan-1,3-dione (XXVIII) are treated with hydrogen peroxide in diethyl ether there is preferential oxidation of the acyl side chain leading to the formation of an ester (XXIX).[78] In acidic or alkaline media, hydrogen peroxide oxidizes 2-acetylindan-1,3-dione to a mixture of acetic and phthalic acids.

[71] Corbett, Hassall, Johnson, and Todd, *Chemistry & Industry*, **1949**, 626.
[72] Blatt and Rytina, *J. Am. Chem. Soc.*, **72**, 403 (1950).
[73] Blatt and Hawkins, *J. Am. Chem. Soc.*, **58**, 81 (1936).
[74] Karrer, Albers-Schonberg, and Kebrle, *Helv. Chim. Acta*, **35**, 1498 (1952).
[75] Karrer, Kebrle, and Thakkar, *Helv. Chim. Acta*, **33**, 1711 (1950).
[76] Karrer, Kebrle, and Albers-Schonberg, *Helv. Chim. Acta*, **34**, 1014 (1951).
[77] Böeseken and Jacobs, *Rec. trav. chim.*, **55**, 804 (1936).
[78] Hassall, *J. Chem. Soc.*, **1948**, 50.

XXVIII



$H_2O_2$ / $H^+$ or $OH^-$          $H_2O_2$ \ $(C_2H_5)_2O$



$+ CH_3CO_2H$

XXIX



XXX

The Baeyer-Villiger reaction has been used in the elucidation of the structure of the natural product leptospermone (XXX).[79]

**Aldehydes.** Peracids generally convert both aliphatic and aromatic aldehydes to carboxylic acids.[80-83] Hydrogen peroxide reacts with aliphatic aldehydes in neutral media to give hydroxyhydroperoxides.[84, 11] It is significant, however, that such peroxides rearrange readily on heating to give a mixture of the corresponding carboxylic acid and the formate of the next lower alcohol. This behavior suggests that the oxidation of aldehydes with peroxides normally follows the Baeyer-Villiger pattern.

$$CH_3(CH_2)_5CHO + H_2O_2 \rightarrow CH_3(CH_2)_5CH(OH)O_2H \xrightarrow{\text{Heat}}$$
$$CH_3(CH_2)_5OCHO + CH_3(CH_2)_5CO_2H$$

The oxidation of citral (XXXI) to the lower aldehyde XXXII is an example of a similar course of reaction.[85]

[79] Briggs, Hassall, and Short, *J. Chem. Soc.*, **1945**, 706.

[80] D'Ans and Kneip, *Ber.*, **48**, 1136 (1915).

[81] Wieland and Richter, *Ann.* **495**, 284 (1932).

[82] Lyubarskii and Kagan, *J. Phys. Chem.*, **39**, 847 (1935).

[83] Ross, Gebhart, and Gerecht, *J. Am. Chem. Soc.*, **67**, 1275 (1945).

[84] Rieche, *Alkylperoxyde und Ozonide*, p. 36, Steinkopf, Leipzig, 1931.

[85] Prilejaeff, *Bull. soc. chim. France*, [4] **42**, 687 (1927).

$$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CHCHO \quad \xrightarrow{C_6H_5CO_3H}$$

XXXI

$$(CH_3)_2\overset{O}{\overbrace{C{-}{-}{-}CH}}(CH_2)_2C(CH_3){=}CHOCHO \;\rightarrow$$

$$(CH_3)_2\overset{O}{\overbrace{C{-}{-}{-}CH}}(CH_2)_2CH(CH_3)CHO \;+\; HCO_2H$$

XXXII

The oxidation of aliphatic aldehydes with hydrogen peroxide in acid and alkaline solution occasionally leads to the formation of hydrogen and hydrocarbons in addition to carboxylic acids.[86-89] Such reactions appear to involve a radical mechanism in addition to the normal ionic process.

Aromatic aldehydes have been oxidized with peroxides in a variety of media. In neutral or acid solution the action of peracids and hydrogen peroxide resembles that with alkyl aryl ketones under similar conditions.[90, 91] Benzaldehyde reacts with hydrogen peroxide in ether to give benzoic acid and only traces of phenol.[92] In aldehydes with electron-releasing substituents such as alkoxyl, hydroxyl, and amino[93] in the *ortho* or *para* positions, the formyl group tends to migrate, producing formates or phenols according to the conditions employed.

The oxidation of aromatic aldehydes in alkaline solution was first studied by Dakin,[52] who indicated that the reaction occurred only when hydroxyl groups were present in the *ortho* or *para* positions. In such cases good yields of polyhydric phenols are obtained through the replacement of formyl by hydroxyl groupings. As Table VI indicates, the Dakin procedure has been applied successfully to a variety of substituted phenolic aldehydes. It has been used for the synthesis of phenols such as morphol[94] (XXIII) which are not readily accessible by other means.

HO   OH   XXXIII

[86] Payne and Lemon, *J. Am. Chem. Soc.*, **63**, 226 (1941).

[87] Fry and Payne, *J. Am. Chem. Soc.*, **53**, 1973 (1931).

[88] Bezzi, *Gazz. chim. ital.*, **63**, 345 (1933).

[89] Bach and Generosov, *Ber.*, **55**, 3560 (1922).

[90] Böeseken and Greup, *Rec. trav. chim.*, **58**, 528 (1939).

[91] Wacek and Bezard, *Ber.*, **74**, 845 (1941).

[92] Späth, Pailer, and Gergeley, *Ber.*, **73**, 935 (1940).

[93] Bamberger, *Ber.*, **36**, 2042 (1903).

[94] Barger, *J. Chem. Soc.*, **113**, 218 (1918).

It is of interest that the aldehydes XXXIV and XXXV, in which there is a nitro group *ortho* to the hydroxyl, are not attacked, while the aldehydes XXXVI and XXXVII react in the normal way.[52]  The inhibiting effect



|         |        |        |         |
|---------|--------|--------|---------|
| XXXIV   | XXXV   | XXXVI  | XXXVII  |

is probably due to intramolecular hydrogen bonding. It has been suggested that the Dakin oxidation follows a different course from the Baeyer-Villiger reaction,[95] but this has not been substantiated.[91]

**Side Reactions.**    Structural elements other than carbonyl groups may be attacked under the conditions used for the Baeyer-Villiger reaction. The susceptibility of olefinic linkages to oxidation by peracids is well known.[96] Aromatic hydrocarbons, such as mesitylene,[97] methylcholanthrene, and benzpyrene,[98] which are particularly sensitive to attack by electrophilic reagents, may be oxidized preferentially. The reactivity of other groupings was reviewed in 1949.[99]

There are some isolated examples of oxidation of the normal products of reaction by Baeyer-Villiger reagents. For example, phenols may react with peracids,[100-102] and demethylation of aromatic ethers may occur.[102] Catechols and hydroquinones may be oxidized through quinones[70] to carboxylic acids.[103, 104]  However, if a large excess of reagent is avoided it is generally possible to obtain substantial yields of phenols from Baeyer-Villiger reactions.[48]  In one example of the Dakin reaction, the oxidation of 2-hydroxy-5-methoxybenzaldehyde, the formation of an unidentified, abnormal product has been reported.[105]

There is evidence, in two cases, of oxidation of secondary alcohols by the action of excess peracetic acid. When 1,3-diketones react with excess of this peracid, a ketone is obtained in the place of the secondary alcohol produced with an equimolar amount.[77]  The steroid hydroxy ketone

[95] Wacek and Eppinger, *Ber.*, **73**, 644 (1940).

[96] Swern, *Org. Reactions*, **7**, 378 (1953).

[97] Friess and Miller, *J. Am. Chem. Soc.*, **72**, 2611 (1950).

[98] Eckhardt, *Ber.*, **73**, 13 (1940).

[99] Swern, *Chem. Revs.*, **45**, 1 (1949).

[100] Böeseken and Engelberts, *Proc. Acad. Sci. Amsterdam*, **34**, 1292 (1931) [*C. A.*, **26**, 2970 (1932)].

[101] Fernholz, *Chem. Ber.*, **84**, 110 (1951).

[102] Friess, Soloway, Morse, and Ingersoll, *J. Am. Chem. Soc.*, **74**, 1305 (1952).

[103] Wacek and Fiedler, *Monatsh.*, **80**, 170 (1949).

[104] Weitz, Schobbert, and Seibert, *Ber.*, **68**, 1163 (1935).

[105] Rosenblatt and Rosenthal, *J. Am. Chem. Soc.*, **75**, 4607 (1953).

XXXVIII is oxidized with excess peracetic acid to the diketone XL and to XLI in addition to the normal product XXXIX.[28] The rearrangement of the double bond from the $\beta,\gamma$ to the $\alpha,\beta$ position resembles that observed in other oxidations of $\Delta^5$-3-hydroxy steroids.[106] The oxidation of *allo*-



COCH₃

HO    XXXVIII

Br₂, excessC₆H₅CO₃H, 2n

OCOCH₃        COCH₃        OCOCH₃

HO    XXXIX    O    XL    O    XLI

pregnan-20-one with persulfuric acid gives, in addition to the normal product androstan-17$\beta$-ol, a significant yield of *allo*pregnan-21-ol-20-one.[47] This arises from the action of the peracid on the enolic form of the C–20 keto group.[18]

## SELECTION OF EXPERIMENTAL CONDITIONS

**Peroxides.**  Hydrogen peroxide, permono- and perdi-sulfuric acid, peracetic acid, perbenzoic acid, and monoperphthalic acid have all been used as reagents in the Baeyer-Villiger reaction.  Although there is little precise information on the relative efficiencies of these peroxides, there is sufficient evidence to permit some general conclusions.

Hydrogen peroxide in dilute acid or in neutral solution sometimes converts carbonyl compounds to normal Baeyer-Villiger oxidation products, but more frequently hydroxyhydroperoxides and their condensation products are formed.  The simple and condensed peroxides XLII–XLV are produced by the action of hydrogen peroxide in diethyl ether on cyclohexanone.[107, 15]  Similar compounds are formed from aliphatic aldehydes[11]

[106] Djerassi, *Org. Reactions*, **6**, 212 (1951).
[107] Milas and Panagiotakos, *J. Am. Chem. Soc.*, **61**, 2430 (1939).

and fluorenone[14] under these conditions, although normal Baeyer-Villiger oxidation products are obtained without difficulty when peracids are used.



From these observations and the fact that the peroxides of cyclohexanone, fluorenone, and aliphatic aldehydes are converted by heating or by treatment with acids to the Baeyer-Villiger reaction products, it appears that hydrogen peroxide in ether or dilute acid is less effective since it does not favor the dissociation and rearrangement steps postulated for the Baeyer-Villiger reaction (p. 75).

In the related rearrangement of esters of the hydroperoxide formed from decahydronaphthalene (XLVI),[2] the dissociation step is influenced both by hydrogen-ion catalysis and by the nature of the acyl group RCO. The



acetate and benzoate rearrange readily on warming. The $p$-nitrobenzoate rearranges more readily than the benzoate, and all attempts to prepare the trichloracetate lead to the rearrangement product. By analogy, it may be expected that the Baeyer-Villiger reaction is favored by conditions leading to the formation of peroxide esters of relatively strong acids. There is little evidence on this point, but the fact that the organic peracids

have proved more generally useful than hydrogen peroxide is in agreement with this view. The more limited applicability of the persulfuric acids is to be attributed in part to the fact that their use in aqueous solution favors the formation of peroxides. Though persulfuric acids and their salts have been used successfully in non-aqueous media, organic peracids are more convenient.

Hydrogen peroxide in alkaline solution differs in reactivity from other Baeyer-Villiger reagents. In the Dakin reaction and the cleavage of $\alpha$-diketones, alkaline conditions are to be preferred. With $\alpha,\beta$-unsaturated ketones, however, these conditions lead exclusively to epoxyketones rather than Baeyer-Villiger reaction products. There has been a useful study of the kinetic course of the oxidation of mesityl oxide and of ethylideneacetone by hydrogen peroxide in an alkaline medium.[107a] It would be desirable to obtain further information on the course and kinetics of reactions involving alkaline hydrogen peroxide.

*In all peroxide oxidations of new compounds the possibility of reactions occurring with explosive violence must be considered.* Trial experiments should be carried out using small quantities of material. Large excesses of reagents should be avoided, and if significant quantities of unconsumed peroxides remain at the end of the reaction they should be destroyed by reducing agents such as sodium bisulfite or ferrous sulfate before isolation of the products is attempted.

It is generally possible to follow the course of the Baeyer-Villiger reaction by estimating the active oxygen at intervals. Blank determinations should be carried out, particularly when long reaction times are involved, as the reagents may decompose under the conditions of the experiment. Information on conditions influencing the stability of peroxides is included in reviews on the general properties of hydrogen peroxide[108-110] and peracids.[99] In addition to temperature and $pH$, such factors as intensity of illumination, solvent polarity, and trace-metal impurities may play an important role.[111-113]

The following procedures are convenient for the preparation of the peroxides used in the Baeyer-Villiger reaction. Further information on methods of preparation of organic peracids is included in reviews,[96,99,114,] and also procedures for the analysis of peroxides have been summarized.[115]

[107a] Bunton and Minkoff, *J. Chem. Soc.*, **1949**, 665.

[108] Shanley and Greenspan, *Ind. Eng. Chem.*, **39**, 1536 (1947).

[109] Medard, *Compt. rend.*, **222**, 1491 (1946).

[110] Schumb, *Ind. Eng. Chem.*, **41**, 992 (1949).

[111] Böeseken and Blumberger, *Rec. trav. chim.*, **44**, 90 (1925).

[112] Calderwood and Lane, *J. Phys. Chem.*, **45**, 108 (1941).

[113] Meerwein, Ogait, Prang, and Serini, *J. prakt. Chem.*, **113**, 9 (1926).

[114] Criegee, *Fortschr. chem. Forsch.*, **1**, 508 (1950).

[115] Swern, *Org. Reactions*, **7**, 392 (1953).

**Hydrogen Peroxide.** In alkaline solution, hydrogen peroxide decomposes relatively rapidly and is particularly sensitive to impurities.[108] These facts must be taken into consideration to ensure that a sufficient excess of reagent is available. The majority of Baeyer-Villiger oxidations involving alkaline hydrogen peroxide employ dilute sodium hydroxide in slight excess of the amount required to keep the reactants and products in solution. Ammonium hydroxide[52] and potassium bicarbonate[68] have also been used, and pyridine has been added in reactions in which the sodium salt of the starting material is relatively insoluble in water.[79, 94]

Hydrogen peroxide in ether is conveniently prepared by shaking 50 g. of 30% hydrogen peroxide with five 100-ml. portions of diethyl ether. The ether extract is dried first with sodium sulfate and then with calcium chloride. It contains approximately 2% hydrogen peroxide. A more concentrated solution (4–6%) may be obtained by evaporation of ether from the dilute solution at room temperature under reduced pressure.[92] The concentration of hydrogen peroxide may be determined iodimetrically. Ceric sulfate is used for the titration of hydrogen peroxide when aldehydes are present.[86, 116]

Hydrogen peroxide has also been used in acetone,[95] in formic acid-chloroform,[117] and in acetic acid.[118] It has been shown in the oxidation of androsterone acetate that a dilute solution of peracetic acid in glacial acetic acid is preferable to hydrogen peroxide in acetic acid.[119]

**Persulfuric Acid.** Baeyer and Villiger's "dry reagent" is prepared by mixing 10 g. of potassium persulfate with 11 g. of concentrated sulfuric acid in a mortar, adding 30 g. of potassium sulfate, and grinding the mixture to a fine powder.[1] This reagent is stable in the absence of moisture.

Oxidations have been carried out using suspensions of the dry reagent[1] or solutions of persulfuric acid in glacial acetic acid,[47] in concentrated and dilute sulfuric acid, in petroleum ether,[34] and in ethanol-sulfuric acid.[35] Methods for the estimation of permono- and perdi-sulfuric acid have been described.[120, 121]

**Perbenzoic Acid.** Details of the preparation of this acid are given in *Organic Reactions.*[122] A product of 99.7% purity is prepared by vacuum sublimation of crude material at 40°.[123]

[116] Willard and Young, *J. Am. Chem. Soc.,* **55,** 3260 (1933).
[117] Prelog and Kocor, *Helv. Chim. Acta,* **31,** 237 (1948).
[118] Mannich, *Ber.,* **74,** 1007 (1941).
[119] Levy and Jacobsen, *J. Biol. Chem.,* **171,** 71 (1947).
[120] D'Ans and Friederich, *Ber.,* **43,** 1880 (1910).
[121] Rius and Zulueta, *Anales real soc. españ. fis. y quim.,* **44B,** 923 (1948) [*C. A.,* **43,** 2121 (1949)].
[122] Swern, *Org. Reactions,* **7,** 394 (1953).
[123] D'Ans, Mattner, and Busse, *Angew. Chem.,* **65,** 57 (1953).

In Baeyer-Villiger oxidations perbenzoic acid is normally used in chloroform solution. Such solutions are fairly stable in the dark at low temperatures. A chloroform solution obtained from a typical *Organic Syntheses* preparation[124] (approximately 8% perbenzoic acid) lost 5.3% active oxygen on standing for twenty-one days at 2° in the dark. In five days at room temperature there was a loss of 38%.

**Monoperphthalic Acid.** The preparation of this acid is discussed in *Organic Reactions*.[125] Monoperphthalic acid is somewhat more stable than perbenzoic acid. At 10–15° it decomposes at the rate of approximately 2% per day. The insolubility of phthalic acid in chloroform is often an advantage in working up reaction mixtures; this property has been utilized where the products of peracid oxidation are decomposed by water.[126]

**Peracetic Acid.** Details of the preparation and estimation of this acid are given in *Organic Reactions*.[115, 125] Solutions containing approximately 40% peracetic acid are commercially available.[127]

Peracetic acid loses active oxygen relatively slowly. A 45% solution retains 75% of its activity after seven weeks at room temperature.[128] More stable solutions may be obtained by the addition of stabilizers or by distillation under reduced pressure.[129] The latter procedure is hazardous and it is not recommended. Peracetic acid explodes violently on heating at 110°.[130]

**Solvents and Catalysts.** As the tables indicate, Baeyer-Villiger reactions may be carried out using a variety of solvents. Many common organic solvents are inert under the conditions of reaction. The choice of a particular solvent is determined largely by the solubilities of the reactants and products. Rate studies have shown that reaction is favored by polar solvents,[23] but this fact has apparently not played an important role in the choice of media.

There is ample evidence that the oxidations are susceptible to catalysis by acids.[4, 5, 91, 131] Solutions containing high concentrations of sulfuric acid and hydrofluoric acid[20] may be employed with advantage. Perchloric acid,[6] sulfuric acid,[4, 29] and toluenesulfonic acid[28, 91, 119] have been used in catalytic amounts in oxidations involving peracetic and perbenzoic acids, and this may have a marked effect in reducing reaction times. As

[124] Braun, *Org. Syntheses*, Coll. Vol. 1, 431, 2nd ed., 1941.

[125] Swern, *Org. Reactions*, **7**, 395 (1953).

[126] Böhme, *Ber.*, **70**, 379 (1937).

[127] Buffalo Electrochemical Co., *Peracetic Acid Data Sheet*, I (1947).

[128] Greenspan, *J. Am. Chem. Soc.*, **68**, 907 (1946).

[129] Böeseken, Cohen, and Kip, *Rec. trav. chim.*, **55**, 815 (1936).

[130] D'Ans and Frey, *Ber.*, **45**, 1845 (1912).

[131] Dilthey, Quint, and Dierichs, *J. prakt. Chem.*, [2] **151**, 25 (1938).

a typical example, benzophenone is oxidized by peracetic acid in glacial acetic acid to phenyl acetate in 44% yield in one hundred and ninety-two hours, but when concentrated sulfuric acid (25%) is added 82% conversion occurs in thirty minutes.[4]

The oxidation of carbonyl compounds with peroxides in the presence of metal catalysts[132, 133] does not appear to follow the same course as the Baeyer-Villiger reaction.

**Temperature and Time.** A wide range of temperatures has been employed in Baeyer-Villiger oxidations. In some earlier applications of the reaction the carbonyl compounds were heated under reflux with peroxides in relatively high-boiling solvents. This is not to be recommended as a general procedure. Temperatures above 45° normally lead to excessive decomposition of peroxides, and under such conditions a large excess of reagent is required to replace the loss and may lead to oxidation of the normal products. There are exceptional cases involving the oxidation of aromatic aldehydes and ketones in which higher reaction temperatures have been used successfully, but in these oxidations short reaction times are involved.[48, 94] The reaction is normally carried out at a temperature of 10-40°. Lower temperatures may lead to excessively long reaction times and to reduced yields.[35]

When oxidations are carried out with organic peracids or hydrogen peroxide in neutral media, reaction times may vary from several hours to several weeks, according to the molecular species. As a typical example, oxidation of 3-ketosteroids with perbenzoic acid in chloroform is complete in sixteen hours at 16°, although under the same conditions 20-ketosteroids require seven to ten days for cleavage.[27]

In general, relatively short reaction times are required when oxidations are carried out in alkaline or strongly acidic media.

### EXPERIMENTAL PROCEDURES

The following examples illustrate typical procedures for the Baeyer-Villiger reaction.

**Catechol (Dakin modification using hydrogen peroxide and sodium hydroxide solution).** Detailed directions for the preparation of catechol from salicylaldehyde (69–73%)[134] and for a similar preparation of 3-methoxycatechol[135] are given in *Organic Syntheses.*

**3,4-Dihydroxyphenanthrene (Dakin modification using alkaline hydrogen peroxide and pyridine).**[94] A solution of 1.11 g. of 3-hydroxy-4-formylphenanthrene (5 millimoles) in 10 ml. of pyridine is placed in a

[132] Treibs, *Ber.*, **72**, 1194 (1939).
[133] Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).
[134] Dakin, *Org. Syntheses, Coll. Vol.* 1, 149, 2nd ed., 1941.
[135] Surrey, *Org. Syntheses*, **26**, 90 (1946).

25-ml. flask equipped with a dropping funnel and an exit tube. After the air has been displaced with hydrogen, 0.55 ml. of 30.8% hydrogen peroxide (50 millimoles) and 0.45 ml. of 12.5 $N$ potassium hydroxide (5.6 millimoles) are added. The addition of potassium hydroxide causes a considerable rise in temperature. The solution is allowed to boil for a few seconds. It is then cooled, acidified with excess hydrochloric acid, and extracted with diethyl ether. The ether solution is washed with dilute hydrochloric acid to remove pyridine, dried, and evaporated. The crude residue (1.05 g.) is recrystallized from benzene and petroleum ether to yield 0.83 g. (80%) of pure 3,4-dihydroxyphenanthrene, m.p. 142–3°.

**Phenyl $p$-Nitrobenzoate (Oxidation of a diaryl ketone using peracetic acid with sulfuric acid as catalyst).**[4]   A solution of 4.54 g. of $p$-nitrobenzophenone (20 millimoles) in a mixture of 50 ml. of glacial acetic acid and 30 ml. of concentrated sulfuric acid is treated with external cooling with 8 ml. of 40% peracetic acid (40 millimoles). After thirty minutes at room temperature the mixture is neutralized with sodium carbonate solution and extracted with diethyl ether. The dried ether extract yields on evaporation 4.6 g. (95%) of phenyl $p$-nitrobenzoate, m.p. 128–130°.

**Etiocholan-3α,12α,17β-triol (Oxidation of a 20-keto steroid using perbenzoic acid with sulfuric acid as catalyst).**[28]   Ninety grams of 3α,12α-diacetoxypregnan-20-one (0.22 mole) and 44 ml. of a 10% solution of sulfuric acid in glacial acetic acid are added separately with external cooling to 440 ml. of a chloroform solution containing 68.6 g. (0.49 mole) of perbenzoic acid. The solution is allowed to stand in the dark at room temperature for ten days. After dilution with diethyl ether, the mixture is washed in turn with water, dilute sodium carbonate solution, and water. The organic layer is dried, and the solvent is evaporated. The residue is saponified by boiling for one hour with a solution of 60 g. of sodium hydroxide in 850 ml. of methanol and 50 ml. of water. After much of the methanol has been removed by distillation under reduced pressure, sufficient ether is added to keep the product in solution. The ether solution is washed with water until neutral, dried, concentrated to 600 ml., and cooled to −10° to precipitate 46.3 g. of etiocholan-3α,12α,17β-triol, m.p. 231–232°. Treatment of the concentrated mother liquor with Girard's Reagent P furnishes an additional 0.73 g. of the triol and 6.17 g. of starting material. The total yield of triol is 71%.

**Diphenic Acid (Cleavage of an α-diketone using alkaline hydrogen peroxide).**[136]   A suspension of 1 g. of 9,10-phenanthraquinone (4.8 millimoles) in 20 ml. of 5% aqueous sodium hydroxide is mixed with 2.5 ml. of 27% hydrogen peroxide (19 millimoles) and allowed to stand with

[136] C. H. Hassall, unpublished observations.

occasional stirring at 30°. Further additions of 2.5 ml. of 27% hydrogen peroxide are made after six hours and again after an additional twelve hours. After a total of forty-eight hours the mixture is filtered from a trace of insoluble material and acidified. The precipitate of pure diphenic acid formed is collected on a filter, washed with water, and dried; the yield is 1.09 g. (94%), m.p., 229–230°.*

**2-Acetoxyindan-1,3-dione (Selective oxidation of a triketo-methane derivative using hydrogen peroxide in ether).**[78] A solution containing 1 g. of 2-acetylindan-1,3-dione (5.3 millimoles) in 80 ml. of diethyl ether is treated with 12 ml. (18 millimoles) of 5% hydrogen peroxide in ether and allowed to stand in a closed flask at 15°. After twenty-one days the ether is evaporated. The residue is triturated with 3 ml. of water, filtered, and extracted with chloroform. The chloroform extract is filtered from a trace of phthalic acid and evaporated. The residue is crystallized twice from ethyl acetate-petroleum ether (40–60°) to give 0.70 g. (64%) of 2-acetoxyindan-1,3-dione, m.p. 96°.

**Lactone $C_{21}H_{32}O_4$ from Isoandrosterone Acetate (Oxidation of a 17-keto steroid using peracetic acid with $p$-toluenesulfonic acid as catalyst).**[119] A solution of 0.274 g. of isoandrosterone acetate (0.83 millimole) in 2 ml. of glacial acetic acid, 5 ml. of 9.5% peracetic acid in acetic acid (6.75 millimoles), and 25 mg. of $p$-toluenesulfonic acid are mixed and allowed to stand for twenty-three hours at 35° in the dark. The mixture is then treated with a large excess of water which precipitates 0.252 g. (88%) of the crude lactone, m.p. 156–158.5°. This product is converted by one crystallization from benzene-neohexane to the pure lactone, $C_{21}H_{32}O_4$, m.p. 158–159.5°.

### TABULAR SURVEY OF THE BAEYER-VILLIGER REACTION

The following tables list all examples of the Baeyer-Villiger reaction noted in a survey of the literature available through December, 1953. The tables also include examples of oxidations of carbonyl compounds under Baeyer-Villiger conditions that have not led to the formation of the normal products of the Baeyer-Villiger reaction. The carbonyl compounds in the tables are arranged in order of increasing size of the empirical formulas. When several references are cited for a particular case, all refer to reactions under similar conditions. The yield quoted is that given in the first reference. The names of several steroids have been altered to conform with accepted conventions.

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*Yields of 70%[69] and 50%[137] are obtained when hydrogen peroxide-acetic acid and chromic acid, respectively, are used as oxidizing agents.

[137] Charrier and Beretta, *Gazz. chim. ital.*, **54**, 765 (1924).

TABLE 1

BAEYER-VILLIGER OXIDATION OF SATURATED ALIPHATIC KETONES

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_3H_6O$ | Acetone | $H_2SO_5$ | Acetone peroxide | 65 | 138, 139, 140, 64 |
| | | $H_2O_2$, $H_2SO_4$ | Acetone peroxide, hydroxyacetone | — | 21 |
| $C_4H_8O$ | Butanone | $H_2O_2$, $H_2SO_4$ | Butanone peroxide, 3-hydroxybutanone | — | 21, 140 |
| $C_5H_8O$ | Acetylcyclopropane | $C_6H_5CO_3H$ | No reaction | — | 141, 23 |
| $C_5H_{10}O$ | 3-Pentanone | $H_2O_2$, $H_2SO_4$ | 3-Pentanone peroxide, 2-hydroxypentan-3-one | — | 21 |
| $C_6H_{10}O$ | Acetylcyclobutane | $C_6H_5CO_3H$ | Cyclobutyl acetate | 58 | 23 |
| $C_7H_{12}O$ | Acetylcyclopentane | $C_6H_5CO_3H$ | Cyclopentyl acetate | 61 | 23 |
| $C_8H_{14}O$ | cis-1-Acetyl-2-methylcyclopentane | $C_6H_5CO_3H$ | cis-2-Methylcyclopentyl acetate | 66 | 7 |
| | trans-1-Acetyl-2-methylcyclopentane | $C_6H_5CO_3H$ | trans-2-Methylcyclopentyl acetate | 64 | 7 |
| | Acetylcyclohexane | $C_6H_5CO_3H$ | Cyclohexyl acetate | 67 | 141, 23 |
| $C_8H_{16}O$ | 2-Octanone | $H_2O_2$, HF | n-Hexyl acetate | 51 | 20 |
| $C_9H_{16}O$ | cis-1-Acetyl-2-methylcyclohexane | $C_6H_5CO_3H$ | cis-2-Methylcyclohexyl acetate | 63 | 7 |
| | trans-1-Acetyl-2-methylcyclohexane | $C_6H_5CO_3H$ | trans-2-Methylcyclohexyl acetate | 55 | 7 |
| | Acetylcycloheptane | $C_6H_5CO_3H$ | Cycloheptyl acetate | 69 | 23 |
| $C_{10}H_{12}O$ | 3-Phenylbutan-2-one | $C_6H_5CO_3H$ | Phenylmethylcarbinyl acetate | 87 | 30 |
| $C_{12}H_{20}O$ | cis-cis-Acetyldecahydronaphthalene | $C_6H_5CO_3H$ | cis-cis-Decahydro-2-naphthol | 65 | 32 |
| $C_{21}H_{34}O$ | Allopregnan-20-one | $K_2S_2O_8$, $CH_3CO_2H$, $H_2SO_4$ | Allopregnan-21-ol-21-one acetate, androstan-17β-ol† | 30–35 | 47 |
| $C_{21}H_{24}O_2$ | Δ5-Pregnen-3β-ol-20-one | $C_6H_5CO_3H$ | Testosterone acetate, progesterone, Δ5-androsten-3β,17β-diol 17-monoacetate | — | 28 |
| $C_{23}H_{34}O_3$ | Δ5-Pregnen-3β-ol-20-one acetate | Monoperphthalic acid, $CHCl_3$‡ | Δ5-Androsten-3β,17β-diol | 63 | 28, 47 |
| | | $C_6H_5CO_3H$, $CHCl_3$, $H_2SO_4$ | Δ5-Androsten-3β,17β-diol | 60 | 28 |
| $C_{23}H_{34}O_4$ | Pregnan-3α-ol-11,20-dione acetate | $C_6H_5CO_3H$ | Etiocholan-3α,17β-diol-11-one diacetate† | 85 | 27 |
| $C_{23}H_{36}O_3$ | Allopregnan-3β-ol-20-one acetate | $C_6H_5CO_3H$ | Androstan-3β,17β-diol† | 3 | 40 |
| | Allopregnan-3α-ol-20-one acetate | $K_2S_2O_8$, $CH_3CO_2H$, $H_2SO_4$ | Androstan-3α,17β-diol diacetate† | — | 142 |
| | Pregnan-3α-ol-20-one acetate | $C_6H_5CO_3H$ | Etiocholan-3α,17β-diol diacetate | 52 | 31, 47 |
| | 17-Isopregnan-3α-ol-20-one acetate | $C_6H_5CO_3H$ | Etiocholan-3α,17α-diol diacetate | 53 | 31 |
| $C_{25}H_{38}O_5$ | Pregnan-3α,12α-diol-20-one diacetate | $C_6H_5CO_3H$, $CHCl_3$, $H_2SO_4$§ | Etiocholan-3α,12α,17β-triol | 77 | 28, 27 |
| $C_{28}H_{36}O_4$ | Pregnan-3α-ol-11,20-dione benzoate | $C_6H_5CO_3H$ | Etiocholan-3α,17β-diol-11-one 3-benzoate 17-acetate† | 18 | 27 |

*Note:* References 138-164 are listed on p. 106.

* Where $CH_3CO_3H$ is indicated, acetic acid is always present; where $H_2SO_5$ is shown, sulfuric acid is present; where $C_6H_5CO_3H$ is shown, chloroform is present.

† The configuration at C–17 assigned by the author has been changed. The correction follows from the unequivocal evidence, only available after the completion of the investigation, that the Baeyer-Villiger reaction occurs with retention of configuration.

‡ A catalytic amount of $p$-$CH_3C_6H_4SO_3H$ was added.

§ Catalytic amount.

## TABLE II

### BAEYER-VILLIGER OXIDATION OF ALICYCLIC KETONES

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_4H_8O$ | Cyclobutanone | $C_6H_5CO_3H$ | Butyrolactone | 70 | 33 |
| $C_5H_8O$ | Cyclopentanone | $H_2O_2$, NaOH | 5-Hydroxyvaleric acid lactone | 18 | 37, 36 |
| | | $H_2O_2$, HF | Polyesters of 5-hydroxyvaleric acid | 86–89 | 20 |
| | | $K_2S_2O_8$, $H_2SO_4$, $C_2H_5OH$ | Ethyl 5-hydroxyvalerate | 70 | 143, 35 |
| | | $C_6H_5CO_3H$ | 5-Hydroxyvaleric acid lactone | 78 | 5 |
| | | $H_2O_2$, $HNO_3$ | Cyclopentanone peroxide | — | 64 |
| $C_6H_{10}O$ | Cyclohexanone | $H_2O_2$, HF | 6-Hydroxycaproic acid lactone, polyesters of 6-hydroxycaproic acid | 8, 81 | 20 |
| | | $H_2SO_5$ | Polyesters of 6-hydroxycaproic acid | — | 140, 69 |
| | | $K_2S_2O_8$, $H_2SO_4$, $C_2H_5OH$ | Ethyl 6-hydroxycaproate | 39–45 | 35 |
| | | $H_2O_2$, NaOH | 6-Hydroxycaproic acid | 19 | 38 |
| | | $C_6H_5CO_3H$ | 6-Hydroxycaproic acid lactone | 71 | 5, 144 |
| $C_7H_{12}O$ | 3-Methylcyclohexanone | $K_2S_2O_8$, $H_2SO_4$ | 3-Methylcyclohexanone peroxide | — | 138 |
| | Cycloheptanone | $K_2S_2O_8$, $H_2SO_4$, $C_2H_5OH$ | Ethyl 7-hydroxyheptanoate | 47 | 35, 138 |
| | | $C_6H_5CO_3H$ | 7-Hydroxyenanthic acid lactone | 97 | 5 |
| $C_8H_{14}O$ | Cycloöctanone | $C_6H_5CO_3H$ | 8-Hydroxycaprylic acid lactone | 61 | 33 |
| $C_{10}H_{10}O$ | α-Tetralone | $H_2SO_5$ | 4-Hydroxy-4-(o-hydroxyphenyl)-butyric acid lactone | — | 145 |
| $C_{10}H_{16}O$ | Camphor | $H_2SO_5$ | Campholide | 22 | 1 |
| $C_{10}H_{18}O$ | p-Menthan-2-one | $H_2SO_5$ | 6-Hydroxy-3-isopropylenanthic acid lactone | 40 | 1 |
| | Menthone | $H_2SO_5$ | 6-Hydroxy-3,7-dimethylcaprylic acid lactone | 82 | 140, 138 |
| $C_{13}H_{24}O$ | Cyclotridecanone | $H_2SO_5$ | 13-Hydroxytridecanoic acid lactone | 41 | 34 |
| $C_{14}H_{26}O$ | Cyclotetradecanone | $H_2SO_5$ | 14-Hydroxymyristic acid lactone | 35 | 34 |
| $C_{15}H_{28}O$ | Cyclopentadecanone (Exaltone) | $H_2SO_5$, $CH_3CO_2H$ | 15-Hydroxypentadecanoic acid lactone | 47 | 34 |
| | | $H_2O_2$, $H_2SO_4$ | Cyclopentadecanone peroxide, 15-hydroxypentadecanoic acid lactone | — | 146 |
| $C_{16}H_{30}O$ | Cyclohexadecanone | $H_2SO_5$ | 16-Hydroxypalmitic acid lactone | 30 | 34 |
| $C_{17}H_{32}O$ | Cycloheptadecanone | $H_2SO_5$ | 17-Hydroxymargaric acid lactone | 53 | 34 |

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{18}H_{22}O_3$ | Estrone | $H_2O_2$, NaOH | Lactone $C_{18}H_{22}O_3$ | 42 | 36 |
| $C_{19}H_{30}O$ | Androstan-3-one | $C_6H_5CO_3H$ | Lactone $C_{19}H_{30}O_2$ | 10 | 43 |



H

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{19}H_{30}O_2$ | Androstan-3-one-17β-ol | $C_6H_5CO_3H$ | Lactone $C_{19}H_{30}O_3$ | 32 | 43 |
| $C_{20}H_{20}O_3$ | Equilenin acetate | $CH_3CO_3H$† | Acetate of lactone $C_{16}H_{16}O_3$ | 55 | 147 |
| | (±)-Isoequilenin acetate | $CH_3CO_3H$† | Acetate of lactone $C_{16}H_{16}O_3$ | 69 | 46 |



$CH_3CO_2$

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{20}H_{24}O_3$ | Estrone acetate | $H_2O_2$, $CH_3CO_2H$ | Acetate of lactone $C_{18}H_{22}O_3$ | 57–63 | 45 |
| $C_{21}H_{32}O_2$ | Δ5-Pregnen-3β-ol-20-one | $Br_2 \rightarrow C_6H_5CO_3H \rightarrow Zn$ | Lactone $C_{21}H_{30}O_3$ | — | 63 |
| $C_{21}H_{32}O_3$ | Androsterone acetate | $CH_3CO_3H$† | Acetate of lactone $C_{19}H_{30}O_3$ | 79 | 119 |
| | Isoandrosterone acetate | $CH_3CO_3H$† | Acetate of lactone $C_{19}H_{30}O_3$ | 89–92 | 119 |
| $C_{23}H_{33}BrO_4$ | 4-Bromo-12α-acetoxypregnan-3,20-dione | $C_6H_5CO_3H \rightarrow$ pyridine | Lactone $C_{23}H_{32}O_5$, lactone $C_{21}H_{30}O_5$ | — | 63 |
| $C_{25}H_{36}O_3$ | Δ11-3-Ketocholenic acid methyl ester | $C_6H_5CO_3H$ | Lactone $C_{25}H_{33}O_5$ | 68 | 148 |
| $C_{25}H_{40}O_3$ | 3-Ketocholanic acid methyl ester | $C_6H_5CO_3H$ | Lactone $C_{25}H_{40}O_4$ | 68 | 40 |
| $C_{26}H_{34}O_3$ | Etiocholan-17β-ol-3-one benzoate | $C_6H_5CO_3H$ | Lactone $C_{26}H_{34}O_4$ | 95 | 41 |
| $C_{27}H_{42}O_5$ | 3-Keto-12β-acetoxycholanic acid methyl ester | $C_6H_5CO_3H$ | Lactone $C_{27}H_{42}O_6$ | — | 40 |
| $C_{27}H_{44}O_2$ | Cholestandione | $(NH_4)_2S_2O_8$, $H_2SO_4$ | Lactone $C_{27}H_{44}O_4$ (?) | 46 | 149 |
| $C_{27}H_{46}O$ | Coprostan-3-one | $C_6H_5CO_3H$ | Lactone $C_{27}H_{46}O_2$ | 80 | 40, 39 |
| | Cholestan-3-one | $C_6H_5CO_3H$ | Lactone $C_{27}H_{46}O_2$ | 59 | 40 |
| $C_{27}H_{46}O_2$ | 7-Ketocholestan-3β-ol | $C_6H_5CO_3H$ | Lactone $C_{27}H_{46}O_3$ | 87 | 44 |

$C_8H_{17}$



HO

| | Carbonyl Compound | Reagent* | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{29}H_{48}O_3$ | 7-Ketocholestan-3β-ol acetate (benzoate or pivalate) | $C_6H_5CO_3H$ | Derivatives of lactone $C_{27}H_{46}O_3$ | 86–100 | 44 |

*Note:* References 138–164 are listed on p. 106.

* Where $CH_3CO_3H$ is indicated, acetic acid is always present; where $H_2SO_5$ is shown, sulfuric acid is present; where $C_6H_5CO_3H$ is shown, chloroform is present.

† A catalytic amount of $p$-$CH_3C_6H_4SO_3H$ was added.

# TABLE III

BAEYER-VILLIGER OXIDATION OF ALIPHATIC AROMATIC, ALICYCLIC AROMATIC, AROMATIC, AND HETEROCYCLIC KETONES

| | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_8H_7ClO$ | p-Chloroacetophenone | $C_6H_5CO_3H$ | p-Chlorophenyl acetate | 57 | 10 |
| $C_8H_8O$ | Acetophenone | $CH_3CO_3H$ | Phenyl acetate | 33 | 48, 4 |
| | | $C_6H_5CO_3H$ | Phenyl acetate | 63 | 141 |
| $C_8H_8O_2$ | o-Hydroxyacetophenone | $H_2O_2, NH_3$ | Catechol | — | 52 |
| | m-Hydroxyacetophenone | $H_2O_2, NH_3$ | No reaction | — | 52 |
| | p-Hydroxyacetophenone | $H_2O_2, NH_3$ | Hydroquinone | 40–50 | 52 |
| $C_8H_8O_3$ | 2,4-Dihydroxyacetophenone | $H_2O_2, NH_3$ | Hydroxyhydroquinone | — | 52 |
| | 2,5-Dihydroxyacetophenone | $H_2O_2, NH_3$ | Hydroxyhydroquinone | — | 52 |
| $C_9H_7O_2Cl$ | 2-Methoxy-4-chloroacetophenone | $CH_3CO_3H\,^\bullet$ | 4-Methoxy-4-chlorophenyl acetate, | 50 | 48 |
| | | | 5-chloroguaiacol | Trace | |
| $C_9H_{10}O$ | p-Methylacetophenone | $C_6H_5CO_3H$ | p-Cresyl acetate | 73 | 10 |
| | Propiophenone | $C_6H_5CO_3H$ | Phenyl propionate | 73 | 141 |
| $C_9H_{10}O_2$ | p-Hydroxypropiophenone | $H_2O_2, NH_3$ | Hydroquinone | — | 52 |
| | o-Methoxyacetophenone | $CH_3CO_3H$ | Guaiacol | — | 48 |
| | m-Methoxyacetophenone | $C_6H_5CO_3H$ | m-Methoxyphenyl acetate | 52 | 10 |
| | p-Methoxyacetophenone | $C_6H_5CO_3H$ | p-Methoxyphenyl acetate | 66 | 10, 48, 90, 91 |
| $C_9H_{10}O_3$ | 2-Hydroxy-4-methoxyacetophenone | $H_2O_2, NH_3$ | 1,2-Dihydroxy-4-methoxybenzene | — | 150 |
| $C_{10}H_{10}O_3$ | p-Acetoxyacetophenone | $C_6H_5CO_3H$ | Hydroquinone diacetate | 80 | 10 |
| $C_{10}H_{11}NO_2$ | p-Acetaminoacetophenone | $C_6H_5CO_3H$ | p-Acetaminophenyl acetate | 80 | 71 |
| $C_{10}H_{12}O_3$ | 2,4-Dimethoxyacetophenone | $CH_3CO_3H$ | 2,4-Dimethoxyphenol | — | 48 |
| | 2,5-Dimethoxyacetophenone | $CH_3CO_3H\,^\bullet$ | 2,5-Dimethoxyphenyl acetate | — | 48 |
| | 2,4-Dihydroxy-3,5-dimethylacetophenone (clavatol) | $H_2O_2, NaOH$ | 3-Hydroxy-2,6-dimethylbenzoquinone | 30 | 151 |

| | | | | | |
|---|---|---|---|---|---|
| $C_{11}H_{14}O$ | Acetomesitylene | $C_6H_5CO_3H$ | No product isolated | — | 97 |
| $C_{11}H_{14}O_4$ | 2,4,5-Trimethoxyacetophenone | $CH_3CO_3H\,^\bullet$ | 2,4,5-Trimethoxyphenyl acetate | — | 48 |
| | 2,3,4-Trimethoxyacetophenone | $CH_3CO_3H\,^\bullet$ | 2,3,4-Trimethoxyphenyl acetate | — | 48 |
| $C_{12}H_{14}O_4$ | 1,3-Diacetyl-4,6-dimethoxybenzene | $CH_3CO_3H\,^\bullet$ | 4,6-Dimethoxyresorcinol diacetate | — | 48 |
| $C_{13}H_8O$ | Fluorenone | $CH_3CO_3H, H_2SO_4$ | 2'-Hydroxybiphenyl-2-carboxylic acid lactone | — | 4 |
| | | $H_2O_2, (C_2H_5)_2O$ | Fluorenone peroxide, | 53 | 14 |
| | | | 2'-Hydroxybiphenyl-2-carboxylic acid lactone | 20 | |
| | | $H_2SO_5, (CH_3CO)_2O$ | 2'-Hydroxybiphenyl-2-carboxylic acid lactone | 96 | 14 |
| $C_{13}H_8N_2O_5$ | o,p'-Dinitrobenzophenone | $CH_3CO_3H, H_2SO_4$ | No reaction | — | 4 |
| | p,p'-Dinitrobenzophenone | $CH_3CO_3H, H_2SO_4$ | p-Nitrophenol, p-nitrobenzoic acid | 54, 82 | 4 |
| $C_{13}H_9BrO$ | p-Bromobenzophenone | $CH_3CO_3H, H_2SO_4$ | Phenyl p-bromobenzoate | 60 | 4 |
| $C_{13}H_9ClO$ | p-Chlorobenzophenone | $CH_3CO_2H, H_2SO_4$ | Phenyl p-chlorobenzoate, phenol, p-chloro-benzoic acid | 77 | 4 |
| $C_{13}H_9NO_3$ | p-Nitrobenzophenone | $CH_3CO_3H, H_2SO_4$ | Phenyl p-nitrobenzoate | 95 | 4, 131 |
| $C_{13}H_{10}O$ | Benzophenone | $H_2SO_5, (CH_3CO)_2O$ | Phenyl benzoate | Quantitative | 140, 4 |
| $C_{13}H_{12}NO$ | p-Aminobenzophenone | $CH_3CO_3H, H_2SO_4$ | Phenyl p-aminobenzoate | 38 | 4 |
| $C_{13}H_{16}O$ | Phenyl cyclohexyl ketone | $CH_3CO_3H$ | Cyclohexanol, benzoic acid, phenol, hexa-hydrobenzoic acid | 6, 33, 5, 5 | 4 |
| | | $C_6H_5CO_3H$ | Cyclohexyl benzoate, phenyl hexahydrobenzoate | 71, 15 | 51 |
| $C_{13}H_{16}O_5$ | 1,3-Diacetyl-4,5,6-trimethoxybenzene | $CH_3CO_3H\,^\bullet$ | 4,5,6-Trimethoxyresorcinol diacetate | — | 48 |
| | 1,3-Diacetyl-2,4,5-trimethoxybenzene | $CH_3CO_3H\,^\bullet$ | 2,4,5-Trimethoxyresorcinol diacetate | — | 48 |
| $C_{14}H_{11}NO_2$ | 3-Phenyldioxindole | $H_2O_2, NaOH$ | o-Aminobenzophenone | — | 152 |
| $C_{14}H_{12}O$ | p-Methylbenzophenone | $CH_3CO_3H$ | p-Cresyl benzoate | 14 | 4 |
| $C_{14}H_{12}O_2$ | p-Methoxybenzophenone | $CH_3CO_3H, H_2SO_4$ | p-Methoxyphenyl benzoate | 96 | 4 |
| $C_{15}H_{13}NO_2$ | 3-(o-Tolyl)dioxindole | $H_2O_2, NaOH$ | o-Methyl-o'-aminobenzophenone | — | 152 |
| | 3-(m-Tolyl)dioxindole | $H_2O_2, NaOH$ | m-Toluic acid | — | 152 |
| | 3-(p-Tolyl)dioxindole | $H_2O_2, NaOH$ | p-Methyl-o'-aminobenzophenone | — | 152 |
| $C_{15}H_{13}NO_3$ | 3-(o-Methoxyphenyl)dioxindole | $H_2O_2, NaOH$ | o-Methoxy-o'-aminobenzophenone | — | 152 |
| | 3-(m-Methoxyphenyl)dioxindole | $H_2O_2, NaOH$ | m-Toluic acid | — | 152 |
| | 3-(p-Methoxyphenyl)dioxindole | $H_2O_2, NaOH$ | p-Methoxy-o'-aminobenzophenone | — | 152 |
| $C_{16}H_{16}O$ | Phenyl mesityl ketone | $CH_3CO_3H, H_2SO_4$ | Benzoic acid | 10 | 4 |

*Note:* References 138-164 are listed on p. 106.

\* A catalytic amount of p-$CH_3C_6H_4SO_3H$ was added.

# TABLE IV

## BAEYER-VILLIGER OXIDATION OF $\alpha,\beta$-UNSATURATED CARBONYL COMPOUNDS

| | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_6H_4O_2$ | Benzoqninone | $H_2O_2$, NaOH | *cis*-Ethylene oxide dicarboxylic acid | 53-6 | 104 |
| $C_6H_{10}O$ | Mesityl oxide | $H_2O_2$, NaOH | 1,1-Dimethyl-2-acetylethylene oxide | — | 63 |
| $C_{10}H_6O_2$ | $\alpha$-Naphthoquinone | $H_2O_2$, NaOH | $\alpha$-Naphthoquinone oxide | — | 104 |
| $C_{10}H_{10}O$ | Benzalacetone | $CH_3CO_3H$ | Enol acetate of phenylacetaldehyde | 38 | 153, 53 |
| | | $H_2O_2$, NaOH | 1-Phenyl-2-acetylethylene oxide | 70 | 63, 56, 153 |
| $C_{10}H_{16}O$ | Citral | $C_6H_5CO_3H$ | Enol formate of 2,6-dimethyl-5,6-epoxyheptaldehyde | — | 85 |
| $C_{11}H_8O_2$ | 2-Methyl-1,4-naphthoquinone | $H_2O_2$, NaOH | 2-Methyl-1,4-naphthoquinone oxide | 67 | 57 |
| $C_{11}H_{12}O$ | Methyl $\beta$-methylstyryl ketone | $CH_3CO_3H$ | Enol acetate of methyl benzyl ketone | — | 77 |
| | Ethyl styryl ketone | $CH_3CO_3H$ | Enol propionate of phenylacetaldehyde | 69 | 77 |
| $C_{15}H_{12}O$ | Benzalacetophenone | $H_2O_2$, NaOH | 1-Phenyl-2-benzoylethylene oxide | 89 | 63 |
| $C_{20}H_{24}O_3$ | ($\pm$)-11-Keto-$\Delta^{16}$-21-norprogesterone | $H_2O_2$, NaOH | ($\pm$)-11-Keto-16$\alpha$,17$\alpha$-epoxy-21-norprogesterone | — | 58 |
| $C_{21}H_{14}O$ | 10-Benzalanthrone | $H_2O_2$, NaOH | 10,11-Epoxybenzalanthrone | — | 63 |
| $C_{21}H_{30}O_2$ | Progesterone | $K_2S_2O_8$, $CH_3CO_2H$, $H_2SO_4$ | Lactone $C_{20}H_{30}O_3$ | 43 | 42, 27 |
| $C_{23}H_{15}NO$ | 2-Dimethylamino-10-benzalanthrone | $H_2O_2$, NaOH | 2-Dimethylaminoanthraquinone, benzoic acid | — | 63 |
| $C_{23}H_{32}O_3$ | Pregna-5,16-dien-3$\beta$-ol-20-one acetate | $C_6H_5CO_3H$ | 16,17-Epoxypregna-5-en-3$\beta$-ol-20-one acetate | 56 | 55 |
| $C_{25}H_{36}O_3$ | Methyl $\Delta^{4,11}$-3-ketocholadienate | $C_6H_5CO_3H$ | Methyl $\Delta^4$-11,12-epoxy-3-ketocholenate | 21 | 148 |
| $C_{27}H_{44}O$ | $\Delta^4$-Cholesten-3-one | $K_2S_2O_8$, $CH_3CO_2H$, $H_2SO_4$ | Lactone $C_{26}H_{44}O_2$ | 68 | 42 |

*Note:* References 138-164 are listed on p. 106.

## TABLE V

### BAEYER-VILLIGER OXIDATION OF POLYCARBONYL COMPOUNDS

| | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| | *α-Diketones* | | | | |
| $C_4H_6O_2$ | Biacetyl | Perphthalic acid | Acetic acid | 24 | 67, 61 |
| $C_5H_8O_3$ | Ethyl pyruvate | Perphthalic acid | Monoethyl ester of acetic-carbonic anhydride | — | 8 |
| $C_6Br_4O_2$ | Tetrabromo-o-benzoquinone | $C_6H_5CO_3H$ | 2,3,5-Tribromo-4-hydroxymuconolactone | 30 | 17, 154 |
| $C_6Cl_4O_2$ | Tetrachloro-o-benzoquinone | Perphthalic acid | 2,3,5-Trichloro-4-hydroxymuconolactone, | 4 | 155 |
| | | | tetrachloromuconic acid | 31 | |
| $C_6H_4O_2$ | o-Benzoquinone | $CH_3CO_3H$ | *cis,cis*-Muconic acid | — | 61 |
| $C_6H_{10}O_2$ | Hexane-3,4-dione | Perphthalic acid | Propionic acid | — | 67 |
| $C_7H_6O_2$ | p-Methyl-o-benzoquinone | Perphthalic acid | β-Methylmuconic anhydride | 22 | 65 |
| $C_8H_6O_3$ | Ethyl phenylglyoxalate | Perphthalic acid | Monoethyl ester of benzoic-carbonic anhydride | — | 8 |
| $C_9H_7NO_5$ | o-Nitrophenylpyruvic acid | $H_2O_2$, NaOH | o-Nitrophenylacetic acid | 92 | 62 |
| $C_9H_{12}O_3$ | 1,2,4-Triketo-3,3,5,5-tetramethylcyclopentane | $H_2O_2$ | Tetramethylacetonedicarboxylic acid | Quantitative | 79 |
| $C_{10}H_6O_2$ | β-Naphthoquinone | $CH_3CO_3H$ | o-Carboxy*allo*cinnamic acid | 76 | 61 |
| | | $C_6H_5CO_3H$ | o-Carboxy*allo*cinnamic anhydride | 22 | 17 |
| | | $CH_3CO_3H$ | Phthalic acid | — | 156 |
| $C_{11}H_8O_3$ | 6-Methoxy-1,2-naphthoquinone | Perphthalic acid | 2-Carboxy-5-methoxycinnamic acid | 23 | 59 |
| | | $CH_3CO_3H$ | 2-Carboxy-5-methoxycinnamic acid | 31 | 59 |
| $C_{12}H_5BrO_6$ | β-Bromolaccain | $H_2O_2$, $CH_3CO_2H$ | 4-Ketocarboxy-2,3,5-tricarboxyphenol (?) | — | 157 |
| $C_{12}H_6O_2$ | Acenaphthenequinone | $CH_3CO_3H$ | Naphthalic acid | — | 156 |
| $C_{14}H_6N_4O_{10}$ | 2,2′,4,4′-Tetranitrobenzil | $H_2O_2$, NaOH | 2,4-Dinitrophenol | 53 | 72 |
| | | $H_2O_2$, $CH_3CO_2H$ | 2,4-Dinitrobenzoic acid | Quantitative | 72 |
| $C_{14}H_6O_9$ | 9,10-Phenanthraquinone | $H_2O_2$, NaOH | Diphenic acid | 94 | 136, 156 |
| $C_{14}H_{10}O_2$ | Benzil | $C_2H_5O_2H$, NaOH | Benzoic acid, ethyl benzoate | 70 | 158 |
| | | $CH_3CO_3H$ | Benzoic acid | 95 | 61, 70 |
| | | $H_2O_2$, $CH_2CO_2H$, $HClO_4$ | Benzoic acid | 83 | 6 |
| $C_{15}H_{12}O_2$ | 1,3-Diphenylpropane-1,2-dione | $C_2H_5O_2H$, NaOH | Benzoic acid, phenylacetic acid | 61 | 158 |
| $C_{15}H_{12}O_3$ | p-Methoxybenzil | $C_2H_5O_2H$, NaOH | Anisic acid, benzoic acid | 79 | 158 |
| $C_{16}H_{14}O_4$ | Anisil | $C_2H_5O_2H$, NaOH | Anisic acid, ethyl anisoate | 70 | 158 |
| | | $H_2O_2$, $CH_3CO_2H$ | Anisic acid | 66 | 6 |
| $C_{16}H_{14}O_2$ | Dicinnamylidenebiacetyl | Perphthalic acid | 2-Styrylacrylic anhydride | 26 | 66 |

*Note:* References 138–164 are listed on p. 106.

## TABLE V—*Continued*

### BAEYER-VILLIGER OXIDATION OF POLYCARBONYL COMPOUNDS

| | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| | *α-Diketones—Continued* | | | | |
| $C_{18}H_{18}O_2$ | 1-Mesityl-3-phenylpropane-1,2-dione | $C_2H_5O_2H$, NaOH | Phenylacetic acid, β-isodurylic acid | 70 | 158 |
| $C_{18}H_{32}O_4$ | 9,10-Diketostearic acid | $CH_3CO_2H$ | Pelargonic acid, azelaic acid | 90–95 | 61 |
| $C_{21}H_{32}O_5$ | 3β,14-Dihydroxy-14-iso-20-keto-17-iso-pregnan-21-carboxylic acid | $H_2O_2$, $CH_3CO_2H$ | 3β,14-Dihydroxy-14-iso-17-isoetiocholanic acid | 27 | 68 |
| | | $H_2O_2$, $KHCO_3$ | 3β,14-Dihydroxy-14-iso-17-isoetiocholanic acid | 90 | 68 |
| $C_{23}H_{32}O_5$ | 3β-Acetoxy-14-hydroxy-14-iso-20-keto-pregnan-21-carboxylic acid lactone | $H_2O_2$, $CH_3CO_2H$ | 3β-Acetoxy-14-hydroxy-14-isoetiocholanic acid | — | 68 |
| | *β-Diketones* | | | | |
| $C_5H_8O_2$ | Acetylacetone | $CH_3CO_3H$ | Ethanol | — | 77 |
| $C_6H_{10}O_3$ | Ethyl acetoacetate | $CH_3CO_3H$ | Ethyl hydrogen oxalate, ethanol | — | 77 |
| $C_7H_{12}O_2$ | 3,3-Dimethylpentane-2,4-dione | $CH_3CO_3H$ | No reaction | — | 77 |
| $C_7H_{12}O_3$ | Ethyl α-methylacetoacetate | $CH_3CO_3H$ | Ethyl hydrogen oxalate | — | 77 |
| $C_8H_{14}O_3$ | Ethyl α,α-dimethylacetoacetate | $CH_3CO_3H$ | No reaction | — | 77 |
| $C_9H_{14}O_5$ | Ethyl acetonedicarboxylate | $CH_3CO_3H$ | Oxalic acid | — | 77 |
| $C_{11}H_8O_3$ | 2-Acetylindan-1,3-dione | $H_2O_2$, $(C_2H_5)_2O$ | 2-Acetoxyindan-1,3-dione | 64 | 78 |
| $C_{11}H_{12}O_3$ | Ethyl benzoylacetate | $CH_3CO_3H$ | Benzoic acid, ethyl oxalate | — | 77 |
| $C_{13}H_{16}O_3$ | Ethyl α-benzylacetoacetate | $CH_3CO_3H$ | Ethyl hydrogen oxalate, methylbenzylcarbinol | — | 77 |
| $C_{14}H_{20}O_2$ | | $H_2O_2$, $CH_3CO_2H$ | | 87 | 118 |
| $C_{15}H_{22}O_4$ | 1-Isovaleryl-2,4,6-triketo-3,3,5,5-tetramethyl-cyclohexane (leptospermone) | $H_2O_2$, pyridine | 2,4,6-Triketo-3,3,5,5-tetramethylcyclohexyl isovalerate | 12 | 79 |
| $C_{16}H_{10}O_3$ | 2-Benzoylindan-1,3-dione | $H_2O_2$, $(C_6H_5)_2O$ | 2-Benzoyloxyindan-1,3-dione | 66 | 78 |
| $C_{17}H_{14}O_3$ | Acetyldibenzoylmethane | $H_2O_2$, $(C_2H_5)_2O$ | No reaction | — | 78 |
| $C_{22}H_{16}O_3$ | Tribenzoylmethane | $H_2O_2$, NaOH | Benzoic acid | 92 | 78 |

*Note:* References 138–164 are listed on p. 106.

## TABLE VI

### BAEYER-VILLIGER OXIDATION OF ALDEHYDES

|  | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $CH_2O$ | Formaldehyde | $CH_3CO_3H$ | Formic acid | Quantitative | 80 |
|  |  | $H_2O_2$, NaOH | Formic acid, hydrogen | — | 89, 87 |
| $C_2H_4O$ | Acetaldehyde | $C_6H_5CO_3H$ | Acetic acid | — | 81 |
|  |  | $H_2O_2$, $H_2SO_4$ | Acetic acid, formic acid, methane, hydrogen, carbon dioxide | — | 88 |
| $C_2H_4O_2$ | Glycolic aldehyde | $H_2O_2$ | Hydrogen, carbon dioxide, formic acid, unidentified acids | — | 86 |
| $C_3H_6O$ | Propionaldehyde | $H_2O_2$, $H_2SO_4$ | Propionic acid, acetic acid, formic acid, hydrogen, carbon dioxide, ethane | — | 88 |
| $C_5H_{10}O$ | Pivalic aldehyde | $H_2O_2$ | Isobutane, hydrogen, carbon monoxide, unidentified acids | — | 86 |
| $C_7H_4Br_2O_2$ | 3,5-Dibromo-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 3,5-Dibromocatechol | — | 52 |
|  | 3,5-Dibromo-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | 3,5-Dibromohydroquinone | — | 52 |
|  | 4,6-Dibromo-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 4,6-Dibromocatechol | — | 52 |
| $C_7H_4Cl_2O_2$ | 3,5-Dichloro-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | 3,5-Dichlorohydroquinone | — | 52 |
|  | 3,5-Dichloro-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 3,5-Dichlorocatechol | — | 159, 52 |
| $C_7H_4I_2O_2$ | 3,5-Diiodo-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | No reaction | — | 52 |
| $C_7H_5BrO_2$ | 5-Bromo-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 5-Bromocatechol | — | 52 |
|  | 3-Bromo-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | Bromohydroquinone | 60–70 | 52 |
| $C_7H_5ClO_2$ | 5-Chloro-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 5-Chlorocatechol | — | 52 |
| $C_7H_5NO_3$ | o-Nitrobenzaldehyde | $CH_3CO_3H$ | o-Nitrobenzoic acid | 99 | 91 |
|  | m-Nitrobenzaldehyde | $CH_3CO_3H$ | m-Nitrobenzoic acid | 90 | 91 |
| $C_7H_5NO_4$ | 3-Nitro-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 3-Nitrocatechol | — | 52 |
|  | 5-Nitro-2-hydroxybenzaldehyde | $H_2O_2$, NaOH | 5-Nitrocatechol | 70 | 52 |
|  | 2-Nitro-3-hydroxybenzaldehyde | $H_2O_2$, NaOH | No reaction | — | 52 |
|  | 2-Nitro-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | Nitrobenzoquinone | — | 52 |
|  | 3-Nitro-4-hydroxybenzaldehyde | $H_2O_2$, NaOH | No reaction | — | 52 |
| $C_7H_6O$ | Benzaldehyde | $H_2SO_5$ | Benzaldehyde peroxide | 40 | 160, 140 |
|  |  | $H_2O_2$, $(C_2H_5)_2O$ | Benzoic acid, phenol | — | 92, 161 |
|  |  | $CH_3CO_3H$ | Benzoic acid | Quantitative | 80, 86 |
| $C_7H_6O_2$ | Salicylaldehyde | $H_2O_2$, $CH_3COCH_3$ | Salicylic acid, catechol | 70, trace | 95 |

*Note:* References 138-164 are listed on p. 106.

## TABLE VI—*Continued*

### BAEYER-VILLIGER OXIDATION OF ALDEHYDES

|  | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_7H_6O_2$ | Salicylaldehyde (Contd.) | $H_2O_2$, pyridine | Salicylic acid, catechol | 75, 20 | 95 |
|  |  | $H_2O_2$, NaOH | Catechol | Quantitative | 52, 134 |
|  |  | $CH_3CO_3H$ | Catechol | 89 | 162, 91, 95 |
|  | m-Hydroxybenzaldehyde | $H_2O_2$, NaOH | No reaction | — | 52 |
|  |  | $CH_3CO_3H$ | m-Hydroxybenzoic acid | 74 | 91 |
|  | p-Hydroxybenzaldehyde | $H_2O_2$, NaOH | Hydroquinone | Quantitative | 52 |
|  |  | $CH_3CO_3H$ | Hydroquinone | 93 | 80, 91 |
| $C_7H_6O_3$ | 2,4-Dihydroxybenzaldehyde | $H_2O_2$, NaOH | Hydroxyhydroquinone | — | 52 |
|  | 3,4-Dihydroxybenzaldehyde | $H_2O_2$, NaOH | Hydroxyhydroquinone | — | 52 |
| $C_7H_7NO$ | o-Aminobenzaldehyde | $H_2SO_5$ | o-Aminophenyl formate, o-aminophenol, anthranil | 31 | 93 |
| $C_7H_{14}O$ | n-Heptanal | $CH_3CO_3H$ | n-Heptanoic acid | 88 | 80 |
|  |  | $H_2O_2$, $(C_2H_5)_2O$ | α-Hydroxyheptylhydroperoxide | — | 11 |
| $C_8H_6O_3$ | Piperonal | $CH_3CO_3H$ | 3,4-Methylenedioxyphenol | 60 | 129 |
|  | 2-Hydroxy-4-methylbenzaldehyde | $CH_3CO_3H$ | 4-Methylcatechol | 70 | 91 |
|  | 2-Hydroxy-5-methylbenzaldehyde | $CH_3CO_3H$ | 5-Methylcatechol | 54 | 91 |
| $C_8H_7BrO_3$ | 3-Bromo-4-hydroxy-5-methoxybenzaldehyde | $H_2O_2$, NaOH | 3-Bromo-5-methoxyhydroquinone | 45 | 52 |
| $C_8H_7NO_5$ | 2-Nitro-4-hydroxy-3-methoxybenzaldehyde | $H_2O_2$, NaOH | 3-Methoxy-2-nitrohydroquinone | — | 52 |
|  | 3-Nitro-4-hydroxy-5-methoxybenzaldehyde | $H_2O_2$, NaOH | No reaction | — | 52 |
| $C_8H_8O$ | Phenylacetaldehyde | $H_2O_2$ | Benzyl alcohol, formic acid | — | 163 |
|  |  | $H_2O_2$, heat | Phenylacetic acid, benzaldehyde, formic acid, benzoic acid | — | 163 |
| $C_8H_8O_2$ | o-Methoxybenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | Guaiacol, o-methoxybenzoic acid | — | 92 |
|  |  | $CH_3CO_3H$ | Guaiacol formate | 99 | 91 |
|  | p-Methoxybenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | Hydroquinone monomethyl ether, p-methoxybenzoic acid | — | 92 |
|  |  | $CH_3CO_3H$ | p-Methoxybenzoic acid | Quantitative | 80 |
| $C_8H_8O_3$ | 2-Hydroxy-3-methoxybenzaldehyde | $H_2O_2$, NaOH | 3-Methoxycatechol | 68–80 | 135 |
|  | 2-Hydroxy-5-methoxybenzaldehyde | $H_2O_2$, NaOH | 4-Methoxycatechol | — | 159 |
|  | 3-Hydroxy-4-methoxybenzaldehyde | $H_2O_2$, NaOH | 4-Methoxyresorcinol (?) | — | 52 |
|  | Vanillin | $H_2O_2$, NaOH | Methoxyhydroquinone | Quantitative | 52 |

## TABLE VI—*Continued*

### BAEYER-VILLIGER OXIDATION OF ALDEHYDES

| | Carbonyl Compound | Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_9H_{10}O_3$ | 2,4-Dimethoxybenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | 2,4-Dimethoxyphenol | 27 | 92 |
| | 3,4-Dimethoxybenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | 3,4-Dimethoxyphenol, 3,4-dimethoxybenzoic acid | — | 92 |
| | | $CH_3CO_3H$ | 3,4-Dimethoxyphenol | 66 | 90, 91 |
| $C_9H_{18}O$ | Pelargonic aldehyde | $H_2O_2$, $(C_2H_5)_2O$ | α-Hydroxynonylhydroperoxide | — | 11 |
| $C_{10}H_{12}O_3$ | 3-Ethoxy-4-methoxybenzaldehyde | $CH_3CO_3H$ | 3-Ethoxy-4-methoxyphenol | — | 90 |
| $C_{10}H_{12}O_4$ | 2,4,5-Trimethoxybenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | 2,4,5-Trimethoxyphenol | 18 | 92 |
| $C_{10}H_{20}O$ | Capric aldehyde | $H_2O_2$, $(C_2H_5)_2O$ | α-Hydroxydecylhydroperoxide | — | 11 |
| $C_{11}H_{14}O_3$ | 3,4-Dimethoxy-6-ethylbenzaldehyde | $H_2O_2$, $(C_2H_5)_2O$ | 3,4-Dimethoxy-6-ethylphenol, 3,4-dimethoxy-6-ethylbenzoic acid | — | 92 |
| $C_{11}H_{22}O$ | Undecylic aldehyde | $H_2O_2$, $(C_2H_5)_2O$ | α-Hydroxyundecylhydroperoxide | — | 11 |
| $C_{12}H_{16}O_3$ | 4-Butoxy-3-methoxybenzaldehyde | $CH_3CO_3H$ | 4-Butoxy-3-methoxyphenol | 68 | 90 |
| $C_{12}H_{24}O$ | Lauric aldehyde | $H_2O_2$, $(C_2H_5)_2O$ | α-Hydroxydodecylhydroperoxide | — | 11 |
| $C_{14}H_{11}NO_3S$ | 4-Nitro-2(p-tolylthio)benzaldehyde | $H_2O_2$, $CH_3CO_2H$ | 4-Nitro-2(p-toluenesulphonyl) benzoic acid | — | 164 |
| $C_{15}H_{10}O_2$ | 3-Hydroxy-4-formylphenanthrene | $H_2O_2$, NaOH | 3,4-Dihydroxyphenanthrene | 80 | 94 |

*Note:* References 138-164 are listed on p. 106.

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# CHAPTER 4

# THE ALKYLATION OF ESTERS AND NITRILES

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## CONTENTS

## INTRODUCTION†

This chapter is concerned with the reactions of metal salts (enolates) of active methylene compounds with alkylating agents such as alkyl halides to produce alkyl derivatives. The first example of this reaction is found in the literature of 1863 when Geuther prepared ethyl α-ethyl

* To avoid confusion in the naming of disubstituted active methylene compounds containing two unlike substituents, the name of one of the substituents has been parenthesized.
† The authors are indebted to Morton Brown, Norman A. Le Bel, and Theodor A. Liss for checking the literature referred to in the final draft of this chapter.

acetoacetate by the reaction of the sodium enolate of ethyl acetoacetate with ethyl iodide.[1] The active methylene compounds considered in this chapter include malonic esters, cyanoacetic esters, malononitriles, monocarboxylic esters, and mononitriles. These classes of compounds are characterized by the presence of one or more acidic hydrogen atoms attached to carbon. Notable omissions from this list include ketones, α-diketones, β-diketones, β-keto esters, aliphatic nitro compounds, acetylenes, cyclopentadienes, diarylmethanes, and triarylmethanes. A discussion of the alkylation of acetylenes appears in a previous volume of this series.[2] The alkylation of ketones, α-diketones, β-diketones, β-keto esters, and aliphatic nitro compounds is complicated by the possibility that the alkyl group may be introduced either on an oxygen atom (O-alkylation) or on a carbon atom (C-alkylation). Only C-alkylation has been observed with the active methylene compounds to be discussed here. Compounds that may serve as alkylating agents include alkyl halides, dialkyl sulfates, alkyl sulfonates, alkyl thiocyanates, alkyl nitrates, epoxides, and aryl halides. The use of amines and quaternary ammonium compounds as alkylating agents has been reviewed earlier.[3]

Several alternative methods for the preparation of alkyl and aryl derivatives of carboxylic esters and nitriles have been included. Among these methods are the reduction of alkylidene derivatives, the addition of Grignard reagents to alkylidene derivatives, and the condensation of aromatic compounds with mesoxalic and tartronic esters.

### MECHANISM

For a successful alkylation reaction the active methylene compound must be converted, at least in part, to the corresponding carbanion, the attendant heterolytic carbon-hydrogen bond cleavage being effected by some basic reagent, $B^{\ominus}$. Common to all active methylene compounds is the possibility that the negative charge of the carbanion may be distributed among several atoms. This distribution of charge is most conveniently represented by the various resonance forms of the carbanion.

$$N \equiv C-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5 + B^{\ominus} \rightleftharpoons BH + \overset{\ominus}{N}=C=CH-\underset{\underset{O}{\|}}{C}-OC_2H_5$$

$$\leftrightarrow N \equiv C-\overset{\ominus}{C}H-\underset{\underset{O}{\|}}{C}-OC_2H_5 \leftrightarrow N \equiv C-CH=\underset{\underset{O^{\ominus}}{|}}{C}-OC_2H_5$$

[1] Geuther, *Jahresber.*, **16**, 324 (1863).

[2] Jacobs in Adams, *Organic Reactions*, Vol. 5, Chapter 1, John Wiley & Sons, New York, 1949, pp. 1–78.

[3] Brewster and Eliel in Adams, *Organic Reactions*, Vol. 7, Chapter 3, John Wiley & Sons, New York, 1953, pp. 99–197.

This ionic resonance hybrid is often called the enolate anion.  It may be
formed by reaction of the base with either the keto or the enol form of the
active methylene compound.[4]

The acidity of active methylene compounds can be attributed to reson-
ance stabilization of the enolate anion, a stabilizing interaction not possible
with the un-ionized form.  The degree to which various substituent groups
enhance the acidity of active methylene compounds appears to decrease in
the    following    order:    $-NO_2 > -C-R > -C{\equiv}N > -CO_2C_2H_5 >$
$$\qquad\qquad\qquad\qquad\quad \overset{||}{O}$$
$-C_6H_5$.  The substitution of two or three such groups on a carbon atom
further augments the acidity of the remaining hydrogen atoms bound to
the same carbon atom.  This effect would be anticipated if the additional
resonance stabilization available to such a polysubstituted enolate anion
is considered (see, however, p. 133).  On the other hand, substitution of
aliphatic groups at the active methylene carbon atom reduces the acidity
of the remaining hydrogen atom.  The effect of a number of substituents
(R) on the acid strength of monosubstituted acetic esters ($RCH_2CO_2C_2H_5$)
has been measured;[5] the compounds decreased in acidity in the following
order:  $R = C_6H_5 > H > CH_3 > C_2H_5 > n\text{-}C_3H_7 > n\text{-}C_{10}H_{21} > n\text{-}C_{16}H_{33}$
$> $ cyclohexyl $> i\text{-}C_3H_7$.  It is noteworthy that branching of the carbon
chain ($R = i\text{-}C_3H_7$) has a greater effect on acidity than the length of the
carbon  chain  ($R = n\text{-}C_{16}H_{33}$).  A  similar  reduction  in  the  acidity  of
substituted acetic acids has been ascribed to steric hindrance to solvation
of the carboxylate anion.[6]  This explanation would appear to be equally
valid for the increased difficulty with which highly substituted acetic
esters are converted to their enolate anions.

The formation of the enolate anion, the reactive derivative of the active
methylene compound in alkylation reactions, results from an equilibrium
reaction between the base and the active methylene compound.  Com-
peting equilibra involve the solvent (i.e., ROH, $NH_3$, etc.) and either the
base or the enolate anion.  As a consequence of these equilibria, both the

$$B^{\ominus} + CH_2(CO_2C_2H_5)_2 \rightleftarrows BH + \overset{\ominus}{C}H(CO_2C_2H_5)_2$$

$$\overset{\ominus}{C}H(CO_2C_2H_5)_2 + ROH \rightleftarrows CH_2(CO_2C_2H_5)_2 + \overset{\ominus}{O}R$$

$$B^{\ominus} + ROH \rightleftarrows BH + \overset{\ominus}{O}R$$

solvent (i.e., ROH) and the conjugate acid (BH) of the base must be much

[4] Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, New York,
1950, pp. 132–134.

[5] Brown and Eberly, *J. Am. Chem. Soc.*, **62**, 113 (1940).

[6] Hammond and Hogle, *J. Am. Chem. Soc.*, **77**, 338 (1955).

weaker acids than the active methylene compound if an adequate concentration of the enolate anion is to be present in the reaction mixture.

All available evidence indicates that the enolate anion of the active methylene compound reacts with the alkylating agent by a bimolecular nucleophilic displacement ($S_N2$) process.[7-9] Therefore the structure of the alkylating agent may be expected to influence the course of the alkylation reaction in a manner analogous to the effect of structure on other



$$(C_2H_5O_2C)_2CH^{\ominus} + \underset{H}{\overset{CH_3}{\underset{H}{C}}} - Br \rightarrow$$

$$(C_2H_5O_2C)_2CH\!-\!C\!-\!-H + Br^{\ominus}$$

$S_N2$ reactions. Thus, inversion of configuration is noted when the displacement occurs at an asymmetric center. Diethyl 3α-cholestanylmalonate was produced by the reaction of 3β-cholestanyl tosylate with



$p\text{-}CH_3C_6H_4SO_3 \qquad + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \longrightarrow$



$(C_2H_5O_2C)_2CH \qquad + p\text{-}CH_3C_6H_4SO_3{}^{\ominus}$



$+ \overset{\ominus}{C}H(CO_2C_2H_5)_2 \longrightarrow$



$H^{\oplus} \longrightarrow$



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[7] Grigsby, Hind, Chanley, and Westheimer, *J. Am. Chem. Soc.*, **64**, 2606 (1942).

[8] Newman and VanderWerf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

[9] Bartlett in Gilman, *Organic Chemistry*, Vol. 3, John Wiley & Sons, New York, 1953, p. 25.

diethyl sodiomalonate.[10]   Similarly, the reaction of cyclopentene oxide
yielded diethyl *trans*-(2-hydroxycyclopentyl)malonate.[7]   The attack of
the enolate anion occurs at the less hindered of the two possible positions
in ethylene oxides; displacement occurred at the primary carbon atom
with both styrene oxide and *p*-nitrostyrene oxide.[11,12]   The hindrance to

$$R\text{—}C_6H_4\text{—}CH\text{—}CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow$$

$$(\text{R} = \text{H or NO}_2)$$

$$R\text{—}C_6H_4\text{—}CHCH_2CHCO_2C_2H_5$$
$$\underset{O\text{——}CO}{|\qquad\quad|}$$

rearward attack presented by tertiary alkyl halides usually limits the
usefulness of the alkylation reaction to primary and secondary alkylating
agents (p. 124).   When treated with a solution of diethyl sodiomalonate in
ethanol, *n*-butyl bromide, *sec*-butyl bromide, and *t*-butyl bromide formed
the corresponding diethyl butylmalonates in yields of 80–90%,[13] 80–81%,[14]
and 6.4%,[15] respectively.

Only in special instances has the course of the reaction deviated from
the path expected on the basis of a normal bimolecular nucleophilic dis-
placement.   The reaction of certain allyl halides with enolate anions
has been observed to yield mixtures of products.   Although 1-chloro-
2-pentene reacted with the diethyl malonate anion to yield only the
expected product, the isomeric 3-chloro-1-pentene formed both the
product of direct displacement and the product resulting from attack of
the enolate at the 1-position in an $S_N2'$ displacement.[16,17]

$$C_2H_5CH\text{=}CHCH_2Cl + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow C_2H_5CH\text{=}CHCH_2CH(CO_2C_2H_5)_2$$

$$\cdot S_N2' \text{ process}$$

$$\underset{\substack{\uparrow \\ |S_N2}}{C_2H_5\text{—}CH}\text{—}\underset{\substack{\uparrow \\ |S_N2'}}{CH}\text{=}CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \xrightarrow{S_N2 \text{ process}} C_2H_5\text{—}CH\text{—}CH\text{=}CH_2$$
$$\underset{Cl}{|}\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\underset{CH(CO_2C_2H_5)_2}{|}$$

[10] Shoppee and Stephenson, *J. Chem. Soc.*, **1954**, 2231.

[11] Van Zyl and van Tamelen, *J. Am. Chem. Soc.*, **72**, 1357 (1950).

[12] Cristol and Helmreich, *J. Am. Chem. Soc.*, **74**, 4083 (1952).

[13] Adams and Kamm, *Org. Syntheses, Coll. Vol.* 1, John Wiley & Sons, New York, 1941,
p. 250.

[14] Vliet, Marvel, and Hsueh, *Org. Syntheses, Coll. Vol.* 2, John Wiley & Sons, New York,
1943, p. 417.

[15] Dox and Bywater, *J. Am. Chem. Soc.*, **58**, 731 (1936).

[16] Winstein, *Bull. soc. chim. France*, **1951**, C43.

[17] Kepner, Winstein, and Young, *J. Am. Chem. Soc.*, **71**, 115 (1949).

When, in similar systems, the halogen was bonded to a tertiary carbon atom, as in linalyl chloride[18] or linalyl bromide,[19] only the product resulting from an $S_N2'$ displacement was observed.

$$(CH_3)_2C{=}CHCH_2CH_2CBr(CH_3)CH{=}CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow$$

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2CH(CO_2C_2H_5)_2$$

[18] Barnard and Bateman, *J. Chem. Soc.*, **1950**, 926.
[19] Dupont and Labaune, *Chem. Zentr.*, **82**, II, 138 (1911).

A displacement of the $S_N2'$ type has been postulated to explain the products formed when 1,4-dibromo-2-butene reacted with diethyl sodiomalonate (p. 141).[20]  A more complicated example of an abnormal alkylation is provided by the reaction of $3\beta$-cholesteryl tosylate with diethyl sodiomalonate.  The products initially reported,[21,22] diethyl 3-cholesterylmalonate (later shown to be the $\alpha$-isomer[10]) and diethyl 3,5-cyclo-6-cholestanylmalonate, seemed best explained by the simultaneous operation of $S_N2$ and $S_N2'$ displacements.[23]  However, the demonstration[10] that the diethyl 3-cholesterylmalonate fraction is composed mainly of the 3 $\beta$-isomer suggests the intervention of an intermediate cholesteryl ion (shown in brackets in the equation on page 113) prior to attack by the enolate anion.  A similar anomaly was observed when $\beta$-haloamines were used as alkylating agents.  When diphenylacetonitrile was alkylated either with 1-dimethylamino-2-chloropropane or with 2-dimethylamino-1-chloropropane similar mixtures of products were obtained.[24–26]  Such a result suggests the formation of a cyclic immonium ion[27] prior to the alkylation step.

$$(CH_3)_2NCH_2CH(CH_3)Cl \rightarrow \left[ \begin{array}{c} CH_2{-}CHCH_3 \\ \diagdown \diagup \\ N \\ \diagup \diagdown \\ CH_3 \quad CH_3 \end{array} \right]^{\oplus} Cl^{\ominus}$$

$$(CH_3)_2NCH(CH_3)CH_2Cl \rightarrow$$

$$(C_6H_5)_2CHCN \begin{array}{c} | NaNH_2 \\ \downarrow C_6H_6 \end{array}$$

$$(C_6H_5)_2C(CN)CH(CH_3)CH_2N(CH_3)_2 + (C_6H_5)_2C(CN)CH_2CH(CH_3)N(CH_3)_2$$

The alkylation of alkylidene derivatives may be considered a variant of the reaction of monoalkylated sodiomalonic esters with alkylating agents.  With the alkylidene derivatives the alkyl group is invariably introduced at the position *alpha* to the activating group with attendant migration of the double bond to the $\beta,\gamma$-position.[28]

[20] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1952**, 3610.
[21] Kaiser and Svarz, *J. Am. Chem. Soc.*, **67**, 1309 (1945).
[22] Svarz and Kaiser, *J. Am. Chem. Soc.*, **69**, 847 (1947).
[23] Corey and Sneen, *J. Am. Chem. Soc.*, **75**, 6234 (1953).
[24] Schultz and Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948).
[25] Attenburrow, Elks, Hems, and Speyer, *J. Chem. Soc.*, **1949**, 510.
[26] Walton, Ofner, and Thorp, *J. Chem. Soc.*, **1949**, 648.
[27] Schultz, Robb, and Sprague, *J. Am. Chem. Soc.*, **69**, 2454 (1947).
[28] Cope, Hartung, Hancock, and Crossley, *J. Am. Chem. Soc.*, **62**, 314 (1940).

$$CH_3CH_2CH{=}C(CO_2C_2H_5)_2 + \overset{\ominus}{O}C_2H_5 \rightleftarrows C_2H_5OH +$$



$$
\begin{array}{c}
\overset{\ominus}{C}H_3CHCH{=}C
\begin{array}{l}
\nearrow COC_2H_5 \\[2pt]
\searrow COC_2H_5
\end{array}
\end{array}
\quad\leftrightarrow\quad
CH_3CH{=}CH{-}\overset{\ominus}{C}
\begin{array}{l}
\nearrow COC_2H_5 \\[2pt]
\searrow COC_2H_5
\end{array}
$$

$$
\leftrightarrow CH_3CH{=}CH{-}C
\begin{array}{l}
\nearrow COC_2H_5 \\[2pt]
\searrow \overset{\ominus}{O}COC_2H_5
\end{array}
$$

$$\Big\downarrow n\text{-}C_3H_7I$$

$$CH_3CH{=}CH{-}\underset{\underset{C_3H_7\cdot n}{|}}{C}(CO_2C_2H_5)_2$$

## SCOPE AND LIMITATIONS

### General Considerations

**Nature of the Base and Solvent.** If an alkylation reaction proceeds by the bimolecular mechanism described earlier (p. 111), the rate of alkylation will be directly proportional to the molar concentration of the enolate ion present in the reaction mixture. When the enolate concentration is small, various side reactions, to be described later (p. 123), will predominate. Since the concentration of the enolate ion is dependent upon equilibria involving the base, the solvent, and the active methylene compound (p. 110), the correct choice of base and solvent is of prime importance if the alkylation reaction is to be successful. Usually the base and solvent chosen are such that both the conjugate acid of the base and the solvent are weaker acids than the active methylene compound. Such a choice assures a high concentration of the enolate anion.

In several instances the rate of alkylation of $\beta$-keto esters has been found to depend on the nature of the cationic portion of the base employed.[29] This effect has been ascribed to the formation of a chelate structure, composed of the cation and the enolate anion, which subsequently reacts

with the alkyl halide.[29]    Alternatively, the effect of the cation on the rate
of alkylation might be attributed to the association of the cation and the
enolate anion as ion pairs in the non-polar solvents where the effect of the
cation is most pronounced.[30]    If such ion pairs are less effective than the
free enolate anions as nucleophilic reagents, then the rate of alkylation
would depend on the extent to which the·cation and enolate anion are
associated as ion pairs, a property which would be a function of the parti-
cular cation employed in a given solvent system.

The reagents most commonly used to prepare the enolates of active
methylene compounds include the metal alkoxides and the more basic
metal amides, sodium triphenylmethide and sodium hydride, as well as
metallic sodium and metallic potassium.    A meaningful comparison of
relative base strengths can best be made in terms of various base-solvent
systems, since the basicity is influenced by the solvent.    Many of the
comparisons of relative basicity made in this chapter are founded on the
success or failure of various bases in certain alkylation reactions, because
data concerning relative basicities are not available.    Consideration of
the enolate-base-solvent equilibria mentioned earlier (p. 110) will make
apparent the possibility of increasing the concentration of the enolate
anion in the reaction mixture if the solvent is replaced by a solvent of
lower acidity.    This possibility has been exploited in several instances[31-33]
where alkylation was either unsuccessful or difficult with alcohol as the
solvent; replacement of the alcohol with a less acidic solvent such as
ether or benzene permitted alkylation to occur.    If possible, the base and
the enolate should be soluble in the solvent chosen.    Otherwise, the
surface of the basic reagent may become coated with the metal enolate,
preventing further reaction.

The metal alkoxides are usually sufficiently strong bases for use in the
alkylation of malonic esters, cyanoacetic esters, malononitriles, and
certain mononitriles.    The commonly employed metal alkoxides appear
to increase in basicity in the following order:[34-37] $CH_3ONa < CH_3CH_2ONa$
$< (CH_3)_2CHONa < (CH_3)_3COK$.    When the active methylene compound
and/or the alkylating agent contain one or more ester functions, the
alkoxide chosen should correspond to the alkoxyl group of the ester.

[29] Brändstrom, *Acta Chem. Scand.*, **7**, 223 (1953).

[30] James Cason, private communication.

[31] Wagner-Jauregg and Arnold, *Ann.*, **529**, 274 (1937).

[32] Adams, Stanley, and Stearns, *J. Am. Chem. Soc.*, **50**, 1475 (1928).

[33] Pearson, *J. Am. Chem. Soc.*, **71**, 2212 (1949).

[34] Janssen, *Ann.*, **250**, 125 (1888).

[35] Kopp and Tchoubar, *Bull. soc. chim. France*, **1951**, 30.

[36] McEwen, *J. Am. Chem. Soc.*, **58**, 1124 (1936).

[37] Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2903 (1938).

Otherwise a nonhomogeneous product will result from the ester inter-change which takes place concurrently with alkylation.[37-41]  This problem

$$CH_2(CN)CO_2C_2H_5 + i\text{-}C_5H_{11}O^{\ominus} \rightleftarrows CH_2(CN)C\overset{\displaystyle /OC_2H_5}{\underset{\displaystyle \backslash OC_5H_{11}\text{-}i}{—O^{\ominus}}}$$

$$\updownarrow$$

$$C_2H_5O^{\ominus} + CH_2(CN)CO_2C_5H_{11}\text{-}i$$

is least serious when the highly branched $t$-butoxide anion is employed. Several cases have been reported in which the use of sodium $t$-butoxide in $t$-butyl alcohol led to the successful alkylation of ethyl esters that could not be alkylated readily with sodium ethoxide in ethanol.[35]

The sodium and potassium alkoxides are normally prepared and used in an excess of the corresponding anhydrous[13,42] alcohol which serves as the solvent.  However, the advantages to be gained from the use of other solvents should not be overlooked.  The decarbethoxylation of malonic and cyanoacetic esters in the presence of ethoxide ion, to be discussed more fully later (p. 127), which sometimes occurs as a side reaction, can be diminished if diethyl carbonate is used as the reaction solvent.[43,44] In addition, the high boiling point of diethyl carbonate permits the reaction time to be shortened.  In general, the low yields obtained from slow alkylation reactions (e.g., with long-chain alkyl halides as the alkylating agents) are improved if the low-boiling solvent, ethanol or ether, is replaced by a higher-boiling solvent such as $n$-butyl alcohol[45,46] or diethyl carbonate,[43,44,47-51] or if the reaction mixture is heated in a sealed tube.[31,52] However, higher reaction temperatures sometimes favor dialkylation[53] and dehydrohalogenation of the alkylating agent.[54]

[38] Hessler, *J. Am. Chem. Soc.*, **38**, 909 (1916).
[39] Hessler and Lamb, *J. Am. Chem. Soc.*, **43**, 205 (1921).
[40] Hessler and Henderson, *J. Am. Chem. Soc.*, **43**, 672 (1921).
[41] Osman and Cope, *J. Am. Chem. Soc.*, **66**, 881 (1944).
[42] Gyngell, Phillips, and Smith, *Ind. Chemist*, **21**, 526 (1945).
[43] Wallingford, Homeyer, and Jones, *J. Am. Chem. Soc.*, **63**, 2056 (1941).
[44] Wallingford, Thorpe, and Homeyer, *J. Am. Chem. Soc.*, **64**, 580 (1942).
[45] Bleyberg and Ulrich, *Ber.*, **64**, 2504 (1931).
[46] Backer and Strating, *Rec. trav. chim.*, **59**, 933 (1940).
[47] Simon, Kaufmann, and Schinz, *Helv. Chim. Acta*, **29**, 1133 (1946).
[48] Plattner, Fürst, Wyss, and Sandrin, *Helv. Chim. Acta*, **30**, 689 (1947).
[49] Wiss and Fuchs, *Helv. Chim. Acta*, **35**, 407 (1952).
[50] Blicke and Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).
[51] Wallingford and Homeyer, U.S. pat. 2,358,768 [*C. A.*, **39**, 1879 (1945)].
[52] Marshall, *J. Chem. Soc.*, **1931**, 2336.
[53] Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).
[54] Cope and McElvain, *J. Am. Chem. Soc.*, **54**, 4311 (1932).

The increase in the enolate concentration which results when an alcohol is replaced by a much less acidic or an inert solvent has already been mentioned (p. 116). However, the sodium and potassium alkoxides are relatively insoluble in such inert solvents. Magnesium ethoxide, being soluble in inert solvents,[55,56] offers an advantage in this respect. This base, which readily converts diethyl malonate to its enolate,[57] is of especial value for the dialkylation of this ester.[55,56]

The use of sodium hydride in benzene, toluene, or dimethylformamide is particularly advantageous in alkylation reactions. Sodium hydride reacts irreversibly with an active methylene compound to form an enolate and hydrogen; it has been shown that any sodium hydride which may remain has no effect upon a wide variety of alkyl halides even after prolonged times at elevated temperatures.[58]

Sodium amide is generally used to prepare the sodium derivatives of mononitriles,[53,59] some monocarboxylic esters,[60-62] some alkylmalonic esters, and alkylidenemalonic esters derived from ketones.[63,64] The lithium, sodium, and bromomagnesium salts of secondary amines have found limited use as bases in the alkylation of mononitriles.[53,65,66] The use of lithium diethylamide rather than sodium amide as the base for the alkylation of nitriles avoids side reactions involving addition of the amide ion to the nitrile group (p. 129).[53] This side reaction is particularly serious with disubstituted acetonitriles.

The alkylation of monocarboxylic esters is usually effected in the presence of the strong base sodium triphenylmethide.[67-70] Reactions which employ either sodium amide or sodium triphenylmethide as the base require an inert solvent such as ether, benzene, toluene, or xylene.

Metallic sodium and metallic potassium in inert solvents have been used

[55] Lund, *Ber.*, **67**, 935 (1934).

[56] Lund, Hansen, and Voigt, *Kgl. Danske Videnskab. Selskab, Mat-fys. Medd.*, **12**, No. 9, 23 (1933) [*C. A.*, **28**, 2333 (1934)].

[57] Walker and Hauser, *J. Am. Chem. Soc.*, **88**, 1386 (1946).

[58] Cristol, Ragsdale, and Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).

[59] Ramart, *Compt. Rend.*, **182**, 1226 (1926).

[60] Ramart and Amagat, *Ann. chim. Paris*, [10] **8**, 273 (1927).

[61] Ramart, *Bull. soc., chim. France*, [4] **35**, 196 (1924).

[62] Ramart, *Compt. rend.*, **178**, 396 (1924).

[63] Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2644 (1938).

[64] Cope, Hofmann, and Hardy, *J. Am. Chem. Soc.*, **63**, 1852 (1941).

[85] Cason, Sumrell, and Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

[66] Ziegler, Fr. pat. 581,728 [*C. A.*, **27**, 4251 (1933)].

[67] Schlenk, Hillemann, and Rodloff, *Ann.*, **487**, 135 (1931).

[68] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).

[69] Hudson and Hauser, *J. Am. Chem. Soc.*, **63**, 3156 (1941).

[70] Polgar and Robinson, *J. Chem. Soc.*, **1943**, 615.

extensively to prepare the enolates of malonic ester, cyanoacetic ester, and 3-aryl-2-benzofuranones. Several attempts to use metallic sodium in the alkylation of aliphatic mononitriles have resulted in dimerization of the nitrile.[71-73] Metallic sodium and metallic potassium must be avoided as bases for the alkylation of alkylidenemalonic and alkylidenecyanoacetic esters because partial reduction of the conjugated system accompanies enolate formation.[28,37,63,74]

Sodium hydroxide and potassium hydroxide have been employed as bases for the alkylation of active methylene compounds. The alkylation of nitriles, in certain instances at least, appears to offer no complications with these bases.[34,75-79] Although extensive saponification would be expected to attend the alkylation of esters in the presence of potassium hydroxide, successful alkylations with this base have been reported by several workers.[80-83] These alkylations were usually effected by treat-ment of the active methylene compound with a suspension-of powdered potassium hydroxide in an inert solvent such as di-n-propyl acetal followed by addition of an alkyl halide. For example, ethyl cyanoacetate was converted to ethyl benzylcyanoacetate in 30% yield by this procedure.[83]

Other bases that have had limited use include benzyltriethylammonium hydroxide,[84] potassium acetate,[85] ammonia,[86,87] potassium carbonate,[88,89] phenylsodium,[90] and various sodium enolates.[91-93] Alkylations have also been effected in the presence of metallic zinc[94] and inorganic salts of

[71] Hanriot and Bouveault, *Bull. soc. chim. France*, [3] **1**, 170 (1889).

[72] Wache, *Jahresber.*, **1889**, 644.

[73] Holtzwart, *J. prakt. Chem.* [2] **39**, 230 (1889).

[74] Hugh and Kon, *J. Chem. Soc.*, **1930**, 775.

[75] von Braun, Fussgänger, and Kühn, *Ann.*, **445**, 201 (1925).

[76] Zelinsky and Feldmann, *Ber.*, **22**, 3290 (1889).

[77] Eisleb, *Ber.*, **74**, 1433 (1941).

[78] Cloke, *J. Am. Chem. Soc.*, **51**, 1174 (1929).

[79] Pickard and Yates, *J. Chem. Soc.*, **95**, 1011 (1909).

[80] Ingold, *J. Chem. Soc.*, **119**, 305 (1921).

[81] Weizmann, Bergmann, and Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).

[82] Michael, *J. prakt. Chem.*, [2] **72**, 537 (1905).

[83] Weizmann, Brit. pat. 582,191 [*C. A.*, **41**, 2436 (1947)].

[84] Jarrousse, *Compt. rend.*, **232**, 1424 (1951).

[85] Kohler, Hill, and Bigelow, *J. Am. Chem. Soc.*, **39**, 2405 (1917).

[86] Kohler and Conant, *J. Am. Chem. Soc.*, **39**, 1404 (1917).

[87] Kötz, *J. prakt. Chem.*, [2] **75**, 433 (1907).

[88] Pettersson, *Acta Chem. Scand.*, **4**, 1319 (1950) [*C. A.*, **47**, 3847 (1953)].

[89] Robinson, *J. Chem. Soc.*, **125**, 226 (1924).

[90] Bockmühl and Ehrhardt, Ger. pat. 622,875 [*C. A.*, **30**, 2991 (1936)].

[91] Bockmühl and Ehrhaert, *Ann.*, **581**, 52 (1948).

[92] Case, *J. Am. Chem. Soc.*, **55**, 2927 (1933).

[93] Bockmühl and Ehrhardt, U.S. pat., 2,230,774 [*C. A.*, **35**, 3391 (1941)].

[94] Shukowski, *J. Russ. Phys. Chem. Soc.*, **1887** (1), 601; *Ber.*, **21**, Ref. 57 (1888).

silver.[95,96]    The yields in several alkylation reactions have been improved
when copper or a copper salt was added to the reaction mixture.[97–100]

**Monoalkylation versus Dialkylation.**  During the alkylation of di-
ethyl sodiomalonate with ethyl bromide, the diethyl ethylmalonate that is

(1) $CH_2(CO_2C_2H_5)_2 + C_2H_5O^{\ominus} \rightleftarrows \overset{\ominus}{C}H(CO_2C_2H_5)_2 + C_2H_5OH$

(2) $\overset{\ominus}{C}H(CO_2C_2H_5)_2 + C_2H_5Br \rightarrow C_2H_5CH(CO_2C_2H_5)_2 + Br^{\ominus}$

(3) $C_2H_5CH(CO_2C_2H_5)_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightleftarrows C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2$
$$+ CH_2(CO_2C_2H_5)_2$$

(4) $C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2 + C_2H_5OH \rightleftarrows C_2H_5CH(CO_2C_2H_5)_2 + C_2H_5O^{\ominus}$

(5) $C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2 + C_2H_5Br \rightarrow (C_2H_5)_2C(CO_2C_2H_5)_2 + Br^{\ominus}$

formed (reaction 2) is in equilibrium with its anion (reactions 3 and 4).  The
question, therefore, arises as to why little dialkylation (reaction 5) is
observed.   In a competitive experiment diethyl malonate was alkylated
by ethyl bromide (reaction 2) at a rate seventy times the rate of alkylation
of diethyl ethylmalonate (reaction 5).[33]  The ratio of the ionization
constants[33] of the two esters

$$\frac{K_{\text{diethyl malonate}}}{K_{\text{diethyl ethylmalonate}}} = \frac{1.6 \times 10^{-18}}{2 \times 10^{-20}} \sim 10^2$$

indicates that the concentration of diethyl malonate enolate exceeds the
concentration of the diethyl ethylmalonate anion.
    Of much greater importance here is the acidity of the solvent, ethanol
($K$ ionization $= 7.28 \times 10^{-20}$).[101]  As can be seen from the enolate-
base-solvent equilibria mentioned earlier (p. 110), a solvent that is more
acidic than the active methylene compound will greatly reduce the

[95] Hessler, *Am. Chem. J.*, **22**, 169 (1899).
[96] Lander, *J. Chem. Soc.*, **77**, 743 (1900).
[97] Tabern and Volwiler, *J. Am. Chem. Soc.*, **58**, 1354 (1936).
[98] Hurtley, *J. Chem. Soc.*, **1929**, 1870.
[99] Hoffmann-LaRoche, A.-G., Ger. pat. 526,854 [*Chem. Zentr.*, **102**, II, 909 (1931)].
[100] Hoffmann-LaRoche, A.-G., Ger. pat. 634,285 [*C. A.*, **31**, 219 (1937)].
[101] Danner, *J. Am. Chem. Soc.*, **44**, 2832 (1922).

concentration of enolate present in the reaction mixture since the molar concentration of the solvent is much larger than the molar concentration of the active methylene compound. In the alkylation of diethyl malonate with ethyl bromide, the presence of a large excess of ethanol in the reaction mixture reduces the concentration of the enolate of diethyl ethylmalonate to such a low level that the rate of dialkylation (reaction 5) becomes negligible. As would be predicted on this basis, the replacement of ethanol with an inert solvent favors dialkylation.[102] As would be expected from the facts mentioned above, the greater acidities of alkylcyanoacetic esters and alkylmalonitriles (for malononitrile $K$ ionization $\sim 10^{-11}$)[103] cause dialkylation to be a more serious problem.[95,104-106]

Dialkylation also becomes an important side reaction in the alkylation of active methylene compounds with very reactive halogen compounds such as benzyl halides,[95,107-119] allyl halides,[53,56,120-122] phenacyl halides,[56,106,123,124] and α-chloro thio ethers.[125,126] The large amount of dialkylation observed with the allyl or benzyl halides or with α-halo ethers may be attributed to the fact that heterolytic cleavage of the carbon-halogen bond in such compounds during bimolecular displacement reactions may occur without substantial aid from the attacking nucleophilic reagent. Therefore, a halide of this type (e.g., benzyl chloride) would be expected to show less discrimination between two nucleophilic

[102] Clemo and Tenniswood, *J. Chem. Soc.*, **1931**, 2549.

[103] Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, New York, 1941, p. 269.

[104] Hesse, *Am. Chem. J.*, **16**, 723 (1896).

[105] Cohen, Marshall, and Woodman, *J. Chem. Soc.*, **107**, 887 (1915).

[106] Rây and Rây, *J. Chem. Soc.*, **127**, 2721 (1925).

[107] Bischoff and Siebert, *Ann.*, **239**, 92 (1887).

[108] Fittig and Röders, *Ann.*, **256**, 87 (1890).

[109] Hausmann, *Ber.*, **22**, 2019 (1889).

[110] Poppe, *Ber.*, **23**, 108 (1890).

[111] Cassirer, *Ber.*, **25**, 3018 (1892).

[112] Reissert, *Ber.*, **29**, 633 (1896).

[113] Maxim, *Bull. soc. chim. France*, [4] **39**, 1024 (1926).

[114] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).

[115] Kenner and Witham, *J. Chem. Soc.*, **119**, 1452 (1921).

[116] Walker, *J. Chem. Soc.*, **125**, 1622 (1924).

[117] Gulland, Haworth, Virden, and Callow, *J. Chem. Soc.*, **1929**, 1666.

[118] Curtius and Mülhäusser, *J. prakt. Chem.*, [2] **125**, 291 (1930).

[119] Marvel, *Org. Syntheses*, **21**, 99 (1941).

[120] Paul and Cottin, *Bull. soc. chim. France*, [5] **4**, 933 (1937).

[121] McBay, Jenkins, and Data, *J. Am. Pharm. Assoc.*, **39**, 138 (1950) [*C. A.*, **44**, 4870 (1950)].

[122] Ziegler, Fr. pat. 728,241 [*C. A.*, **26**, 5573 (1932)].

[123] Klobb, *Ann. chim. Paris*, [7] **10**, 168 (1897).

[124] Thorpe, *J. Chem. Soc.*, **91**, 1004 (1907).

[125] Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 655 (1945).

[126] Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 657 (1945).

reagents (e.g., the sodium enolate of diethyl malonate and the more hindered sodium enolate of diethyl benzylmalonate) than would a saturated alkyl halide (e.g., $n$-butyl chloride; cleavage of the carbon-chlorine bond in this case would be greatly facilitated by the attacking nucleophilic reagent).

In addition to the foregoing suggestion, a second factor may account for the large amount of dialkylation observed with phenacyl halides. A monoalkylated product such as diethyl phenacylmalonate would be expected to be more acidic than a monoalkyl derivative such as diethyl ethylmalonate because of the proximity of an electron-withdrawing carbonyl function in the former example. For this reason the proportion of diethyl phenacylmalonate converted to its sodium enolate, a necessary intermediate for dialkylation, would be larger than the proportion of diethyl ethylmalonate converted to its sodium enolate under comparable conditions.

As the reaction leading to the alkylation of an active methylene compound ($Z$—$CH_2$—$Y$) proceeds, the ratio of the concentration of the mono-substituted enolate [$R$—$\overset{\ominus}{C}(Z)Y$] to the concentration of the unsubstituted enolate ($Z$—$\overset{\ominus}{CH}$—$Y$) must necessarily increase. An increase in this ratio will increase the proportion of dialkylation that occurs. This unfavorable

$$Z-\overset{\ominus}{C}H-Y + R-CH(Z)Y \rightleftharpoons Z-CH_2-Y + R-\overset{\ominus}{C}(Z)Y$$

$$\frac{[R-\overset{\ominus}{C}(Z)Y]}{[Z-\overset{\ominus}{C}H-Y]} = \frac{K[R-CH(Z)Y]}{[Z-CH_2-Y]}$$

concentration ratio may be overcome to a large extent if an excess of the active methylene compound ($Z$—$CH_2$—$Y$) is used,[7,33,105,116,118,127–135] a possibility first realized by Leuchs.[136] Dialkylation has also been diminished by the addition of an excess of both the active methylene

[127] Gagnon, Boivin, and Boivin, *Can. J. Research*, **28B**, 207 (1950).

[128] Gagnon, Boivin, and Giguère, *Can. J. Research*, **28B**, 352 (1950).

[129] Skinner, *J. Am. Chem. Soc.*, **59**, 322 (1937).

[130] Huber, Clinton, Boehme, and Jackman, *J. Am. Chem. Soc.*, **67**, 1618 (1945).

[131] Gol'mov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **19**, 1679 (1949) [*C. A.*, **44** 1030 (1950)].

[132] Olynyk, Camp, Griffith, Woislowski, and Helmkamp, *J. Org. Chem.*, **13**, 465 (1948).

[133] Curtius and Gaier, *J. prakt. Chem.*, [2] **125**, 279 (1930).

[134] Brigl, *Hoppe-Seyler's Z. physiol. Chem.*, **95**, 161 (1915).

[135] Weitzel and Wojahn, *Hoppe-Seyler's Z. physiol. Chem.*, **285**, 220 (1950).

[136] Leuchs, *Ber.*, **44**, 1507 (1911).

compound and the base; such additions serve to increase the concentration of the active methylene enolate $(Z—\overset{\ominus}{CH}—Y)$.[112,124,137-139]

Other factors reported to favor monoalkylation include the use of low-boiling solvents[53] and the use of alkyl chlorides rather than alkyl bromides.[140]

**Order of Introduction of Groups.** If two alkyl groups are to be introduced into malonic or cyanoacetic ester, the order of introduction of groups may have a profound influence on the yield and purity of the product. When the two alkyl groups are identical best results have been obtained by adding one equivalent of the base and alkyl halide, allowing the reaction mixture to become approximately neutral, and then adding the second equivalent of base and alkyl halide.[141] Where two different alkyl residues are to be introduced, it is advisable to introduce the larger group first if both alkylation steps involve displacement at a primary carbon atom.[142-145] This order is of particular importance if the smaller alkyl residue is a methyl or an ethyl group; in these cases the boiling points of the unchanged ester, the monoalkylated ester, and the dialkylated ester are too close to one another to permit separation without recourse either to very precise fractional distillation[135] or to a chemical separation (p. 157).

In the dialkylation of malonic ester the introduction of a primary alkyl group should always *precede* the introduction of a secondary alkyl group. If this precaution is not observed the introduction of a second alkyl group is often unsuccessful,[35,145-149] because of the low acidity of the intermediate *sec*-alkylmalonic ester (p. 110) and the sterically hindered nature of the corresponding enolate anion. This difficulty accompanying the alkylation of *sec*-alkylmalonic esters has occasionally been overcome by the use of a strong base such as sodium *t*-butoxide in *t*-butyl alcohol.[35]

**Side Reactions.** Aside from dialkylation, a wide variety of side reactions may attend the alkylation of an active methylene compound. Among these side reactions are the reactions of the alkylating agent with the base

[137] Hinegardner and Johnson, *J. Am. Chem. Soc.*, **52,** 3724 (1930).

[138] Levene and Allen, *J. Biol. Chem.*, **27,** 433 (1916).

[139] Zaheer and Sidhu, *J. Indian Chem. Soc.*, **24,** 134 (1947).

[140] Hinegardner and Johnson, *J. Am. Chem. Soc.*, **52,** 4139 (1930).

[141] Levene and Cretcher, *J. Biol. Chem.*, **33,** 505 (1918).

[142] Dolique, *Ann. chim. Paris*, [10], **15,** 429 (1931).

[143] Dolique, *Compt. rend.*, **190,** 878 (1930).

[144] Dox and Yoder, *J. Am. Chem. Soc.*, **44,** 1141 (1922).

[145] Crossley and Le Sueur, *J. Chem. Soc.*, **77,** 83 (1900).

[146] Kondakova and Katsnel'son, *Compt. rend. acad. sci.* (*U.R.S.S.*) *N.S.*, **4,** 403 (1936) [*C. A.*, **31,** 3448 (1937)].

[147] Zelinskii, Bondar, Kost, and Lifshits, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk,* (**1951**), No. 2, 96 [*C. A.*, **45,** 10205 (1951)].

[148] Shonle, Keltch, and Swanson, *J. Am. Chem. Soc.*, **52,** 2440 (1930).

[149] Hope and Perkin, *J. Chem. Soc.*, **95,** 1360 (1909).

and solvent. Provided that an adequate concentration of the enolate anion is present (p. 115) the interaction of the alkylating agent and the solvent and/or the base to produce an ether becomes a serious competing reaction only with very reactive halides such as allyl,[150-152] benzyl,[153,154] and benzhydryl halides. The low yields obtained in the synthesis of benzhydrylmalonic esters, presumably attributable to solvolysis of the benzhydryl halides in the alcoholic reaction mixture,[155] may be avoided if the reaction is conducted in benzene solution.[156] Triphenylmethyl chloride also has served as an effective alkylating agent in ether solution.[56]

As was noted earlier (p. 112) tertiary alkyl halides that can undergo dehydrohalogenation usually do so more rapidly than they undergo the displacement reaction leading to alkylation; accordingly, they are poor alkylating agents.[157,159] Olefin formation is less important with secondary alkyl halides[160] and is not a serious side reaction with primary alkyl halides. Halogen compounds like ethyl $\alpha$-bromoisobutyrate[161-167] and ethyl $\beta$-bromolevulinate[168] whose dehydrohalogenation leads to an $\alpha,\beta$-unsaturated ester or ketone introduce a further complication; the initially formed unsaturated products may add the active methylene compound in a Michael reaction.[161,162]

$$\overset{\ominus}{CH(CO_2C_2H_5)_2}$$
$$+ \ (CH_3)_2CBrCO_2C_2H_5 \ \Big\{$$

$$\xrightarrow{\text{Alkylation}} \ (C_2H_5O_2C)_2CHC(CH_3)_2CO_2C_2H_5$$

$$\xrightarrow{\text{Dehydrohalogenation}} \ CH_2{=}C(CH_3)CO_2C_2H_5$$

$$\overset{CH_2(CO_2C_2H_5)_2}{\Big\downarrow}$$

$$(C_2H_5O_2C)_2CHCH_2CH(CH_3)CO_2C_2H_5$$

[150] Mousseron and Winternitz, *Bull. soc. chim. France*, **1946**, 604.

[151] Perkins and Cruz, *J. Am. Chem. Soc.*, **49**, 517 (1927).

[152] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1953**, 1803.

[153] Mayer, Sieglitz, Fischer, Hagen, Jung, Knies, Kohl, Listmann, Neugebauer, and Schulte, *Ber.*, **55**, 1835 (1922).

[154] de Benneville, Clagett, and Connor, *J. Org. Chem.*, **6**, 690 (1941).

[155] Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, p. 167.

[156] Cope, *J. Am. Chem. Soc.*, **56**, 721 (1934).

[157] Widegvist, *Arkiv Kemi, Mineral. Geol.*, **B23**, No. 4, 6 (1946) [*C. A.*, **41**, 1615 (1947)].

[158] St. Pfau and Plattner, *Helv. Chim. Acta*, **22**, 202 (1939).

[159] Alexander, McCollum, and Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

[160] Kazanskii and Lukina, *Doklady Akad. Nauk S.S.S.R.*, **83**, 693 (1952) [*C. A.*, **47**, 2712 (1953)].

[161] Bischoff and von Kuhlberg, *Ber.*, **23**, 634 (1890).

[162] Bischoff and Mintz, *Ber.*, **23**, 647 (1890).

[163] Auwers and Jackson, *Ber.*, **23**, 1599 (1890).

[164] Zelinsky and Besredka, *Ber.*, **24**, 459 (1891).

[165] Bischoff, *Ber.*, **24**, 1041 (1891).

[166] Auwers and Köbner, *Ber.*, **24**, 1923 (1891).

[167] Bone and Sprankling, *J. Chem. Soc.*, **75**, 839 (1899).

[168] Emery, *J. prakt. Chem.*, [2] **53**, 308 (1896).

Decarbalkoxylation (p. 127) and side reactions which involve the alkylating agent and the base may be minimized if a mixture of the alkylating agent and the active methylene compound is treated with the base at a rate equal to that at which the base is consumed in the reaction.[42,121,169,170]

Similarly, the slow addition of the sodium derivatives of mononitriles to allylic halides has been found to minimize the extent of polymerization of both the alkylating agent and the product.[171]

Certain vicinal dihalides tend to lose their halogen atoms with the simultaneous production of the corresponding olefin under the conditions of the alkylation reaction. Such dihalides include ethylene iodide (but not ethylene bromide),[92] 2,3-dibromo-2-methylbutane,[172,173] $o,o'$-dinitro-stilbene dibromide,[174] and diethyl $erythro$-$\alpha,\alpha'$-dibromosuccinate.[175] For each molecule of halogen lost, two molecules of the active methylene compound are coupled in a reaction similar to the coupling of active methylene compounds in the presence of iodine (p. 137). Certain of the olefins produced in this way may add an additional equivalent of the active methylene compound in a Michael reaction.[175] The reaction of



dimethyl $erythro$-$\alpha,\alpha'$-dibromosuccinate is illustrative. In addition to the major products, dimethyl fumarate, tetramethyl 1,1,2,2-ethanetetra-carboxylate, and tetramethyl 1,1,2,3-propanetetracarboxylate, a small amount of racemic tetramethyl 1,1,2,3-cyclopropanetetracarboxylate was formed. The cyclopropane tetracarboxylic ester is believed to arise from

[169] Phillips, *Ind. Chemist*, **21**, 678 (1945).
[170] Mariella and Raube, *Org. Syntheses*, **33**, 23 (1953).
[171] Whyte and Cope, *J. Am. Chem. Soc.*, **65**, 1999 (1943).
[172] Bischoff, *Ber.*, **28**, 2824 (1895).
[173] Ipatiew, *J. Russ. Phys. Chem. Soc.*, **30**, 391 (1898) (*Chem. Zentr.*, **1898**, II, 660).
[174] Bischoff, *Ber.*, **21**, 2071 (1888).
[175] Ing and Perkin, *J. Chem. Soc.*, **125**, 1814 (1924).

the partial base-catalyzed isomerization of the dimethyl *erythro*-α,α'-dibromosuccinate to the *threo* isomer; dimethyl *threo*-α,α'-dibromo-succinate, when treated with dimethyl sodiomalonate, was converted to



the racemic cyclopropane tetracarboxylic ester in 80–90% yield.[175]  A similar base-catalyzed epimerization of the isomeric α,α'-dibromoglutaric esters has been observed.[176]

Another side, reaction which involves the transfer of a halogen atom is exemplified by the attempted alkylation of methyl diphenylacetate with methyl α-bromophenylacetate in the presence of sodium triphenylmethide.[67]  The product was dimethyl α,α'-diphenylsuccinate.

$$(C_6H_5)_3C^{\ominus} + C_6H_5CHBrCO_2CH_3 \rightarrow (C_6H_5)_3CBr + C_6H_5\overset{\ominus}{C}HCO_2CH_3$$

$$C_6H_5\overset{\ominus}{C}HCO_2CH_3 + C_6H_5CHBrCO_2CH_3 \rightarrow Br^{\ominus}$$
$$+ CH_3O_2CCH(C_6H_5)CH(C_6H_5)CO_2CH_3$$

Similarly, 2-bromo-2-nitropropane and diethyl sodiomalonate underwent partial halogen interchange, the products being tetraethyl 1,1,2,2-ethanetetracarboxylate and 2,3-dimethyl-2,3-dinitrobutane.[177]  However, normal alkylation was observed when 2-chloro-2-nitropropane was allowed to react with the sodium enolate of diethyl ethylmalonate.[177]  Halogenated nitroalkanes in which the nitro group is bonded to a carbon atom

$$(CH_3)_2C(NO_2)Br + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} (CH_3)_2C(NO_2)C(NO_2)(CH_3)_2$$

bearing a hydrogen atom cannot be employed as alkylating agents. Instead, the enolate of the nitro compound is formed, since it is less basic than the enolate of malonic ester.

In addition to the side reactions that can occur with the alkylating agent, both the initial active methylene compound and the alkylated product can undergo a number of transformations.  The possibility of ester interchange when the alkoxyl group of the ester and the alkoxide ion differ has already been mentioned (p. 117).  When sodium amide is

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[176] Ing and Perkin, *J. Chem. Soc.*, **127**, 2387 (1925).

[177] van Tamelen and Van Zyl, *J. Am. Chem. Soc.*, **71**, 835 (1949).

used as the base for the alkylation of esters, amide formation may be a serious side reaction.[178,179]

$$C_6H_5CH_2CO_2C_2H_5 + H_2N^\ominus \rightleftarrows C_6H_5CH_2C\begin{smallmatrix}OC_2H_5\\|\\—O^\ominus\\|\\NH_2\end{smallmatrix} \rightleftharpoons C_6H_5CH_2CONH_2 + C_2H_5O^\ominus$$

A related side reaction results in the loss of the carbalkoxyl group as the corresponding dialkyl carbonate.[180] Similarly, cyanoacetic esters are converted to mononitriles.[181] Among the malonic esters the importance

$$C_6H_5CH(CO_2C_2H_5)_2 \underset{\longleftarrow}{\overset{C_2H_5O^\ominus}{\longrightarrow}} C_6H_5CH(CO_2C_2H_5)C\begin{smallmatrix}OC_2H_5\\|\\—O^\ominus\\|\\OC_2H_5\end{smallmatrix} \rightleftarrows$$

$$C_6H_5\overset{\ominus}{C}HCO_2C_2H_5 + (C_2H_5O)_2CO$$

$$C(CH_3)(CN)CO_2C_2H_5 + C_2H_5O^\ominus \rightleftarrows$$

$$\overset{\ominus}{C}(CH_3)CN + (C_2H_5O)_2CO$$

of this side reaction decreases in the following order: diethyl diphenyl-malonate > diethyl ethyl(phenyl)malonate > diethyl diethylmalonate.[180]

$$(C_6H_5)_2C(CO_2C_2H_5)C\begin{smallmatrix}OC_2H_5\\|\\—O^\ominus\\|\\OC_2H_5\end{smallmatrix} \rightarrow (C_2H_5O)_2CO +$$

(six o- and p-quinoid forms of this type)

[178] Cutler, Surrey, and Cloke, *J. Am. Chem. Soc.*, **71**, 3375 (1949).

[179] Hauser and Hudson in Adams, *Organic Reactions*, Vol. 1, John Wiley & Sons, New York, 1942, p. 266.

[180] Cope and McElvain, *J. Am. Chem. Soc.*, **54**, 4319 (1932).

[181] Ingold and Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

Such an order is understandable when the resonance stabilization available to the carbanion formed after loss of diethyl carbonate is considered. Substituents other than the phenyl group[180,182] which have been observed to enhance the cleavage reaction include the nitro group,[183] the vinyl group,[54] the 2,4-dinitrophenyl group,[184] and the 2- or 3-indenyl group.[181] On the other hand, bulky groups that impede the approach of the ethoxide ion or substituents that reduce the stability of a carbanion diminish the amount of decarbethoxylation. Malonic esters and monoalkylmalonic esters are less readily cleaved to monocarboxylic esters and dialkyl carbonates because they react readily with sodium alkoxides to form stable enolates.

The reversible nature of the decarbethoxylation of diethyl phenyl-malonate has been demonstrated.[43] In fact, the reverse reaction, carbethoxylation, has been found valuable both in the synthesis of diethyl phenylmalonate from ethyl phenylacetate and in the synthesis of cyano-acetic esters from mononitriles.[185-189] As mentioned previously (p. 117), the use of diethyl carbonate as a solvent for the alkylation reaction offers special advantages where cleavage might be an important side reaction. The extent of decarbethoxylation is diminished and the reaction time is shortened by virtue of the high boiling point of the diethyl carbonate.

The decarbethoxylation of disubstituted malonic esters at high temperatures in the presence of ethanol-free sodium ethoxide or sodium or potassium metal (p. 150) would constitute a serious side reaction where the alkylation of an alkylmalonic ester was attempted under such conditions.

In the alkylation of malononitriles (see Table X), the addition of ethanol to one of the cyano groups to produce stable imido esters is often observed.[95,104] The mononitriles are usually stable to ethanolic sodium

$$C_6H_5CH_2CH(CN)_2 + CH_3I + C_2H_5OH \xrightarrow{\text{NaOC}_2\text{H}_5}$$

$$C_6H_5CH_2C(CH_3)(CN)COC_2H_5$$
$$\overset{\|}{\text{NH}}$$

ethoxide, 4-cyano-1-methyl-4-phenylpiperidine being an exception;[190] an imido ester presumably is an intermediate in the cleavage. The stronger

[182] Wislicenus and Goldstein, *Ber.*, **28**, 815 (1895).

[183] Boyd and Kelly, *J. Am. Chem. Soc.*, **74**, 4600 (1952).

[184] von Richter, *Ber.*, **21**, 2470 (1888).

[185] Gagnon and Boivin, *Can. J. Research*, **26B**, 503 (1948).

[186] Wallingford, Jones, and Homeyer, *J. Am. Chem. Soc.*, **64**, 576 (1942).

[187] Leonard and Simet, *J. Am. Chem. Soc.*, **74**, 3218 (1952).

[188] Bergel, Hindley, Morrison, and Rinderknecht, *J. Chem. Soc.*, **1944**, 269.

[189] Horning and Finelli, *Org. Syntheses*, **30**, 43 (1950).

[190] Bergel, Haworth, Morrison, and Rinderknecht, *J. Chem. Soc.*, **1944**, 261.

base, sodium amide, does attack the cyano group in such solvents as boiling benzene,[191] toluene,[192] or xylene.[191-194] Under such conditions

$$\text{H}_3\text{CN}\underset{\text{C}\equiv\text{N}}{\overset{\text{C}_6\text{H}_5}{\bigcirc}} \xrightarrow{\text{C}_2\text{H}_5\text{OH, NaOC}_2\text{H}_5} \text{H}_3\text{CN}\bigcirc\text{C}_6\text{H}_5$$

86%

the nitrile function may be eliminated as sodium cyanamide.

$$(\text{C}_6\text{H}_5)_2\text{C(CN)CH}_2\text{CH}_2\text{N(CH}_3)_2 + 2\text{NaNH}_2 \xrightarrow{\text{Xylene}}$$
$$\text{NH}_3 + \text{Na}_2\text{N}_2\text{C} + (\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{CH}_2\text{N(CH}_3)_2$$
91%

The loss of the nitrile function has also been observed with substituted nitriles which have no hydrogen atom on the carbon atom *alpha* to the nitrile group and which have a hydrogen atom and a phenyl group on the carbon atom *beta* to the cyano group.[195] This elimination of hydrogen cyanide may be likened to other bimolecular elimination processes as is shown in the accompanying equation. In the presence of basic catalysts

$$\text{C}_6\text{H}_5\text{CH}\overset{\overset{\displaystyle \overset{\ominus}{\text{NH}}_2}{\downarrow}}{\underset{\underset{\text{CN}}{|}}{-}}\text{C(C}_6\text{H}_5)_2 \rightarrow \text{C}_6\text{H}_5\text{CH}=\text{C(C}_6\text{H}_5)_2 + \text{NH}_3 + \text{CN}^{\ominus}$$

both acetic esters and mono- and di-substituted acetic esters can condense with themselves in a reaction of the acetoacetic ester type[179] to produce β-keto esters with a consequent diminished yield of the alkylated product.[178,196] A similar condensation, the Thorpe reaction, occurs as a side reaction and results in poor yields in the alkylation of certain mono-nitriles.[71-73] Such Claisen-type condensations become particularly important with compounds where intramolecular condensation is possible.[176,197-201] The accompanying example[198] illustrates both a

[191] Ruddy, *J. Am. Chem. Soc.*, **73**, 4096 (1951).

[192] Jackman, Nachod, and Archer, *J. Am. Chem. Soc.*, **72**, 716 (1950).

[193] Jackman, Bolen, Nachod, Tullar, and Archer, *J. Am. Chem. Soc.*, **71**, 2301 (1949).

[194] Kleiderer, *Report No. P.B.* 981, Office of the Publication Board, Dept. of Commerce, Washington, D.C.

[195] Hauser and Brasen, to be published.

[196] Scheibler, Marhenkel, and Bassanoff, *Ber.*, **58**, 1198 (1925).

[197] Perkin and Thorpe, *J. Chem. Soc.*, **79**, 729 (1901).

[198] Mitchell and Thorpe, *J. Chem. Soc.*, **97**, 2261 (1910).

[199] Goss and Ingold, *J. Chem. Soc.*, **1928**, 1268.

[200] Acheson and Robinson, *J. Chem. Soc.*, **1952**, 1127.

[201] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1953**, 1799.

Claisen condensation and the subsequent elimination of a carbethoxyl group.



Active methylene compounds having alkoxyl[202-204] or alkylthio[205] functions bonded to the carbon atom *beta* to the activating group have been observed to undergo base-catalyzed elimination under the conditions of the alkylation reaction. The unsaturated compounds initially formed are susceptible to polymerization and Michael reactions.



Polymer                    $(C_2H_5O_2C)_2CHCH_2CH(CO_2C_2H_5)_2$

During the alkylation of certain malonic esters a reverse Michael reaction competes with the alkylation reaction. In such cases the alkylation products of diethyl malonate or diethyl monoalkylmalonates are isolated.[87,154,206,207] For example, the products of the alkylation of ethyl $\gamma$-benzoyl-$\alpha$-carbethoxy-$\beta$-phenylbutyrate (I) were dependent on the alkylating agent employed.[154] With methyl iodide both the keto

[202] Ziegler, Schenck, Krockow, Siebert, Wenz, and Weber, *Ann.*, **551**, 1 (1942).
[203] McElvain and Burkett, *J. Am. Chem. Soc.*, **64**, 1831 (1942).
[204] Simonsen, *J. Chem. Soc.*, **93**, 1777 (1908).
[205] Böhme and Greve, *Chem. Ber.*, **85**, 409 (1952).
[206] Perkin, *J. Chem. Soc.*, **69**, 1500 (1896).
[207] Rydon, *J. Chem. Soc.*, **1935**, 420.

ester II (R = CH₃) and diethyl methylmalonate (III, R = CH₃) were formed. If the less reactive ethyl iodide was employed, only diethyl ethylmalonate (III, R = C₂H₅) was produced since the reaction mixture remained basic sufficiently long for the reverse Michael reaction to predominate. Whether the cleavage occurred before or after the alkylation step is not known.

If the active methylene compound employed contains other reactive functions additional side reactions are possible. In the case of diethyl chloromalonate the rate of displacement of the chloride ion by the ethoxide anion exceeds the rate of alkylation except with very reactive alkylating agents such as benzyl chloride[208] or 4-(or 5-)chloromethylimidazole.[209] Small amounts (1.5%) of diethyl 5-ethoxyhexylmalonate were formed along with diethyl 2-methylcyclohexane-1,1-dicarboxylate when diethyl 5-bromohexylmalonate was cyclized in the presence of sodium ethoxide.[210]

Additional side reactions may accompany the alkylation of alkylidene-malonic esters, alkylidenecyanoacetic esters, and alkylidenemalononitriles. These include polymerization[28,37,211,212] and reverse aldol reactions.[28] If sodium in an inert solvent is used to prepare the enolates of alkylidene esters partial reduction may occur (p. 119).

The products obtained from the alkylation of alkylidene derivatives of malonic ester,[64,213] cyanoacetic ester,[64,214-217] malononitriles,[215,216] and mononitriles[171] with allylic halides have been found to undergo thermal isomerization in certain cases, and the products must be distilled at temperatures that do not cause rearrangement. For the various active methylene compounds used, the rates of such rearrangements fall in the order: malononitriles > cyanoacetic esters > malonic esters.[171,213,215,216]

$$CH_2=C-CH_3$$
$$\begin{array}{c} CH_2=C-CH_3 \\ \diagdown \\ C(CO_2C_2H_5)_2 \\ \diagup \\ CH_3CH=CHCH_2 \end{array} \xrightarrow{185°} \begin{array}{c} CH_2-CCH_3 \\ | \quad \| \\ | \quad C(CO_2C_2H_5)_2 \\ | \\ CH_3CH-CH=CH_2 \\ 90\% \end{array}$$

Steric effects influence markedly the ease of these rearrangements.[213,215]

[208] Conrad, *Ann.*, **209**, 241 (1881).

[209] Pyman, *J. Chem. Soc.*, **99**, 1386 (1911).

[210] Gol'mov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **23**, 1162 (1953) [*C. A.*, **47**, 12255 (1953)].

[211] Cope and Hoyle, *J. Am. Chem. Soc.*, **63**, 733 (1941).

[212] Cope, U.S. pat. 2,222,455 [*C. A.*, **35**, 1802 (1941)].

[213] Aldridge and Murphy, *J. Am. Chem. Soc.*, **73**, 1158 (1951).

[214] Cope and Hardy, *J. Am. Chem. Soc.*, **62**, 441 (1940).

[215] Cope, Hoyle, and Heyl, *J. Am. Chem. Soc.*, **63**, 1843 (1941).

[216] Foster, Cope, and Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).

[217] Cope and Field, *J. Am. Chem. Soc.*, **71**, 1589 (1949).

## The Active Methylene Compound

**Malonic Esters (Table I).** In the many alkylations reported to yield monoalkylmalonic esters, the base-solvent combination generally employed was sodium ethoxide in ethanol. As noted previously (p. 120) such reaction conditions inhibit dialkylation since, in most cases, the monoalkyl derivative is less acidic than ethanol. This advantage, which is not shared with cyanoacetic ester and malononitrile, recommends malonic ester if only the monoalkyl compound is desired. The separation problem that arises in the preparation of methylmalonic esters and ethylmalonic esters (p. 123) is best avoided by employing an alternative synthetic method (p. 147) for these esters. The use of the ethoxymagnesium salt of malonic ester rather than sodiomalonic ester is a valuable modification[55,56,150,218-220] if the alkylation is to be run in an inert solvent such as ether or benzene (p. 116). Diethyl carbonate (pp. 117, 128) offers advantages as the solvent in some instances.

**Substituted Malonic Esters (Tables II, III, and IV) and Alkylidenemalonic Esters (Table V).** The reduced acidity[5] of monoalkylmalonic esters (p. 110) in which the alkyl group is secondary or tertiary[44,52,145-149,221-226] has resulted in low yields during alkylations in the presence of ethanolic sodium ethoxide. This difficulty, which is much less serious with the analogous cyanoacetic esters (p. 134), has been overcome by recourse to stronger bases and less acidic solvents. The use of sodium $t$-butoxide in $t$-butyl alcohol has permitted the alkylation of diethyl isopropylmalonate,[35] diethyl (1-ethylbutyl)malonate,[35] and diethyl cyclohexylmalonate.[35] Diethyl diisopropylmalonate was prepared by the use of sodium and ether at elevated temperatures in a sealed tube.[52] Diethyl ethyl-($sec$-butyl)malonate was obtained in 95% yield when the ethanol-free sodium enolate of diethyl $sec$-butylmalonate was heated with ethyl bromide in diethyl carbonate.[44,51,227]Another striking demonstration of the value of this method is found in the alkylation of diethyl $t$-butylmalonate with allyl bromide, the reaction being effected in 36% yield in the presence of sodium ethoxide and diethyl carbonate.[44] Benzene and toluene have

[218] Fuson and Jackson, *J. Am. Chem. Soc.*, **72**, 351 (1950).
[219] Ali-Zade and Arbuzov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **13**, 113 (1943) [*C. A.*, **38**, 352 (1944)].
[220] Terent'ev, *J. Russ. Phys.-Chem. Soc.*, **60**, 85 (1928) [*C. A.*, **22**, 3880 (1928)].
[221] Conrad and Guthzeit, *Ann.*, **222**, 249 (1883).
[222] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).
[223] Bischoff, *Ber.*, **29**, 972 (1896).
[224] Cope and Lyman, *J. Am. Chem. Soc.*, **75**, 3312 (1953).
[225] Marshall, *J. Chem. Soc.*, **1930**, 2754.
[226] Weizmann, Sulzbacher, and Bergmann, *J. Chem. Soc.*, **1947**, 772.
[227] Wallingford and Homeyer, U.S. pat. 2,391,530 [*C. A.*, **40**, 3770 (1946)].

served as solvents for the alkylation of the sodium salts of diethyl benz-hydrylmalonate[156] and dibenzhydryl benzhydrylmalonate[224] with benz-hydryl bromide.

The introduction of a phenyl group reduces the acidity of diethyl malonate or ethyl phenylacetate, the reduction in acidity being comparable with that resulting from the introduction of a methyl group (p. 110).[5] An explanation for this phenomenon may be the non-coplanarity of the phenyl derivative, which inhibits effective resonance stabilization of the enolate anion.

Alkylation of chloromalonic ester is successful only with very reactive alkylating agents (p. 131).[209,228-230] With less reactive alkylating agents, coupling of the malonic ester residues[231] or ether formation is the predominant reaction. In the alkylation of nitromalonic ester, the alkyl group is introduced on the carbon atom[183] rather than on an oxygen atom. Whereas the alkylation of aminomalonic esters results in both C- and N-alkylation,[232] formamido, acetamido, benzamido, and phthalimido derivatives of malonic ester can be alkylated without N-alkylation. The formamido- and acetamido-malonates are most useful since the phthalimido derivatives are hydrolyzed and decarboxylated with difficulty[233] and many of the alkyl(benzamido)malonic esters are oils.[232] The facile deacylation of formamidomalonates and acetamidomalonates may be disadvantageous if the alkylation reaction is slow. The yields of the isopropyl derivative obtained with diethyl acetamidomalonate (37%)[234,235] and with diethyl benzamidomalonate (66%)[233] are explicable in terms of the greater susceptibility of the acetamido group to alcoholysis. The absence of alcohol in the reaction mixture has proved advantageous in the alkylation of diethyl phthalimidomalonate with 1,3-dibromopropane and with γ-phthalimidopropyl bromide.[236]

The alkylation of alkylidenemalonic esters produces the α-alkyl derivative of the corresponding β,γ-unsaturated ester. The accompanying

$$CH_3CH_2C(CH_3)\!\!=\!\!C(CO_2C_2H_5)_2 + n\text{-}C_3H_7Br \xrightarrow{\ NaNH_2\ }$$
$$CH_3CH\!\!=\!\!C(CH_3)C(n\text{-}C_3H_7)(CO_2C_2H_5)_2$$

example[237] illustrates the shift of the double bond to yield the more highly

[228] Perkin, J. Chem. Soc., **53**, 1 (1888).

[229] Kipping, J. Chem. Soc., **53**, 21 (1888).

[230] Titley, J. Chem. Soc., **1928**, 2571.

[231] Kötz and Zörnig, J. prakt. Chem., [2] **74**, 425 (1906).

[232] Albertson, J. Am. Chem. Soc., **68**, 450 (1946).

[233] Redemann and Dunn, J. Biol. Chem., **130**, 341 (1939).

[234] Atkinson and Scott, J. Chem. Soc., **1949**, 1040.

[235] Snyder, Shekleton, and Lewis, J. Am. Chem. Soc., **67**, 310 (1945).

[236] Sörensen, Hoppe-Seyler's Z. physiol. Chem., **44**, 448 (1905).

[237] Cope and Hancock, J. Am. Chem. Soc., **60**, 2901 (1938).

substituted vinyl derivative, which occurs when the double bond can migrate into either of two positions. As with saturated alkylmalonic ester derivatives, chain branching markedly reduces the acidity of alkylidenemalonic esters. Although sodium ethoxide may serve as the base for the alkylation of alkylidenemalonic esters derived from aldehydes,[28] the branched alkylidene derivatives prepared from ketones require a stronger base.[237] Since the use of sodium in an inert solvent causes reduction of the alkylidene derivative (p. 119), sodium amide in liquid ammonia or in an inert solvent has proved to be most satisfactory for the preparation of enolates from alkylidenemalonic esters derived from ketones.

**Cyanoacetic Esters** (Table VI). Like malonic esters, cyanoacetic esters are usually alkylated in the presence of ethanolic sodium ethoxide. The increased importance of dialkylation (p. 121) as a side reaction attending the alkylation of cyanoacetic esters has been discussed. The high order of reactivity of the ethyl cyanoacetate enolate has been utilized advantageously to prevent side reactions with very reactive alkylating agents;[238] in such cases reaction of the alkylating agent with the enolate anion is apparently more rapid than the reaction of the alkylating agent with the base or the solvent.

**Substituted Cyanoacetic Esters** (Tables VII and VIII) **and Alkylidenecyanoacetic Esters** (Table IX). The use of cyanoacetic esters rather than malonic esters is recommended if the preparation of a dialkyl derivative is desired. Monoalkyl derivatives of cyanoacetic ester are readily alkylated in the presence of ethanol and sodium ethoxide even if the first alkyl group introduced is branched.[145,225,226,238-240] This property both simplifies the preparation of dialkylcyanoacetic esters and eliminates the need to introduce the primary alkyl group in the first stage of the alkylation as often must be done with malonic esters (p. 123). For example, ethyl ethyl(isopropyl)cyanoacetate was prepared in 86% yield from ethyl isopropylcyanoacetate and ethyl iodide,[239] whereas diethyl ethyl(isopropyl)malonate was obtained from diethyl isopropylmalonate under similar conditions in very poor yield.[145]

Ethyl acetamidocyanoacetate[232,241,242] and methyl (phenylacetamido)-cyanoacetate[243-245] have been alkylated in the presence of alcoholic

[238] Tabern and Volwiler, *J. Am. Chem. Soc.*, **56**, 1139 (1934).
[239] Fischer, Rohde, and Brauns, *Ann.*, **402**, 364 (1914).
[240] Fischer and Flatau, *Ber.*, **42**, 2981 (1909).
[241] Albertson and Tullar, *J. Am. Chem. Soc.*, **67**, 502 (1945).
[242] Fields, Walz, and Rothchild, *J. Am. Chem. Soc.*, **73**, 1000 (1951).
[243] Ehrhart, *Chem. Ber.*, **82**, 60 (1949).
[244] Ehrhart, *Chem. Ber.*, **82**, 387 (1949).
[245] Horner and Medem, *Chem. Ber.*, **85**, 520 (1952).

sodium alkoxides without difficulty. Sodium hydride has been recommended as the base for the alkylation of acetamidomalonic ester and acetamidocyanoacetic ester.[246]

The alkylation of alkylidenecyanoacetic esters derived from aldehydes has failed because these alkylidene derivatives are rapidly polymerized in the presence of bases.[212] Aside from the fact that only the alkylidene-malonic esters derived from the simplest ketones are available,[37,74] the use of alkylidenecyanoacetic esters derived from ketones rather than the malonic ester analogs offers an advantage in that the cyanoacetate derivatives may be alkylated in the presence of ethanolic sodium ethoxide.[37] However, sodium isopropoxide in isopropyl alcohol has been recommended for the alkylation of secondary alkylidenecyanoacetic esters.[37,211,247]

**Malononitriles (Table X) and Alkylidenemalononitriles (Table IX).** Malononitrile, monoalkylmalononitriles, and alkylidene-malononitriles have been alkylated in the presence of ethanolic sodium ethoxide. However, the usefulness of the reaction is often limited by the simultaneous addition of the alcohol to one of the nitrile groups of the product[95,104,211] to produce an imido ester (p. 128). In addition the alkylidenemalononitriles derived from aldehydes polymerize very readily.[211] The use of malononitrile to form monoalkyl derivatives is limited by the ease with which it is dialkylated.[95]

**Monocarboxylic Esters (Table XI), 3-Aryl-2-benzofuranones (Table XII), and Succinic, Glutaric and Glutaconic Esters (Table XIII).** Either sodium amide or sodium triphenylmethide in an inert solvent is the base most often used to produce the enolates of monocarboxylic esters. These sodium enolates have been alkylated with alkyl and allyl halides, with dihalogenated alkanes[248] with phenacyl bromide,[248] with nitroaryl halides,[248] with 4,7-dichloroquinoline,[178] with epoxides,[69] with dialkyl sulfates,[249] and with alkyl sulfonates.[69] In contrast to the mono-nitriles (p. 136), dialkylation is not a serious problem. The 3-aryl-2-benzofuranones most often have been alkylated by treatment with sodium or potassium metal in an inert solvent followed by treatment with an alkylating agent. Several α-bromoglutaric esters have been converted to the corresponding cyclopropane derivatives by self-alkylation, the base used being sodium carbonate or potassium hydroxide.[80,250]

As cited previously (p. 110), the acidity of acetic esters is reduced by alkyl substitution especially if the alkyl group is branched.[5] Although the acidity of ethyl acetate is enhanced by the substitution of one phenyl group

[246] Shapira, Shapira, and Dittmer, *J. Am. Chem. Soc.*, **75**, 3655 (1953).

[247] Mitter and Dutta, *J. Indian Chem. Soc.*, **25**, 306 (1948).

[248] Wislicenus and Mocker, *Ber.*, **46**, 2772 (1913).

[249] Bowden, *J. Am. Chem. Soc.*, **60**, 131 (1938).

[250] Perkin and Thorpe, *J. Chem. Soc.*, **75**, 48 (1899).

on the $\alpha$-carbon atom, further substitution diminishes the acidity, the order of decreasing acidity being $C_6H_5CH_2CO_2C_2H_5 > (C_6H_5)_2CHCO_2C_2H_5 > C_6H_5CH(CH_3)CO_2C_2H_5.$[5]

Glutaconic esters, which are vinylogs of malonic ester, may be converted to their enolate anions with less basic reagents (sodium ethoxide or potassium ethoxide) than are required for saturated dicarboxylic esters. The greater acidity of the glutaconic esters may be ascribed to the increased resonance stabilization of their enolate anions. The reaction mixtures obtained from the alkylation of glutaconic esters may be complex, since four different isomers, two of which are racemic mixtures, may be formed. The structures of the alkylated products are difficult to determine, since the hydrolytic conditions required to convert the esters to the solid dicarboxylic acids often cause further isomerization. The isomer that predominates in the reaction product obtained from the alkylation of a glutaconic ester is apparently determined by the nature of the substituents in the product.[251] The alkylation of $\alpha$- (or $\gamma$-)-substituted glutaconic

$$C_2H_5O_2CCH\!\!=\!\!CH\!\!-\!\!CH_2CO_2C_2H_5 \xrightarrow{\text{B}^{\ominus}}$$
$$\underset{\gamma}{} \quad \underset{\beta}{} \quad \underset{\alpha}{}$$



esters has led to the formation of $\alpha,\gamma$-disubstituted glutaconic esters.[252,253]

$$C_2H_5O_2CCH\!\!=\!\!CHCH(CH_2C_6H_5)CO_2C_2H_5 \xrightarrow{\text{KOC}_2\text{H}_5,\ \text{CH}_3\text{I}}$$
$$C_2H_5O_2CC(CH_3)\!\!=\!\!CHCH(CH_2C_6H_5)CO_2C_2H_5$$
$$+\ C_2H_5O_2CCH(CH_3)CH\!\!=\!\!C(CH_2C_6H_5)CO_2C_2H_5$$

**Mononitriles (Table XIV) and Alkylideneacetonitriles (Table XV).** Acetonitrile as well as mono- and di-substituted acetonitriles have been alkylated in the presence of sodium amide in an inert solvent. The use

[251] Gidvani and Kon, *J. Chem. Soc.*, **1932**, 2443.

[252] Thorpe and Wood, *J. Chem. Soc.*, **103**, 1752 (1913).

[253] Kon and Watson, *J. Chem. Soc.*, **1932**, 2434.

of the base potassium amide in a mixture of liquid ammonia and ether as the solvent has proved advantageous for the alkylation of phenylacetonitrile and diphenylacetonitrile.[195] The alkylating agents employed include alkyl and allyl halides, dihalogenated alkanes, chloropyridines, chloroquinolines, epoxides, dialkyl sulfates, and alkyl sulfonates. In some instances elevated reaction temperatures favor dialkylation,[53] elimination of the cyano group,[91,191-193] or dimerization of the nitrile.[71-73] When 2- or 4-chloropyridines or 4-chloroquinolines were employed as the alkylating agent for phenylacetonitrile the yield of product did not exceed 50% unless two equivalents of sodium amide were used.[178,254] This result has been attributed to the formation of an insoluble sodium salt which removed an additional equivalent of base from the reaction mixture.[178]

The metal salts of primary and secondary amines have been used as bases for the alkylation of mononitriles.[53,66,255] Sodium hydroxide and potassium hydroxide have also served as bases for the alkylation of nitriles.[34,75-79,256,257]



Aldehydes[258,259] and ketones[171,193,259] condense readily with mononitriles. The alkylidene derivatives formed from ketones are best converted to their sodium enolates with sodium amide. Thus the alkylation of cyclohexylidene(phenyl)acetonitrile failed in ethanolic sodium ethoxide;[259] with the stronger base sodium amide in benzene or ether, alkylated products were obtained in yields of 77–82%.[171]

## Alkylating Agents

**Halogens.** The addition of bromine or iodine to an enolate often results in the coupling of two molecules of the active methylene compound. The

[254] Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951).
[255] Ziegler, Ger. pat. 583,561 [*C. A.*, **28**, 1057 (1934)].
[256] Meyer, *Ann.*, **250**, 118 (1888).
[257] Haller and Benoist, *Ann. chim. Paris*, [9] **17**, 25 (1922).
[258] Murray and Cloke, *J. Am. Chem. Soc.*, **58**, 2014 (1936).
[259] McRae and Manske, *J. Chem. Soc.*, **1928**, 484.
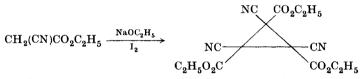
probable course of the reaction[107,260,261] will be seen to resemble the course of an analogous side reaction involving vicinal dihalides (p. 125). Similar dimeric products have been formed from monocarboxylic esters,[67,69,248] 3-aryl-2-benzo-furanones,[262,263] and mononitriles.[264] However, the enolates of some monosubstituted malonic esters formed only the iodinated derivative of the active methylene compound when treated with iodine.[265] That monosubstitution need not always inhibit this coupling reaction is indicated by the treatment of various polymethylene-$\alpha,\omega$-dimalonic esters with iodine and a base; the corresponding carbocycles are formed.[87,266-269]

$$C_2H_5CH[CH(CO_2C_2H_5)_2]_2 + 2NaOC_2H_5 + I_2 \rightarrow$$

$$H_5C_2CH \begin{array}{c} C(CO_2C_2H_5)_2 \\ | \\ C(CO_2C_2H_5)_2 \end{array} + 2NaI + 2C_2H_5OH$$

When the sodium enolate of ethyl cyanoacetate is treated with iodine a cyclic trimer is formed;[270-272] the same product results when ethyl bromocyanoacetate is heated with aniline in ether.[273]

$$CH_2(CN)CO_2C_2H_5 \xrightarrow[I_2]{NaOC_2H_5}$$

**Alkyl Halides.** In reactivity as alkylating agents for active methylene compounds the various halogenated organic compounds lie in the order observed for other bimolecular nucleophilic displacement reactions; the allyl and benzyl halides are more reactive than the alkyl halides,[274] which in turn are more reactive than the vinyl[54,275-277] and aryl[142,278] halides.

[260] Bischoff and Rach, *Ber.*, **17**, 2781 (1884).
[261] Lennon and Perkin, *J. Chem. Soc.*, **1928**, 1513.
[262] Löwenbein and Simonis, *Ber.*, **57**, 2040 (1924).
[263] Löwenbein, *Ber.*, **58**, 601 (1925).
[264] Auwers and Meyer, *Ber.*, **22**, 1227 (1889).
[265] Bischoff and Hausdörfer, *Ann.*, **239**, 110 (1887).
[266] Perkin, *J. Chem. Soc.*, **51**, 1 (1887).
[267] Perkin, *J. Chem. Soc.*, **51**, 240 (1887).
[268] Perkin, *J. Chem. Soc.*, **65**, 572 (1894).
[269] Haworth and Perkin, *J. Chem. Soc.*, **65**, 591 (1894).
[270] Errera and Perciabosco, *Ber.*, **33**, 2976 (1900).
[271] Engler and Meyer, *Ber.*, **38**, 2486 (1905).
[272] Thorpe and Young, *J. Chem. Soc.*, **77**, 937 (1900).
[273] Goldthwaite, *Am. Chem. J.*, **30**, 447 (1903).
[274] Noller and Adams, *J. Am. Chem. Soc.*, **48**, 2444 (1926).
[275] Benary and Schinkopf, *Ber.*, **56**, 354 (1923).
[276] V. Voorhees, Ph.D. Dissertation, University of Wisconsin, 1924.
[277] Heyl and Cope, *J. Am. Chem. Soc.*, **65**, 669 (1943).
[278] Dox and Thomas, *J. Am. Chem. Soc.*, **45**, 1811 (1923).

Likewise, for a given alkyl group the iodide is more reactive than the bromide,[34,37,40,142,234,279-281] which is more reactive than the chloride,[282-284] the fluoride being almost inert.[285] Since very reactive halogen compounds favor dialkylation (p. 121), it is usually advisable to select the least reactive halide as an alkylating agent where dialkylation is expected to be a serious side reaction.[140,280]

Alkyl halides that are readily dehydrohalogenated (e.g., tertiary alkyl halides) are unsuitable alkylating agents (p. 124), since the yield of alkylated product is materially reduced by the loss of both base and alkyl halide which accompanies dehydrohalogenation.[44,149,168,286] For example, one-third of the cyclohexyl bromide employed in the alkylation of diethyl malonate was converted to cyclohexene.[286]

Although the alkyl bromides are usually the most satisfactory alkylating agents, the alkyl chloride is recommended when the corresponding alkyl bromide is very reactive. If the alkyl bromide is relatively unreactive, use of the corresponding alkyl iodide is preferable. If the desired alkyl iodide is not available a satisfactory alternative employs mixtures of the alkyl bromide or alkyl chloride with sodium iodide[70,287-289,291] or potassium iodide[290,292] in alcoholic media.

**Di- and Poly-halides.** Alkylation reactions involving methylene chloride,[293,294] methylene bromide,[295] and methylene iodide[296-300] have been found to proceed normally. Such dihalides have been especially valuable for the preparation of cyclic systems.[296,299-302] However, a

[279] Rossolymo, *Ber.*, **22**, 1233 (1889).
[280] Bischoff, *Ber.*, **28**, 2616 (1895).
[281] Kuhn, Köhler, and Köhler, *Hoppe-Seyler's Z. physiol. Chem.*, **242**, 171 (1936).
[282] Rothstein, *Bull. soc. chim. France*, [5] **2**, 80 (1935).
[283] Noyes and Cox, *J. Am. Chem. Soc.*, **25**, 1093 (1903).
[284] Dey and Doraiswami, *J. Ind. Chem. Soc.*, **10**, 309 (1933).
[285] Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).
[286] Eykman, *Chem. Weekblad*, **6**, 699 (1909).
[287] Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **9**, 99 (1942).
[288] Gagnon, Savard, Gaudry, and Richardson, *Can. J. Research*, **25B**, 28 (1947).
[289] Birch and Robinson, *J. Chem. Soc.*, **1942**, 488.
[290] Rajzman, *Bull. soc. chim. France*, **1948**, 754.
[291] Buu-Hoï, Cagniant, and Janicaud, *Compt. rend.*, **212**, 1105 (1941).
[292] Pineau, *J. recherches centre natl. recherche sci.*; *Labs. Bellevue Paris*, **1951**, 292 [*C. A.*, **46**, 416 (1952)].
[293] Perkin and Prentice, *J. Chem. Soc.*, **59**, 990 (1891).
[294] Tutin, *J. Chem. Soc.*, **91**, 1141 (1907).
[295] Perkin and Scarborough, *J. Chem. Soc.*, **119**, 1400 (1921).
[296] Dressel and Guthzeit, *Ann.*, **256**, 171 (1890).
[297] Guthzeit and Dressel, *Ber.*, **21**, 2233 (1888).
[298] Zelinsky, *Ber.*, **22**, 3294 (1889).
[299] Perkin, *J. Chem. Soc.*, **59**, 798 (1891).
[300] Kötz and Stalmann, *J. prakt. Chem.*, [2] **68**, 156 (1903).
[301] Pospischill, *Ber.*, **31**, 1950 (1898).
[302] Thole and Thorpe, *J. Chem. Soc.*, **99**, 2183 (1911).

similar reaction involving benzylidene chloride and tetraethyl 1,1,5,5-pentanetetracarboxylate led to the formation of the doubly unsaturated

$$\text{CH}_2[\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2]_2 + \text{CH}_2\text{I}_2 \xrightarrow{\text{NaOC}_2\text{H}_5}$$

acid $\alpha,\alpha'$-dibenzylidenepimelic acid, after saponification and decarboxylation,[303] rather than a cyclic compound.

Chloroform, bromoform, iodoform, ethyl trichloroacetate, carbon tetrachloride, and carbon tetrabromide all react with diethyl sodiomalonate to form diethyl $\alpha,\gamma$-dicarbethoxyglutaconate, although a similar reaction with 1,1,1-trichloroethane failed. Analogous products are formed with

$$\text{CHCl}_3 + 2\text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{\text{NaOC}_2\text{H}_5} (\text{C}_2\text{H}_5\text{O}_2\text{C})_2\text{CHCH}=\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2$$

other active methylene compounds including ethyl cyanoacetate and malononitrile.[231] If monoalkylmalonic esters are utilized in a similar reaction, a mixture of products is formed in which either one or two of the halogen atoms of the haloform is retained.[231]

$$\text{CH}_3\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2 + \text{CHCl}_3 \xrightarrow{\text{Na, (C}_2\text{H}_5)_2\text{O}} \text{Cl}_2\text{CHC}(\text{CH}_3)(\text{CO}_2\text{C}_2\text{H}_5)_2$$
$$+ (\text{C}_2\text{H}_5\text{O}_2\text{C})_2\text{C}(\text{CH}_3)\text{CHClC}(\text{CH}_3)(\text{CO}_2\text{C}_2\text{H}_5)_2$$

$\alpha,\omega$-Polymethylene dihalides have served as useful alkylating agents for the preparation of carbocyclic compounds with ring sizes ranging from three to seven.[92,170,269,304-310] A competing reaction results in the

$$\text{Br}(\text{CH}_2)_5\text{Br} + \text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow{\text{NaOC}_2\text{H}_5, \text{C}_2\text{H}_5\text{OH}}$$
$$+ (\text{C}_2\text{H}_5\text{O}_2\text{C})_2\text{CH}(\text{CH}_2)_5\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$$

[303] Perkin and Prentice, *J. Chem. Soc.*, **59**, 818 (1891).

[304] Dox and Yoder, *J. Am. Chem. Soc.*, **43**, 1366 (1921).

[305] Knowles and Cloke, *J. Am. Chem. Soc.*, **54**, 2028 (1932).

[306] Case, *J. Am. Chem. Soc.*, **56**, 715 (1934).

[307] Weston, *J. Am. Chem. Soc.*, **68**, 2345 (1946).

[308] Haworth and Perkin, *J. Chem. Soc.*, **65**, 86 (1894).

[309] Carpenter and Perkin, *J. Chem. Soc.*, **75**, 921 (1899).

[310] Best and Thorpe, *J. Chem. Soc.*, **95**, 685 (1909).

simultaneous formation of the tetralkyl polymethylene-$\alpha,\omega$-dimalonate.[311] Although this tetracarboxylic ester is usually formed by attack of two diethyl malonate anions on the dihalide,[312] the cyclopropane derivative obtained when ethylene dibromide serves as the alkylating agent has been found to be susceptible to attack by the enolate of an active methylene compound.[310,312-314] Thus the tetracarboxylic ester could be formed by either of two routes. The yield of the cyclopropane is better if ethyl cyanoacetate is substituted for diethyl malonate. As would be anticipated, the use of a large volume of solvent favors intramolecular alkylation leading to a cyclic product.[210,307]

$$BrCH_2CH_2Br + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow Br(CH_2)_2CH(CO_2C_2H_5)_2 + Br^{\ominus}$$

$$Br(CH_2)_2CH(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} \begin{array}{c} CH_2 \\ \diagdown \\ \diagup \\ CH_2 \end{array}\hspace{-0.3em} C(CO_2C_2H_5)_2$$

$$Br(CH_2)_2CH(CO_2C_2H_5)_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow (C_2H_5O_2C)_2CH(CH_2)_2\overset{\overset{\displaystyle CO_2C_2H_5}{|}}{\underset{\underset{\displaystyle CO_2C_2H_5}{|}}{C}H}$$

$$\begin{array}{c} CH_2 \\ \diagdown \\ \diagup \\ CH_2 \end{array}\hspace{-0.3em} C(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5}$$

A similar synthesis of cyclopropane derivatives utilizes 1,4-dibromo-2-butene as the alkylating agent.[20] The major products are tetraethyl 2-vinyl-1,1,4,4-butanetetracarboxylate and diethyl 2-vinyl-1,1-cyclopropanedicarboxylate, the cyclopropane derivative apparently having been formed by an intramolecular $S_N2'$ process (p. 112).

$$BrCH_2CH{=}CHCH_2Br + CH_2(CO_2C_2H_5)_2 \xrightarrow[C_2H_5OH]{NaOC_2H_5}$$

$$CH_2{=}CH{-}\underset{\diagdown\ \ \diagup}{\underset{CH_2}{CH{-}C}}(CO_2C_2H_5)_2 + CH_2{=}CH{-}\underset{\underset{\displaystyle CH_2CH(CO_2C_2H_5)_2}{|}}{CHCH}(CO_2C_2H_5)_2$$

$$+ (C_2H_5O_2C)_2CHCH_2CH{=}CHCH_2CH(CO_2C_2H_5)_2$$

It has proved difficult to arrest the reaction of polymethylene dihalides and sodiomalonic ester at the monoalkylation stage, since the intramolecular and intermolecular dialkylation reactions described previously

[311] Freer and Perkin, *J. Chem. Soc.*, **53**, 215 (1888).
[312] Bone and Perkin, *J. Chem. Soc.*, **67**, 108 (1895).
[313] Mitchell and Thorpe, *J. Chem. Soc.*, **97**, 997 (1910).
[314] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1952**, 3616.

often predominate.   However, diethyl $\gamma$-bromopropylmalonate has been prepared in 70% yield by the use of a large excess of 1,3-dibromopropane with diethyl malonate.[131]   An alternative synthesis for such compounds involves the initial formation of a terminal methylene derivative of malonic ester followed by the peroxide-catalyzed addition of hydrogen bromide.[210,315]

$$CH_2{=}CHCH_2Br + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow CH_2{=}CHCH_2CH(CO_2C_2H_5)_2 + \overset{\ominus}{Br}$$

$$CH_2{=}CHCH_2CH(CO_2C_2H_5)_2 + HBr \xrightarrow[\text{catalyst}]{\text{Peroxide}} Br(CH_2)_3CH(CO_2C_2H_5)_2$$

Monoalkylation of diethyl sodiomalonate with 1-chloro-3-iodopropane would be expected to produce diethyl $\gamma$-chloropropylmalonate, displacement having involved the more reactive carbon-iodine bond.   However, the alcohol-soluble sodium iodide produced in the reaction mixture converted the chloro ester in part to the corresponding iodo compound. When excess sodium iodide was added to the reaction mixture, only diethyl $\gamma$-iodopropylmalonate could be isolated.[92]   In the preparation of diethyl ($\beta$-chloroethyl)isoamylmalonate from 1-chloro-2-iodoethane and diethyl isoamylmalonate this problem was avoided by the use of a benzene solution in which sodium iodide is insoluble.[316]

Where one of the halogens of the dihalide is bonded to a secondary carbon atom, some dehydrohalogenation may be expected to accompany alkylation.[160]   Halogen atoms bonded to tertiary carbon atoms are lost as the corresponding hydrogen halide.[173,317,318]

As described earlier (p. 125) certain vicinal dihalides, especially those compounds in which the halogen atoms are bonded to secondary and tertiary carbon atoms, tend to lose the halogen with the resulting formation of an olefin and the coupled product from two molecules of the active methylene compound.   Other vicinal dihalides such as 1,2-dichlorocyclohexane,[150] 1,2-dibromocyclohexane,[150,286,319] 1,2-dibromotetrahydronaphthalene,[150,320] and   2,3-dibromodecahydronaphthalene[150]   undergo

$$\langle \rangle \text{Cl} + NaOC_2H_5 \rightarrow \langle \rangle \text{Cl} + NaCl + C_2H_5OH$$

$$\langle \rangle \text{Cl} + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow \langle \rangle CH(CO_2C_2H_5)_2 + Cl^{\ominus}$$

[315] Walborsky, *J. Am. Chem. Soc.*, **71**, 2941 (1949).

[316] Rosenberg, Kneeland, and Skinner, *J. Am. Chem. Soc.*, **56**, 1339 (1934).

[317] Polgar and Robinson, *J. Chem. Soc.*, **1945**, 389.

[318] Ipatiew, *J. prakt. Chem.*, [2] **59**, 542 (1899).

[319] Gunstone and Heggie, *J. Chem. Soc.*, **1952**, 1354.

[320] Mousseron and Du, *Bull. soc. chim. France*, [5] **11**, 118 (1944).

both alkylation and dehydrohalogenation reactions. Thus the product formed from the 1,2-dihalocyclohexanes was the same as the product formed from 2-cyclohexenyl chloride[150] or 2-cyclohexenyl bromide.[319] Since the alkylation of 1,2-dichlorocyclohexane with diethyl sodiomalonate proceeds much more rapidly than the analogous reaction with cyclohexyl chloride,[150] dehydrochlorination is presumed to be the first step in the reaction sequence. With 2,3-dibromotetrahydronaphthalene only dehydrohalogenation occurred, the product being naphthalene.[320]

The reaction of 1,2-dithiocyanocyclohexane with diethyl malonate is completely analogous to the reaction of the 1,2-dihalocyclohexanes. One thiocyano group is lost in an elimination reaction, and the other group is displaced with the production of diethyl 2-cyclohexenylmalonate.[322]

**Vinyl and Aryl Halides.** Although vinyl and aryl halides, being inert to nucleophilic displacement reactions, are generally of no value as alkylating agents, several successful alkylation reactions involving such halides have been reported. Thus 1,2-dibromoethylene reacted with diethyl ethylmalonate to yield diethyl ethyl-($\beta$-bromovinyl)malonate.[54] However, 1,2-dichloroethylene failed to alkylate malonic ester.[275] The successful alkylation of acetonitrile with chlorobenzene in the presence of potassium amide and liquid ammonia[323] may be likened to the conversion of chlorobenzene to aniline under similar conditions,[324] in which the amino group may become attached either to the carbon atom from which the chlorine atom is displaced or to an adjacent carbon atom. It is not known whether the position at which the cyanomethyl group enters and the position occupied by the leaving chlorine atom are the same.

If the carbon-halogen bond of the aryl halide is activated by the introduction of electron-attracting groups *ortho* and *para* to the halogen atom, then successful arylation will occur. For example, ethyl *p*-nitrophenylcyanoacetate has been prepared from *p*-nitrochlorobenzene and ethyl cyanoacetate.[325] However, it will be recalled that such electron-attracting substituents also promote decarbethoxylation (p. 127). When diethyl 2,4-dinitrophenylmalonate was treated with 2,4-dinitrobromobenzene in ethanolic sodium ethoxide, only ethyl *bis*-(2,4-dinitrophenyl)acetate could be isolated.[184] Replacement of halogen atoms situated on negatively substituted benzene rings by hydrogen has also been observed during alkylation reactions.[326–328]

[321] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **9**, 111 (1942).
[322] Mousseron and Winternitz, *Bull. soc. chim. France*, [5] **11**, 120 (1944).
[323] Bergstrom and Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).
[324] Roberts, Simmons, Carlsmith, and Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).
[325] Fairbourne and Fawson, *J. Chem. Soc.*, **1927**, 46.
[326] Jackson and Robinson, *Am. Chem. J.*, **11**, 93 (1889).
[327] Jackson and Robinson, *Am. Chem. J.*, **11**, 541 (1889).
[328] Jackson and Robinson, *Ber.*, **21**, 2034 (1888).

The 2- and 4-halopyridines and the 2- and 4-chloroquinolines, whose reactivity may be likened to that of the nitrochlorobenzenes just described, also serve as effective alkylating agents.

**Epoxides.** Epoxides have served as alkylating agents for malonic esters, cyanoacetic esters, monocarboxylic esters, and mononitriles. Except in sterically unfavorable instances,[7] the intermediate hydroxy esters or hydroxy nitriles are converted to the corresponding lactones or cyclic imido esters.[27,329] The same products are formed if the corresponding alkene halohydrins are utilized.

**Dialkyl Carbonates.** The dialkyl carbonates cannot be used to alkylate malonic ester,[330] monocarboxylic esters,[43,129,331,332] or mononitriles[185,186,189,333] because carbethoxylation of the intermediate anion (p. 128) takes precedence over alkylation. With primary alkylmalonic esters the dialkyl carbonates may be used as alkylating agents, the dialkylated product being obtained in yields of 25–80%.[330] The dialkyl carbonates are unsatisfactory alkylating agents for secondary alkylmalonic esters and for alkylcyanoacetic esters.[330]

**Dialkyl Sulfates, Alkyl Sulfonates, and Nitrates.** Both dimethyl sulfate and diethyl sulfate have been used extensively for the alkylation of all types of active methylene compounds. The yields obtained with these alkylating agents and with the corresponding alkyl iodides are usually similar. In addition the high boiling points of the dialkyl sulfates permit the use of higher reaction temperatures without loss of the alkylating agent.[249]

The alkyl benzenesulfonates and the alkyl $p$-toluenesulfonates have been used to advantage as alkylating agents.[69] As in the case of the alkyl halides the yields of alkylated products derived from primary alkyl sulfonates are good, but only fair yields are obtained with the sulfonate esters of secondary alcohols. In addition to their high boiling points, the alkyl sulfonates are valuable alkylating agents where conversion of the corresponding alcohol to the alkyl halide is difficult or involves rearrangement.[238,334,335]

Benzyl nitrate has served as an alkylating agent for malonic ester, both mono- and di-alkylation products being obtained.[336]

[329] Easton, Gardner, and Stevens, *J. Am. Chem. Soc.*, **69**, 2941 (1947).

[330] Wallingford and Jones, *J. Am. Chem. Soc.*, **64**, 578 (1942).

[331] Nelson and Cretcher, *J. Am. Chem. Soc.*, **50**, 2758 (1928).

[332] Hauser, Abramovitch, and Adams, *J. Am. Chem. Soc.*, **64**, 2714 (1942).

[333] Hessler, *Am. Chem. J.*, **32**, 119 (1904).

[334] Braker, Pribyl, and Lott, *J. Am. Chem. Soc.*, **69**, 866 (1947).

[335] Peacock and Tha, *J. Chem. Soc.*, **1928**, 2303.

[333] Nef, *Ann.*, **309**, 171 (1899).

## ALTERNATIVE METHODS OF ALKYLATION

**Reduction of Alkylidene Derivatives (Tables XVI and XVII).**
Synthetic methods applicable to the preparation of alkylidene derivatives of malonic esters,[337-343] cyanoacetic esters,[37, 74, 290, 340, 344-346] and acetonitriles[258,347,348] have been described.   Since alkylidenecyanoacetic esters derived from aldehydes of low molecular weight undergo rapid polymerization,[212] malonic ester is the reagent of choice when an alkylidene derivative is to be prepared from an aldehyde.   However, only the alkylidenemalonic esters derived from acetone, methyl ethyl ketone,[37] cyclopentanone,[74] and cyclohexanone[349] can be prepared easily, a fact that demands the use of cyanoacetic ester for the preparation of the alkylidene derivatives from less reactive ketones.   The reduction of these compounds to the saturated esters or nitriles has been achieved with aluminum amalgam[343,350-353] and with sodium amalgam.[346,354-358]   Alkylidenemalonic esters have been reduced by catalytic hydrogenation in the presence of nickel[340,360] and copper chromite,[340] and both alkylidenemalonic and alkylidenecyanoacetic esters have been reduced in the presence of platinum[340,] or palladium.[217,317,340,346,361,362]   Most alkylidenemalonic esters and alkylidenecyanoacetic esters may be reduced successfully by catalytic hydrogenation over palladium.
The condensation and reduction stages of this type of synthesis may sometimes be combined if a solution of cyanoacetic ester and the carbonyl

[337] Knoevenagel, *Ber.*, **31**, 2585 (1898).
[338] Giral and Guzmán, *Ciencia e invest. Buenos Aires*, **2**, 39 (1946) [*C. A.*, **40**, 5025 (1946)].
[339] Breslow and Hauser, *J. Am. Chem. Soc.*, **62**, 2385 (1940).
[340] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
[341] Goss, Ingold, and Thorpe, *J. Chem. Soc.*, **123**, 3353 (1923).
[342] Baker and Eccles, *J. Chem. Soc.*, **1927**, 2125.
[343] Vogel, *J. Chem. Soc.*, **1928**, 1013.
[344] Hancock and Cope, *Org. Syntheses*, **25**, 44 (1945).
[345] Bagchi, Bergmann, and Bannerjee, *J. Am. Chem. Soc.*, **71**, 989 (1949).
[346] Higginbotham and Lapworth, *J. Chem. Soc.*, **123**, 1618 (1923).
[347] Bodroux, *Bull. soc. chim. France*, [4] **11**, 336 (1912).
[348] Bodroux, *Compt. rend.*, **153**, 350 (1911).
[349] Kon and Speight, *J. Chem. Soc.*, **1926**, 2727.
[350] Henle, *Ann.*, **348**, 16 (1906).
[351] Vogel, *J. Chem. Soc.*, **1928**, 2010.
[352] Vogel and Oommen, *J. Chem. Soc.*, **1930**, 768.
[353] Desai and Sahariya, *J. Univ. Bombay*, **8**, III, 239 (1939) [*C. A.*, **34**, 2803 (1940)].
[354] Claisen and Crismer, *Ann.*, **218**, 139 (1883).
[355] Marckwald, *Ber.*, **21**, 1080 (1888).
[356] Sandelin, *Ber.*, **33**, 489 (1900).
[357] Baker and Lapworth, *J. Chem. Soc.*, **125**, 2333 (1924).
[358] Owen and Nord, *J. Org. Chem.*, **15**, 988 (1950).
[359] Hastings and Cloke, *J. Am. Chem. Soc.*, **56**, 2136 (1934).
[360] Bowden and Adkins, *J. Am. Chem. Soc.*, **62**, 2422 (1940).
[361] Smith and Agre, *J. Am. Chem. Soc.*, **60**, 648 (1938).
[362] Warner and Moe, *J. Am. Chem. Soc.*, **74**, 371 (1952).

component in an acetic acid-piperidine mixture is hydrogenated over palladium on charcoal. This process, termed reductive alkylation, has been found to produce certain alkylcyanoacetic esters in yields of 39–98%.[362-364]

Reductions of alkylidene derivatives and reductive alkylation are advantageous in that dialkylation, a side reaction in alkylation procedures, is avoided.[363] The use of platinum oxide as the catalyst for reductive alkylation may result in partial reduction of the nitrile group in addition to the expected reductive alkylation.[363]

**Addition of Grignard Reagents to Alkylidene Derivatives (Tables XVIII and XIX).** Extensive dehydrohalogenation precludes the use of tertiary alkyl halides for the preparation of tertiary alkyl derivatives of active methylene compounds (pp. 112, 124, 139). Such tertiary alkyl derivatives can be prepared by the addition of Grignard reagents to the alkylidene derivatives obtained by the condensation of malonic or cyano-acetic esters with a ketone. The mode of addition of Grignard reagents to

$$(CH_3)_2C = C(CO_2C_2H_5)_2 + CH_3MgI \rightarrow (CH_3)_3CCH(CO_2C_2H_5)_2$$



substituted cinnamonitriles is dependent on the structure of the unsaturated compound. Normally, 1,2 addition occurs forming an imino compound;[365,366] however, if a large group is bonded to the α-carbon atom, 1,4 addition leading to a saturated nitrile has been observed.[365,366] The addition of aliphatic Grignard reagents to alkylidene derivatives is often accompanied by reduction of the double bond in the alkylidene compound as a side reaction.[367] The substitution of the appropriate dialkyl- or diaryl-cadmium for the Grignard reagent has resulted in the formation of the alkylated product in poor yield.[367] The addition of copper salts to the reaction mixture has been reported to favor the 1,4-addition of Grignard reagents to alkylidenemalonic esters.[368]

**Condensation of Aromatic Compounds with Mesoxalic and Tartronic Esters (Table XX).** Direct alkylation methods usually cannot be applied to the preparation of aryl- and diaryl-malonic esters (p. 143).

[363] Alexander and Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).

[364] Sharp and Dohme, Brit. pat. 606,962 [*C. A.*, **43**, 1436 (1949)].

[365] Kohler, *Am. Chem. J.*, **35**, 386 (1906).

[366] Henze and Swett, *J. Am. Chem. Soc.*, **73**, 4918 (1951).

[367] Prout, Huang, Hartman, and Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).

[368] Brandström and Forsblad, *Arkiv Kemi*, **6**, 561 (1954).

Aryl-substituted malonic esters have been obtained from diethyl mesoxalate, an oxidation product of diethyl malonate.[369]  The aryltartronic esters have been obtained either by the condensation of mesoxalic ester with aromatic hydrocarbons in the presence of sulfuric acid or stannic chloride[370,371] or by the addition of Grignard reagents to mesoxalic ester



at $-70\%$.[372]  Diethyl 9-phenanthryltartronate has been converted to 9-phenanthrylmalonic ester by the replacement of the hydroxyl group by a chlorine atom followed by reduction.[372]

The diarylmalonic esters have been prepared by the condensation of aromatic hydrocarbons with either mesoxalic esters or aryltartronic esters in the presence of sulfuric acid or phosphorus oxychloride.[373]

$$\underset{\text{OH}}{p\text{-}(CH_3)_2NC_6H_4\overset{|}{C}(CO_2C_2H_5)_2} + (CH_3)_2NC_6H_5 \xrightarrow{\text{POCl}_3}$$

$$[p\text{-}(CH_3)_2NC_6H_4]_2C(CO_2C_2H_5)_2$$

**Other Methods.**  Among other methods available for the preparation of alkyl- or aryl-malonic esters is the condensation of diethyl oxalate with the appropriately substituted acetic ester.[179]  The resultant ethoxalyl derivative is then decarbonylated thermally with [374] or without[375-378] powdered soft glass.  This method is of value not only for the preparation

$$C_6H_5CH_2CO_2C_2H_5 + (CO_2C_2H_5)_2 \xrightarrow{\text{NaOC}_2\text{H}_5} C_6H_5CH(CO_2C_2H_5)COCO_2C_2H_5$$

$$C_6H_5CH(CO_2C_2H_5)COCO_2C_2H_5 \rightarrow CO + C_6H_5CH(CO_2C_2H_5)_2$$

[369] Dox, *Org. Syntheses, Coll. Vol.* 1, John Wiley & Sons, New York, 1941, p. 266.
[370] Riebsomer and Irvine, *Org. Syntheses*, **25**, 33 (1945).
[371] Riebsomer, Wiseman, and Condike, *Proc. Indiana Acad. Sci.*, **50**, 80 (1940) [*C. A.*, **35**, 5476 (1941)].
[372] Cope and Field, *J. Org. Chem.*, **14**, 856 (1949).
[373] Guyot and Michel, *Compt. rend.*, **148**, 229 (1909).
[374] Blicke and Zienty, *J. Am. Chem. Soc.*, **63**, 2779 (1941).
[375] Rising and Stieglitz, *J. Am. Chem. Soc.*, **40**, 723 (1918).
[376] Keach, *J. Am. Chem. Soc.*, **55**, 3440 (1933).
[377] Lauer and Hansen, *J. Am. Chem. Soc.*, **61**, 3039 (1939).
[378] Levene and Meyer, *Org. Syntheses, Coll. Vol.* 2, John Wiley & Sons, New York, 1943, p. 288.

of arylmalonic esters unobtainable by direct alkylation,[379] but also for the preparation of low-molecular-weight monoalkylmalonic esters whose separation from the malonic ester and dialkylmalonic ester present in the product obtained by direct alkylation is difficult (p. 123).[69,380,381]

A more direct method of carbethoxylation involves the use of diethyl carbonate in the presence of sodium ethoxide. This method is applicable to the synthesis of alkyl and aryl derivatives of malonic ester[43,129,330–332] and cyanoacetic ester,[185–189,331,333] the best yields being obtained in the case of the aryl derivatives. Dialkylacetic esters cannot be carbethoxylated by this method.[43]

The alkylation of aromatic hydrocarbons with $\alpha$-bromoarylacetic esters, $\alpha$-bromoarylacetonitriles, or $\alpha$-bromodiarylacetonitriles in a Friedel-Crafts reaction has served to produce diarylacetic esters,[382] diarylacetonitriles,[27,382,383] and triarylacetonitriles.[383]

Diethyl cyclopropylmalonate has been prepared from cyclopropane-carboxylic acid by means of the reaction sequence illustrated with the accompanying equations.[384]

$$\begin{array}{c} CH_2 \\ | \rangle CHCOBr \\ CH_2 \end{array} + N_2CHCO_2C_2H_5 \rightarrow \begin{array}{c} CH_2 \\ | \rangle CHCOCN_2CO_2C_2H_5 \\ CH_2 \end{array}$$

$$\begin{array}{c} CH_2 \\ | \rangle CHCOCN_2CO_2C_2H_5 \\ CH_2 \end{array} \xrightarrow{Ag_2O} \begin{array}{c} CH_2 \\ | \rangle CHC{=}C{=}O \\ CH_2 \quad CO_2C_2H_5 \end{array}$$

$$\begin{array}{c} CH_2 \\ | \rangle CHC{=}C{=}O \\ CH_2 \quad CO_2C_2H_5 \end{array} + C_2H_5OH \rightarrow \begin{array}{c} CH_2 \\ | \rangle CHCH(CO_2C_2H_5)_2 \\ CH_2 \end{array}$$

The alkylation of cyanoketene dimethyl acetal with benzyl bromide gave, after acidification, methyl benzylcyanoacetate (21%) and methyl dibenzylcyanoacetate (26%).[385]

[379] Reichstein and Morsman, Helv. Chim. Acta, 17, 1119 (1934).

[380] Floyd and Miller, J. Am. Chem. Soc., 2354 (1947).

[381] Cox and McElvain, Org. Syntheses, Coll. Vol. 2, John Wiley & Sons, New York, 1943, p. 279.

[382] Hoch, Compt. rend., 196, 1617 (1933).

[383] Hoch, Compt. rend., 197, 770 (1933).

[381] Smith and McKenzie, J. Org. Chem., 15, 74 (1950).

[385] McElvain and Schroeder, J. Am. Chem. Soc., 71, 47 (1949).

## SYNTHETIC APPLICATIONS OF THE ALKYLATION REACTION

The alkylation of active methylene compounds affords a convenient synthetic route to mono-, di-, and tri-substituted derivatives of acetic acid and acetonitrile in which the carbon chain of the alkylating agent has been lengthened by two atoms. Substituted acetic acids are often prepared from the corresponding malonic esters by saponification with aqueous alkali (p. 157) followed by decarboxylation of the substituted malonic acid. With ethyl esters the course of the saponification step may be followed by distilling the ethanol from the reaction mixture as it is formed. With low-molecular-weight substituted malonic acids, decarboxylation is most easily effected by boiling a solution of the malonic acid in 20% (constant-boiling) aqueous hydrochloric acid or aqueous sulfuric acid. The saponification and decarboxylation may be done in the same reaction vessel if a calculated excess of concentrated hydrochloric or sulfuric acid is added to the reaction mixture obtained from the saponification.[14,386] It is usually more satisfactory to isolate substituted malonic acids of high molecular weight. These acids lose carbon dioxide when they are heated above their melting points.[387] Alternatively, a solution of the substituted malonic acid in a high-boiling solvent such as xylene may be boiled under reflux until decarboxylation is complete.

$$\begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CO_2C_2H_5)_2 \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CO_2{}^{\ominus}Na^{\oplus})_2 \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CO_2H)_2 \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle CHCO_2H + CO_2$$

The saponification of substituted cyanoacetic esters followed by the thermal decarboxylation of the corresponding cyanoacetic acid yields substituted acetonitriles.

$$\begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CN)CO_2C_2H_5 \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CN)CO_2{}^{\ominus}Na^{\oplus} \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle C(CN)CO_2H \rightarrow \begin{array}{c} R \\ R' \end{array}\!\!\Big\rangle CHCN + CO_2$$

Substituted malonic and cyanoacetic esters may be hydrolyzed and decarboxylated to yield substituted acetic acids in one step by treatment with boiling aqueous acids.[388]

[386] Reid and Ruhoff, *Org. Syntheses, Coll. Vol. 2*, John Wiley & Sons, New York, 1943, p. 474.

[387] Marvel and du Vigneaud, *Org. Syntheses, Coll. Vol. 2*, John Wiley & Sons, New York, 1943, p. 94.

[388] Clarke and Murray, *Org. Syntheses, Coll. Vol. 1*, John Wiley & Sons, New York, 1941, p. 523.

*t*-Butyl,[389] tetrahydropyranyl,[390] and benzhydryl[224] esters of substituted malonic acids undergo fission of the carbon-oxygen bond of the ester in acidic media.   This rapid fission of *t*-butyl esters[392] and tetrahydropyranyl esters[390] has been utilized for the synthesis of easily reducible ketones,[390,393]

$$p\text{-}O_2NC_6H_4COC(CH_2C_6H_5)(CO_2C_4H_9\text{-}t)_2 \xrightarrow{\ H^{\oplus}\ } p\text{-}O_2NC_6H_4COCH_2CH_2C_6H_5$$

$$+ 2CO_2 + 2(CH_3)_2C{=}CH_2$$

by the acidic hydrolysis and decarboxylation of acylmalonic esters.   The use of benzyl esters[394-396] which can be cleaved by hydrogenolysis[397] is not feasible for the synthesis of compounds with easily reducible groups. The use of the acid-labile *t*-butyl and tetrahydropyranyl esters is to be recommended for the preparation of substituted malonic or cyanoacetic acids containing other functions which would not survive the reaction conditions required for the hydrolysis of the ethyl esters.   The reversible nature of the acidic cleavage permits the synthesis of *t*-butyl esters by the condensation of carboxylic acids and isobutylene in an acidic medium;[393] tetrahydropyranyl esters may be prepared similarly from dihydropyran.

$$CH_2(CO_2H)_2 + 2(CH_3)_2C{=}CH_2 + 2H^{\oplus} \rightleftarrows CH_2(CO_2C_4H_9\text{-}t)_2$$

An alternative method for the conversion of diethyl dialkylmalonates to ethyl dialkylacetates involves the removal of a carbethoxyl group at high temperatures.   This change is most easily effected by heating an ethanolic solution of the diethyl dialkylmalonate to 250° in the presence of sodium ethoxide (p. 127).   Under such conditions diethyl diethyl-malonate was converted to ethyl diethylacetate in 82% yield.[180]   When an ethereal solution of diethyl diethylmalonate was heated with 2 gram atoms of sodium metal, carbon monoxide (85%) was evolved and ethyl

[389] Cohen and Schneider, *J. Am. Chem. Soc.*, **63**, 3382 (1941).

[390] Bowman and Fordham, *J. Chem. Soc.*, **1952**, 3945.

[391] Strain, Plati, and Warren, *J. Am. Chem. Soc.*, **64**, 1436 (1942).

[392] Breslow, Baumgarten, and Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

[393] Fonken and Johnson, *J. Am. Chem. Soc.*, **74**, 831 (1952).

[394] Bowman, *J. Chem. Soc.*, **1950**, 325.

[395] Ames and Bowman, *J. Chem. Soc.*, **1951**, 1079.

[396] Bowman and Fordham, *J. Chem. Soc.*, **1951**, 2758.

[397] Hartung and Simonoff in Adams, *Organic Reactions*, Vol. 7, Chapter 5, John Wiley & Sons, New York, 1953, pp. 263–326.

diethylacetate was formed in 46% yield.[398]    Similarly, diethyl diethyl-
malonate, when heated with ethanol-free sodium ethoxide to 220–230°,
yielded ethyl diethylacetate (67%), ether (8%), diethyl carbonate (16%),
ethylene (14%), carbon monoxide (25%), and ethanol.[180]    The diethyl
carbonate was presumably formed from the ethanol generated in the
reaction mixture (p. 127).

Substituted acetic acids prepared by means of the alkylation
reaction have been used to prepare long-chain hydrocarbons of known
structure,[46,141,399,400]    hydrindones,[114,401–410]    tetralones,[321,411–423]    and
hydrotetralones.[424–426]

A number of amino acid syntheses have utilized such starting materials
as chloromalonic ester,[209] alkylmalonic esters,[118,119,132,427–433] aminomalonic

[398] Krollpfeiffer and Rosenberg, *Ber.*, **69**, 465 (1936).

[399] Levene and Taylor, *J. Biol. Chem.*, **54**, 351 (1922).

[400] Grimshaw, Guy, and Smith, *J. Chem. Soc.*, **1940**, 68.

[401] Lecocq, *Ann. chim. Paris*, [12] **3**, 62 (1948).

[402] von Braun and Friedsam, *Ber.*, **65**, 1680 (1932).

[403] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **9**, 119 (1942).

[404] Cagniant, *Bull. soc. chim. France*, [5] **9**, 884 (1942).

[405] Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **10**, 151 (1943).

[406] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

[407] Bruce and Kahn, *J. Am. Chem. Soc.*, **60**, 1017 (1938).

[408] Bruce and Todd, *J. Am. Chem. Soc.*, **61**, 157 (1939).

[409] Fieser and Gates, *J. Am. Chem. Soc.*, **62**, 2335 (1940).

[410] Martin, *J. Chem. Soc.*, **1941**, 679.

[411] Lévy, *Ann. chim. Paris*, [11] **9**, 44 (1938).

[412] Buchta, Galster, and Luther, *Chem. Ber.*, **82**, 126 (1949).

[413] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **9**, 841 (1942).

[414] Buu-Hoï and Cagniant, *Compt. rend.*, **214**, 115 (1942).

[415] Ruzicka and Mingazzini, *Helv. Chim. Acta*, **5**, 710 (1922).

[416] Ruzicka and Ehmann, *Helv. Chim. Acta*, **15**, 140 (1932).

[417] Ruzicka, Ehmann, and Mörgeli, *Helv. Chim. Acta*, **16**, 314 (1933).

[418] Rapson and Short, *J. Chem. Soc.*, **1933**, 128.

[419] Kon, Narracott, and Reid, *J. Chem. Soc.*, **1938**, 778.

[420] Cocker and Hayes, *J. Chem. Soc.*, **1951**, 844.

[421] Chakravarti, *J. Indian Chem. Soc.*, **20**, 393 (1943).

[422] Dhekne and Bhide, *J. Indian Chem. Soc.*, **28**, 504 (1951).

[423] Späth and Hromatka, *Monatsh. Chem.*, **60**, 117 (1932).

[424] Chuang, Tien, and Ma, *Ber.*, **69**, 1494 (1936).

[425] Cook and Lawrence, *J. Chem. Soc.*, **1935**, 1637.

[426] Cook and Lawrence, *J. Chem. Soc.*, **1937**, 817.

[427] Fischer and Schmitz, *Ber.*, **39**, 351 (1906).

[428] Fischer and Schmitz, *Ber.*, **39**, 2209 (1906).

[429] von Braun and Kruber, *Ber.*, **45**, 384 (1912).

[430] Curtius and Sieber, *Ber.*, **55**, 1543 (1922).

[431] Sayles and Degering, *J. Am. Chem. Soc.*, **71**, 3161 (1949).

[432] Carter, *J. Biol. Chem.*, **108**, 619 (1935).

[433] Barry and Hartung, *J. Org. Chem.*, **12**, 460 (1947).

esters,[434, 435] formamidomalonic ester,[246, 436, 437] acetamidomalonic ester,[49,232,234,235,438-452,454-457] benzamidomalonic ester,[233,453,458,459] phthalimidomalonic ester,[236,460-468] alkylcyanoacetic esters,[127,128,185,288, 469-472] and acylaminocyanoacetie esters.[241,242,448] The reaction sequence utilized for the preparation of amino acids from aminomalonic esters, acylaminomalonic esters, or acylaminocyanoacetic esters involves alkylation followed by saponification and decarboxylation. Finally the acyl group is removed by acid hydrolysis. By the appropriate

$$RCONHCH(CO_2C_2H_5)_2 \rightarrow RCONHC(R')(CO_2C_2H_5)_2$$

$$\rightarrow RCONHCH(R')CO_2H \rightarrow R'CH(NH_2)CO_2H$$

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choice of the alkyl group introduced, this method was found applicable to the synthesis of $\delta$-hydroxylysine.[437]

An alternative synthetic method for amino acids involves bromination of the appropriate alkylmalonic acid followed by decarboxylation and treatment with ammonia.[119,427-429,431,432,473] In the synthesis of several amino acids the nitrogen atom bonded to the $\alpha$-carbon atom was introduced as a nitroso group.[132,474]

$$NC(CH_2)_3CH(CO_2C_2H_5)_2 \xrightarrow{C_2H_5ONO,NaOC_2H_5} \left[ \begin{array}{c} CO_2C_2H_5 \quad OC_2H_5 \\ | \qquad\qquad | \quad \ominus \\ NC(CH_2)_3C\text{------}C\text{---}O \\ | \qquad\qquad | \\ N{=}O \qquad OC_2H_5 \end{array} \right] \rightarrow$$

$$NC(CH_2)_3\underset{\underset{NOH}{\parallel}}{C}CO_2C_2H_5 \xrightarrow[(b)\ H_2O]{(a)\ H_2/Pt} H_2N(CH_2)_4CH(NH_2)CO_2H$$

Alkylmalonic esters[118,430] and alkylcyanoacetic esters[127,128,185,288,469-472] can also be converted to amino acids by way of the intermediate monoacid azides. The malonic esters are first selectively hydrolyzed to their monopotassium salts. The ester function is then converted to the corresponding acid azide which affords the desired amino acid after decomposition and acidic hydrolysis (p. 154). With cyanoacetic esters the reaction sequence terminates with hydrolysis of the nitrile group.

Many small-ring compounds[20,160,170,175,266-268,295,300,305-307,309,475-491]

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$$RCH(CO_2K)CO_2C_2H_5 \xrightarrow{N_2H_4} RCH(CO_2K)CONHNH_2 \xrightarrow{HNO_2}$$

$$RCH(CO_2K)CON_3 \rightarrow RCH \begin{array}{c} CO—O \\ | \\ NH—CO \end{array} \rightarrow RCH(NH_2)CO_2H$$

$$RCH(CN)CO_2C_2H_5 \xrightarrow{N_2H_4} RCH(CN)CONHNH_2 \xrightarrow{HNO_2} RCH(CN)CON_3$$

$$\rightarrow RCH(NH_2)CN \rightarrow RCH(NH_2)CO_2H$$

and some large-ring compounds[219,269,306,492,493] are readily accessible with the use of dihalogenated alkylating agents or $\omega$-haloalkyl derivatives of active methylene compounds. Alkylating agents of the type $Z(CH_2CH_2Cl)_2$, where Z is an oxygen, sulfur, or nitrogen atom, have been used to synthesize tetrahydropyrans,[77,494,496-499] tetrahydrothiopyrans,[77,499] and piperidines.[77,495,501,503-505] The synthesis of certain polynuclear hydrocarbons by the method of Darzens[506-516] and by related

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methods[517-520] requires as intermediates suitably substituted allylmalonic esters.



Lactones are readily prepared by the treatment of epoxides with the metal enolates of malonic esters,[8,11,12,282,521-527] cyanoacetic esters,[528] or ethyl isobutyrate.[69] Similarly, mononitriles are converted to cyclic imido esters,[27,329] which may be hydrolyzed to lactones.[25] The reaction of α-bromoisobutyraldehyde with diethyl malonate produced an unsaturated lactone rather than a normal alkylation product.[529]

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In the synthesis of barbituric acids, malonic esters[15,35,125,126,129,144,203,278, 334,376,379,484,530-561] cyanoacetic esters,[562,563] and malononitriles[211] have found extensive use. The barbituric acids are formed when one of the aforementioned active methylene compounds is treated with urea or guanidine[563] in the presence of a base. The thiobarbituric acids[35,126,552-555] have been prepared from thiourea in an analogous manner. The intermediate imino com-

$$R_2C(CO_2C_2H_5)_2 + NH_2CONH_2 \xrightarrow{NaOC_2H_5} \begin{array}{c} CO-NH \\ | \quad\quad | \\ R_2C \quad\quad CO \\ | \quad\quad | \\ CO-NH \end{array} + 2C_2H_5OH$$

pounds formed in the reaction of substituted cyanoacetic esters or substituted malononitriles with urea or a urea derivative have been hydrolyzed with aqueous acid.

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## EXPERIMENTAL CONDITIONS AND PROCEDURES

If optimum yields are to be obtained from an alkylation reaction the apparatus, solvent, and reactants must be anhydrous. Although the maintenance of an inert (nitrogen) atmosphere in the reaction is advisable, this precaution is of prime importance if a high-boiling solvent is used or if the reaction is run at a temperature below the boiling point of the solvent. Without protection from the atmosphere afforded by solvent vapor or by an inert gas, many of the alkoxides and enolates are rapidly attacked by molecular oxygen.

If the alkylating agent is relatively volatile an excess of the reagent must be employed if the reaction is to go to completion. In such instances a desirable alternative is the use of dimethyl sulfate, diethyl sulfate, or the appropriate alkyl sulfonate. Although the completion of an alkylation can sometimes be determined by allowing the reaction to proceed until the reaction mixture becomes neutral, in many reactions complete neutrality is never reached. To determine the extent of alkylation in such cases it is advisable to remove aliquots of the reaction mixture periodically and to titrate them with a standard acid. To simplify subsequent extraction procedures the majority of the alcohol should be distilled from an alkylation reaction mixture before the mixture is poured into water.

Whenever dialkylation is possible, it will occur to some extent. The separation of the monoalkylated from the dialkylated product and the unchanged active methylene compound is most often achieved by fractional distillation. However, this method of separation has proved to be very difficult when the alkylating agent contained no more than three carbon atoms.[135] In such cases the use of an excess of the active methylene compound to minimize dialkylation is not a desirable procedure since the separation of the unchanged starting material and the monoalkylated product is equally difficult. A number of separation techniques have been employed which are applicable only to specific types of compounds.[124,184,256,313,564-566] A more general method, especially for malonic and cyanoacetic esters, involves the selective saponification of certain components of the reaction mixture with sodium or potassium hydroxide or the selective conversion of the more reactive ester functions to amides with ammonium hydroxide.[63,82,95,567-569] Shaking with 25% aqueous sodium hydroxide for one minute saponifies diethyl malonate.[82,570]

[564] Neure, *Ann.*, **250**, 140 (1888).
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Monoalkylmalonic esters must be boiled with 50% aqueous potassium hydroxide for two hours to effect saponification,[82,571] and dialkylmalonic esters require ten hours under similar conditions.[82,571]   With less concentrated alkali longer reaction periods are required.   The cyanoacetic esters are more rapidly hydrolyzed, the ester group of ethyl methylcyanoacetate being saponified almost instantly with 10% aqueous sodium hydroxide.[568]   Similarly, ethyl dimethylcyanoacetate is saponified within twenty minutes.[568]

The ease with which alkylidenecyanoacetic esters form water-soluble sodium bisulfite adducts permits these esters to be separated from their alkylation products, which do not react with sodium bisulfite.[37,64,214,344] Unchanged alkylidenemalonic esters also may be removed by treatment with aqueous ammonium hydroxide.   Under such conditions the alkylidene derivative is converted to the aldehyde or ketone and malonic ester in a reverse aldol reaction.   The malonic ester so formed is converted to malonamide.[63]

**Diethyl *n*-Butylmalonate.**[13]   This *Organic Syntheses* procedure illustrates the standard method used for the alkylation of malonic and cyanoacetic esters.   The monoalkylated product is obtained in 80–90% yield from 5.15 moles of diethyl malonate and 5.0 moles of *n*-butyl bromide in the presence of ethanolic sodium ethoxide prepared from 2.5 l. of ethanol and 5 gram atoms of sodium.

**Diethyl Benzylmalonate.**[136]   If the standard alkylation procedure for malonic esters (cf. diethyl *n*-butylmalonate, above) is applied to a reactive halide such as benzyl chloride, diethyl benzylmalonate is obtained in 51–57% yield, the remainder of the product being diethyl dibenzylmalonate.[119]   In the procedure of Leuchs an excess of diethyl malonate is used to reduce dialkylation (p. 122).

To an ethanolic solution of diethyl sodiomalonate prepared from 11.5 g. (0.5 gram atom) of sodium, 150 ml. of absolute ethanol, and 160 g. (1.0 mole) of diethyl malonate, is added dropwise, with stirring, 63.2 g. (0.5 mole) of benzyl chloride.   The reaction mixture is boiled under reflux until it is neutral to litmus.   After most of the ethanol has been distilled from the mixture under reduced pressure, water is added to the residual oil and the mixture is extracted with ether.   The ether solution is dried and fractionally distilled.   The diethyl benzylmalonate, collected at 163–170°/12 mm., amounts to 107 g. (85%).

**Diethyl Ethyl(phenyl)malonate (Inverse Addition Procedure).**[42] In a 2-l. three-necked flask equipped with a dropping funnel, a mechanical stirrer, and an efficient reflux condenser connected to a trap chilled in solid carbon dioxide are placed 264 g. (1.1 moles) of diethyl phenylmalonate

[571] Norris and Tucker, *J. Am. Chem. Soc.*, **55**, 4697 (1933).

and 131 g. (1.2 moles) of ethyl bromide. While the contents of the flask are maintained at 45°, a solution of sodium ethoxide, prepared by the addition of 25 g. (1.1 gram atoms) of sodium to 450 ml. of absolute ethanol and followed by dilution of the solution with 10 ml. of ethyl acetate, is added dropwise with stirring. The sodium ethoxide solution is added at such a rate that the reaction mixture never becomes more than slightly basic to moist phenolphthalein paper. Near the end of the addition period any ethyl bromide which has collected in the solid carbon dioxide trap is returned to the reaction vessel. After the addition is complete (time required one and one-half to two hours) the reaction mixture is heated to 45° with stirring for one hour, and then the bulk of the ethanol is distilled from the reaction mixture. After water has been added to the residual oil and the mixture extracted with ether, the ether solution is dried over sodium sulfate and fractionally distilled. The diethyl ethyl-(phenyl)malonate is collected at 166–168°/12–13 mm.; yield 248 g. (97%).

**Diethyl Ethyl(isopropyl)malonate.** (A) *Alkylation of Diethyl Ethylmalonate.*[145] To a solution of the sodium enolate of diethyl ethylmalonate, prepared from 24.8 g. (1.08 gram atoms) of sodium, 300 ml. of absolute ethanol, and 200 g. (1.08 moles) of diethyl ethylmalonate, 190 g. (1.12 moles) of isopropyl iodide is added dropwise. After the reaction mixture has been boiled under reflux with stirring for fifteen hours, most of the ethanol is distilled from the mixture and water is added. The product is extracted with ether, and the ether solution is dried over calcium chloride and fractionally distilled. The yield of diethyl ethyl(isopropyl)-malonate, b.p. 230–235°, is 113 g. (46%). If the lower-boiling fractions are realkylated, the yield of diethyl ethyl(isopropyl)malonate may be raised to 75%.

(B) *Alkylation of Diethyl Isopropylmalonate.*[35] In a 2-l. three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a gas inlet tube is placed 800 ml. of dry *t*-butyl alcohol. Sodium (23 g., 1.0 gram atom) is then added in small pieces while a nitrogen atmosphere is maintained in the flask. The mixture is boiled under reflux until solution of the sodium is complete. After the gas inlet tube has been replaced by a dropping funnel, 202 g. (1.0 mole) of diethyl isopropylmalonate is added dropwise, with stirring, to the hot solution. After the solution of the sodium enolate of diethyl isopropylmalonate has been allowed to cool, 170 g. (1.1 moles) of ethyl iodide is added dropwise and with stirring. The resulting mixture is boiled under reflux, with stirring, for three hours, and then the *t*-butyl alcohol is distilled under reduced pressure. After the addition of 1 l. of water the mixture is extracted with ether and the ether extract is dried over sodium sulfate and fractionally distilled. The

diethyl ethyl(isopropyl)malonate, collected at 112–115°/18 mm., amounts to 150 g. (65%).

**Diethyl Isopropyl(formamido)malonate.**[246]    Diethyl formamido-malonate[572] (11.5 g., 0.056 mole) is added in small portions to 1.44 g. (0.06 mole) of sodium hydride in 25 g. of anhydrous dimethylformamide. After the mixture has been allowed to stand for thirty minutes it is filtered and the filtrate is treated with 12.3 g. (0.10 mole) of isopropyl bromide. The resulting mixture is boiled under reflux for two hours, and then most of the solvent is removed by distillation under reduced pressure.  The residue is mixed with 125 ml. of water and allowed to stand in an ice bath until the oil that initially separates has solidified.  The crude product is collected on a filter, washed with water, dried, and recrystallized from an ether-petroleum ether mixture.  The yield of diethyl isopropyl(forma-mido)malonate, m.p. 67–73°, is 6.95 g. (50%).  An additional recrystallization raises the melting point to 73.5–74°.

**Diethyl 1,1-Cyclobutanedicarboxylate.**[573]    A solution of sodium ethoxide is prepared by the addition of 23 g. (1 gram atom) of sodium to 500 ml. of absolute ethanol contained in a three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a long-stemmed dropping funnel.  A 200-ml. portion of the solution is drawn into the dropping funnel with suction, and the dropping funnel is attached to the top of the reflux condenser.  Diethyl malonate (96 g., 0.6 mole) is then added to the flask, and the mixture is heated to boiling with stirring.  Over a period of one hour the sodium ethoxide solution and 101 g. (0.5 mole) of tri-methylenebromide are added concurrently to the boiling reaction mixture. After the addition is complete the mixture is boiled under reflux with stirring for ninety minutes, and then about 400 ml. of ethanol is distilled from the reaction mixture.   The residue is mixed with water and extracted with three portions of benzene.   After the benzene has been distilled from the extract the residue is distilled under reduced pressure.   The diethyl 1,1-cyclobutanedicarboxylate, collected at 105–112°/15 mm., amounts to 60–65 g. (60–67%).

**Ethyl α-Ethyl-α-methylvalerate.**[68]    Ethyl α-methylbutyrate (23.5 g., 0.18 mole) is added to an ethereal solution containing 0.18 mole of sodium triphenylmethide.   After the reaction mixture has been shaken for five minutes, 30.7 g. (0.18 mole) of n-propyl iodide is added, and the reaction flask is stoppered, shaken, and allowed to stand overnight.   The ethereal solution is washed with 200 ml. of water and dried, first over sodium sulfate and then over anhydrous calcium sulfate ("Drierite").   After the ether has been removed, the residue is distilled and the crude ester is

[572] Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).
[573] Cason and Allen, *J. Org. Chem.*, **14**, 1036 (1949).

redistilled; b.p. 180–185°, yield 19 g. (61%). Redistillation affords pure ethyl α-ethyl-α-methylvalerate, b.p. 81°/20 mm.

**3-(β-Diethylaminoethyl)-3-phenyl-2-benzofuranone.**[574]   To a stirred suspension of 34.5 g. (1.5 gram atoms) of finely divided sodium in 300 ml. of toluene, diluted with 2 l. of benzene, is added 315 g. (1.5 moles) of 3-phenyl-2-benzofuranone. After the mixture has been heated to boiling and then cooled to room temperature, 227 g. (1.67 moles) of diethylaminoethyl chloride is added slowly with stirring. After the addition is complete, the mixture is stirred for sixty hours and then washed, first with ice water and then with dilute mineral acid. The combined acidic extracts are treated with excess aqueous sodium carbonate, and the resulting mixture is extracted with ether. The ether extract is dried and distilled. The 3-(β-diethylaminoethyl)-3-phenyl-2-benzofuranone, b.p. 192–194°/2 mm., amounts to 402 g. (87%).

**Diethyl Ethyl(1-isopentenyl)malonate.**[28]   To a solution of sodium ethoxide, prepared from 8.05 g. (0.35 gram atom) of sodium and 300 ml. of ethanol and cooled to −5°, 79.8 g. (0.35 mole) of diethyl isopentylidene-malonate is added, dropwise and with stirring, over a period of ten minutes. The reaction mixture, maintained at a temperature of −5° to −10°, is stirred for an additional twenty minutes. Ethyl iodide (65.5 g., 0.42 mole) is added in one portion, and the reaction mixture is rapidly heated to boiling. An ice bath should be available in case the exothermic reaction becomes too vigorous. After the reaction mixture has been boiled for twenty minutes, the contents of the flask are cooled and diluted with 800 ml. of water. The organic layer is separated, and the aqueous phase is extracted with four portions of benzene. The combined organic layers are washed with two portions of water, and the benzene is removed by distillation. Upon fractional distillation the residue yields 80 g. (88%) of diethyl ethyl(1-isopentenyl)malonate, b.p. 141–142°/19 mm.

**Ethyl (1-Ethylpropenyl)methylcyanoacetate.**[344]   The alkylation of an alkylidenecyanoacetic ester in the presence of sodium ethoxide is exemplified by this *Organic Syntheses* procedure. The sodium enolate of the alkylidenecyanoacetic ester is prepared from 0.40 mole of ethyl (1-ethylpropylidene)cyanoacetate and sodium ethoxide obtained by the solution of 0.40 gram atom of sodium in 400 ml. of absolute ethanol. After the enolate has been allowed to react with 0.44 mole of methyl iodide, the ethyl (1-ethylpropenyl)methylcyanoacetate is isolated in 81–87% yield.

**Ethyl *n*-Butyl(isopropyl)cyanoacetate.**[575]   To a solution of sodium ethoxide prepared from 11.5 g. (0.5 gram atom) of sodium and 300 ml. of absolute ethanol is added, dropwise and with stirring, 84.6 g. (0.5 mole)

[574] Weston and Brownell, *J. Am. Chem. Soc.*, **74**, 653 (1952).
[575] A. C. Cope and E. M. Hancock, to be published.

of ethyl $n$-butylcyanoacetate. After the mixture has been stirred for five minutes, 73.8 g. (0.6 mole) of isopropyl bromide is added during a period of two minutes. The mixture is boiled under reflux with stirring for three hours, and then about 200 ml. of ethanol is distilled from the mixture under reduced pressure. The residue is diluted with 3 volumes of water, acidified by addition of a few drops of hydrochloric acid, and extracted with three portions of benzene. The combined benzene extracts are washed with water and distilled. The crude ester, b.p. 113–115°/6 mm., is shaken with 160 ml. of 5% aqueous sodium hydroxide for one and one-half hours to hydrolyze any unchanged monoalkyl ester present. The ester is extracted with ether, and the extract is washed with water, diluted with benzene, and distilled. The pure ethyl $n$-butyl(isopropyl)cyano-acetate is collected at 115–116°/7 mm., $n_D^{25}$ 1.4327, yield 91.5 g. (87%).

α-Cyclohexylphenylacetonitrile.[576] This *Organic Syntheses* procedure illustrates the alkylation of a mononitrile in the presence of sodium amide. The reaction of a suspension in toluene of the sodium enolate of phenyl-acetonitrile (prepared in liquid ammonia from 0.35 mole of phenylaceto-nitrile and 0.35 mole of sodium amide) with 0.40 mole of cyclohexyl bromide produces α-cyclohexylphenylacetonitrile in 65–77% yield.

## TABULAR SURVEY OF THE ALKYLATION OF ESTERS AND NITRILES

The compounds listed in Tables I to XV have been arranged according to the nature of the active methylene compound. Malonic esters precede cyanoacetic esters, which in turn are followed by monocarboxylic esters and mononitriles. In Tables XVI to XX are surveyed several alternative methods of alkylation. Within each table the compounds are listed in order of increasing number of carbon atoms, monoalkyl derivatives preceding dialkyl derivatives. Among the monoalkyl derivatives acyclic groups are found first, followed in turn by saturated carbocyclic, aromatic, and then heterocyclic substituents. The straight-chain alkyl derivatives have been placed before branched-chain derivatives, the latter groups being listed in order of increased branching; the unsaturated substituents follow. Monocyclic precede bicyclic derivatives, the isomers with the smallest rings always being listed first. Oxygen heterocycles will be found before heterocycles containing sulfur. Next are listed the nitrogen heterocycles, followed by substituents containing two or more hetero atoms.

The alkylating agents employed have also been arranged in the order of increasing number of carbon atoms. Within a group of alkylating agents with the same number of carbon atoms the order of arrangement is

[576] Hancock and Cope, *Org. Syntheses*, **25**, 25 (1945).

chlorides, bromides, iodides, unsaturated halides, carbonates, sulfates, sulfonates, dihalides, and epoxides. Ethers have been placed just after their hydrocarbon analogs. For example, $n\text{-}C_3H_7O(CH_2)_3Br$ would follow $n\text{-}C_6H_{13}Br$, and $p$-methoxybenzyl bromide would follow $p$-methylbenzyl bromide.

In those reactions where more than one reference is cited the experimental data are taken from the first reference, the remaining references being arranged in numerical order. Where two figures are listed in the column headed "Yield" the first figure refers to the actual yield or conversion, and the second, enclosed in parentheses, is based on the amount of starting material consumed. In cases listed in the tables in which a compound resulting from hydrolysis, decarboxylation, or some other transformation was isolated rather than the initial alkylation product, the formula of the product actually isolated is listed and the yield cited is the yield of that compound. The literature has been reviewed through 1952 with the occasional inclusion of more recent work.

Because of the extent of the literature on alkylation and complexity of searching this literature by subject, there are undoubtedly many examples of alkylation that were not found. To avoid confusion in the nomenclature of disubstituted active methylene compounds with unlike substituents attached to the same carbon atom one of the groups is enclosed in parentheses. For example the ester $C_2H_5C(C_6H_5)(CO_2C_2H_5)_2$ would be named diethyl ethyl(phenyl)malonate.

## TABLE I

### ALKYLATION OF MALONIC ESTERS, CH$_2$(CO$_2$R)$_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| I$_2$ | (C$_2$H$_5$O$_2$C)$_2$CHCH(CO$_2$C$_2$H$_5$)$_2$ | 100 | NaOC$_2$H$_5$ | Ethanol–ether | 260, 107, 261 |
| I$_2$ | (C$_2$H$_5$O$_2$C)$_2$C=C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 260 |
| **C$_1$** | | | | | |
| CH$_3$Br | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | 79–83 | NaOC$_2$H$_5$ | Ethanol | 570 |
| CH$_3$I | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | 94 | NaOC$_2$H$_5$ | Ethanol | 169, 280, 577–582 |
| CH$_3$I | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | 82 | KOH | None | 82 |
| CH$_3$I | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 583 |
| (CH$_3$)$_2$SO$_4$ | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 336 |
| p-CH$_3$C$_6$H$_4$SO$_3$CH$_3$ | CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | 80 | NaOC$_2$H$_5$ | Ethanol | 335 |
| CH$_2$Cl$_2$ | (C$_2$H$_5$O$_2$C)$_2$CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Ethanol | 293, 294 |
| CH$_2$I$_2$ | (C$_2$H$_5$O$_2$C)$_2$CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 84 | NaOC$_2$H$_5$ | Ethanol | 296, 297, 298 |
| CHCl$_3$ | (C$_2$H$_5$O$_2$C)$_2$CHCH=C(CO$_2$C$_2$H$_5$)$_2$ | 56 | NaOC$_2$H$_5$ | Ethanol | 221, 584–587 |
| CCl$_4$ | (C$_2$H$_5$O$_2$C)$_2$CHCH=C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 588, 172, 589, 590 |
| CBr$_4$ | (C$_2$H$_5$O$_2$C)$_2$CHCH=C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 591, 590 |
| CCl$_3$NO$_2$ | (C$_2$H$_5$O$_2$C)$_2$CHCH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 591, 590 |
| **C$_2$** | | | | | |
| C$_2$H$_5$Br | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 80 | Na | None | 280 |
| C$_2$H$_5$Br | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 90–94 | NaOC$_2$H$_5$ | Ethanol | 536, 545 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 83 | NaOC$_2$H$_5$ | Ethanol | 399, 433, 540, 541, 592–594 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ and (C$_2$H$_5$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 595 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | — | Mg(OC$_2$H$_5$)$_2$ | Ethanol | 596 |
| C$_2$H$_5$I | (C$_2$H$_5$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | Good | Mg(OC$_2$H$_5$)$_2$ | Ethanol | 56 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 60 | KOH | None | 82 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | Poor | Ag$_2$O | None | 96 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 75 | Na | None | 280 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 100 | Zn | None | 597, 598 |
| C$_2$H$_5$I | (C$_2$H$_5$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 100 | Zn | None | 597, 94, 599 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | — | MgHg$_x$ | C$_6$H$_6$ | 596 |
| (C$_2$H$_5$)$_2$SO$_4$ | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 249 |
| (C$_2$H$_5$)$_2$SO$_4$ | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 59 | Mg(OC$_2$H$_5$)$_2$ | Ethanol | 220 |
| p-CH$_3$C$_6$H$_4$SO$_3$C$_2$H$_5$ | C$_2$H$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 68 | NaOC$_2$H$_5$ | Ethanol | 335 |
| CH$_2$ClCH$_2$Cl | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 268 |
| CH$_2$ClCH$_2$Cl | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$, C$_2$H$_5$O$_2$CCH$_2$(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$, and C$_2$H$_5$O$_2$CCH$_2$(CH$_2$)$_2$CH$_2$CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 600 |
| CH$_2$BrCH$_2$Br | BrCH$_2$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 35–40 | Na | C$_6$H$_6$ | 54 |
| CH$_2$BrCH$_2$Br | BrCH$_2$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 601 |
| CH$_2$BrCH$_2$Br | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 27–30 | Na | Toluene | 602 |
| CH$_2$BrCH$_2$Br | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 603, 266 |
| CH$_2$BrCH$_2$Br | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | { 60–65 (65–70) } | Mg(OC$_2$H$_5$)$_2$ | Ethanol | 602 |
| CH$_2$BrCH$_2$Br | CH$_2$<br>>C(CO$_2$C$_2$H$_5$)$_2$<br>CH$_2$ | 40 | NaOC$_2$H$_5$ | Ethanol | 484, 485, 488, 604 |
| BrCH$_2$OCH$_2$Br | (C$_2$H$_5$O$_2$C)$_2$CHCH$_2$OCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 35 | Mg(OC$_2$H$_5$)$_2$ | Ethanol | 219 |
| CH$_2$ClCH$_2$OH | HOCH$_2$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Ethanol | 605, 148 |
| CH$_2$ClCH$_2$OH | OC——O<br>&#124; &#124;<br>CH$_2$CH$_2$CCH$_2$CH$_2$<br>&#124; &#124;<br>O——CO | 5–10 | NaOC$_2$H$_5$ | Ethanol | 606 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $CH_2BrCH_2OH$ | OC——O<br>&#124; &#124;<br>$CH_2CH_2CCH_2CH_2$<br>&#124; &#124;<br>O———CO | 5–10 | $NaOC_2H_5$ | Ethanol | 606 |
| $CH_2ClCH_2O_2CCH_3$ | OC——O<br>&#124; &#124;<br>$CH_2CH_2CCH_2CH_2$<br>&#124; &#124;<br>O———CO | 5–10 | $NaOC_2H_5$ | Ethanol | 606 |
| $CH_2BrCH_2O_2CCH_3$ | OC——O<br>&#124; &#124;<br>$CH_2CH_2CCH_2CH_2$<br>&#124; &#124;<br>O———CO | — | $NaOC_2H_5$ | Ethanol | 606, 607 |
| $CH_2$—$CH_2$<br>\ /<br>O | $HOCH_2CH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 521 |
| $CH_2$—$CH_2$<br>\ /<br>O | α-Carbethoxybutyrolactone | — | $NaOC_2H_5$ | Ethanol | 522 |
| $CH_3CCl_3$ | None | — | $NaOC_2H_5$ | Ethanol | 608 |
| $CH_3OCH_2Cl$ | $CH_3OCH_2CH(CO_2C_2H_5)_2$ | 49 | Na | Ether | 204, 542, 609 |
| $CH_3SCH_2Cl$ | $CH_3SCH_2CH(CO_2CH_3)_2$* | 9 | Na | Ether | 205 |
| $ClCH_2CN$ | $NCCH_2CH(CO_2C_2H_5)_2$ | 30 | Na | $C_6H_6$ | 610 |

$C_3$

| | | | | | |
|---|---|---|---|---|---|
| $n$-$C_3H_7Br$ | $n$-$C_3H_7CH(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 611, 541 |
| $n$-$C_3H_7Br$ | $n$-$C_3H_7CH(CO_2C_2H_5)_2$ | 80 | Na | None | 280 |
| $n$-$C_3H_7Br$ | $(n$-$C_3H_7)_2C(CO_2C_2H_5)_2$ | 30 | $NaOC_2H_5$ | Ethanol | 612 |
| $n$-$C_3H_7I$ | $n$-$C_3H_7CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 613, 50, 540 |
| $n$-$C_3H_7I$ | $n$-$C_3H_7CH(CO_2C_2H_5)_2$ | — | Zn | None | 614 |
| $n$-$C_3H_7I$ | $(n$-$C_3H_7)_2C(CO_2C_2H_5)_2$ | 33 | $NaOC_2H_5$ | Ethanol | 612 |
| $n$-$C_3H_7I$ | $(n$-$C_3H_7)_2C(CO_2C_2H_5)_2$ | — | Zn | None | 614 |
| $C_2H_5OCH_2Cl$ | $(C_2H_5OCH_2)_2C(CO_2C_2H_5)_2$ | 25 | Na | Ether | 542 |
| $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2CH(CO_2C_2H_5)_2$ | — | Na | Ether | 205 |
| $CH_3O(CH_2)_2I$ | OC——O<br>&#124; &#124;<br>$CH_2CH_2CCH_2CH_2$<br>&#124; &#124;<br>O———CO | 40 | $NaOC_2H_5$ | Ethanol | 606 |
| $CH_3CH(OCH_3)Cl$ | $CH_3CH(OCH_3)CH(CO_2C_2H_5)_2$ | 70 | Na | Ether | 535 |
| $i$-$C_3H_7Cl$ | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 100 | $NaOC_2H_5$ | Ethanol | 87 |
| $i$-$C_3H_7Br$ | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 95 | $NaOC_2H_5$ | Ethanol | 169, 47, 387, 545 |
| $i$-$C_3H_7Br$ | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 227, 51 |
| $i$-$C_3H_7I$ | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 77 | Na | None | 280 |
| $i$-$C_3H_7I$ | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 63 | $NaOC_2H_5$ | Ethanol | 577, 569 |
| Not stated | $i$-$C_3H_7CH(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 540, 35, 571, 615 |
| $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2CH(CO_2C_2H_5)_2$ | 91 | $NaOC_2H_5$ | Ethanol | 121, 506, 571, 615–618 |
| $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2CH(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 51 |
| $CH_2$=$CHCH_2Br$ | $(CH_2$=$CHCH_2)_2C(CO_2C_2H_5)_2$ | Good | $Mg(OC_2H_5)_2$ | Ethanol | 56 |
| $CH_2$=$CHCH_2I$ | $CH_2$=$CHCH_2CH(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | Ethanol | 619 |
| $CH_2$=$CHCH_2I$ | $(CH_2$=$CHCH_2)_2C(CO_2C_2H_5)_2$ | 100 | $NaOC_2H_5$ | Ethanol | 619 |
| $CH_2$=$CHCH_2I$ | $(CH_2$=$CHCH_2)_2C(CO_2C_2H_5)_2$ | — | Zn | None | 620 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $p$-$CH_3C_6H_4SO_3CH_2CH_2CN$ | $NCCH_2CH_2CH(CO_2C_2H_5)_2$ | 34 | $NaOC_2H_5$ | Ethanol | 102 |
| $F(CH_2)_3Br$ | $F(CH_2)_3CH(CO_2C_2H_5)_2$ | 52 | $NaOCH_3$ | Ethanol | 285 |
| $ClCH{=}CHCH_2Cl$ | $ClCH{=}CHCH_2CH(CO_2C_2H_5)_2$ | 26 | $NaOC_2H_5$ | Ethanol | 621 |
| | $(ClCH{=}CHCH_2)_2C(CO_2C_2H_5)_2$ | 32 | | | |
| $Cl(CH_2)_3Br$ | $Cl(CH_2)_3CH(CO_2C_2H_5)_2$ | 93 | $NaOC_2H_5$ | Ethanol -ether | 622, 480, 490, 623 |
| $Cl(CH_2)_3Br$ | $[Cl(CH_2)_3]_2C(CO_2C_2H_5)_2$ | 62 | $NaOC_2H_5$ | Ethanol | 623, 624 |
| $Cl(CH_2)_3Br$ | Diethyl cyclobutane-1,1-dicarboxylate | 8–10 | $NaOC_2H_5$ | Ethanol | 624 |
| $Cl(CH_2)_3Br$ | Diethyl cyclobutane-1,1-dicarboxylate | 55† | $NaOC_2H_5$ | Ethanol | 170, 625 |
| $Cl(CH_2)_3I$ | $I(CH_2)_3CH(CO_2C_2H_5)_2$ | 38 | $NaOC_2H_5$ | Ethanol | 92 |
| $Br(CH_2)_3Br$ | $Br(CH_2)_3CH(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 131, 136, 627–629 |
| $Br(CH_2)_3Br$ | $(C_2H_5O_2C)_2CH(CH_2)_3CH(CO_2C_2H_5)_2$ | 15 | $NaOC_2H_5$ | Ethanol | 131, 172, 267, 630–632 |
| $Br(CH_2)_3Br$ | Diethyl cyclobutane-1,1-dicarboxylate | 60–65 | $NaOC_2H_5$ | Ethanol | 573, 160, 172, 266, 483, 488, 491, 627, 633 |
| $CH_3CHBrCH_2Br$ | $\begin{array}{c}H_3CCH\\ \ \ \mid\ \ \ \ >C(CO_2C_2H_5)_2\\ CH_2\end{array}$ | — | $NaOC_2H_5$ | Ethanol | 336, 626 |
| $CH_3COCH_2Br$ | $CH_3COCH_2CH(CO_2C_2H_5)_2$ | 70 | Na | Ether | 593, 634 |
| | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | | | |
| $CH_3COCH_2Br$ | $CH_3COCH_2CH(CO_2C_2H_5)_2$ | 20 | $NaOC_2H_5$ | Ethanol | 593 |
| $CH_3O_2CCH_2Cl$ | $CH_3O_2CCH_2CH(CO_2CH_3)_2$* | 27 | $NaOCH_3$ | $CH_3OH$ | 635 |

| | | | | | |
|---|---|---|---|---|---|
| $CH_3CH_2CCl_3$ | $CH_2{=}CClCH_2CH(CO_2C_2H_5)_2$ | 22 | $NaOC_2H_5$ | Ethanol | 636 |
| $CH_2{-}CHCH_2Cl$ (epoxide) | α-Carbethoxy-δ-chloro-γ-valerolactone | 78 | $NaOC_2H_5$ | Ethanol | 136, 522 |
| $CH_2{-}CHCH_2Cl$ (epoxide) | $ClCH_2CHOHCH_2CH(CONH_2)_2$ | — | $NaOC_2H_5$ | Ethanol | 521 |
| $CH_2OHCHOHCH_2Cl$ | $CH_2OHCHOHCH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 637 |
| $CH_2BrCHBrCH_2Br$ | $CH_2{=}CBrCH_2CH(CO_2C_2H_5)_2$ and $(CH_2{=}CBrCH_2)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 638, 639 |
| $C_4$ | | | | | |
| $n$-$C_4H_9Br$ | $n$-$C_4H_9CH(CO_2C_2H_5)_2$ | 80–90 | $NaOC_2H_5$ | Ethanol | 13, 121, 142, 540, 541, 640, 641 |
| $n$-$C_4H_9I$ | $n$-$C_4H_9CH(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 399, 141 |
| $n$-$C_3H_7OCH_2Cl$ | $n$-$C_3H_7OCH_2CH(CO_2C_2H_5)_2$ | 21 | Na | Ether | 542 |
| $n$-$C_3H_7OCH_2Cl$ | $(n$-$C_3H_7OCH_2)_2C(CO_2C_2H_5)_2$ | 21 | Na | Ether | 542 |
| $C_6H_5SO_3(CH_2)_2OC_2H_5$ | $C_2H_5O(CH_2)_2CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 646 |
| $i$-$C_4H_9Br$ | $i$-$C_4H_9CH(CO_2C_2H_5)_2$ | 77 | $NaOC_2H_5$ | Ethanol | 427, 540, 555 642 |
| $sec$-$C_4H_9Br$ | $sec$-$C_4H_9CH(CO_2C_2H_5)_2$ | 80–81 | $NaOC_2H_5$ | Ethanol | 14, 148, 540, 571, 643, 645 |
| $sec$-$C_4H_9Br$ | $(sec$-$C_4H_9)_2C(CO_2C_4H_9$-$sec)_2$‡ | 78 | $NaOC_4H_9$-$sec$ | $(sec$-$C_4H_9O)_2CO$ | 51 |
| $sec$-$C_4H_9I$ | $sec$-$C_4H_9CH(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 582 |
| $CH_3CH(OC_2H_5)Cl$ | $CH_3CH(OC_2H_5)CH(CO_2C_2H_5)_2$ | 28 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| $CH_3CH(OC_2H_5)Cl$ | $CH_3CH(OC_2H_5)CH(CO_2C_2H_5)_2$ | 27 | Na | Ether | 535 |
| $t$-$C_4H_9Br$ | $t$-$C_4H_9CH(CO_2C_2H_5)_2$ | 6 | $NaOC_2H_5$ | Ethanol | 15, 473 |
| $CH_3CH{=}CHCH_2Cl$ | $CH_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 18 |
| $CH_3CH{=}CHCH_2Br$ | $CH_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 647, 648 |

*Note:* References 577–1080 are on pp. 322–331.

\* Dimethyl malonate was used in this experiment.

† The reactants were added in inverse order.

‡ Di-*sec*-butyl malonate was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $CH_2=CH(CH_2)_2Br$ | $CH_2=CH(CH_2)_2CH(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 647 |
| $CH_2=CHCH(CH_3)Cl$ | $\{CH_2=CHCH(CH_3)CH(CO_2C_2H_5)_2$ | 54 | $NaOC_2H_5$ | Ethanol | 18 |
| | $\{CH_3CH=CHCH_2CH(CO_2C_2H_5)_2$ | 2 | | | |
| $CH_2=C(CH_3)CH_2Br$ | $CH_2=C(CH_3)CH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 552 |
| $\begin{smallmatrix}CH_2\\ \diagdown\\ \diagup\\ CH_2\end{smallmatrix}CHCH_2Br$ | $\begin{smallmatrix}CH_2\\ \diagdown\\ \diagup\\ CH_2\end{smallmatrix}CHCH_2CH(CO_2C_2H_5)_2$ | 66–70 | $NaOC_2H_5$ | Ethanol | 649 |
| $Cl(CH_2)_4Br$ | $Cl(CH_2)_4CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 431 |
| $ClCH_2CH(CH_3)CH_2Br$ | $ClCH_2CH(CH_3)CH_2CH(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 481, 482 |
| $Br(CH_2)_4Br$ | Diethyl cyclopentane-1,1-dicarboxylate | 55 | $NaOC_2H_5$ | Ethanol | 488, 308, 650 |
| $CH_3CHBr(CH_2)_2Br$ | Diethyl 2-methylcyclobutane-1,1-dicarboxylate | 50–55§ | $NaOC_2H_5$ | Ethanol | 160 |
| $C_2H_5CHOHCH_2Cl$ | $\alpha$-Carbethoxy-$\gamma$-ethyl-$\gamma$-butyrolactone | 58 | $NaOC_2H_5$ | Ethanol | 651 |
| $C_2H_5OCHClCH_2Cl$ | $(C_2H_5O_2C)_2C=CHCH_2CH(CO_2C_2H_5)_2$ | 69 | Na | Ether | 275 |
| $C_2H_5OCHClCH_2Cl$ | $ClCH_2CH(OC_2H_5)CH(CO_2C_2H_5)_2$ | — | Na | Ether | 275 |
| $Cl(CH_2)_2O(CH_2)_2Cl$ | Diethyl tetrahydropyran-4,4-dicarboxylate | 26 | $NaOC_2H_5$ | Ethanol | 496, 498 |
| $CH_2=CHO(CH_2)_2Cl$ | $[CH_2=CHO(CH_2)_2]_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 541 |
| $I(CH_2)_2O(CH_2)_2I$ | Diethyl tetrahydropyran-4,4-dicarboxylate | 65 | $NaOC_2H_5$ | Ethanol | 494 |
| $n$-$C_3H_7SCH_2Cl$ | $(n$-$C_3H_7SCH_2)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| $C_2H_5SCH(CH_3)Cl$ | $\{C_2H_5SCH(CH_3)CH(CO_2C_2H_5)_2$ and | 55 | $NaOC_2H_5$ | Toluene | 126 |
| | $\{[C_2H_5SCH(CH_3)]_2C(CO_2C_2H_5)_2$ | | | | |
| $CH_3CH=CHCHCl_2$ | $ClCH=CHCH(CH_3)CH(CO_2C_2H_5)_2$ | 41 | $NaOC_2H_5$ | Ethanol | 636 |
| $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2CH(CO_2C_2H_5)_2$ | 62 | $NaOC_2H_5$ | Ethanol | 533, 561, 652 |
| $BrCH_2CH=CHCH_2Br$ | $(C_2H_5O_2C)_2CHCH_2CH=CHCH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 20 |

| | | | | | |
|---|---|---|---|---|---|
| $BrCH_2CH=CHCH_2Br$ | $(C_2H_5O_2C)_2CHCH(CH=CH_2)$- $CH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 20 |
| $BrCH_2CH=CHCH_2Br$ | $CH_2=CHC\underset{\diagdown\diagup}{\underset{CH_2}{—}}C(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 20 |
| $CH_2=CHCH\underset{\diagdown O \diagup}{—CH_2}$ | $\alpha$-Carbethoxy-$\gamma$-vinyl-$\gamma$-butyrolactone | 73 | $NaOC_2H_5$ | Ethanol | 11, 526 |
| $CH_3OCH_2CH\underset{\diagdown O \diagup}{—CH_2}$ | $CH_3OCH_2CH\underset{\underset{O——CO}{|\quad\quad|}}{—CH_2CH_2}$ | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $Cl(CH_2)_3CN$ | $NC(CH_2)_3CH(CO_2C_2H_5)_2\|$ | 75 | $NaOC_2H_5$ | Ether | 132 |
| $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2CH(CO_2C_2H_5)_2$ | — | Na | Ether | 653 |
| $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2CH(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 653, 161, 654 |
| $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2CH(CO_2C_2H_5)_2$ | 67 | $NaOC_2H_5$ | Ethanol | 655, 594, 635 |
| $ClCH_2CO_2C_2H_5$ | $(C_2H_5O_2CCH_2)_2C(CO_2C_2H_5)_2$ | 87 | $Mg(OC_2H_5)_2$ | Ethanol | 55 |
| 4-Chloromethylimidazole hydrochloride | Diethyl (4-imidazolemethyl)malonate | 49 | $NaOC_2H_5$ | Ethanol | 209 |
| $C_5$ | | | | | |
| $n$-$C_5H_{11}Br$ | $n$-$C_5H_{11}CH(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545, 148, 543, 656 |
| $CH_3O(CH_2)_4Br$ | $CH_3O(CH_2)_4CH(CO_2C_2H_5)_2$ | 80–84 | $NaOC_2H_5$ | Ethanol | 662 |
| $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}CH(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | Ethanol | 657, 35, 148, 540, 545, 555, 571, 616, 658 |
| $n$-$C_3H_7CH(CH_3)Br$ | $n$-$C_3H_7CH(CH_3)CH(CO_2C_2H_5)_2$ | 51 | $NaOC_2H_5$ | Ethanol | 148, 659 |
| $sec$-$C_4H_9CH_2Br$ | $sec$-$C_4H_9CH_2CH(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545, 659 |
| $i$-$C_3H_7(CH_2)_2Br$ | $i$-$C_3H_7(CH_2)_2CH(CO_2H)_2$ | 83 | $NaOC_2H_5$ | Ethanol | 138 |
| $(C_2H_5)_2CHBr$ | $(C_2H_5)_2CHCH(CO_2C_2H_5)_2$ | 36 | $NaOC_2H_5$ | Ethanol | 148 |

*Note:* References 577–1080 are on pp. 322–331.

§ The product contained up to 18% of unsaturated material.

‖ The cyanide group has $-C^{14}N$.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $(+)$-$CH_3CH$=$CHCH(CH_3)Cl$ | $rac$-$CH_3CH$=$CHCH(CH_3)CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 660 |
| $CH_2$=$CH(CH_2)_3Br$ | $CH_2$=$CH(CH_2)_3CH(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 661 |
| $(CH_3)_2C$=$CHCH_2Br$ | $(CH_3)_2C$=$CHCH_2CH(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 666, 47, 616, 663 |
| $HC$≡$CC(CH_3)_2Cl$ | $HC$≡$CC(CH_3)_2CH(CO_2C_2H_5)_2$ | 45 | $NaOC_2H_5$ | Ethanol | 664 |
| $Br(CH_2)_5Br$ | $(C_2H_5O_2C)_2CH(CH_2)_5CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 304 308, |
|  | Diethyl cyclohexane-1,1-dicarboxylate | 30 |  |  |  |
| $Br(CH_2)_3CH(CH_3)Br$ | Diethyl 2-methylcyclopentane-1,1-dicarboxylate | — | $NaOC_2H_5$ | Ethanol | 665 |
| $(CH_3)_2CBr(CH_2)_2Br$ | $(CH_3)_2C$=$CHCH_2CH(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 318, 173, 616 |
|  | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — |  |  | 667 |
| $F(CH_2)_5Br$ | $F(CH_2)_5CH(CO_2C_2H_5)_2$ | 74 | $NaOCH_3$ | Ethanol | 285 |
| $NC(CH_2)_4Br$ | $NC(CH_2)_4CH(CO_2C_2H_5)_2$ | 56–59 | $NaOC_2H_5$ | Ethanol | 668 |
| $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)CH(CO_2C_2H_5)_2$ | — | Na | — | 161 |
| $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)CH(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 223, 669 |
| $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2CH(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_3$ | Ethanol | 610, 670 |
| $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2CH(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_5$ | Ethanol | 671 |
|  | $[C_2H_5O_2C(CH_2)_2]_2C(CO_2C_2H_5)_2$ | 28 |  |  |  |
| $I(CH_2)_2CO_2C_2H_5$ | $[C_2H_5O_2C(CH_2)_2]_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 672 |
| $CH_2BrCHBrCO_2C_2H_5$ | $CH_2$—$C(CO_2C_2H_5)_2$ (with CHCO$_2$C$_2$H$_5$ bridge) | 77 | $NaOC_2H_5$ | Ethanol | 673 |
| $Br_2C$=$CHCO_2C_2H_5$ | Not established | Poor | $NaOC_2H_5$ | Ethanol | 674 |
| $BrCH(CO_2CH_3)_2$ | $(CH_3O_2C)_2CHCH(CO_2CH_3)_2$* | — | $NaOCH_3$ | $CH_3OH$ | 675 |
|  | $(CH_3O_2C)_2CHC(CO_2CH_3)_2CH(CO_3CH_3)_2$* | Low |  |  |  |
| Cyclobutylmethyl tosylate | Diethyl (cyclobutylmethyl)malonate | 50 | $NaOC_2H_5$ | Ethanol | 334 |
| Cyclopentyl bromide | Diethyl cyclopentylmalonate | 70 | $NaOC_2H_5$ | Ethanol | 31, 148, 677 |
| Cyclopentyl iodide | Diethyl cyclopentylmalonate | 50 | $NaOC_2H_5$ | Ethanol | 676 |
| 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenylmalonate | 70 | Na | $C_6H_6$ | 287 |
| 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenylmalonate | 70 | Na | Toluene | 678, 151 |
| 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenylmalonate | 84–88 | $NaOC_2H_5$ | Ethanol | 274, 286, 287, 679–681 |
| *trans*-1,4-Dibromo-2-cyclopentene | Diethyl bicyclo-[3.1.0]-hex-2-ene-6,6-dicarboxylate | 33 | $NaOC_2H_5$ | Ethanol | 152 |
|  | Diethyl (ethoxycyclopentenyl)malonate (isomers) | 14 |  |  |  |
|  | $(C_2H_5O_2C)_2HC$〔 〕$CH(CO_2C_2H_5)_2$ | — |  |  |  |
| *cis*-1,4-Dibromo-2-cyclopentene | Diethyl bicyclo-[3.1.0]-hex-2-ene-6,6-dicarboxylate | 16 | $NaOC_2H_5$ | Ethanol | 152 |
| $C_2H_5OCH_2CH$—$CH_2$ (epoxide) | $C_2H_5OCH_2CHCH_2CHCO_2C_2H_5$ (O—CO) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $H_5C_2C(CH_3)$—$CH_2$ (epoxide) | $H_5C_2C(CH_3)CH_2CHCO_2C_2H_5$ (O—CO) | 50–60 | $NaOC_2H_5$ | Ethanol | 525 |
| Cyclopentene oxide | *trans*-Diethyl (2-hydroxycyclopentyl)malonate | 27 | Na | $C_6H_6$ | 7 |
| Cyclopentene oxide | *trans*-Diethyl (2-hydroxycyclopentyl)malonate | 70–75 | $NaOC_2H_5$ | Ethanol | 7 |
| Tetrahydrofurfuryl bromide | Diethyl tetrahydrofurfurylmalonate | 70 | $NaOC_2H_5$ | Ethanol | 682 |
| Furfuryl chloride | Diethyl furfurylmalonate | 76 | $NaOC_2H_5$ | Ethanol | 544 |
| 2-Chlorotetrahydropyran | Diethyl 2-tetrahydropyranylmalonate | — | NaH | Toluene | 683 |

*Note:* References 577–1080 are on pp. 322–331.
* Dimethyl malonate was used in this experiment.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $C_6$ | | | | | |
| $n\text{-}C_6H_{13}Br$ | $n\text{-}C_6H_{13}CH(CO_2C_2H_5)_2$ | 80–85 | $NaOC_2H_5$ | Ethanol | 282, 538 |
| $n\text{-}C_6H_{13}Br$ | $(n\text{-}C_6H_{13})_2C(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 121 |
| $n\text{-}C_6H_{13}I$ | $n\text{-}C_6H_{13}CH(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 684 |
| $n\text{-}C_6H_{13}I$ | $(n\text{-}C_6H_{13})_2C(CO_2C_2H_5)_2$ | 92 | $NaOC_4H_9\text{-}n$ | $n\text{-}C_4H_9OH$ | 685 |
| $CH_3O(CH_2)_5Br$ | $CH_3O(CH_2)_5CH(CO_2C_2H_5)_2$ | 62 | — | — | 691 |
| $C_2H_5O(CH_2)_4Br$ | $C_2H_5O(CH_2)_4CH(CO_2C_2H_5)_2$ | 87 | $NaOC_2H_5$ | Ethanol | 646 |
| $n\text{-}C_4H_9CH(CH_3)Br$ | $n\text{-}C_4H_9CH(CH_3)CH(CO_2C_2H_5)_2$ | 83 | $NaOC_2H_5$ | Ethanol | 686 |
| $i\text{-}C_3H_7(CH_2)_3I$ | $i\text{-}C_3H_7(CH_2)_3CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 138 |
| $n\text{-}C_3H_7CH(CH_3)CH_2Br$ | $n\text{-}C_3H_7CH(CH_3)CH_2CH(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 555 |
| $n\text{-}C_3H_7CH(C_2H_5)Br$ | $n\text{-}C_3H_7CH(C_2H_5)CH(CO_2C_2H_5)_2$ | 55 | $NaOC_2H_5$ | Ethanol | 35 |
| $(C_2H_5)_2CHCH_2Br$ | $(C_2H_5)_2CHCH_2CH(CO_2C_2H_5)_2$ | 80–85 | $NaOC_2H_5$ | Ethanol | 282, 555, 687, 688 |
| $(C_2H_5O)_2CHCH_2Br$ | $(C_2H_5O)_2CHCH_2CH(CO_2C_2H_5)_2$ | 57 | $NaOC_2H_5$ | Ethanol | 689 |
| $t\text{-}C_4H_9(CH_2)_2Br$ | $t\text{-}C_4H_9(CH_2)_2CH(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | Ethanol | 690 |
| $C_2H_5CH(OCH_3)(CH_2)_2Cl\text{-}KI$ | $C_2H_5CH(OCH_3)(CH_2)_2CH(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 292 |
| $trans\text{-}C_2H_5CH{=}CH(CH_2)_2Br$ | $C_2H_5CH{=}CH(CH_2)_2CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol-toluene | 692 |
| $cis\text{-}C_2H_5CH{=}CH(CH_2)_2I$ | $cis\text{-}C_2H_5CH{=}CH(CH_2)_2CH(CO_2C_2H_5)_2$ | 54 | Not stated | — | 693 |
| $CH_2{=}CH(CH_2)_4Br$ | $CH_2{=}CH(CH_2)_4CH(CO_2C_2H_5)_2$ | 73 | $NaOC_2H_5$ | Ethanol | 210 |
| $CH_3O(CH_2)_2CH{=}CHCH_2Cl$ | $CH_3O(CH_2)_2CH{=}CHCH_2CH(CO_2C_2H_5)_2$ | 5 | $NaOC_2H_5$ | Ethanol | 694 |
| $CH_3O(CH_2)_2CH{=}CHCH_2Cl$ | $\begin{cases} CH_3O(CH_2)_2CH{=}CHCH_2CH(CO_2C_2H_5)_2 \\ [CH_3O(CH_2)_2CH{=}CHCH_2]_2C(CO_2C_2H_5)_2 \end{cases}$ | 23<br>20 | $Mg(OC_2H_5)_2$ | Ethanol | 694 |
| $CH_3O(CH_2)_2CHClCH{=}CH_2$ | $CH_3O(CH_2)_2CH{=}CHCH_2CH(CO_2C_2H_5)_2$ | 7 | $NaOC_2H_5$ | Ethanol | 694 |

| | | | | | |
|---|---|---|---|---|---|
| $CH_3O(CH_2)_2CHClCH{=}CH_2$ | $\begin{cases} CH_3O(CH_2)_2CH{=}CHCH_2CH(CO_2C_2H_5)_2 \\ [CH_3O(CH_2)_2CH{=}CHCH_2]_2C(CO_2C_2H_5)_2 \end{cases}$ | 29<br>5 | $Mg(OC_2H_5)_2$ | Ethanol | 694 |
| $n\text{-}C_3H_7C{\equiv}CCH_2Br$ | $\begin{cases} n\text{-}C_3H_7C{\equiv}CCH_2CH(CO_2C_2H_5)_2 \\ [n\text{-}C_3H_7C{\equiv}CCH_2]_2C(CO_2C_2H_5)_2 \end{cases}$ | 57<br>13 | $NaOC_2H_5$ | Ethanol | 695 |
| $CH_3CHBr(CH_2)_4Br$ | Tetraethyl 2-methylheptane-1,1,7,7-tetracarboxylate<br>Diethyl 2-methylcylcohexane-1,1-dicarboxylate | —<br><br>— | $NaOC_2H_5$ | Ethanol | 696 |
| $CH_3CHBr(CH_2)_4Br$ | $CH_3CHBr(CH_2)_4CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 210 |
| $Br(CH_2)_6Br$ | Diethyl cycloheptane-1,1-dicarboxylate and tetraethyl octane-1,1,8,8-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 269 |
| $C_2H_5C(CH_3)Br(CH_2)_2Br$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ and $C_2H_5C(CH_3){=}CHCH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 697, 318 |
| $CH_3CO(CH_2)_4Br$ | $CH_3CO(CH_2)_4CH(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 698 |
| $(CH_3)_2N(CH_2)_2CH(CH_3)Cl$ | $(CH_3)_2N(CH_2)_2CH(CH_3)CH(CO_2C_2H_5)_2$ | 72 | $NaOC_2H_5$ | Ethanol | 699 |
| $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2CH(CO_2C_2H_5)_2$ | 45 | Na | $C_6H_6$ | 610 |
| $Br(CH_2)_5CN$ | $NC(CH_2)_5CH(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 700 |
| $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)CH(CO_2C_2H_5)_2$ | — | Na | None | 161 |
| $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)CH(CO_2C_2H_5)_2$ | 55 | $NaOC_2H_5$ | Ethanol | 223 |
| $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2CH(CO_2C_2H_5)_2$ | — | Na | None | 161 |
| $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2CH(CO_2C_2H_5)_2$ $CHCO_2CH_3$ | 60 | $NaOC_2H_5$ | Ethanol | 701, 223, 702 |
| $CH_3O_2CCHBrCHBrCO_2CH_3$ | $CH_3O_2CCH{-}C(CO_2CH_3)_2$ * | 80–90 | $NaOHC_3$ | Methanol | 175, 703 |
| Cyclohexyl bromide | Diethyl cyclohexylmalonate | 60 | $NaOC_2H_5$ | Ethanol | 35, 31, 50, 149, 286, 704, 705 |
| Cyclohexyl bromide | Di-$t$-butyl cyclohexylmalonate¶ | 77 | NaH | $t\text{-}C_4H_9OH$ | 393 |
| 1-Chloro-2-cyclohexene | Diethyl 2-cyclohexenylmalonate | — | — | — | 150 |

*Note:* References 557–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

¶ Di-$t$-butyl malonate was used in this experiment.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| 1,2-Dichlorocyclohexane | Diethyl 2-cyclohexenylmalonate | <60 | $NaOC_2H_5$ | Ethanol | 150 |
| 1-Chloro-2-bromocyclohexane | Diethyl 2-cyclohexenylmalonate | ca. 40 | $NaOC_2H_5$ | Ethanol | 150 |
| 1,2-Dibromocyclohexane | {Diethyl 2-cyclohexenylmalonate | 66 | $NaOC_2H_5$ | Ethanol | 287, 150, 286, 706 |
| | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | | | |
| Cyclohexene bromohydrin | Diethyl (2-hydroxycyclohexyl)malonate | — | $NaOC_2H_5$ | Ethanol | 706 |
| Cyclohexene oxide | Lactone from 2-hydroxycyclohexylacetic acid | — | $NaOC_2H_5$ | Ethanol | 706 |
| Cyclohexene oxide | Lactone from diethyl (2-hydroxy-cyclohexyl)malonate | >77 | $NaOC_2H_5$ | Ethanol | 8, 707 |
| $\beta$-(2-Thienyl)ethyl chloride | Diethyl [$\beta$-(2-thienyl)ethyl]malonate | 51 | $NaOC_2H_5$ | Ethanol | 50, 708, 709 |
| 4-Bromomethylpiperidine | None | — | — | — | 710 |
| 1-Nitroso-4-bromo-methylpiperidine | Di-(1-nitroso-4-piperidylmethyl)malonic acid | 79 | $NaOC_2H_5$ | Ethanol | 710 |
| 2,4-Dinitrochlorobenzene | Diethyl (2,4-dinitrophenyl)malonate | 90 | Na | Ether | 139, 284 |
| Picryl chloride | Diethyl (2,4,6-trinitrophenyl)malonate | — | $NaOC_2H_5$ | Ethanol | 711 |
| 2,4-Dinitrobromobenzene | Diethyl (2,4-dinitrophenyl)malonate | — | $NaOC_2H_5$ | Ethanol | 184, 712 |
| 2,5-Dichloro-1,3-dinitro-benzene | Diethyl (2,6-dinitro-4-chlorophenyl)malonate | 22 | Na | Ether | 713, 714 |
| 1-Chloro-4-bromo-2,6-dinitrobenzene | Diethyl (2,6-dinitro-4-bromophenyl)malonate | 90 | Na | Ether | 715 |
| 2,4-Dinitro-1,3,5-trichlorobenzene | Dimethyl (2,4-dinitro-3,5-dichlorophenyl)malonate* | — | Na | Ether | 714 |
| 2,4-Dinitro-1,3,5-tribromobenzene | Diethyl (2,4-dinitro-5-bromophenyl)malonate | 40 (53) | $NaOC_2H_5$ | Ethanol-$C_6H_6$ | 327, 326, 328 |
| $n$-$C_3H_7OCH_2CH\overset{\diagup CH_2}{\underset{\diagdown O}{}}$ | $n$-$C_3H_7OCH_2CHCH_2CHCO_2C_2H_5$ <br> $\underset{O\!-\!-\!CO}{\mid\quad\mid}$ | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $i$-$C_3H_7OCH_2CH\overset{\diagup CH_2}{\underset{\diagdown O}{}}$ | $i$-$C_3H_7OCH_2CHCH_2CHCO_2C_2H_5$ <br> $\underset{O\!-\!-\!CO}{\mid\quad\mid}$ | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $i$-$C_3H_7C(CH_3)\overset{\diagup CH_2}{\underset{\diagdown O}{}}$ | $i$-$C_3H_7C(CH_3)CH_2CHCO_2C_2H_5$ <br> $\underset{O\!-\!-\!-\!CO}{\mid\quad\quad\mid}$ | 50–60 | $NaOC_2H_5$ | Ethanol | 525 |
| **$C_7$** | | | | | |
| $n$-$C_7H_{15}Br$ | $n$-$C_7H_{15}CH(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 656, 282 |
| $C_2H_5O(CH_2)_5Br$ | $C_2H_5O(CH_2)_5CH(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 716 |
| $CH_3CO_2(CH_2)_5Cl\cdot NaI$ | $CH_2(CH_2)_4CHCO_2C_2H_5$ <br> $\underset{O\!-\!-\!-\!-\!-\!CO}{\mid\quad\quad\quad\mid}$ | — | $NaOC_2H_5$ | Ethanol | 717 |
| $i$-$C_3H_7(CH_2)_4I$ | $i$-$C_3H_7(CH_2)_4CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 138 |
| $i$-$C_5H_{11}CH(CH_3)I$ | $i$-$C_5H_{11}CH(CH_3)CH(CO_2C_2H_5)_2$ | 21 | $NaOC_2H_5$ | Ethanol | 718 |
| $i$-$C_4H_9CH(CH_3)CH_2Br$ | $i$-$C_4H_9CH(CH_3)CH_2CH(CO_2C_2H_5)_2$ | 62 | $NaOC_2H_5$ | Ethanol | 686 |
| $t$-$C_4H_9(CH_2)_3Br$ | $t$-$C_4H_9(CH_2)_3CH(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_5$ | Ethanol | 690 |
| $C_2H_5CH(CH_3)CH(CH_3)CH_2Br$ | $C_2H_5CH(CH_3)CH(CH_3)CH_2CH(CO_2C_2H_5)_2$ | 79 | $NaOC_2H_5$ | Ethanol | 686 |
| $n$-$C_3H_7CH(CH_3)CH(CH_3)Br$ | $n$-$C_3H_7CH(CH_3)CH(CH_3)CH(CO_2C_2H_5)_2$ | 12 | $NaOC_2H_5$ | Ethanol | 686 |
| $(C_2H_5)_2CBr(CH_2)_2Br$ | $(C_2H_5)_2C\!=\!CHCH_2CH(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 697, 318, 667 |
| $n$-$C_4H_9CH(CH_2Br)_2$ | {$BrCH_2CH(C_4H_9$-$n)CH_2CH(CO_2C_2H_5)_2$ | 41 | $NaOC_2H_5$ | Ethanol | 489 |
| | {Diethyl 3-$n$-butylcyclobutane-1,1-dicarboxylate | 24 | | | |
| Chloropentamethylethane | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 719 |
| $CH_2\!=\!CH(CH_2)_5Br$ | $CH_2\!=\!CH(CH_2)_5CH(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 661 |
| $n$-$C_4H_9C\!\equiv\!CCH_2Br$ | $n$-$C_4H_9C\!\equiv\!CCH_2CH(CO_2C_2H_5)_2$ | 66 | $NaOC_2H_5$ | Ethanol | 695 |
| $CH_3CHBr(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2CH(CH_3)CH(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 720 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—*Continued*

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ORGANIC REACTIONS

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $Br(CH_2)_4CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_4CH(CO_2C_2H_5)_2$ | 84 | $NaOC_2H_5$ | Ethanol-$C_6H_6$ | 668 |
| $i\text{-}C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7\text{-}i)CH(CO_2C_2H_5)_2$ | 38 | $NaOC_2H_5$ | Ethanol | 223 |
| $C_2H_5OCH_2CHBrCO_2C_2H_5$ | $C_2H_5OCH_2CHCO_2C_2H_5$ <br> \| <br> $CH(CO_2C_2H_5)_2$ | 64 | Na | — | 721 |
| $ClCH(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | >50 | $NaOC_2H_5$ | Ethanol | 722 |
| $BrCH(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 675 |
| $CH_3COCHBrCH_2CO_2C_2H_2$ | $CH_3COCHCH(CO_2C_2H_5)_2$ <br> \| <br> $CH_2CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 723, 168 |
| $\beta$-Cyclopentylethyl bromide | Diethyl ($\beta$-cyclopentylethyl)malonate | — | Na | Xylene | 724 |
| $\beta$-Cyclopentylethyl bromide | Diethyl ($\beta$-cyclopentylethyl)malonate | 50–60 | $NaOC_2H_5$ | Ethanol | 725 |
| $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl [$\beta$-(2-cyclopentenyl)ethyl]malonate | — | Na | Xylene | 726 |
| $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl [$\beta$-(2-cyclopentenyl)ethyl]malonate | — | $NaOC_2H_5$ | Ethanol | 727 |
| $\gamma$-Tetrahydrofurfurylpropyl bromide | Diethyl ($\gamma$-tetrahydrofurfurylpropyl)malonate | 65–66 | — | — | 728 |
| Bromomethylcyclohexane | Diethyl (cyclohexylmethyl)malonate | 71 | $NaOC_2H_5$ | Ethanol | 704 |
| 1-Methylcyclohexyl chloride | Diethyl (1-methylcyclohexyl)malonate | — | $NaOC_2H_5$ | Ethanol | 150 |
| 2-Methylcyclohexyl bromide | Diethyl (2-methylcyclohexyl)malonate | 49 | Na | — | 147 |
| 3-Methylcyclohexyl bromide | Diethyl (3-methylcyclohexyl)malonate (*cis* and *trans* isomers) <br> Diethyl di-(3-methylcyclohexyl)malonate | Good <br><br> — | $NaOC_2H_5$ | Ethanol | 729 |
| 3-Methylcyclohexyl iodide | Diethyl (3-methylcyclohexyl)malonate | 40 | $NaOC_2H_5$ | Ethanol | 352 |
| 4-Methylcyclohexyl bromide | Diethyl (4-methylcyclohexyl)malonate | — | $NaOC_2H_5$ | Ethanol | 149 |
| 4-Methylcyclohexyl iodide | Diethyl (4-methylcyclohexyl)malonate | 55 | $NaOC_2H_5$ | Ethanol | 352 |
| 1-Bromomethyl-1-bromocyclohexane | $\bigcirc CH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 150 |
| 1-Methyl-1,2-dibromocyclohexane | Diethyl (2-methyl-2-cyclohexenyl)malonate | — | $NaOC_2H_5$ | Ethanol | 150, 730 |
| 4-Methyl-1,2-dibromocyclohexane | Diethyl (5-methyl-2-cyclohexenyl)malonate (isomers) | — | — | — | 730 |
| (+)-5-Methyl-1,2-dibromocyclohexane | Two products, no analyses given | — | $NaOC_2H_5$ | Ethanol | 150 |
| 1-Cyano-1,2-dibromocyclohexane | Structure of product not determined | — | $NaOC_2H_5$ | Ethanol | 150 |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CO_2C_2H_5)_2$ | 80 | NaH | $t\text{-}C_4H_9OH$ | 393 |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CO_2C_2H_5)_2$ | 24 | KOH | $CH_3CH(OC_2H_5)_2$ | 83 |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CO_2C_2H_5)_2$ <br><br><br> $(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$ | 85 <br><br><br><br><br> 12 | $NaOC_2H_5$ | Ethanol | 136, 107, 108, 113, 119, 121, 142, 411, 430, 433, 571, 732, 734, 735 |
| $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$ | 84–87 | $NaOC_2H_5$ | Ethanol | 733 |
| $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$ | — | $Mg(OC_2H_5)_2$ | Ethanol | 56 |
| $o\text{-}ClC_6H_4CH_2Cl$ | $o\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$ <br> $(o\text{-}ClC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 76 <br> 7 | $NaOC_2H_5$ | Ethanol | 736, 737 |
| $m\text{-}ClC_6H_4CH_2Cl$ | $m\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$ <br> $(m\text{-}ClC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 35 <br> — | $NaOC_2H_5$ | Ethanol | 115 |
| $p\text{-}ClC_6H_4CH_2Cl$ | $p\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$ <br> $(p\text{-}ClC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 50 <br> — | — | — | 738 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| o-BrC$_6$H$_4$CH$_2$Cl | o-BrC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | Good | NaOC$_2$H$_5$ | Ethanol | 406 |
| p-BrC$_6$H$_4$CH$_2$Br | p-BrC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 70 | NaOC$_2$H$_5$ | Ethanol | 738 |
| | (p-BrC$_6$H$_4$CH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | | | |
| p-IC$_6$H$_4$CH$_2$Br | p-IC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 54 | NaOC$_2$H$_5$ | Ethanol | 391 |
| o-O$_2$NC$_6$H$_4$CH$_2$Cl | (o-O$_2$NC$_6$H$_4$CH$_2$)$_2$C(CO$_2$CH$_3$)$_2$* | — | NaOCH$_3$ | CH$_3$OH | 739 |
| o-O$_2$NC$_6$H$_4$CH$_2$Cl | o-O$_2$NC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 54 | NaOC$_2$H$_5$ | Ethanol | 112, 740, 741 |
| | (o-O$_2$NC$_6$H$_4$CH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 46 | | | |
| m-O$_2$NC$_6$H$_4$CH$_2$Cl | m-O$_2$NC$_6$H$_4$CH$_2$CH(CO$_2$CH$_3$)$_2$* and (m-O$_2$NC$_6$H$_4$CH$_2$)$_2$C(CO$_2$CH$_3$)$_2$* | — | NaOCH$_3$ | CH$_3$OH | 342 |
| m-O$_2$NC$_6$H$_4$CH$_2$Cl | m-O$_2$NC$_6$H$_4$CH$_2$CH(CO$_2$H)$_2$ and (m-O$_2$NC$_6$H$_4$CH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 117 |
| p-O$_2$NC$_6$H$_4$CH$_2$X** | p-O$_2$NC$_6$H$_4$CH$_2$CH(CO$_2$CH$_3$)$_2$* | — | NaOCH$_3$ | CH$_5$OH | 342 |
| p-O$_2$NC$_6$H$_4$CH$_2$Cl | p-O$_2$NC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Ethanol | 118, 112, 740–742 |
| | (p-O$_2$NC$_6$H$_4$CH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 18 | | | |
| 2-Nitro-4-cyanobromobenzene | Dimethyl (2-nitro-4-cyanophenyl)malonate* | — | Na | Ether | 712 |
| o-Bromobenzoic acid | Diethyl (o-carboxyphenyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 98 |
| n-C$_4$H$_9$OCH$_2$CH——CH$_2$ (O bridge) | n-C$_4$H$_9$OCH$_2$CHCH$_2$CHCO$_2$C$_2$H$_5$ (O——CO) | 50–60 | NaOC$_2$H$_5$ | Ethanol | 524 |
| n-C$_4$H$_9$C(CH$_3$)——CH$_2$ (O bridge) | n-C$_4$H$_9$C(CH$_3$)CH$_2$CHCO$_2$C$_2$H$_5$ (O——CO) | 50–60 | NaOC$_2$H$_5$ | Ethanol | 525 |
| i-C$_4$H$_9$OCH$_2$CH——CH$_2$ (O bridge) | i-C$_4$H$_9$OCH$_2$CHCH$_2$CHCO$_2$C$_2$H$_5$ (O——CO) | 50–60 | NaOC$_2$H$_6$ | Ethanol | 524 |
| i-C$_4$H$_9$C(CH$_3$)——CH$_2$ (O bridge) | i-C$_4$H$_9$C(CH$_3$)CH$_2$CHCO$_2$C$_2$H$_5$ (O——CO) | 50–60 | NaOC$_2$H$_5$ | Ethanol | 525 |

$C_8$

| | | | | | |
|---|---|---|---|---|---|
| n-C$_8$H$_{17}$Br | n-C$_8$H$_{17}$CH(CO$_2$C$_4$H$_9$-t)$_2$¶ | 71 | NaH | t-C$_4$H$_9$OH | 393 |
| n-C$_8$H$_{17}$Br | n-C$_8$H$_{17}$CH(CO$_2$C$_2$H$_6$)$_2$ | 80–85 | NaOC$_2$H$_6$ | Ethanol | 282, 743 |
| n-C$_8$H$_{17}$I | n-C$_8$H$_{17}$CH(CO$_2$C$_2$H$_5$)$_2$ | 68 | NaOC$_2$H$_5$ | Ethanol | 744 |
| n-C$_8$H$_{17}$I | (C$_8$H$_{17}$-n)$_2$C(CO$_2$C$_2$H$_6$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 745, 615 |
| n-C$_6$H$_{13}$CH(CH$_3$)Br | n-C$_6$H$_{13}$CH(CH$_3$)CH(CO$_2$C$_2$H$_5$)$_2$ | 70–85 | NaOC$_2$H$_5$ | Ethanol | 545, 746 |
| n-C$_6$H$_{13}$CH(CH$_3$)I | n-C$_6$H$_{13}$CH(CH$_3$)CH(CO$_2$C$_2$H$_5$)$_2$ | 80 | NaOC$_2$H$_5$ | Ethanol | 399, 317 |
| n-C$_5$H$_{11}$CH(CH$_3$)CH$_2$I | n-C$_5$H$_{11}$CH(CH$_3$)CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 82 | NaOC$_2$H$_5$ | Ethanol | 747 |
| i-C$_3$H$_7$(CH$_2$)$_5$I | i-C$_3$H$_7$(CH$_2$)$_5$CH(CO$_2$C$_2$H$_5$)$_2$ | 73 | NaOC$_2$H$_5$ | Ethanol | 138 |
| i-C$_3$H$_7$(CH$_2$)$_5$CH(C$_2$H$_5$)Br | i-C$_3$H$_7$(CH$_2$)$_5$CH(C$_2$H$_5$)CH(CO$_2$C$_2$H$_5$)$_2$ | 43 | NaOC$_2$H$_5$ | Ethanol | 718, 748 |
| n-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$Br | n-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_9$ | n-C$_4$H$_9$OH | 749 |
| i-C$_3$H$_7$(CH$_2$)$_3$CH(CH$_3$)I | i-C$_3$H$_7$(CH$_2$)$_3$CH(CH$_3$)CH(CO$_2$C$_2$H$_5$)$_2$ | 77 | NaOC$_2$H$_5$ | Ethanol | 750 |
| i-C$_3$H$_7$CH$_2$COC(CH$_3$)$_2$Br | i-C$_3$H$_7$CH$_2$COC(CH$_3$)$_2$CH$_2$CO$_2$H | — | NaOC$_2$H$_5$ | Ethanol | 751 |
| (C$_2$H$_5$)$_2$CBrCO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CC(C$_2$H$_5$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | Na | — | 162 |
| CH$_3$CCl(CO$_2$C$_2$H$_5$)$_2$ | (C$_2$H$_6$O$_2$C)$_2$CHCH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 752 |
| CH$_3$CBr(CO$_2$C$_2$H$_5$)$_2$ | (C$_2$H$_5$O$_2$C)$_2$C=C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 752 |
| | CH$_3$C(CO$_2$C$_2$H$_5$)$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | Low | | | |
| (+,−)-C$_2$H$_5$O$_2$CCHBr-CHBrCO$_2$C$_2$H$_5$ | CHCO$_2$C$_2$H$_5$ (——) C$_2$H$_5$O$_2$CCH–C(CO$_2$C$_2$H$_5$)$_2$ | 80–90 | NaOC$_2$H$_5$ | Ethanol | 175, 485 |
| CH$_3$O$_2$CCHBr(CH$_2$)$_2$-CHBrCO$_2$CH$_3$ (low-melting isomer) | Tetramethyl cyclopentane-1,2,2,3-tetracarboxylate* | — | NaOCH$_3$ | CH$_3$OH | 753 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

** The halogen was not specified.

¶ Di-t-butyl malonate was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $CH_3O_2CCHBr(CH_2)_2\cdot$ CHBrCO$_2$CH$_3$ (high-melting isomer) | Tetramethyl cyclo-pentane-1,2,2,3-tetracarboxylate* | — | NaOCH$_3$ | CH$_3$OH | 753 |
| $(CH_3O_2CCHBr)_2CHCH_3$ |  | 68 | NaOCH$_3$ | CH$_3$OH | 199, 200 |
| $\gamma$-Cyclopentylpropyl bromide | Diethyl ($\gamma$-cyclopentylpropyl)malonate | 83 | NaOC$_2$H$_5$ | Ethanol | 754 |
| $\beta$-Cyclohexylethyl bromide | Diethyl ($\beta$-cyclohexylethyl)malonate | 50 | NaOC$_2$H$_5$ | Ethanol | 704 |
| $\beta$-Cyclohexylideneëthyl bromide | Diethyl ($\beta$-cyclohexylideneëthyl)malonate | 50 | NaOC$_2$H$_5$ | Ethanol | 663 |
| $\beta$-(1-Cyclohexenyl)ethyl bromide | Diethyl [$\beta$-(1-cyclohexenyl)ethyl]malonate | 58 | K | C$_6$H$_6$ | 425 |
| 1-Bromo-1-ethylcyclohexane | Diethyl (1-ethylcyclohexyl)malonate | 2 | Na | Toluene | 147 |
| 1-Ethyl-1,2-dibromocyclo-hexane | Diethyl (2-ethyl-2-cyclohexenyl)malonate | Poor | — | — | 730 |
| 1,2-Dithiocyanocyclohexane | Diethyl 2-cyclohexenylmalonate | 30 | NaOC$_2$H$_5$ | Ethanol | 150, 322 |
| $C_6H_5(CH_2)_2Cl$ | $C_6H_5(HC_2)_2CH(CO_2C_2H_5)_2$ | — | NaOC$_2$H$_5$ | Ethanol | 427 |
| $C_6H_5CH(CH_3)Br$ | $[C_6H_5CH(CH_3)]_2C(CO_2C_2H_5)_2$ | — | Na | Toluene | 508 |
| $C_6H_5(CH_2)_2Br$ | $C_6H_5(CH_2)_2CH(CO_2C_2H_5)_2$ | 65 | Na | Toluene | 411 |
| $C_6H_5(CH_2)_2Br$ | $C_6H_5(CH_2)_2CH(CO_2C_2H_5)_2$ | 80 | NaOC$_2$H$_5$ | Ethanol | 755, 142, 428, 539, 756, 757 |
| $C_6H_5O(CH_2)_2Br$ | $C_6H_5O(CH_2)_2CH(CO_2C_2H_5)_2$ | 89 | NaOC$_2$H$_5$ | Ethanol | 136, 758 |
| $C_6H_5O(CH_2)_2Br$ | $[C_6H_5O(CH_2)_2]_2C(CO_2C_2H_5)_2$ | — | NaOC$_2$H$_5$ | Ethanol | 758 |
| $\beta$-Phenoxyethyl p-toluenesulfonate | $C_6H_5O(CH_2)_2CH(CO_2C_2H_5)_2$ | — | NaOC$_2$H$_5$ | Ethanol | 335 |
| $o$-CH$_3$C$_6$H$_4$CH$_2$Cl | $o$-CH$_3$C$_6$H$_4$CH$_2$CH(CO$_2$H)$_2$ | 60–70 | NaOC$_2$H$_5$ | Ethanol | 759, 760 |
| Chloromethyl-p-bromotoluene (mixture) | Diethyl [2(and 3)-bromo-5(and 6)-methylbenzyl]malonate | 88 | NaOC$_2$H$_5$ | Ethanol | 114 |
| $o$-CH$_3$C$_6$H$_4$CH$_2$Br | $o$-CH$_3$C$_6$H$_4$CH$_2$CH(CO$_2$H)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 761 |
| $o$-CH$_3$C$_6$H$_4$CH$_2$Br | $o$-CH$_3$C$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 57 | Na | Benzene | 421 |
| $m$-CH$_3$C$_6$H$_4$CH$_2$Br | $m$-CH$_3$C$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 66 | NaOC$_2$H$_5$ | Ethanol | 133, 110, 762 |
| $p$-CH$_3$C$_6$H$_4$CH$_2$Cl | $p$-CH$_3$C$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Toluene | 507 |
| 2-Methoxy-5-nitrobenzyl chloride | Diethyl (2-methoxy-5-nitrobenzyl)malonate | — | — | — | 763 |
| $m$-CH$_3$OC$_6$H$_4$CH$_2$Br | $[m$-CH$_3$OC$_6$H$_4$CH$_2]_2C(CO_2C_2H_5)_2$ | — | NaOC$_2$H$_5$ | Ethanol | 764 |
| $p$-CH$_3$OC$_6$H$_4$CH$_2$Cl | $p$-CH$_3$OC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Toluene | 511 |
| $o$-NCC$_6$H$_4$CH$_2$Cl | $o$-NCC$_6$H$_4$CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ {$(o$-NCC$_6$H$_4$CH$_2)_2C(CO_2C_2H_5)_2$ | Good — | NaOC$_2$H$_5$ | Ethanol | 198, 109 |
| $C_6H_5COCH_2Br$ | $C_6H_5COCH_2CH(CO_2H)_2$ | — | NaOC$_2$H$_5$ | Ethanol | 765, 106, 766 |
| 3-Nitro-4-bromoacetophenone | Dimethyl (2-nitro-4-acetylphenyl)malonate* | 70 | Na | Ether | 712 |
| 3-Nitro-4-methyl-6-bromobenzonitrile | Dimethyl (2-cyano-4-nitro-5-methyl-phenyl)malonate* | Poor | Na | Ether | 712 |
| $o$-Xylylene dibromide | Diethyl hydrindene-2,2-dicarboxylate | 75 | NaOC$_2$H$_5$ | Ethanol | 767, 302, 486 |
| $i$-C$_6$H$_{11}$OCH$_2$CH——CH$_2$ \ / O | $i$-C$_5$H$_{11}$OCH$_2$CHCH$_2$CHCO$_2$C$_2$H$_5$ — O——CO | 50–60 | NaOC$_2$H$_5$ | Ethanol | 524 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $i\text{-}C_6H_{11}C(CH_3)\text{—}CH_2$ (epoxide) | $i\text{-}C_5H_{11}C(CH_3)CH_2CHCO_2C_2H_5$ (O—CO ring) | 50–60 | $NaOC_2H_6$ | Ethanol | 525 |
| $C_6H_5CH\text{—}CH_2$ (epoxide) | $C_6H_6CHCH_2CH_2$ (O—CO ring) | 76 | $NaOC_2H_6$ | Ethanol | 526, 11 |
| $p\text{-}O_2NC_6H_4CH\text{—}CH_2$ (epoxide) | $p\text{-}O_2NC_6H_4CHCH_2CHCO_2C_2H_5$ (O—CO ring) | 46 | $NaOC_2H_5$ | Ethanol | 12 |
| $C_9$ | | | | | |
| $n\text{-}C_9H_{19}Br$ | $n\text{-}C_9H_{19}CH(CO_2C_2H_5)_2$ | 80–85 | $NaOC_2H_5$ | Ethanol | 282 |
| $n\text{-}C_7H_{15}CH(CH_3)I$ | $n\text{-}C_7H_{15}CH(CH_3)CH(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 317 |
| $n\text{-}C_5H_{11}CH(CH_3)(CH_2)_2Br$ | $n\text{-}C_5H_{11}CH(CH_3)(CH_2)_2CH(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | Ethanol | 317 |
| $i\text{-}C_3H_7(CH_2)_6I$ | $i\text{-}C_3H_7(CH_2)_6CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 138 |
| $i\text{-}C_3H_7(CH_2)_4CH(CH_3)Br$ | $i\text{-}C_3H_7(CH_2)_4CH(CH_3)CH(CO_2H)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 686 |
| $n\text{-}C_3H_7CH(CH_3)CH\text{-}(C_2H_5)CH_2Br$ | $n\text{-}C_3H_7CH(CH_3)CH(C_2H_5)CH_2CH(CO_2C_2H_5)_2$ | 63 | $NaOC_2H_5$ | Ethanol | 686 |
| $CH_2\text{=}CH(CH_2)_7Br$ | $CH_2\text{=}CH(CH_2)_7CH(CO_2C_2H_5)_2$ | 81 | $NaOC_2H_5$ | Ethanol | 661 |
| $C_2H_5CH\text{=}CH(CH_2)_2\text{-}CH\text{=}CHCH_2Cl$ | $C_2H_5CH\text{=}CH(CH_2)_2CH\text{=}CH\text{-}CH_2CH(CO_2C_2H_5)_2$ | 50 | — | — | 693 |
| $C_2H_5CH\text{=}C(CH_3)(CH_2)_4Br$ | $C_2H_5CH\text{=}C(CH_3)(CH_2)_4CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 317 |
| $Br(CH_2)_6CO_2C_2H_5\text{-}NaI$ | $C_2H_5O_2C(CH_2)_6CH(CO_2C_2H_5)_2$ | 83 | $NaOC_2H_6$ | Ethanol | 717 |
| $C_2H_5O_2CCHBrCH_2CHBr\text{-}CO_2C_2H_5$ | Tetraethyl cyclobutane-1,2,2,3-tetracarboxylate | 50 | $NaOC_2H_5$ | Ethanol | 176 |
| $\delta$-Cyclopentylbutyl bromide | Diethyl ($\delta$-cyclopentylbutyl)malonate | 40 | $NaOC_2H_6$ | Ethanol | 725 |
| $\delta$-Cyclopentylbutyl bromide | Diethyl ($\delta$-cyclopentylbutyl)malonate | — | Na | Toluene | 724 |

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $\delta$-(2-Cyclopentenyl)butyl bromide | Diethyl [$\delta$-(2-cyclopentenyl)butyl]malonate | — | Na | Toluene | 724 |
| $\gamma$-Cyclohexylpropyl bromide | Diethyl ($\gamma$-cyclohexylpropyl)malonate | 53 | $NaOC_2H_5$ | Ethanol | 704 |
| $\beta$-(2-Methyl-1-cyclohexenyl)-ethyl bromide | Diethyl [$\beta$-(2-methyl-1-cyclo-hexenyl)ethyl]malonate | 71 | K | $C_6H_6$ | 424 |
| $C_6H_5(CH_2)_3Br$ | $C_6H_5(CH_2)_3CH(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | Ethanol | 768, 429, 769, 770 |
| $C_6H_5(CH_2)_3I$ | $C_6H_5(CH_2)_3CH(CO_2C_2H_5)_2$ | — | — | — | 771 |
| $C_6H_5CH_2O(CH_2)_2Cl$ | $[C_6H_5CH_2O(CH_2)_2]_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 606 |
| $C_6H_5O(CH_2)_3Cl$ | $C_6H_5O(CH_2)_3CH(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 772–774 |
| $C_6H_5O(CH_2)_3Br$ | $C_6H_5O(CH_2)_3CH(CO_2C_2H_5)_2$ | 84 | $NaOC_2H_5$ | Ethanol | 775, 698, 776, 777 |
| $C_6H_5CH_2CH(CH_3)Br\text{-}KI$ | $C_6H_5CH_2CH(CH_3)CH(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 432 |
| $C_6H_5CH\text{=}CHCH_2Cl$ | $C_6H_5CH\text{=}CHCH_2CH(CO_2C_2H_5)_2$ | 51 | $NaOC_2H_5$ | Ethanol | 18 |
| $m\text{-}CH_3C_6H_4(CH_2)_2Br$ | $m\text{-}CH_3C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | Ethanol | 517 |
| $p\text{-}CH_3C_6H_4(CH_2)_2Br$ | $p\text{-}CH_3C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$ | Good | — | — | 760 |
| $m\text{-}CH_3OC_6H_4(CH_2)_2Br$ | $m\text{-}CH_3OC_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$ | 82–85 | K | Toluene | 412 |
| 2-Bromo-5-ethylbenzyl chloride | Diethyl (2-bromo-5-ethylbenzyl)malonate | 78 | $NaOC_2H_5$ | Ethanol | 407 |
| 2,4-Dimethylbenzyl chloride | Diethyl (2,4-dimethylbenzyl)malonate | 49 | Na | Xylene | 778, 760 |
| 3,5-Dimethylbenzyl bromide | Diethyl (3,5-dimethylbenzyl)malonate | 30 | $NaOC_2H_5$ | Ethanol | 779, 738 |
| 2-Methyl-5-methoxybenzyl chloride | Diethyl (2-methyl-5-methoxybenzyl)malonate | 77 | $NaOC_2H_5$ | Ethanol | 404 |
| 2-Chloro-5-nitro-4-methylacetophenone | Diethyl (2-acetyl-4-nitro-5-methylphenyl)malonate | — | Na | Ether | 712 |
| Methyl $p$-chloromethylbenzoate | Diethyl ($p$-carbomethoxybenzyl)malonate | 66 | $NaOC_2H_5$ | Ethanol | 780 |
| $C_6H_5CH_2COCH_2Cl$ | $(C_6H_5CH_2COCH_2)_2C(CO_2C_2H_5)_2$ | — | $Mg(OC_2H_5)_2$ | Ethanol | 56 |
| 2,3-Dichloroindenone | Diethyl (2-chloro-3-indenonyl)malonate | — | $NaOC_2H_5$ | Ethanol | 781 |
| $n\text{-}C_6H_{13}OCH_2CH\text{—}CH_2$ (epoxide) | $n\text{-}C_6H_{13}OCH_2CHCH_2CHCO_2C_2H_5$ (O—CO ring) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

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ORGANIC REACTIONS

## ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $n\text{-}C_6H_{13}C(CH_3)\text{—}CH_2$ over $O$ | $n\text{-}C_6H_{13}C(CH_3)CH_2CHCO_2C_2H_5$ with $O\text{———}CO$ | 50–60 | $NaOC_2H_5$ | Ethanol | 525 |
| $C_6H_5OCH_2CH\text{——}CH_2$ over $O$ | $C_6H_5OCH_2CHCH_2CHCO_2C_2H_5$ with $O\text{———}CO$ | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $C_6H_5C(CH_3)\text{—}CH_2$ over $O$ | $C_6H_5C(CH_3)CH_2CHCO_2C_2H_5$ with $O\text{———}CO$ | 50–60 | $NaOC_2H_5$ | Ethanol | 525 |
| 3-Chloromethylthianaphthene | Diethyl (3-thianaphthenemethyl)malonate | 45 | Na | $C_6H_6$ | 782 |
| $C_{10}$ | | | | | |
| $n\text{-}C_{10}H_{21}Br\text{-}KI$ | $n\text{-}C_{10}H_{21}CH(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | Ethanol | 70, 282, 289 |
| $n\text{-}C_{10}H_{21}I$ | $n\text{-}C_{10}H_{21}CH(CO_2C_2H_5)_2$ | 93 | $NaOC_2H_5$ | Ethanol | 684 |
| $n\text{-}C_8H_{17}CH(CH_3)Br$ | $n\text{-}C_8H_{17}CH(CH_3)CH(CO_2C_4H_9)_2$†† | 82 | — | — | 784 |
| $n\text{-}C_5H_{11}CH(C_4H_9\text{-}n)I$ | $n\text{-}C_5H_{11}CH(C_4H_9\text{-}n)CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 141 |
| $i\text{-}C_3H_7(CH_2)_3CH(CH_3)(CH_2)_2Br$ | $i\text{-}C_3H_7(CH_2)_3CH(CH_3)(CH_2)_2CH(CO_2C_2H_5)_2$ | 50 | — | — | 743 |
| Geranyl chloride | Diethyl geranylmalonate | 43 | $NaOC_2H_5$ | Ethanol | 18, 282, 785 |
| Geranyl bromide | Diethyl geranylmalonate | 52 | $NaOC_2H_5$ | Ethanol | 19 |
| Linalyl bromide | Diethyl geranylmalonate | 52 | $NaOC_2H_5$ | Ethanol | 19 |
| $i\text{-}C_3H_7(CH_2)_3CH(CH_3)COCH_2Br$ | $i\text{-}C_3H_7(CH_2)_3CH(CH_3)COCH_2CH(CO_2C_2H_5)_2$ | 84 | Na | $C_6H_6$ | 786 |
| $C_2H_5O_2C(CH_2)_3CHBrCO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_3CH(CO_2C_2H_5)CH(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 787 |
| $C_2H_5O_2C(CH_2)_3CHBrCO_2C_2H_5$ | $[C_2H_5O_2C(CH_2)_3CH(CO_2C_2H_5)]_2C(CO_2C_2H_5)_2$ | 10 | $NaOC_2H_5$ | Ethanol | 787 |
| $Br(CH_2)_{10}Br$ | $Br(CH_2)_{10}CH(CO_2C_2H_5)_2$ | 33 | $NaOC_2H_5$ | Ethanol | 788 |
| $Br(CH_2)_{10}Br$ | Diethyl cycloundecane-1,1-dicarboxylate and $(C_2H_5O_2C)_2CH(CH_2)_{10}CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 493 |
| $C_2H_5O_2CCHBr(CH_2)_2CHBrCO_2C_2H_5$ (low-melting) | Tetraethyl cyclopentane-1,2,2,3-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 753 |
| $C_2H_5O_2CCHBr(CH_2)_2CHBrCO_2C_2H_5$ (high-melting) | Tetraethyl cyclopentane-1,2,2,3-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 789 |
| $\beta$-(1-Carbethoxycyclopentyl)ethyl bromide | Diethyl $\alpha,\alpha$-tetramethylene-$\alpha'$-carbethoxyadipate | — | Na | None | 790 |
| $\delta$-Cyclohexylbutyl chloride | Diethyl ($\delta$-cyclohexylbutyl)malonate | 85 | $NaOC_2H_5$ | Ethanol | 704 |
| $\beta$-(4-Methyl-1-cyclohexenyl)propyl bromide | Diethyl [$\beta$-(4-methyl-1-cyclohexenyl)propyl]malonate | 8 | K | Benzene | 426 |
| $C_6H_5(CH_2)_4Br$ | $C_6H_5(CH_2)_4CH(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 432, 429 |
| $C_6H_5O(CH_2)_4Br$ | $C_6H_5O(CH_2)_4CH(CO_2C_2H_5)_2$ | 65–75 | $NaOC_2H_5$ | Ethanol | 792 |
| $C_6H_5CH_2O(CH_2)_3Cl$ | $C_6H_5CH_2O(CH_2)_3CH(CO_2C_2H_5)_2$ | 77 | $NaOC_2H_5$ | Ethanol | 698 |
| $C_6H_5(CH_2)_2CH(CH_3)Br$ | $C_6H_5(CH_2)_2CH(CH_3)CH(CO_2C_2H_5)_2$ | 68 | $NaOC_2H_5$ | Ethanol | 432 |
| $C_6H_5CH(CH_3)(CH_2)_2Br$ | $C_6H_5CH(CH_3)(CH_2)_2CH(CO_2C_2H_5)_2$ | 51 | — | — | 791 |
| $C_6H_5CH_2CH(C_2H_5)Br$ | $C_6H_5CH_2CH(C_2H_5)CH(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_5$ | Ethanol | 432 |
| $C_6H_5OCH_2CH(C_2H_5)X^{**}$ | $C_6H_5OCH_2CH(C_2H_5)CH(CO_2C_2H_5)_2$ | 54 | $NaOC_2H_5$ | Ethanol | 793 |
| $C_6H_5CH_2SCH_2CH(CH_3)Br$ | $C_6H_5CH_2SCH_2CH(CH_3)CH(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 794 |
| $p\text{-}CH_3C_6H_4C(CH_3)_2Cl$ | $p\text{-}CH_3C_6H_4C(CH_3)_2CH(CO_2C_2H_5)_2$ | 9 | Na | $C_6H_6$ | 795 |
| $p\text{-}CH_3OC_6H_4CH_2CH(CH_3)Br$ | $p\text{-}CH_3OC_6H_4CH_2CH(CH_3)CH(CO_2C_2H_5)_2$ | 54 | $NaOC_2H_5$ | Ethanol | 796 |
| 2-Isopropyl-5-bromobenzyl chloride | Diethyl (and dimethyl) (2-isopropyl-5-bromobenzyl)malonate | 85 | $NaOCH_3$ | Ethanol | 408 |
| 2,4,6-Trimethylbenzyl chloride | Diethyl (2,4,6-trimethylbenzyl)malonate | Good | $NaOC_2H_5$ | Ethanol | 760 |
| 2,3,6-Trimethylbenzyl bromide | Diethyl (2,3,6-trimethylbenzyl)malonate | 64 | $NaOC_2H_5$ | Ethanol | 797 |
| $p\text{-}CH_3OC_6H_4COCH(CH_3)Br$ | $p\text{-}CH_3OC_6H_4COCH(CH_3)CH(CO_2C_2H_5)_2$ | 30 | Na | $C_6H_6$ | 422 |
| Teresantalyl chloride | Diethyl teresantalylmalonate | 13 | $KOC_2H_5$ | Xylene | 798 |

*Note:* References 577–1080 are on pp. 322–331.

†† Di-$n$-butyl malonate was used in this experiment.

** The halogen was not specified.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| 3-Bromomethylindene | Diethyl (3-indenylmethyl)malonate | 79 | $NaOC_2H_5$ | Ethanol | 799 |
| $C_6H_5CHBrCHBrCO_2CH_3$ | $CHCO_2CH_3$* $H_5C_6CH—C(CO_2CH_3)_2$ | — | $NaOCH_3$ | $CH_3OH$ | 800 |
| Dibromothymoquinone | $CH(CO_2C_2H_5)_2$ (quinone structure) | — | $NaOC_2H_5$ | Ethanol | 801 |
| $n$-$C_7H_{15}OCH_2CH$——$CH_2$ \ O / | $n$-$C_7H_{15}OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $C_6H_5CH_2OCH_2CH$——$CH_2$ \ O / | $C_6H_5CH_2OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $o$-$CH_3C_6H_4OCH_2CH$——$CH_2$ \ O / | $o$-$CH_3C_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $o$-$CH_3OC_6H_4OCH_2CH$——$CH_2$ \ O / | $o$-$CH_3OC_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $m$-$CH_3C_6H_4OCH_2CH$——$CH_2$ \ O / | $m$-$CH_3C_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $p$-$CH_3C_6H_4OCH_2CH$——$CH_2$ \ O / | $p$-$CH_3C_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ (lactone) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| 4-Chloromethyl-2-phenylthiazole | Diethyl [(2-phenyl-4-thiazole)methyl]malonate and diethyl di-[(2-phenyl-4-thiazole)methyl]malonate | 70 | — | — | 137 |
| 2,3-Dibromo-decahydronaphthalene | $CH(CO_2C_2H_5)_2$ (structure) | 70 | $NaOC_2H_5$ | Ethanol | 150, 320 |
| 1,2-Dibromo-1,2,3,4-tetrahydronaphthalene | 3,4(and 1,4-)-Dihydro-1-naphthylacetic acid, 3,4-(and 1,4-)-dihydro-2-naphthylacetic acid and naphthalene | — | $NaOC_2H_5$ | Ethanol | 320 |
| 2,3-Dibromo-1,2,3,4-tetrahydronaphthalene | Naphthalene | — | $NaOC_2H_5$ | Ethanol | 150 |
| 2,3-Dibromo-1,2,3,4-tetrahydronaphthalene | Naphthalene | — | $Mg(OC_2H_5)_2$ | Ethanol | 150 |
| 1,4-Dibromo-1,2,3,4-tetrahydronaphthalene | $CH(CO_2H)_2$ (structure) | 10 | $NaOC_2H_5$ | Ethanol | 150 |
| 2,3-Dichloro-α-naphthoquinone | $CH(CO_2C_2H_5)_2$ Cl (quinone structure) | — | $NaOC_2H_5$ | Ethanol | 781 |
| 2,3-Dibromo-α-naphthoquinone | $CH(CO_2C_2H_5)_2$ Br (quinone structure) | Good | $NaOC_2H_5$ | Ethanol | 781 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| 3,4-Dibromo-$\beta$-naphthoquinone | Diethyl [(?) -bromo-$\beta$-naphtho-quinone]malonate | — | $NaOC_2H_5$ | Ethanol | 781 |
| $C_{11}$ | | | | | |
| $n$-$C_{11}H_{23}Br$ | $n$-$C_{11}H_{23}CH(CO_2C_2H_5)_2$ | 80–85 | $NaOC_2H_5$ | Ethanol | 282, 802 |
| $n$-$C_9H_{19}CH(CH_3)Br$-NaI | $n$-$C_9H_{19}CH(CH_3)CH(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 70 |
| $CH_2$=$CH(CH_2)_9Cl$-KI | $CH_2$=$CH(CH_2)_9CH(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 804 |
| $n$-$C_4H_9CH(C_2H_5)$-$(CH_2)_2CH(CH_3)Br$ | $n$-$C_4H_9CH(C_2H_5)(CH_2)_2CH(CH_3)$-$CH(CO_2C_2H_5)_2$ | 71 | $NaOC_2H_5$ | Ethanol | 686 |
| $\varepsilon$-Cyclohexylpentyl bromide | Diethyl ($\varepsilon$-cyclohexylpentyl)malonate | 79 | $NaOC_2H_5$ | Ethanol | 704 |
| $C_6H_5O(CH_2)_5Br$ | $C_6H_5O(CH_2)_5CH(CO_2C_2H_5)_2$ | 53 | $NaOC_2H_5$ | Ethanol | 803 |
| $n$-$C_4H_9CH(C_6H_5)Cl$ | $n$-$C_4H_9CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 805 |
| $t$-$C_4H_9CH(C_6H_5)Br$ | $t$-$C_4H_9CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 24 | $NaOC_2H_5$ | Ethanol | 806 |
| $p$-$t$-$C_4H_9C_6H_4CH_2Cl$ | $p$-$t$-$C_4H_9C_6H_4CH_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 403 |
| $\gamma$-(2-Methyl-5-methoxyphenyl)propyl bromide | Diethyl [$\gamma$-(2-methyl-5-methoxyphenyl)propyl]malonate | 49 | $NaOC_2H_5$ | Ethanol | 404 |
| $\beta$-(2,5-Dimethyl-4-methoxyphenyl)ethyl bromide | Diethyl [$\beta$-(2,5-dimethyl-4-methoxyphenyl)ethyl]malonate | 54 | $NaOC_2H_5$ | Ethanol | 807 |
| 2-Methyl-5-isopropylbenzyl chloride | Diethyl (2-methyl-5-isoproplbenzyl)-malonate | 60 | Na | $C_6H_6$ | 808, 418, 779 |
| 2,3,5,6-Tetramethylbenzyl chloride | Diethyl (2,3,5,6-tetramethylbenzyl)malonate | 66 | Na | $C_6H_6$ | 809 |
| 2,3,5,6-Tetramethylbenzyl chloride | $\beta$-(2,3,5,6-Tetramethylphenyl)propionic acid | 72 | $NaOC_2H_5$ | Ethanol | 810 |
| $\omega$-Chloro-2,5-dimethyl-propiophenone | Diethyl [$\beta$-(2,5-dimethylbenzoyl)ethyl]-malonate | — | $NaOC_2H_5$ | Ethanol | 779 |
| $n$-$C_8H_{17}OCH_2CH$——$CH_2$ (epoxide) | $n$-$C_8H_{17}OCH_2CHCH_2CHCO_2C_2H_5$ (O——CO) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $C_6H_5(CH_2)_2OCH_2CH$——$CH_2$ (epoxide) | $C_6H_5(CH_2)_2OCH_2CHCH_2CHCO_2C_2H_5$ (O——CO) | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
| $\gamma$-Bromopropylphthalimide | Diethyl ($\gamma$-phthalimidopropyl)malonate | — | $NaOC_2H_5$ | Ethanol | 811 |
| 4-Chloromethyl-2-(4-methoxyphenyl)thiazole | Diethyl [2-(4-methoxyphenyl)-4-thiazolemethyl]malonate | 52 | — | — | 140 |
| $C_6H_5CHBr(CH_2)_4Br$ | Diethyl 2-phenylcyclohexane-1,1-dicarboxylate | — | $NaOC_2H_5$ | Ethanol | 812 |
| $C_6H_5CHBrCHBrCO_2C_2H_5$ | $H_5C_6CH$—$C(CO_2C_2H_5)_2$ ($CHCO_2C_2H_5$) | — | $NaOC_2H_5$ | Ethanol | 813 |
| $C_6H_5C$=$CCO_2C_2H_5$ (Br Br) | $C_2H_5O_2CCH$=$C(C_6H_5)CBr(CO_2C_2H_5)_2$ | — | Na | Ether | 813 |
| $C_6H_5C$=$CCO_2C_2H_5$ (Br Br) | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 813 |
| (phthalimido-epoxide) NCH₂CH——CH₂ | $\alpha$-Carbethoxy-$\delta$-phthalimido-$\gamma$-valerolactone | 60 | $NaOC_2H_5$ | Ethanol | 464 |
| 2-Chloromethyl-5,6,7,8-tetrahydronaphthalene | (tetrahydronaphthalenyl)$CH_2CH(CO_2C_2H_5)_2$ | — | — | — | 513 |
| 1-Chloromethylnaphthalene | Diethyl (1-naphthylmethyl)malonate | 82 | $NaOC_2H_5$ | Ethanol | 409, 512, 738 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| 1-Bromomethylnaphthalene | Diethyl (1-naphthylmethyl)malonate | 55 | Na | $C_6H_6$ | 153 |
| 4-Bromo-1-bromomethyl-naphthalene | Diethyl (4-bromo-1-naphthylmethyl)malonate | — | Na | $C_6H_6$ | 153 |
| 2-Bromomethylnaphthalene | Diethyl (2-naphthylmethyl)malonate | — | Na | $C_6H_6$ | 153 |
| 1-Bromo-2-bromomethyl-naphthalene | Diethyl (1-bromo-2-naphthylmethyl)malonate | — | Na | $C_6H_6$ | 153 |

$C_{12}$

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $n\text{-}C_{12}H_{25}I$ | $(n\text{-}C_{12}H_{25})_2C(CO_2H)_2$ | 61 | $NaOC_2H_5$ | Ethanol | 684 |
| $n\text{-}C_6H_{13}CH(CH_3)CH\text{-}(C_2H_5)CH_2Br$ | $n\text{-}C_6H_{13}CH(CH_3)CH(C_2H_5)CH_2CH(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 686 |
| $Br(CH_2)_3C(CO_2C_2H_5)_2$<br>$\mid$<br>$C_2H_5$ | $(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_3CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 814, 656 |
| $cyclo\text{-}C_6H_{11}(CH_2)_6Br$ | $cyclo\text{-}C_6H_{11}(CH_2)_6CH(CO_2C_2H_5)_2$ | 63 | $NaOC_2H_5$ | Ethanol | 704 |
| $C_6H_5O(CH_2)_6Br$ | $C_6H_5O(CH_2)_6CH(CO_2C_2H_5)_2$ | 71 | $NaOC_2H_5$ | Ethanol | 815, 816 |
| $p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2Br$ | $p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$ <br> $[p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2]_2C(CO_2C_2H_5)_2$ | 50 <br> — | Na | $C_6H_6$ | 321 |
| 2-Bromoethyl-4-isopropyl-1-methylbenzene |  | 30 | Na | $C_6H_6$ | 415 |
| 5-Isopropyl-2-methyl-4-methoxybenzyl chloride | Diethyl (2-methyl-4-methoxy-5-isopropylbenzyl)malonate | 63 | $NaOC_2H_5$ | Ethanol | 404 |

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| Pentamethylbenzyl chloride | Diethyl (pentamethylbenzyl)malonate | 62 | Na | $C_6H_6$ | 809 |
| $C_6H_5(CH_2)_3OCH_2CH{-\!\!-}CH_2$<br>$\diagdown_O\diagup$ | $C_6H_5(CH_2)_3OCH_2CHCH_2CHCO_2C_2H_5$<br>$\mid\qquad\mid$<br>$O{-\!\!-\!\!-}CO$ | 50–60 | $NaOC_2H_5$ | Ethanol | 524 |
|  |  | 30 | Na | Pyridine | 818 |
|  |  | — | Na | Acetone | 818 |
| $\beta\text{-}(1\text{-Naphthyl})$ethyl bromide | Diethyl $[\beta\text{-}(1\text{-naphthyl})$ethyl]malonate | 37 | $NaOC_2H_5$ | Ethanol | 546, 517 |
| $\beta\text{-}(2\text{-Naphthyl})$ethyl bromide | Diethyl $[\beta\text{-}(2\text{-naphthyl})$ethyl]malonate | 89 | Na | $C_6H_6$ | 819 |
| $\beta\text{-}(2\text{-Naphthyl})$ethyl bromide | Diethyl $[\beta\text{-}(2\text{-naphthyl})$ethyl]malonate | 64 | $NaOC_2H_5$ | Ethanol | 820, 817 |
| 1-Chloromethyl-2-methylnaphthalene | Diethyl (2-methyl-1-naphthyl-methyl)malonate | — | — | — | 821 |
| 1-Chloromethyl-4-methylnaphthalene | Diethyl (4-methyl-1-naphthyl-methyl)malonate | — | $NaOC_2H_5$ | Toluene | 514 |
| 1-Chloromethyl-6-methoxynaphthalene | Diethyl (6-methoxy-1-naphthyl-methyl)malonate | — | $NaOC_2H_5$ | None | 822 |
| 2-Bromomethyl-3-methylnaphthalene | Diethyl (3-methyl-2-naphthyl-methyl)malonate | 39 | $NaOC_2H_5$ | Ethanol | 401, 823 |
| 1-Chloroacenaphthene | Diethyl 1-acenaphthenylmalonate | 67 | $NaOC_2H_5$ | Ethanol | 824 |
| 1-Bromoacenaphthene | Diethyl 1-acenaphthenylmalonate | >82 | $NaOC_2H_5$ | Ethanol | 825 |
| 1,5-Dibromoacenaphthene | Diethyl (1-bromo-5-acenaphthenyl)malonate | — | — | — | 826 |

$C_{13}$

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $Br(CH_2)_3C(C_2H_7\text{-}n)\text{-}(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C(C_3H_7\text{-}n)(CH_2)_3CH(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 656 |
| $\beta\text{-}(p\text{-}t\text{-Amylphenyl})$ethyl bromide | Diethyl $[\beta\text{-}(p\text{-}t\text{-amylphenyl})$ethyl]malonate | 48 | $NaOC_2H_5$ | Ethanol | 413 |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE I—*Continued*

### ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $\beta$-(2-Methyl-4-$t$-butylphenyl)-ethyl bromide | Diethyl [$\beta$-(2-methyl-4-$t$-butylphenyl)ethyl]-malonate | 80 | $NaOC_2H_5$ | Ethanol | 827, 414 |
| $\beta$-(2-Methoxy-5-$t$-butylphenyl)ethyl bromide | Diethyl [$\beta$-(2-methoxy-5-$t$-butyl-phenyl)ethyl]malonate | 52 | $NaOC_2H_5$ | Ethanol | 827 |
| 2,4-Dimethyl-5-$t$-butylbenzyl chloride | Diethyl (2,4-dimethyl-5-$t$-butylbenzyl)-malonate | 19 | $NaOC_2H_5$ | Ethanol | 405 |
| $i$-$H_7C_3$ ⬡ $(CH_2)_2Br$ / $CH_3O$ $CH_3$ | $i$-$H_7C_3$ ⬡ $(CH_2)_2CH(CO_2C_2H_5)_2$ / $CH_3O$ $CH_3$ | — | $NaOC_2H_5$ | Ethanol | 321 |
| $i$-$H_7C_3$ ⬡ $(CH_2)_2Br$ / $CH_3O$ $CH_3$ | $i$-$H_7C_3$ ⬡ $(CH_2)_2CH(CO_2C_2H_5)_2$ / $CH_3O$ $CH_3$ | 61 | Na | Toluene | 413 |
| 1-Benzoyl-4-bromo-methylpiperidine | Diethyl [(1-benzoyl-4-piperidyl)-methyl]malonate | — | $NaOC_2H_5$ | Ethanol | 828 |
| Benzhydryl bromide | Diethyl benzhydrylmalonate | 49 | $NaOC_2H_5$ | Ethanol | 516, 829 |
| $o$-$C_6H_5C_6H_4CH_2Br$ | $o$-$C_6H_5C_6H_4CH_2CH(CO_2C_2H_5)_2$ | 80 | — | — | 830 |
| $p$-$C_6H_5C_6H_4CH_2Cl$ | $p$-$C_6H_5C_6H_4CH_2CH(CO_2C_2H_5)_2$ and $(p$-$C_6H_5C_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 65 | — | — | 738 |
| 3-Nitro-4-bromobenzophenone | Diethyl (2-nitro-4-benzoylphenyl)malonate | — | Na | Ether | 712 |
| $\beta$-(5-Methoxy-1-naphthyl)-ethyl bromide | Diethyl [$\beta$-(5-methoxy-1-naphthyl)ethyl]-malonate | 65 | $NaOC_2H_5$ | Ethanol | 520 |
| $\beta$-(7-Methoxy-2-naphthyl)-ethyl bromide | Diethyl [$\beta$-(7-methoxy-2-naphthyl)ethyl]-malonate | 80 | Na | $C_6H_6$ | 819 |
| $\beta$-(6-Methoxy-1-naphthyl)-ethyl bromide | Diethyl [$\beta$-(6-methoxy-1-naphthyl)ethyl]-malonate | 37 | K | Toluene | 831 |
| ⬡⬡$C(CH_3)_2Cl$ | ⬡⬡$C(CH_3)_2CH(CO_2H)_2$ | 15 | Na | Ether | 832 |
| 1-Chloromethyl-2-ethyl-naphthalene | Diethyl (2-ethyl-1-naphthylmethyl)malonate | — | — | — | 821 |
| 1-Chloromethyl-2,3-dimethylnaphthalene | Diethyl (2,3-dimethyl-1-naphthylmethyl)-malonate | — | — | — | 821 |
| 1-Chloromethyl-3,4-dimethylnaphthalene | Diethyl (3,4-dimethyl-1-naphthylmethyl)-malonate | — | — | — | 821 |
| 9-Bromofluorene | Fluorenyl-9-acetic acid | 89 | $NaOC_2H_5$ | Ethanol | 833, 516 |
| $C_{14}$–$C_{18}$ | | | | | |
| $n$-$C_{14}H_{29}I$ | $n$-$C_{14}H_{29}CH(CO_2C_2H_5)_2$ | 96 | Na | None | 684 |
| $n$-$C_4H_9CH(C_2H_5)(CH_2)_2$-$CH(C_4H_9$-$i)Br$ | $n$-$C_4H_9CH(C_2H_5)(CH_2)_2CH(C_4H_9$-$i)$-$CH(CO_2C_2H_5)_2$ | 31 | $NaOC_2H_5$ | Ethanol | 686 |
| $n$-$C_4H_9CH(C_6H_5)(CH_2)_3Br$ | $n$-$C_4H_9CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$ | 66 | $NaOC_2H_5$ | Ethanol | 805 |
| $p$-$C_6H_5COC_6H_4CH_2Br$ | $(p$-$C_6H_5COC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | $C_6H_6$ | 834 |
| ⬡$CH_2Br$ / ⬡$CH_2Br$ | ⬡$CH_2$\$C(CO_2C_2H_5)_2$ / ⬡$CH_2$ | — | $NaOC_2H_5$ | Ethanol | 492 |
| $t$-$H_9C_4$ ⬡ $(CH_2)_2Br$ / $CH_3O$ $CH_3$ | $t$-$H_9C_4$ ⬡ $(CH_2)_2CH(CO_2C_2H_5)_2$ / $CH_3O$ $CH_3$ | — | — | — | 414 |
| $p$-$CH_3OC_6H_4SO_2C_6H_4CH_2Br$-$p$ | $p$-$CH_3OC_6H_4SO_2C_6H_4CH_2CH(CO_2C_2H_5)_2$ | 40 | Na | $C_6H_6$ | 245 |
| 1-Chloromethyl-4-isopropylnaphthalene | Diethyl (4-isopropyl-1-naphthylmethyl)malonate | — | $NaOC_2H_5$ | Ethanol | 515 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| (acenaphthene structure) $(CH_2)_2Br$ | (acenaphthene structure) $(CH_2)_2CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 835 |
| $Br(CH_2)_3C(C_7H_{15}\text{-}n)(CO_2CH_3)_2$ | $(CH_3O_2C)_2C(C_7H_{15}\text{-}n)(CH_2)_3CH(CO_2CH_3)_2*$ | — | Na | None | 656 |
| 3,7,11-Trimethyl-2-dodecenyl bromide | Diethyl (3,7,11-trimethyl-2-dodecenyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 836 |
| Farnesyl bromide | Diethyl farnesylmalonate | 56 | $NaOC_2H_5$ | Ethanol | 837 |
| $Br(CH_2)_3C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C(C_5H_{11}\text{-}n)(CH_2)_3CH(CO_2C_2H_5)_2$ | — | — | — | 656 |
| $(C_2H_5O_2C)_2CBrCH_2\text{-}CBr(CO_2C_2H_5)_2$ | $C(CO_2C_2H_5)_2$ (cyclopropane) $CH_2\text{—}C(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 261 |
| $n\text{-}C_8H_{17}CH(C_6H_5)Cl$ | $n\text{-}C_8H_{17}CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 805 |
| 1-Chloromethyl-2-t-butylnaphthalene | Diethyl (2-t-butyl-1-naphthyl-methyl)malonate | — | — | — | 821 |
| β-(5-Isopropyl-1-naphthyl)-ethyl bromide | Diethyl [β-(5-isopropyl-1-naphthyl)ethyl]-malonate | 59 | $NaOCH_3$ | Xylene | 838 |
| (octahydrophenanthrenone structure) $CH_3Br$ | (octahydrophenanthrenone structure) $CH_3CH_2CO_2H$ | 24 | Na | $C_6H_6$-ethanol | 839 |
| $n\text{-}C_{16}H_{33}Br$ | $n\text{-}C_{16}H_{33}CH(CO_2C_2H_5)_2$ | 94 | $NaOC_2H_5$ | Ethanol | 679, 840, 841 |
| $n\text{-}C_{16}H_{33}I$ | $n\text{-}C_{16}H_{33}CH(CO_2C_2H_5)_2$ and $(n\text{-}C_{16}H_{33})_2C(CO_2C_2H_5)_2$ | 40 | $NaOC_2H_5$ | Ethanol | 842 |
| $n\text{-}C_6H_{13}CH{=}CH(CH_2)_8Br$ | $n\text{-}C_6H_{13}CH{=}CH(CH_2)_8CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 843 |
| $C_2H_5CH{=}CH(CH_2)_{12}Br$ | $C_2H_5CH{=}CH(CH_2)_{12}CH(CO_2C_2H_5)_2$ | 40–50 | $NaOC_4H_9\text{-}n$ | $n\text{-}C_4H_9OH$ | 844 |
| $n\text{-}C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_6I$ | $n\text{-}C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_6CH(CO_2C_2H_5)_2$ | >29 | $NaOC_2H_5$ | Ethanol | 845, 846 |
| Hydnocarpyl bromide | Diethyl hydnocarpylmalonate | 59 | $NaOC_2H_5$ | Ethanol | 847 |
| $(C_2H_5O_2C)_2CBr(CH_2)_2\text{-}CBr(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ and $CH_2\text{—}C(CO_2C_2H_5)_2$ / $CH_2\text{—}C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 261 |
| $n\text{-}C_9H_{19}CH(C_6H_5)Cl$ | $n\text{-}C_9H_{19}CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 61 | $NaOC_2H_5$ | Ethanol | 805 |
| $n\text{-}C_4H_9CH(C_6H_5)(CH_2)_5Br$ | $n\text{-}C_4H_9CH(C_6H_5)(CH_2)_5CH(CO_2C_2H_5)_2$ | 67 | $NaOC_2H_5$ | Ethanol | 805 |
| $n\text{-}C_{17}H_{35}I$ | $n\text{-}C_{17}H_{35}CH(CO_2C_2H_5)_2$ | 92 | Na | $C_6H_6$ | 400 |
| $n\text{-}C_{15}H_{31}CH(CH_3)Br$ | $n\text{-}C_{15}H_{31}CH(CH_3)CH(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 281 |
| $n\text{-}C_{15}H_{31}CH(CH_3)I$ | $n\text{-}C_{15}H_{31}CH(CH_3)CH(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 281 |
| 3-Chloromethylpyrene | Diethyl (3-pyrenylmethyl)malonate | 76 | Na | $C_6H_6$ | 848 |
| $n\text{-}C_{18}H_{37}I$ | $n\text{-}C_{18}H_{37}CH(CO_2C_2H_5)_2$ | 100 | $NaOC_4H_9\text{-}n$ | $n\text{-}C_4H_9OH$ | 46, 45, 684 |
| Oleyl bromide | Diethyl oleylmalonate | 53 | — | — | 849 |
| Oleyl tosylate | Diethyl oleylmalonate | 60 | — | — | 849 |
| Chaulmoogryl bromide | Diethyl chaulmoogrylmalonate | — | $NaOC_2H_5$ | Ethanol | 850 |
| $n\text{-}C_4H_9CH(C_6H_5)(CH_2)_7Cl$ | $n\text{-}C_4H_9CH(C_6H_5)(CH_2)_7CH(CO_2C_2H_5)_2$ | 61 | $NaOC_2H_5$ | Ethanol | 805 |
| 3-(α-Bromoethyl)pyrene | Diethyl [α-(3-pyrenyl)ethyl]malonate | >93 | Na | $C_6H_6$ | 848 |

*Note:* References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $C_{19}$–$C_{24}$ | | | | | |
| $n$-$C_9H_{19}CH(C_6H_5)(CH_2)_3Br$ | $n$-$C_9H_{19}CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$ | 72 | $NaOC_2H_5$ | Ethanol | 805 |
| Dimesitylchloromethane | Diethyl (dimesitylmethyl)malonate | 84 | $Mg(OC_2H_5)_2$ | Ether-ethanol | 218 |
| $(C_6H_5)_3CCl$ | $(C_6H_5)_3CCH(CO_2C_2H_5)_2$ | 86 | $Mg(OC_2H_5)_2$ | Ether | 56 |
| $(C_6H_5)_3CBr$ | $(C_6H_5)_3CCH(CO_2C_2H_5)_2$ | — | Na | Ether | 851 |
| $n$-$C_8H_{17}CH(C_6H_5)(CH_2)_5Cl$ | $n$-$C_8H_{17}CH(C_6H_5)(CH_2)_5CH(CO_2C_2H_5)_2$ | 42 | $NaOC_2H_5$ | Ethanol | 805 |
| Diphenyl-$o$-tolylmethyl bromide | Diethyl (diphenyl-$o$-tolylmethyl)malonate | 69 | $Mg(OC_2H_5)_2$ | Ethanol | 829 |
| Diphenyl-$p$-tolylmethyl bromide | Diethyl (diphenyl-$p$-tolylmethyl)malonate | 77 | $Mg(OC_2H_5)_2$ | Ethanol | 829 |
| Diphenyl-$o$-methoxyphenyl-methyl bromide | Diethyl (diphenyl-$o$-methoxyphenylmethyl)-malonate | 82 | $Mg(OC_2H_5)_2$ | Ethanol | 829 |
| Diphenyl-$p$-methoxy-phenylmethyl bromide | Diethyl (diphenyl-$p$-methoxyphenylmethyl)-malonate | — | $Mg(OC_2H_5)_2$ | Ethanol | 829 |



| | | | | | 852 |
|---|---|---|---|---|---|
| | | — | — | — | |

| | | | | | |
|---|---|---|---|---|---|
| $n$-$C_{22}H_{45}I$ | $n$-$C_{22}H_{45}CH(CO_2C_2H_5)_2$ | 92 | $NaOC_2H_5$ | Ethanol | 802, 134, 684 |
| $n$-$C_8H_{17}CH=CH(CH_2)_{12}Br$ | $n$-$C_8H_{17}CH=CH(CH_2)_{12}CH(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | Ethanol | 853 |
| $n$-$C_9H_{19}CH(C_6H_5)(CH_2)_6Cl$ | $n$-$C_9H_{19}CH(C_6H_5)(CH_2)_6CH(CO_2C_2H_5)_2$ | 57 | $NaOC_2H_5$ | Ethanol | 805 |
| $n$-$C_8H_{17}CH(C_6H_5)(CH_2)_7Br$ | $n$-$C_8H_{17}CH(C_6H_5)(CH_2)_7CH(CO_2C_2H_5)_2$ | 73 | $NaOC_2H_5$ | Ethanol | 805 |
| $i$-$C_3H_7(CH_2)_{20}I$ | $i$-$C_3H_7(CH_2)_{20}CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 854 |
| $n$-$C_{10}H_{21}CH(C_{10}H_{21}$-$n)(CH_2)_2I$ | $n$-$C_{10}H_{21}CH(C_{10}H_{21}$-$n)(CH_2)_2CH(CO_2C_2H_5)_2$ | 16 | $NaOC_2H_5$ | Ethanol | 70 |
| $n$-$C_7H_{15}CH(CH_3)CH_2CH=$ $C(CH_3)(CH_2)_8CH(CH_3)I$ | $n$-$C_7H_{15}CH(CH_3)CH_2CH=C(CH_3)(CH_2)_8$-$CH(CH_3)CH(CO_2C_2H_5)_2$ | 13 | $NaOC_2H_5$ | Ethanol | 855 |
| $n$-$C_9H_{19}CH=C(CH_3)(CH_2)_9$-$CH(CH_3)I$ | $n$-$C_9H_{19}CH=C(CH_3)(CH_2)_9CH(CH_3)CH$-$(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 856 |
| Diphenyl-$\alpha$-naphthylmethyl bromide | Diethyl (diphenyl-$\alpha$-naphthylmethyl)-malonate | 38 | $Mg(OC_2H_5)_2$ | Ethanol | 829 |
| $n$-$C_9H_{19}CH(CH_3)(CH_2)_2$-$CH(CH_3)(CH_2)_{10}Br$ | $n$-$C_9H_{19}CH(CH_3)(CH_2)_2CH(CH_3)(CH_2)_{10}$-$CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 317 |
| $n$-$C_3H_7CH=C(CH_3)(CH_2)_4$-$CH=C(CH_3)(CH_2)_9CH(CH_3)I$ | $n$-$C_3H_7CH=C(CH_3)(CH_2)_4CH=C(CH_3)(CH_2)_9$-$CH(CH_3)CH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 856 |
| $C_{25}$ | | | | | |
| Diphenyl-4-biphenylylmethyl bromide | Diethyl (diphenyl-4-biphenylylmethyl)malonate | 89 | $Mg(OC_2H_5)_2$ | Ethanol | 829 |
| $3\beta$-Cholestanyl $p$-toluenesulfonate | Diethyl $3\alpha$-cholestanylmalonate | — | Na | Toluene | 10 |
| $3\beta$-Cholesteryl $p$-toluenesulfonate | Diethyl 3-cholesterylmalonate and diethyl 3,5-cyclo-6-cholestanylmalonate | — | Na | Xylene | 21, 22 |
| $3\beta$-Cholesteryl $p$-toluenesulfonate | Diethyl $3\alpha$- and $3\beta$-cholesterylmalonate†† | — | Na | Toluene | 10 |

*Note:* References 577–1080 are on pp. 322–331.

†† The ratio of the $\beta$-isomer to the $\alpha$-isomer was about 9 to 1.

# TABLE II

## ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| X | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Cl | None | $(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ | <60 | $NaOC_2H_5$ | Ethanol | 857 |
| | $CHCl_3$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 231 |
| | $CHBr_3$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 231 |
| | $CHI_3$ | $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 231 |
| | 4-Imidazoylmethyl chloride hydrochloride | Diethyl [4-(or 5-)-imidazoylmethyl]-chloromalonate | 60 | $NaOC_2H_5$ | Ethanol | 209 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CCl(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 208 |
| | o-Xylylene dibromide | $o\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$ | — | $NaOC_2H_5$ | Ethanol-ether | 228 |
| | m-Xylylene dibromide | $m\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$ | 100 | $NaOC_2H_5$ | Ethanol-ether | 229 |
| | p-Xylylene dibromide | $p\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$ | — | $NaOC_2H_5$ | Ethanol-ether | 229 |
| | p-Carbethoxybenzyl bromide | Diethyl (p-carbethoxybenzyl)-chloromalonate | Fair | — | — | 230 |
| $NO_2$ | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2C(NO_2)(CO_2C_2H_5)_2$ | 34 | $KOC_2H_5$ | Ethanol | 183 |
| | $CH_3CH{=}CHCH_2Cl$ | $CH_3CH{=}CHCH_2C(NO_2)(CO_2C_2H_5)_2$ | 25 | $KOC_2H_5$ | Ethanol | 183 |
| $NH_2$ | $CH_3Br$ | $CH_3C(NH_2)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 858 |
| | $CH_3I$ | $CH_3C(NH_2)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 858 |
| | $(CH_3)_2SO_4$ | $CH_3C(NH_2)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 858 |
| | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2C(NH_2)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 859 |
| | $Br(CH_2)_3Br$ | $\begin{array}{c}CH_2{-}CH_2\\ \vert \quad\ \vert \\ CH_2 \quad CHCO_2H \\ \diagdown N \diagup \\ H\end{array}$ | 25 | $NaOC_2H_5$ | Ethanol | 434 |
| | $i\text{-}C_4H_9I$ | $i\text{-}C_4H_9C(NH_2)(CO_2C_2H_5)_2$ | 55 | Na | $i\text{-}C_4H_9OCH_3$ | 859 |
| | $C_6H_5CH_2Br$ | $C_6H_5CH_2C(NH_2)(CO_2C_2H_5)_2$ | 60 | Na | Ether | 859 |
| HCONH | $i\text{-}C_3H_7Br$ | $i\text{-}C_3H_7C(NHCHO)(CO_2C_2H_5)_2$ | 50 | NaH | $(CH_3)_2NCHO$ | 246 |
| | $CH_2{=}CHCH_2Cl$ | $CH_2{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 69 | NaH | Toluene | 860 |
| | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | — | — | — | 861 |
| | $Cl(CH_2)_3Br$ | $Cl(CH_2)_3C(NHCHO)(CO_2C_2H_5)_2$ | — | — | — | 436 |
| | cis-$ClCH{=}CHCH_2Cl$ | cis-$ClCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 84 | NaH | Toluene | 860 |
| | trans-$ClCH{=}CHCH_2Cl$ | trans-$ClCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 86 | NaH | Toluene | 860 |
| | $CH_2{=}CClCH_2Cl$ | $CH_2{=}CClCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 83 | NaH | Toluene | 246 |
| | $CH_2{=}CBrCH_2Br$ | $CH_2{=}CBrCH_2C(NHCHO)(CO_2C_2H_5)_2$ | — | — | — | 862 |
| | $CH_2{=}CBrCH_2Br$ | $CH_2{=}CBrCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 81 | NaH | Toluene | 246 |
| | $BrCH{=}CHCH_2Br$ | $BrCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | — | — | — | 862 |
| | $BrCH{=}CHCH_2Br$ | $BrCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 73 | NaH | $(CH_3)_2NCHO$ | 860 |
| | $Cl_2C{=}CHCH_2Br$ | $Cl_2C{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 83 | NaH | $(CH_3)_2NCHO$ | 860 |
| | $HC{\equiv}CCH_2Br$ | $HC{\equiv}CCH_2C(NHCHO)(CO_2C_2H_5)_2$ | 82 | NaH | $C_6H_6$ | 246 |
| | $\begin{array}{c}BrCH_2CH{-}CH_2\\ \diagdown\ \diagup\\ O\end{array}$ | $\begin{array}{c}BrCH_2CHCH_2C(NHCHO)CO_2C_2H_5\\ \vert\qquad \vert\\ O{-}{-}{-}CO\end{array}$ | — | — | — | 436 |
| | $n\text{-}C_4H_9Br$ | $n\text{-}C_4H_9C(NHCHO)(CO_2CH_3)_2$* | 37 | $NaOCH_3$ | $CH_3OH$ | 863 |
| | $n\text{-}C_4H_9Br$ | $n\text{-}C_4H_9C(NHCHO)(CO_2C_2H_5)_2$ | 62 | $NaOC_2H_5$ | Ethanol | 863 |
| | $CH_2{=}CH(CH_2)_2Br$ | $CH_2{=}CH(CH_2)_2C(NHCHO)(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 864, 437 |
| | $BrCH_2CO_2CH_3$ | $CH_3O_2CCH_2C(NHCHO)(CO_2CH_3)_2$* | 47 | $NaOCH_3$ | $CH_3OH$ | 863 |
| | $\begin{array}{c}CH_2\diagdown\\ \vert\quad CHCH_2Br\\ CH_2\diagup\end{array}$ | $\begin{array}{c}CH_2\diagdown\\ \vert\quad CHCH_2C(NHCHO)(CO_2C_2H_5)_2\\ CH_2\diagup\end{array}$ | 53 | $NaOC_2H_5$ | Ethanol | 864 |
| | 3-Bromomethylthiophene | Diethyl (3-thenyl)formamidomalonate | 80 | NaH | $C_6H_6$ | 246 |
| | 3-Bromomethylthiophene | Diethyl (3-thenyl)formamidomalonate | 80 | NaH | Toluene | 246 |
| | 3-Bromomethylthiophene | Diethyl (3-thenyl)formamidomalonate | 93 | NaH | $(CH_3)_2NCHO$ | 246 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(NHCHO)(CO_2CH_3)_2$* | 75 | $NaOCH_3$ | $CH_3OH$ | 863 |
| | $p\text{-}CH_3OC_6H_4CH_2Cl$ | $p\text{-}CH_3OC_6H_4CH_2C(NHCHO)(CO_2CH_3)_2$* | 73 | $NaOCH_3$ | $CH_3OH$ | 863 |

Note: References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.

TABLE II—*Continued*

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| X | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| HCONH (*cont.*) | 3-Nitro-4-methoxybenzyl chloride | Diethyl (3-nitro-4-methoxybenzyl)-formamidomalonate | 80 | NaH | Toluene | 246 |
| | 2,4-Dimethylbenzyl chloride | Diethyl (2,4-dimethylbenzyl)-formamidomalonate | 89 | NaH | Toluene | 246 |
| | $BrCH\!=\!CHCH_2C(NHCHO)\text{-}$ $(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C(NHCHO)CH_2\text{-}$ $CH\!=\!CHC(NHCHO)(CO_2C_2H_5)_2$ | — | — | — | 862 |
| | $(C_6H_5)_2CHBr$ | $(C_6H_5)_2CHC(NHCHO)(CO_2C_2H_5)_2$ | 43 | Na | Xylene | 865 |
| | 1-Chloromethyl-naphthalene | Diethyl (1-naphthylmethyl)-formamidomalonate | 96 | NaH | Toluene | 246 |
| | $C_1\text{-}C_2$ | | | | | |
| $CH_3CONH$ | $CH_3I$ | $CH_3C(NHCOCH_3)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 232 |
| | $(CH_3)_2SO_4$ | $CH_3C(NHCOCH_3)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 232 |
| | $C_2H_5Br$ | $C_2H_5C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232 |
| | $C_3$ | | | | | |
| | $n\text{-}C_3H_7Br$ | $n\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$ | 71 | $NaOC_2H_5$ | Ethanol | 235, 232 |
| | $CH_3S(CH_2)_2Cl$ | $CH_3S(CH_2)_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | >56 | $NaOC_2H_5$ | Ethanol | 866 |
| | $CH_3S(CH_2)_2Cl$ | $CH_3S(CH_2)_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | >60 | $NaOC_4H_9\text{-}t$ | $t\text{-}C_4H_9OH$ | 866 |
| | $i\text{-}C_3H_7Br$ | $i\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$ | 37 | $NaOC_2H_5$ | Ethanol | 234 |
| | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232, 867 |
| | $CH_3COCH_2Br$ | $CH_3COCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 66 | $NaOC_2H_5$ | $C_6H_6$ | 49 |
| | $ClCH\!=\!CHCH_2Cl$ | $ClCH\!=\!CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 60 | — | — | 449 |
| | $C_4$ | | | | | |
| | $n\text{-}C_4H_9Br\text{-}NaI$ | $n\text{-}C_4H_9C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 442, 232, 235 |
| | $n\text{-}C_4H_9I$ | $n\text{-}C_4H_9C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232 |
| | $i\text{-}C_4H_9Br$ | $i\text{-}C_4H_9C(NHCOCH_3)(CO_2C_2H_5)_2$ | 46 | $NaOC_2H_5$ | Ethanol | 235, 232 |
| | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Toluene | 868 |
| | $CH_3CH\!=\!CHCH_2Cl$ | $CH_3CH\!=\!CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 442 |
| | $CH_2\!=\!C(CH_3)CH_2Cl$ | $CH_2\!=\!C(CH_3)CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232 |
| | $Cl(CH_2)_3CN$ | $NC(CH_2)_3C(NHCOCH_3)(CO_2C_2H_5)_2$ | 22 | $NaOC_2H_5$ | Ethanol | 447 |
| | 4-Chloromethylthiazole hydrochloride | Diethyl acetamido-(4-thiazolyl-methyl)malonate | 53 | $NaOC_2H_5$ | Ethanol | 450, 446 |
| | 2-Chloromethylthiazole | 2-Amino-3-(2-thiazolyl)propionic acid | 29 | $NaOC_2H_5$ | Ethanol | 446 |
| | $C_5$ | | | | | |
| | $n\text{-}C_5H_{11}Br$ | $n\text{-}C_5H_{11}C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232 |
| | 2-Chloromethylfuran | Diethyl acetamido(furfuryl)malonate | 60–70 | $NaOC_2H_5$ | Ethanol | 452 |
| | 2-Chloromethylthiophene | Diethyl acetamido-(2-thenyl)malonate | 88 | $NaOC_2H_5$ | Ethanol | 869 |
| | 2-Chloromethylthiophene | Diethyl acetamido-(2-thenyl)malonate | 71 | NaH | Toluene | 860 |
| | 2-Bromomethylthiophene | Diethyl acetamido-(2-thenyl)malonate | 67 | $NaOC_2H_5$ | Ethanol | 870 |
| | 3-Bromomethylthiophene | Diethyl acetamido-(3-thenyl)malonate | 85 | NaH | Toluene | 246 |
| | 5-Bromo-2-bromomethyl-thiophene | Diethyl acetamido-(5-bromo-2-thenyl)-malonate | 60 | $NaOC_2H_5$ | Ethanol | 870 |
| | 2-Bromo-3-bromomethyl-thiophene | Diethyl acetamido-(2-bromo-3-thenyl)-malonate | 90 | $NaOC_2H_5$ | Ethanol | 870 |
| | 5-Chloromethyl-1-methylimidazole hydrochloride | Ethyl $\alpha$-acetamido-$\alpha$-carbethoxy-$\beta$-(1-methyl-5-imidazolyl)propionate | 68 | $NaOC_2H_5$ | Ethanol | 443 |
| | $C_6$ | | | | | |
| | $n\text{-}C_6H_{13}I$ | $n\text{-}C_6H_{13}C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 232 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE II—*Continued*

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| X | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| CH₃CONH | $C_7$ | | | | | |
| (*Cont.*) | $n\text{-}C_7H_{15}Br$ | $n\text{-}C_7H_{15}C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | NaOC₂H₅ | Ethanol | 232 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 82 | NaOC₂H₅ | Ethanol | 235 |
| | $o\text{-}FC_6H_4CH_2Cl$ | $o\text{-}FC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 89 | NaOC₂H₅ | Ethanol | 444 |
| | $m\text{-}FC_6H_4CH_2Cl$ | $m\text{-}FC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 68 | NaOC₂H₅ | Ethanol | 444 |
| | $p\text{-}FC_6H_4CH_2Cl$ | $p\text{-}FC_6H_4CH_2C(NHCOCH_6)(CO_2C_2H_5)_2$ | 76 | NaOC₂H₅ | Ethanol | 444 |
| | $o\text{-}ClC_6H_4CH_2Cl$ | $o\text{-}ClC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_6)_2$ | 81 | NaOC₂H₅ | Ethanol | 448 |
| | $p\text{-}ClC_6H_4CH_2Cl$ | $p\text{-}ClC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 84 | NaOC₂H₆ | Ethanol | 448 |
| | 2,4-Dichlorobenzyl chloride | $2,4\text{-}Cl_2C_6H_3CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 80 | NaOC₂H₅ | Ethanol | 451 |
| | 3,4-Dichlorobenzyl chloride | $3,4\text{-}Cl_2C_6H_3CH_2C(NHCOCH_6)(CO_2C_2H_6)_2$ | 89 | NaOC₂H₅ | Ethanol | 448 |
| | $p\text{-}O_2NC_6H_4CH_2Cl$ | $p\text{-}O_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 88 | NaOC₂H₅ | Ethanol | 448 |
| | $p\text{-}O_2NC_6H_4CH_2Br$ | $p\text{-}O_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 100 | NaOC₂H₅ | Ethanol | 454 |
| | 2-Hydroxy-5-nitrobenzyl chloride | Diethyl acetamido-(2-hydroxy-5-nitrobenzyl)malonate | 20 | NaOC₂H₅ | Ethanol | 448 |
| | $p\text{-}H_2NC_6H_4CH_2Cl$ | $p\text{-}H_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 97 | NaOC₂H₆ | Ethanol | 448 |
| | $C_8$ | | | | | |
| | $n\text{-}C_8H_{17}I$ | $n\text{-}C_8H_{17}C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | NaOC₂H₅ | Ethanol | 232 |
| | $C_6H_5S(CH_2)_2Cl$ | $C_6H_5S(CH_2)_2CH(NH_2)CO_2H$ | >20 | NaOC₂H₆ | Ethanol | 457 |
| | 3-Nitro-4-methylbenzyl chloride | 2-Amino-3-(3-nitro-4-methylphenyl)-propionic acid | 34 | NaOC₂H₅ | Ethanol | 451 |
| | 2-Fluoro-4-methoxybenzyl chloride | Diethyl acetamido-(2-fluoro-4-methoxybenzyl)malonate | 85 | NaOC₂H₅ | Ethanol | 445 |
| | $C_6H_5COCH_2Br$ | $C_6H_5COCH_2C(NHCOCH_6)(CO_2C_2H_5)_2$ | 71 | NaOC₂H₅ | $C_6H_6$ | 49, 456 |
| | $o\text{-}O_2NC_6H_4COCH_2Br$ | $o\text{-}O_2NC_6H_4COCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 41 | NaOC₂H₅ | Ethanol | 456 |
| | $o\text{-}O_2NC_6H_4COCH_2Br$ | $o\text{-}O_2NC_6H_4COCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | 19 | NaOC₂H₆ | $(C_2H_5O)_3CO$ | 49 |
| | 5-Chloromethyl-1-isopropylimidazole hydrochloride | 2-Amino-3-(1-isopropyl-5-imidazolyl)-propionic acid | 44 | NaOC₂H₅ | Ethanol | 443 |
| | 1-Chloromethyl-benzimidazole hydrochloride | 2-Amino-3-(1-benzimidazolyl)propionic acid | — | NaOC₂H₅ | Ethanol | 455 |
| | 2-Chloromethyl-benzimidazole hydrochloride | Diethyl acetamido-(2-benzimidazolyl-methyl)malonate | 65 | NaOC₂H₃ | Ethanol | 455 |
| | $C_9$ | | | | | |
| | $n\text{-}C_9H_{19}Br$ | $n\text{-}C_9H_{19}C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | NaOC₂H₅ | Ethanol | 232 |
| | 2-Ethoxy-5-nitrobenzyl chloride | Diethyl acetamido-(2-ethoxy-5-nitrobenzyl)malonate | 82 | NaOC₂H₆ | Ethanol | 448 |
| | 2-Bromo-3-bromo-methylcoumarone | Diethyl acetamido-(2-bromo-3-coumaronylmethyl)malonate | 73 | NaOC₂H₅ | Ethanol | 440 |
| | 2-Chloromethyl-4-methylbenzimidazole hydrochloride | Ethyl 2-acetamido-3-(4-methyl-2-benzimidazolyl)propionate | 40 | NaOC₂H₅ | Ethanol | 455 |
| | 2-Chloromethyl-5-methyl-benzimidazole hydrochloride | Ethyl 2-acetamido-3-(5-methyl-2-benzimidazolyl)propionate | 50 | NaOC₂H₅ | Ethanol | 455 |
| | $C_{10}$ | | | | | |
| | β-3-Indolylethyl bromide | Diethyl acetamido-[β(3-indolyl)-ethyl]malonate | 58 | NaOC₂H₅ | Ethanol | 441 |
| | 5-Chloromethyl-1-cyclohexylimidazole hydrochloride | 2-Amino-3-(1-cyclohexyl-5-imidazolyl)-propionic acid | 49 | NaOC₂H₆ | Ethanol | 443 |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE II—*Continued*

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

| X | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $CH_3CONH$ (*Cont.*) | 5-Chloromethyl-1-phenylimidazole hydrochloride | 2-Amino-3-(1-phenyl-5-imidazolyl)-propionic acid | 49 | $NaOC_2H_5$ | Ethanol | 443 |
| | 2-Chloromethyl-5,6-dimethylbenzimidazole hydrochloride | Ethyl 2-acetamido-3-(5,6-dimethyl-2-benzimidazolyl)propionate | *ca.* 40 | $NaOC_2H_5$ | Ethanol | 455 |
| | $C_{11}$ | | | | | |
| | $C_6H_5CH(CO_2C_2H_5)CH_2Br$ | $C_6H_5CH(CO_2C_2H_5)CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | — | — | 439 |
| | 1-Chloromethylnaphthalene | Diethyl acetamido-(1-naphthyl-methyl)malonate | 92 | $NaOC_2H_5$ | Ethanol | 440 |
| | 5-Chloromethyl-1-benzylimidazole hydrochloride | 2-Amino-3-(1-benzyl-5-imidazolyl)-propionic acid | 45 | $NaOC_2H_5$ | Ethanol | 443 |
| | $C_{13}$-$C_{14}$ | | | | | |
| | 4-(4-Nitrophenyl-sulfonyl)benzyl bromide | Diethyl acetamido-[4-(4-nitro-phenylsulfonyl)benzyl]malonate | 74 | $NaOC_2H_5$ | Ethanol-dioxane | 454 |
| | 3,5-Diiodo-4-(4-methoxyphenyl-sulfonyl)benzyl chloride | Diethyl acetamido-[3,5-diiodo-4-(4-methoxyphenylsulfonyl)benzyl]-malonate | 84 | $NaOC_2H_5$ | Ethanol-dioxane | 438 |
| $C_6H_5CONH$ | $C_3$-$C_8$ | | | | | |
| | $i$-$C_3H_7I$ | $C_6H_5CONHC(C_3H_7$-$i)(CO_2C_2H_5)_2$ | 66 | $NaOC_2H_5$ | Ethanol | 233 |
| | $i$-$C_4H_9I$ | $C_6H_5CONHC(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 233 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(NHCOC_6H_5)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 233 |
| | $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(NHCOC_6H_5)(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 459 |
| | 2-Chloromethylpyridine | 2-Amino-3-(2-pyridyl)propionic acid | 17 | $NaOC_2H_5$ | Ethanol | 458 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CONHC(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 95 | $NaOC_2H_5$ | Ethanol | 233 |
| | $p$-$HOC_6H_4(CH_2)_2Br$ | $p$-$HOC_6H_4(CH_2)_2CH(NH_2)CO_2H$ | 7 | $NaOC_2H_5$ | Ethanol | 453 |
| Phthalimido ($=C_8H_4O_2N$) | $C_2$-$C_3$ | | | | | |
| | $CH_3OCH_2Cl$ | $CH_3OCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 73 | Na | $C_6H_6$ | 871 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 95–99 | $NaOC_2H_5$ | $ClCH_2CO_2C_2H_5$ | 467 |
| | $ClCH_2SCH_2Cl$ | $(C_2H_5O_2C)_2C(C_8H_4O_2N)CH_2S$-$CH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 81 | Na | Xylene | 460 |
| | $CH_3S(CH_2)_2Cl$ | $CH_3S(CH_2)_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 76–80 | $NaOC_2H_5$ | None | 466, 465 |
| | $CH_2=CHCH_2I$ | $CH_2=CHCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | None | 462, 435 |
| | $Br(CH_2)_3Br$ | $(C_2H_5O_2C)_2C(C_8H_4O_2N)(CH_2)_3C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | None | 462, 236, 463 |
| | $C_4$-$C_{11}$ | | | | | |
| | $C_2H_5S(CH_2)_2Cl$ | $C_2H_5S(CH_2)_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 68 | Na | None | 461 |
| | $Cl(CH_2)_3CN$ | $NC(CH_2)_3C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 75–80 | $NaOC_2H_5$ | None | 462 |
| | 2-Chloromethylthiophene | Diethyl phthalimido(2-thenyl)malonate | 93 | Na | Toluene | 869 |
| | 2-Chloromethylpyridine | Diethyl phthalimido-(2-pyridylmethyl)-malonate | 10 | Na | Xylene | 468 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$ | 75–80 | $NaOC_2H_5$ | None | 462 |
| | $\gamma$-Bromopropylphthalimide | Diethyl ($\gamma$-phthalimidopropyl)-phthalimidomalonate | 75 | Na | None | 236, 462 |

*Note:* References 577–1080 are on pp. 322–331.

# TABLE III

## ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

### (The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_1$ | $C_1$ | | | | | |
| $CH_3$ | $CH_3I$ | $(CH_3)_2C(CO_2C_2H_5)_2$ | 55 | KOH | None | 82 |
| | $CH_3I$ | $(CH_3)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 571 |
| | $CH_2I_2$ | $CH_2[C(CH_3)(CO_2C_2H_5)_2]_2$ | — | $NaOC_2H_5$ | Ethanol | 872 |
| | $CHCl_3$ | $Cl_2CHC(CH_3)(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2C(CH_3)CHClC(CH_3)(CO_2C_2H_5)_2$ | — | Na | Ether | 231 |
| | $CHCl_3$ | $Cl_2CHCH(CH_3)(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2C(CH_3)CHClC(CH_3)(CO_2C_2H_5)_2$ | — | K | Ether | 231 |
| | $CHBr_3$ | $Br_2CHC(CH_3)(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2C(CH_3)CHBrC(CH_3)(CO_2C_2H_5)_2$ | — | Na | Ether | 231 |
| | $CHI_3$ | $I_2CHC(CH_3)(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2C(CH_3)CHIC(CH_3)(CO_2C_2H_5)_2$ | — | Na | Ether | 231 |
| | $C_2$ | | | | | |
| | $C_2H_5I$ | $C_2H_5C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 577 |
| | $CH_3SCH_2Cl$ | $CH_3SCH_2C(CH_3)(CO_2C_2H_5)_2$ | 51 | Na | Ether | 205 |
| | $CH_2ClCH_2Br$ | $Cl(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 70 | Na | Toluene | 873 |
| | $CH_2BrCH_2Br$ | $Br(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ <br> $CH_2C(CH_3)(CO_2C_2H_5)_2$ <br> &#124; <br> $CH_2C(CH_3)(CO_2C_2H_5)_2$ | 15 <br><br> 70 | $NaOC_2H_5$ | Ethanol | 874, 172 <br><br> 626 |
| | $CH_2BrCH_2Br$ | $Br(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 32 | Na | $C_6H_6$ | 875 |
| | $C_3$ | | | | | |
| | $n$-$C_3H_7I$ | $n$-$C_3H_7C(CH_3)(CO_2C_2H_5)_2$ | 87 | $NaOC_2H_5$ | Ethanol | 582, 488 |
| | Not stated | $n$-$C_3H_7C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 571 |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(CH_3)(CO_2C_2H_5)_2$ | 64 | Na | Ether | 205 |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | Not stated | $i$-$C_3H_7C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 571 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(CH_3)(CO_2C_2H_5)_2$ | — | — | — | 629, 172 |
| | $(CH_3)_2CClNO_2$ | $(CH_3)_2C(NO_2)C(CH_3)(CO_2C_2H_5)_2$ | 45 | Na | Ether | 556 |
| | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(CH_3)(CO_2C_2H_5)_2$ | 87–89 | — | — | 876, 571 |
| | $ClCH_2CO_2C_2H_5$ | Diethyl α-carbethoxy-α-methylsuccinate | — | Na | Ether | 653, 161 |
| | $ClCH_2CO_2C_2H_5$ | Diethyl α-carbethoxy-α-methylsuccinate | — | Na | $C_6H_6$ | 653 |
| | $C_4$ | | | | | |
| | Not stated | $n$-$C_4H_9C(CH)_3(CO_2C_2H_5)_2$ | — | Na | — | 571 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(CH_3)(CO_2CH_3)_2$* | 43 | Na | Ether | 205 |
| | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 533 |
| | $C_5$ | | | | | |
| | $n$-$C_5H_{11}Br$ | $n$-$C_5H_{11}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $n$-$C_3H_7CH(CH_3)Br$ | $n$-$C_3H_7CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $n$-$C_4H_9SCH_2Cl$ | $n$-$C_4H_9SCH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $CH_3CHBrCO_2C_2H_5$ | Diethyl α,α'-dimethyl-α-carbethoxysuccinate | — | Na | None | 877 |
| | $CH_3CHBrCO_2C_2H_5$ | Diethyl α,α'-dimethyl-α-carbethoxysuccinate | 37 | $NaOC_2H_5$ | Ethanol | 223, 702 |
| | $ClCH(CO_2CH_3)_2$ | $(CH_3O_2C)_2CHCH(CO_2CH_3)_2$* and $(CH_3O_2C)_2C=C(CO_2CH_3)_2$* | — <br> — | $NaOCH_3$ | $CH_3OH$ | 752 |
| | Cyclobutylmethyl tosylate | Diethyl (cyclobutylmethyl)-methylmalonate | 18 | $NaOC_2H_5$ | Ethanol | 334 |
| | α-Chloromethylthiophene | Diethyl (α-thenyl)methylmalonate | Good | — | — | 878 |
| | $C_6$ | | | | | |
| | $n$-$C_6H_{13}Br$ | $n$-$C_6H_{13}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $i$-$C_6H_{13}I$ | $i$-$C_6H_{13}C(CH_3)(CO_2C_2H_5)_2$ | 83 | Na | $C_6H_6$ | 247 |
| | $n$-$C_4H_9CH(CH_3)Br$ | $n$-$C_4H_9CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $n$-$C_4H_9S(CH_2)_2Cl$ | $n$-$C_4H_9S(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $C_2H_5CHBrCO_2C_2H_5$ | Diethyl α-methyl-α'-ethyl-α-carbethoxysuccinate | 26 | $NaOC_2H_5$ | Ethanol | 223, 162 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | Diethyl α,α,α'-trimethyl-α'-carbethoxysuccinate | 57 | Na | None | 872, 162, 223 |

*Note:* References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.

## TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $CH_3$ (*Cont.*) | 2-Cyclohexenyl bromide | Diethyl (2-cyclohexenyl)methylmalonate | 73 | $NaOC_2H_5$ | Ethanol | 319 |
| | 1,2-Dibromocyclohexane | Diethyl (2-cyclohexenyl)methylmalonate | >60 | $NaOC_2H_5$ | Ethanol | 319, 150 |
| | $C_7$ | | | | | |
| | $i$-$C_3H_7CHBrCO_2C_2H_5$ | Diethyl $\alpha$-isopropyl-$\alpha'$-methyl-$\alpha'$-carbethoxysuccinate | 8 | $NaOC_2H_5$ | Ethanol | 223 |
| | $ClCH(CO_2C_2H_5)_2$ | $(C_2H_5O_2)_2CHCH(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 752 |
| | $BrCH(CO_2C_2H_5)_2$ | $\{(C_2H_5O_2C)_2CHC(CH_3)(CO_2C_2H_5)_2$ <br> $\{(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ | Poor <br> — | $NaOC_2H_5$ | Ethanol | 752 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl methyl-[$\beta$-(2-cyclopentenyl)-ethyl]malonate | 56 | $NaOC_2H_5$ | Ethanol | 334 |
| | $\beta$-(2-Cyclopentenyl)ethyl tosylate | Diethyl methyl-[$\beta$-(2-cyclopentenyl)-ethyl]malonate | 56 | $NaOC_2H_5$ | Ethanol | 334 |
| | Cyclohexylmethyl iodide | Diethyl methyl(cyclohexylmethyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 334 |
| | Cyclohexylmethyl iodide | Diethyl methyl(cyclohexyl-methyl)malonate | 65 | $NaOC_4H_9$-$n$ | $n$-$C_4H_9OH$ | 334 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 615 |
| | $C_8$ | | | | | |
| | $n$-$C_8H_{17}I$ | $n$-$C_8H_{17}C(CH_3)(CO_2C_2H_5)_2$ | 63 | $NaOC_2H_5$ | Ethanol | 879 |
| | $n$-$C_4H_9CH(C_2H_5)CH_2Br$ | $n$-$C_4H_9CH(C_2H_5)CH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $(CH_3)_2CBr(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(CH_3)_2C(CH_3)(CO_2C_2H_5)_2$ | 6 | $NaOC_2H_5$ | Ethanol | 880 |
| | $CH_3CCl(CO_2C_2H_5)_2$ | $(C_2H_5O_2)_2C(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 5 | $NaOC_2H_5$ | Ethanol | 578 |
| | $\alpha$-Chloroethylcyclohexyl sulfide | Diethyl [$\alpha$-(cyclohexylthio)-ethyl]methylmalonate | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $\beta$-(1-Cyclohexenyl)ethyl bromide | Diethyl methyl-[$\beta$-(1-cyclohexenyl)-ethyl]malonate | 53 | K | $C_6H_6$ | 426 |
| | $C_6H_5(CH_2)_2Br$ | $C_6H_5(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 60 | K | Xylene | 881 |
| | $C_6H_5O(CH_2)_2Br$ | $C_6H_5O(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 65 | Na | Toluene | 873, 758 |
| | $C_9$ | | | | | |
| | $n$-$C_9H_{19}I$ | $n$-$C_9H_{19}C(CH_3)(CO_2C_2H_5)_2$ | 94 | — | — | 882 |
| | $Br(CH_2)_3CH(C_2H_5)CO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)(CH_2)_3C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 814 |
| | $C_6H_5O(CH_2)_3Cl$ | $C_6H_5O(CH_2)_3C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOCH_3$ | $CH_3OH$ | 581 |
| | $o$-$CH_3C_6H_4(CH_2)_2Br$ | $o$-$CH_3C_6H_4(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 50 | Na | $C_6H_6$ | 883 |
| | $p$-$CH_3C_6H_4(CH_2)_2Br$ | $p$-$CH_3C_6H_4(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 87 | Na | $C_6H_6$ | 416 |
| | $p$-$CH_3C_6H_4(CH_2)_2Br$ | $p$-$CH_3C_6H_4(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$ | 35 | $NaOC_2H_5$ | Ethanol | 423 |
| | $C_{10}$ | | | | | |
| | Geranyl chloride | Diethyl methyl(geranyl)malonate | 50 | $NaOC_2H_5$ | Ethanol | 31 |
| | $C_6H_5CH_2SCH_2CH(CH_3)Br$ | $C_6H_5CH_2SCH_2CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 794 |
| | $\beta$-(2,3-Dimethylphenyl)ethyl bromide | Diethyl methyl-[$\beta$-(2,3-dimethylphenyl)-ethyl]malonate | 50 | Na | $C_6H_6$ | 417 |
| | $\beta$-(2,4-Dimethylphenyl)ethyl bromide | Diethyl methyl-[$\beta$-(2,4-dimethylphenyl)-ethyl]malonate | 56 | Na | $C_6H_6$ | 417 |
| | $p$-$C_2H_5C_6H_4COCH_2Cl$ | $p$-$C_2H_5C_6H_4COCH_2C(CH_3)(CO_2C_2H_5)_2$ | 12 | Na | Ether | 420 |
| | $C_6H_5CHBrCO_2C_2H_5$ | $C_6H_5CH(CO_2C_2H_5)C(CH_3)(CO_2C_2H_5)_2$ | 45 | Na | None | 583 |
| | $m$-Carbethoxybenzyl chloride | Diethyl methyl-($m$-carbethoxybenzyl)-malonate | — | — | — | 230 |
| | $\beta$-Bromoethylphthalimide | Diethyl methyl-($\beta$-phthalimidoethyl)-malonate | 40–46 | Na | $C_6H_6$ | 884 |
| | $C_{11}$ | | | | | |
| | Chloromethyltetralin† | Diethyl methyl(tetrahydronaphthyl-methyl)malonate | 51 | Na | $C_6H_6$ | 410 |
| | $\alpha$-Chloromethylnaphthalene | Diethyl methyl-($\alpha$-naphthylmethyl)-malonate | 71 | $NaOC_2H_5$ | Ethanol | 885, 886 |
| | $\beta$-Chloromethylnaphthalene | Diethyl methyl-($\beta$-naphthylmethyl)-malonate | — | — | — | 886 |
| | $C_{12}$-$C_{24}$ | | | | | |
| | $n$-$C_{12}H_{25}X$‡ | $n$-$C_{12}H_{25}C(CH_3)(CO_2C_2H_5)_2$ | — | — | — | 887 |
| | $n$-$C_{13}H_{27}X$‡ | $n$-$C_{13}H_{27}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $n$-$C_{14}H_{29}X$‡ | $n$-$C_{14}H_{29}C(CH_3)(CO_2C_2H_5)_2$ | — | — | — | 887 |

*Note:* References 577–1080 are on pp. 322–331.

† This halide was probably a mixture of isomers.

‡ The halogen was not specified.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| CH₃ (*Cont.*) | Ethyl α-chloro-β-(4-methoxy-2,5-dimethylbenzoyl)-propionate | Triethyl 1-(4-methoxy-2,5-dimethyl-benzoyl)butane-2,2,3-tricarboxylate | 92 | Na | C₆H₆ | 807 |
| | n-C₁₅H₃₁X‡ | n-C₁₅H₃₁C(CH₃)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 888 |
| | Cetyl iodide | Diethyl (cetyl)methylmalonate | 93 | NaOC₂H₅ | Ethanol | 135, 889 |
| | Hydnocarpyl chloride | Diethyl (hydnocarpyl)methylmalonate | 40 | K | Toluene | 291 |
| | ClCH[C(CH₃)(CO₂C₂H₅)₂]₂ | None | — | Na | None | 231 |
| | n-C₇H₁₅CH(CH₃)CH₂-CH=C(CH₃)(CH₂)₉Br | n-C₇H₁₅CH(CH₃)CH₂CH=C(CH₃)-(CH₂)₉C(CH₃)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 855 |
| | 1,11-Dibromo-11,15,19-trimethyleicosane | Diethyl (11,15,19-trimethyl-11-eicosenyl)methylmalonate | — | NaOC₂H₅ | Ethanol | 317 |
| | 1,11-Dibromo-11-methyltricosane | Diethyl (11-methyl-11-tricosenyl)-methylmalonate | — | NaOC₂H₅ | Ethanol | 317 |
| CH₃O | n-C₈H₁₇Br | n-C₈H₁₇C(OCH₃)(CO₂C₂H₅)₂ | 77 | KOC₄H₉-t | t-C₄H₉OH | 395 |
| C₂ | C₁ | | | | | |
| C₂H₅ | CH₃X‡ | C₂H₅C(CH₃)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 615, 571 |
| | CH₂Cl₂ | ClCH₂C(C₂H₅)(CO₂C₂H₅)₂ | — | Na | Ether | 231 |
| | CH₂I₂ | ICH₂C(C₂H₅)(CO₂C₂H₅)₂ | — | Na | Ether | 231 |
| | C₂ | | | | | |
| | C₂H₅X‡ | (C₂H₅)₂C(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 571 |
| | C₂H₅I | (C₂H₅)₂C(CO₂C₂H₅)₂ | 73 | NaOC₂H₅ | Ethanol | 592, 594 |
| | C₂H₅I | (C₂H₅)₂C(CO₂C₂H₅)₂ | — | Mg(OC₂H₅)₂ | Ethanol | 596 |
| | C₂H₅I | (C₂H₅)₂C(CO₂C₂H₅)₂ | 83 | Mg(OC₂H₅)₂ | (C₂H₅O)₂CO | 44, 51, 227 |
| | (C₂H₅O)₂CO | (C₂H₅)₂C(CO₂C₂H₅)₂ | 54 (71)§ | NaOC₂H₅ | (C₂H₅O)₂CO | 330, 890 |
| | (C₂H₅O)₂CO | (C₂H₅)₂C(CO₂C₂H₅)₂ | 83 | Mg(OC₂H₅)₂ | (C₂H₅O)₂CO | 227, 890 |
| | CH₃OCH₂Cl | CH₃OCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 69 | Na | Ether | 542, 374 |
| | CH₃SCH₂Cl | CH₃SCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 44 | Na | Ether | 205 |
| | CH₂OHCH₂Cl | HO(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂ | 27 | NaOC₂H₅ | Ethanol | 148 |
| | CH₂BrCH₂Br | CH₂CH₂C(C₂H₅)CO₂C₂H₅ (with O—CO ring) | — | Na | C₆H₆ | 555 |
| | CH₂BrCH₂Br | Br(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 172 |
| | BrCH=CHBr | { BrCH=CHC(C₂H₅)(CO₂C₂H₅)₂ | 25 | Na | Ether | 54 |
| | | { 3,6,6-Tricarbethoxy-3-octene | 31 | | | |
| | C₃ | | | | | |
| | CH₃O(CH₂)₂Cl | CH₃O(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂ | — | — | — | 374 |
| | C₂H₅OCH₂Cl | C₂H₅OCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 74 | Na | Ether | 542 |
| | C₂H₅SCH₂Cl | C₂H₅SCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 61 | Na | Ether | 205 |
| | C₂H₅SCH₂Cl | C₂H₅SCH₂C(C₂H₅)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Toluene | 125 |
| | CH₃COCH₂Cl | CH₃COCH₂C(C₂H₅)(CO₂C₂H₅)₂ | — | Na | Ether | 891 |
| | CH₃COCH₂Cl | CH₃COCH₂C(C₂H₅)(CO₂C₂H₅)₂ | — | Na | C₆H₆ | 891 |
| | i-C₃H₇I | i-C₃H₇C(C₂H₅)(CO₂C₂H₅)₂ | 46 (75)§ | NaOC₂H₅ | Ethanol | 145 |
| | CH₂=CHCH₂Cl | CH₂=CHCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 70-80 | NaOC₂H₅ | Ethanol | 558 |
| | Cl(CH₂)₃Br | Cl(CH₂)₃C(C₂H₅)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 814 |
| | Cl(CH₂)₃I | I(CH₂)₃C(C₂H₅)(CO₂C₂H₅)₂ | 46 | NaOC₂H₅ | Ethanol | 92 |
| | Br(CH₂)₃Br | Br(CH₂)₃C(C₂H₅)(CO₂C₂H₅)₂ | 32 | Na | C₆H₆ | 537, 656 |
| | Br(CH₂)₃Br | Br(CH₂)₃C(C₂H₅)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 814 |
| | (CH₃)₂CClNO₂ | { (CH₃)₂CNO₂C(C₂H₅)(CO₂C₂H₅)₂ | 40 (65)§ | Na | Ether | 177 |
| | | { (CH₃)₂CHC(C₂H₅)(CO₂C₂H₅)₂ | 8 (13)§ | | | |
| | cis-ClCH=CHCH₂Cl | cis-ClCH=CHCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 70-80 | NaOC₂H₅ | Ethanol | 558 |
| | trans-ClCH=CHCH₂Cl | trans-ClCH=CHCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 70-80 | NaOC₂H₅ | Ethanol | 558, 621 |
| | CH₂=CClCH₂Cl | CH₂=CClCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 70-80 | NaOC₂H₅ | Ethanol | 558 |
| | C₄ | | | | | |
| | n-C₄H₉Br | n-C₄H₉C(C₂H₅)(CO₂C₂H₅)₂ | ca. 80 | NaOC₂H₅ | Ethanol | 536 |
| | n-C₄H₉I | n-C₄H₉C(C₂H₅)(CO₂C₂H₅)₂ | 62 | NaOC₂H₅ | Ethanol | 399, 892 |
| | (C₄H₉O-n)₂CO | n-C₄H₉C(C₂H₅)(CO₂C₄H₉-n)₂¶ | 42 (68)§ | NaOC₄H₉-n | (n-C₄H₉O)₂CO | 890, 330 |
| | CH₃O(CH₂)₃Cl | CH₃O(CH₂)₃C(C₂H₅)(CO₂CH₃)₂* | — | NaOCH₃ | Methanol | 814 |
| | (C₄H₉O-i)₂CO | i-C₄H₉C(C₂H₅)(CO₂C₄H₉-i)₂‖ | 45 (70)§ | NaOC₄H₉-i | (i-C₄H₉O)₂CO | 890, 330 |

*Note:* References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.
‡ The halogen was not specified.
§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.
‖ The diisobutyl ester was used in this experiment.
¶ The di-n-butyl ester was used in this experiment.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R′CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

| R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_2H_5$ (*Cont.*) | $C_2H_5CH(CH_3)Br$ | $C_2H_5CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | ca. 80 | $NaOC_2H_5$ | Ethanol | 536, 148 |
| | $(CH_3)_3CBr$ | $(CH_3)_3CC(C_2H_5)(CO_2C_2H_5)_2$ | 4 | Na | Toluene | 15 |
| | $CH_2=C(CH_3)CH_2Cl$ | $CH_2=C(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 70–80 | $NaOC_2H_5$ | Ethanol | 558 |
| | $CH_2=CHCH-CH_2$ over O | $CH_2=CHCHCH_2C(C_2H_5)CO_2C_2H_5$ (O——CO) | 60 | $NaOC_2H_5$ | Ethanol | 11 |
| | $n\text{-}C_3H_7OCH_2Cl$ | $n\text{-}C_3H_7OCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 50 | Na | Ether | 542 |
| | $C_2H_5O(CH_2)_2Cl$ | $C_2H_5O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $C_2H_5OCH(CH_3)Cl$ | $C_2H_5OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 60 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $CH_2=CHO(CH_2)_2Cl$ | $CH_2=CHO(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 40–45 | $NaOC_2H_5$ | Ethanol | 541 |
| | $n\text{-}C_3H_7SCH_2Cl$ | $n\text{-}C_3H_7SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 73 | Na | Ether | 205 |
| | $i\text{-}C_3H_7SCH_2Cl$ | $i\text{-}C_3H_7SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $CH_2=CHCH_2SCH_2Cl$ | $CH_2=CHCH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125, 893 |
| | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 70–80 | $NaOC_2H_5$ | Ethanol | 558 |
| | $C_2H_5OCHBrCH_2Br$ | $C_2H_5CH(OC_2H_5)C(C_2H_5)CO_2C_2H_5$ (O————CO) | 66 | $NaNH_2$ | Ether | 277 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 653, 161, 891 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 653, 891 |
| | $BrCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 894 |
| | $BrCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 894 |
| $C_5$ | | | | | | |
| | $n\text{-}C_5H_{11}Br$ | $n\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 56 | $NaOC_2H_5$ | Ethanol | 543, 895 |
| | $i\text{-}C_5H_{11}Br$ | $i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 75 | Na | Toluene | 51 |
| | $i\text{-}C_5H_{11}Br$ | $i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | ca. 80 | $NaOC_2H_5$ | Ethanol | 536 |
| | $i\text{-}C_5H_{11}Br$ | $i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44, 51, 227 |
| | $(i\text{-}C_5H_{11}O)_2CO$ | $i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_5H_{11}\text{-}i)_2$** | 60 | $KOC_5H_{11}\text{-}i$ | $(i\text{-}C_5H_{11}O)_2CO$ | 890, 330 |
| | $n\text{-}C_3H_7CH(CH_3)Br$ | $n\text{-}C_3H_7CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 617 |
| | $(+)\text{-}n\text{-}C_3H_7CH(CH_3)Br$ | $(+)\text{-}n\text{-}C_3H_7CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 549 |
| | $(-)\text{-}n\text{-}C_3H_7CH(CH_3)Br$ | $(-)\text{-}n\text{-}C_3H_7CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 549 |
| | $(C_2H_5)_2CHBr$ | $(C_2H_5)_2CHC(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 617, 148 |
| | $(C_2H_5)_2CHOSO_2C_6H_4CH_3\text{-}p$ | $(C_2H_5)_2CHC(C_2H_5)(CO_2C_2H_5)_2$ | Poor | Na | $C_6H_6$ | 238 |
| | $[(C_2H_5)_2CHO]_2CO$ | $(C_2H_5)_2CHC(C_2H_5)(CO_2C_2H_5)_2$ | 35 | $KOCH(C_2H_5)_2$ | $[(C_2H_5)_2CHO]_2CO$ | 890, 330 |
| | $C_2H_5CH(CH_3)CH_2Br$ | $C_2H_5CH(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 30 | $NaOC_2H_5$ | Ethanol | 148 |
| | $C_2H_5C(CH_3)_2Br$ | $C_2H_5C(CH_3)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 5 | $NaOC_2H_5$ | Ethanol | 15 |
| | $CH_3CH=CHCH(CH_3)X‡$ | $CH_3CH=CHCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 547 |
| | $(CH_3)_2C=CHCH_2Br$ | $(CH_3)_2C=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 62 | $NaOC_2H_5$ | Ethanol | 557 |
| | $n\text{-}C_4H_9OCH_2Cl$ | $n\text{-}C_4H_9OCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 50 | Na | Ether | 542 |
| | $i\text{-}C_4H_9OCH_2Cl$ | $i\text{-}C_4H_9OCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 56 | Na | Ether | 542 |
| | $n\text{-}C_3H_7OCH(CH_3)Cl$ | $n\text{-}C_3H_7OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 62 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $(CH_3)_3COCH_2Cl$ | $(CH_3)_3COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $n\text{-}C_4H_9SCH_2Cl$ | $n\text{-}C_4H_9SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5CH(CH_3)SCH_2Cl$ | $C_2H_5CH(CH_3)SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125, 893 |
| | $i\text{-}C_4H_9SCH_2Cl$ | $i\text{-}C_4H_9SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5SCH_2CH(CH_3)Cl$ | $C_2H_5SCH_2CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–75 | $NaOC_2H_5$ | Toluene | 554 |
| | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | None | 162 |
| | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 30 | $NaOC_2H_5$ | Ethanol | 223 |
| | $I(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 894 |
| | $I(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 894 |
| | Cyclobutylmethyl tosylate | Diethyl ethyl(cyclobutylmethyl)malonate | 65 | $NaOC_2H_5$ | Ethanol | 334 |
| | Cyclopentyl bromide | Diethyl ethyl(cyclopentyl)malonate | — | Na | Toluene | 896 |
| | Cyclopentyl bromide | Diethyl ethyl(cyclopentyl)malonate | — | $NaOC_2H_5$ | Ethanol | 617 |
| | Tetrahydrofurfuryl bromide | Diethyl ethyl(tetrahydrofurfuryl)malonate | — | $NaOC_2H_5$ | Ethanol | 543 |
| | 2-Chlorotetrahydropyran | Diethyl ethyl-(2-tetrahydropyranyl)-malonate | — | NaH | Toluene | 683 |
| | 2-Chloromethylthiophene | Diethyl ethyl-(2-thenyl)malonate | — | Na | None | 897 |
| | 2-Methyl-4-chloro-methylthiazole | Diethyl ethyl-(2-methyl-4-thiazolyl-methyl)malonate | 59 | $NaOC_2H_5$ | Ethanol | 548 |
| $C_6$ | | | | | | |
| | $n\text{-}C_6H_{13}Br$ | $n\text{-}C_6H_{13}C(C_2H_5)(CO_2C_2H_5)_2$ | 64 | $NaOC_2H_5$ | Ethanol | 538 |
| | $n\text{-}C_4H_9CH(CH_3)Br$ | $n\text{-}C_4H_9CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 617 |
| | $n\text{-}C_3H_7CH(C_2H_5)X‡$ | $n\text{-}C_3H_7CH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 547 |

*Note:* References 577–1080 are on pp. 322–331.
** The diisoamyl ester was used in this experiment.
‡ The halogen was not specified.

## TABLE III—*Continued*

### Alkylation of Monoalkylmalonic Esters, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_2H_5$ (*Cont.*) | $n\text{-}C_3H_7CH(CH_3)CH_2Br$ | $n\text{-}C_3H_7CH(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 33–43 | $NaOC_2H_5$ | Ethanol | 148, 550 |
| | $i\text{-}C_9H_{12}Br$ | $i\text{-}C_9H_{12}C(C_2H_5)(CO_2C_2H_5)_2$ | 34 | $NaOC_2H_5$ | Ethanol | 718, 550 748 |
| | $(C_2H_5)_2CHCH_2Br$ | $(C_2H_5)_2CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $i\text{-}C_4H_9CH(CH_3)Br$ | $i\text{-}C_4H_9CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $(CH_3)_3C(CH_2)_2Br$ | $(CH_3)_3C(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 44 | $NaOC_2H_5$ | Ethanol | 690 |
| | $CH_3CH{=}CHCH(C_2H_5)X\ddagger$ | $CH_3CH{=}CHCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 547 |
| | $CH_2{=}C(CH_3)CH(C_2H_5)Cl$ | $CH_2{=}C(CH_3)CH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 898 |
| | $n\text{-}C_4H_9O(CH_2)_2Cl$ | $n\text{-}C_4H_9O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $n\text{-}C_4H_9OCH(CH_3)Cl$ | $n\text{-}C_4H_9OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 76 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $n\text{-}C_5H_{11}SCH_2Cl$ | $n\text{-}C_5H_{11}SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $i\text{-}C_5H_{11}SCH_2Cl$ | $i\text{-}C_5H_{11}SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $n\text{-}C_3H_7CH(CH_3)SCH_2Cl$ | $n\text{-}C_3H_7CH(CH_3)SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $n\text{-}C_4H_9S(CH_2)_2Cl$ | $n\text{-}C_4H_9S(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $n\text{-}C_4H_9SCH(CH_3)Cl$ | $n\text{-}C_4H_9SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126, 899 |
| | $C_2H_5SCH(C_3H_7\text{-}n)Cl$ | $C_2H_5SCH(C_3H_7\text{-}n)C(C_2H_5)(CO_2C_2H_5)_2$ | 30–40 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_2H_5SCH(C_3H_7\text{-}i)Cl$ | $C_2H_5SCH(C_3H_7\text{-}i)C(C_2H_5)(CO_2C_2H_5)_2$ | 30–40 | $NaOC_2H_5$ | Toluene | 126, 899 |
| | $i\text{-}C_3H_7SCH(C_2H_5)Cl$ | $i\text{-}C_3H_7SCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 30–40 | $NaOC_2H_5$ | Toluene | 126, 899 |
| | $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | None | 162 |
| | $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 23 | $NaOC_2H_5$ | Ethanol | 223 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | None | 162 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 22 | $NaOC_2H_5$ | Ethanol | 223 |
| | $(C_2H_5)_2NCOCH_2Cl$ | $(C_2H_5)_2NCOCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 530 |
| | Cyclopentylmethyl tosylate | Diethyl ethyl(cyclopentylmethyl)malonate | 60 | $NaOC_2H_5$ | Ethanol | 334 |
| | $C_7$ | | | | | |
| | $(n\text{-}C_3H_7)_2CHBr$ | $(n\text{-}C_3H_7)_2CHC(C_2H_5)(CO_2C_2H_5)_2$ | 31 | $NaOC_2H_5$ | Ethanol | 148, 550 617 |
| | $C_2H_5CH(CH_3)CH_2CH(CH_3)Br$ | $C_2H_5CH(CH_3)CH_2CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $i\text{-}C_5H_{11}CH(CH_3)Br$ | $i\text{-}C_5H_{11}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $i\text{-}C_4H_9CH(CH_3)CH_2Br$ | $i\text{-}C_4H_9CH(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $i\text{-}C_5H_{11}OCH(CH_3)Cl$ | $i\text{-}C_5H_{11}OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 71 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $n\text{-}C_6H_{13}SCH_2Cl$ | $n\text{-}C_6H_{13}SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125, 893 |
| | $n\text{-}C_5H_{11}S(CH_2)_2Cl$ | $n\text{-}C_5H_{11}S(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $n\text{-}C_5H_{11}SCH(CH_3)Cl$ | $n\text{-}C_5H_{11}SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $i\text{-}C_5H_{11}SCH(CH_3)Cl$ | $i\text{-}C_5H_{11}SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_2H_5CH(C_2H_5)CH_2SCH_2Cl$ | $C_2H_5CH(C_2H_5)CH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $n\text{-}C_3H_7CH(CH_3)S(CH_2)_2Cl$ | $n\text{-}C_3H_7CH(CH_3)S(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $n\text{-}C_4H_9SCH_2CH(CH_3)Cl$ | $n\text{-}C_4H_9SCH_2CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70–75 | $NaOC_2H_5$ | Toluene | 554 |
| | $n\text{-}C_4H_9SCH(C_2H_5)Cl$ | $n\text{-}C_4H_9SCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 30–40 | $NaOC_2H_5$ | Toluene | 126 |
| | $i\text{-}C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7\text{-}i)C(C_2H_5)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 223 |
| | $C_2H_5O_2C(CH_2)_4I$ | $C_2H_5O_2C(CH_2)_4C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 777 |
| | $CHCl(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2CHC(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 260 |
| | $\beta$-Cyclopentylethyl bromide | Diethyl ethyl-($\beta$-cyclopentylethyl)malonate | 50–60 | $NaOC_2H_5$ | Ethanol | 725 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl ethyl-[$\beta$-(2-cyclopentenyl)ethyl]-malonate | 46 | $NaOC_2H_5$ | Ethanol | 334 |
| | $(C_6H_5CH_2O)_2CO$ | $C_6H_5CH_2O_2CC(C_2H_5)(CO_2C_2H_5)_2$ | 53 | $NaOCH_2C_6H_5$ | $(C_6H_5CH_2O)_2CO$ | 890, 330 |
| | $p\text{-}O_2NC_6H_4CH_2Cl$ | $p\text{-}O_2NC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 740 |
| | $p\text{-}IC_6H_4CH_2Br$ | $p\text{-}IC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 64 | $NaOC_2H_5$ | Ethanol | 900 |
| | Chloromethyl cyclohexyl sulfide | Diethyl ethyl[(cyclohexylthio)methyl]-malonate | — | $NaOC_2H_5$ | Toluene | 125, 899 |
| | $C_8$ | | | | | |
| | $n\text{-}C_6H_{17}Br$ | $n\text{-}C_6H_{17}C(C_2H_5)(CO_2C_2H_5)_2$ | 85 | Na | Ether | 769 |
| | $(+)\text{-}n\text{-}C_6H_{13}CH(CH_3)Br$ | $(+)\text{-}n\text{-}C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 41 | $NaOC_2H_5$ | Ethanol | 901 |
| | $(-)\text{-}n\text{-}C_6H_{13}CH(CH_3)Br$ | $(-)\text{-}n\text{-}C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 41 | $NaOC_2H_5$ | Ethanol | 901 |
| | $(+\,-)\text{-}n\text{-}C_6H_{13}CH(CH_3)Br$ | $(+\,-)\text{-}n\text{-}C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 43 | $NaOC_2H_5$ | Ethanol | 901 |
| | $n\text{-}C_3H_7CH(CH_3)(CH_2)_3Br$ | $n\text{-}C_3H_7CH(CH_3)(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $n\text{-}C_4H_9CH(C_2H_5)CH_2Br$ | $n\text{-}C_4H_9CH(C_2H_5)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $C_2H_5CH(CH_3)CH_2CH(CH_3)CH_2Br$ | $C_2H_5CH(CH_3)CH_2CH(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $n\text{-}C_4H_9O(CH_2)_2O(CH_2)_2Br$ | $n\text{-}C_4H_9O(CH_2)_2O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $(C_2H_5)_2CHCH(SC_2H_5)Cl$ | $(C_2H_5)_2CHCH(SC_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 30–40 | $NaOC_2H_5$ | Toluene | 126 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl ethyl-($\beta$-cyclohexylethyl)malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $\beta$-Cyclohexylideneethyl bromide | Diethyl ethyl-($\beta$-cyclohexylideneethyl)-malonate | 65 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |

*Note:* References 577–1080 are on pp. 322–331.

$\ddagger$ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_2H_5$ (*Cont.*) | $C_6H_5(CH_2)_2Br$ | $C_6H_5(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 48 | K | Xylene | 881 |
| | $C_6H_5O(CH_2)_2Cl$ | $C_6H_5O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $C_6H_5CH_2SCH_2Cl$ | $C_6H_5CH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 55 | Na | Ether | 205 |
| | $C_6H_5CH(CH_3)X\ddagger$ | $C_6H_5CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $p\text{-}CH_3OC_6H_4CH_2Cl$ | $p\text{-}CH_3OC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 903 |
| | $C_6H_5CH_2OCH_2Cl$ | $C_6H_5CH_2OCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 56 | Na | Ether | 542 |
| | $C_6H_5COCH_2Cl$ | $C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 891 |
| | $C_6H_5COCH_2Cl$ | $C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 891 |
| | $C_6H_5COCH_2Br$ | $C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 904, 894 |
| | $C_6H_5COCH_2Br$ | $C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 894 |
| | $C_6H_5COCH_2Br$ | $H_5C_6C\overset{\displaystyle O}{\diagup}\begin{smallmatrix}CO\\ \|\quad\ \|\\ HC\text{——}C(C_2H_5)CO_2C_2H_5\end{smallmatrix}$ | — | $NaOC_2H_5$ | Ethanol | 106 |
| | $H_5C_6CH\text{——}CH_2$ with O epoxide | $H_5C_6CHCH_2C(C_2H_5)CO_2C_2H_5$<br>$\ \ \ \ \ \|\qquad\ \|$<br>$\ \ \ \ \ O\text{——}CO$ | 65 | $NaOC_2H_5$ | Ethanol | 11 |
| | $C_9$ | | | | | |
| | $n\text{-}C_3H_7CH(CH_3)CH\text{-}(C_2H_5)CH_2Br$ | $n\text{-}C_3H_7CH(CH_3)CH(C_2H_5)CH_2C(C_2H_5)\text{-}(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $i\text{-}C_5H_{11}CH(C_2H_5)CH_2Br$ | $i\text{-}C_5H_{11}CH(C_2H_5)CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 550 |
| | $C_6H_5(CH_2)_3Br$ | $C_6H_5(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_5$ | Ethanol | 900 |
| | $C_6H_5O(CH_2)_3Cl$ | $C_6H_5O(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $C_{10}$ | | | | | |
| | $\delta\text{-}Cyclohexylbutyl bromide$ | Diethyl ethyl-($\delta$-cyclohexylbutyl)malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | 5-Methoxy-2,4-dimethyl-benzyl chloride-KI | Diethyl ethyl-(5-methoxy-2,4-dimethylbenzyl)malonate | 84 | $NaOC_2H_5$ | Ethanol | 905 |
| | 2-Phenyl-4-chloromethyl-thiazole | Diethyl ethyl-(2-phenyl-4-thiazolylmethyl)malonate | 50 | $NaOC_2H_5$ | Ethanol | 548 |
| | $C_{11}$ | | | | | |
| | $n\text{-}C_{11}H_{23}X\ddagger$ | $n\text{-}C_{11}H_{23}C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | 1-Bromomethylnaphthalene | Diethyl ethyl-(1-naphthylmethyl)malonate | 63 | Na | $C_6H_6$ | 153 |
| | 2-Bromomethylnaphthalene | Diethyl ethyl-(2-naphthylmethyl)malonate | — | Na | $C_6H_6$ | 153 |
| | $C_{12}$ | | | | | |
| | $n\text{-}C_{12}H_{25}X\ddagger$ | $n\text{-}C_{12}H_{25}C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $\beta\text{-}(p\text{-}t\text{-}Butylphenyl)ethyl-bromide$ | Diethyl ethyl-[$\beta$-($p$-$t$-butylphenyl)ethyl]-malonate | 60 | Na | Toluene | 413 |
| | 1-Acenaphthenyl chloride | Diethyl ethyl-(1-acenaphthenyl)malonate | 91 | $NaOC_2H_5$ | Ethanol | 824 |
| | $C_{13}$–$C_{16}$ | | | | | |
| | $n\text{-}C_{13}H_{27}Br$ | $n\text{-}C_{13}HC_{27}(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | $n\text{-}C_{14}H_{29}I$ | $n\text{-}C_{14}HC_{29}(C_2H_5)(CO_2C_2H_5)_2$ | 73 | — | — | 684, 888 |
| | $n\text{-}C_{16}H_{33}I$ | $n\text{-}C_{16}HC_{33}(C_2H_5)(CO_2C_2H_5)_2$ | 75 | Na | Toluene | 906 |
| | $n\text{-}C_{16}H_{33}I$ | $n\text{-}C_{16}HC_{33}(C_2H_5)(CO_2C_2H_5)_2$ | 83 | $NaOC_2H_5$ | Ethanol | 135 |
| | $C_{10}$–$C_{16}$ | | | | | |
| †† | $n\text{-}C_{10}H_{21}Br$ | $(CH_2)_2C(C_{10}H_{21}\text{-}n)CO_2C_2H_5$<br>$\ \ \|\qquad\ \|$<br>$\ \ O\text{——}CO$ | — | $NaOC_2H_5$ | Ethanol | 527 |
| †† | $n\text{-}C_{12}H_{25}Br$ | $(CH_2)_2C(C_{12}H_{25}\text{-}n)CO_2C_2H_5$<br>$\ \ \|\qquad\ \|$<br>$\ \ O\text{——}CO$ | — | $NaOC_2H_5$ | Ethanol | 527 |
| †† | $n\text{-}C_{13}H_{27}Br$ | $(CH_2)_2C(C_{13}H_{27}\text{-}n)CO_2C_2H_5$<br>$\ \ \|\qquad\ \|$<br>$\ \ O\text{——}CO$ | — | $NaOC_2H_5$ | Ethanol | 527 |
| †† | $n\text{-}C_{14}H_{29}Br$ | $(CH_2)_2C(C_{14}H_{29}\text{-}n)CO_2C_2H_5$<br>$\ \ \|\qquad\ \|$<br>$\ \ O\text{——}CO$ | — | $NaOC_2H_5$ | Ethanol | 527 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

†† The lactone $CH_2CH_2CHCO_2C_2H_5$ was used as the ester to be alkylated.
$\quad\quad\ \ \|\qquad\ \|$
$\quad\quad\ \ O\text{——}CO$

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| †† (*Cont.*) | $n$-$C_{15}H_{33}Br$ | $(CH_2)_2C(C_{16}H_{33}$-$n)CO_2C_2H_5$<br>  \|    \|<br>  O——CO | — | $NaOC_2H_5$ | Ethanol | 527 |
| | $C_3$–$C_{11}$ | | | | | |
| $C_2H_5O$ | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 907 |
| | $i$-$C_4H_9CH$=$CHCH_2Br$ | $i$-$C_4H_9CH$=$CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 907 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(OC_2H_5)(CO_2C_2H_5)_2$ and<br>$(C_2H_5O_2C)_2C(OC_2H_5)(CH_2)_3$-<br>$C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene-ethanol | 908 |
| | $Br(CH_2)_4Br$ | $Br(CH_2)_4C(OC_2H_5)(CO_2C_2H_5)_2$ and<br>$(C_2H_5O_2C)_2C(OC_2H_5)(CH_2)_4$-<br>$C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene-ethanol | 908 |
| | $C_6H_5CH$=$CHCH_2Br$ | $C_6H_5CH$=$CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 907 |
| | $Br(CH_2)_{10}Br$ | $Br(CH_2)_{10}C(OC_2H_5)(CO_2C_2H_5)_2$ and<br>$(C_2H_5O_2C)_2C(OC_2H_5)(CH_2)_{10}C(OC_2H_5)$-<br>$(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene-ethanol | 908 |
| | $CH_2$=$CH(CH_2)_9Br$ | $CH_2$=$CH(CH_2)_9C(OC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 907 |
| $CH_3OCH_2$ | $CH_3I$ | $(C_2H_5O_2C)_2C(CH_3)CH_2CH(CH_3)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 204 |
| $C_3$ | $C_1$ | | | | | |
| $n$-$C_3H_7$ | $CH_3I$ | $n$-$C_3H_7C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 613 |
| | $CHCl_3$ | $Cl_2CHC(C_3H_7$-$n)(CO_2C_2H_5)_2$ and<br>$(C_2H_5O_2C)_2C(C_3H_7$-$n)CHCl$-<br>$C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | Na | Ether | 231 |
| | $C_2$ | | | | | |
| †† | $Br(CH_2)_3Br$ | $(CH_2)_3C(C_3H_7$-$n)CO_2C_2H_5$<br>  \|    \|<br>  O——CO | — | Na | $C_6H_6$ | 555 |
| $n$-$C_3H_7$ | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 172 |
| †† | $CH_2$—$CH_2$<br>   \\ /<br>    O | $(CH_2)_2CH(C_3H_7$-$n)$<br>  \|    \|<br>  O——CO | 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $C_3$ | | | | | |
| $n$-$C_3H_7$ | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $CH_3SCH(CH_3)Cl$ | $CH_3SCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 45 | Na | — | 656 |
| | $C_4$ | | | | | |
| | $C_2H_5CH(CH_3)Br$ | $C_2H_5CH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 53 | $NaOC_2H_5$ | Ethanol | 909, 547 |
| | $C_2H_5O(CH_2)_2Br$ | $C_2H_5O(CH_2)_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 43 | $NaOC_2H_5$ | Ethanol | 910 |
| | $C_2H_5OCH(CH_3)Cl$ | $C_2H_5OCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 66 | $NaNH_2$ | $C_4H_6$-ether | 203 |
| | $CH_2$=$CHO(CH_2)_2Cl$ | $CH_2$=$CHO(CH_2)_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 40–50 | $NaOC_2H_5$ | Ethanol | 541 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | Na | Ether | 653 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | Na | $C_2H_6$ | 653 |
| | $C_5$ | | | | | |
| | $n$-$C_5H_{11}Br$ | $n$-$C_5H_{11}C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 73 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $n$-$C_4H_9SCH_2Cl$ | $n$-$C_4H_9SCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5CH(CH_3)CH_2Br$ | $C_2H_5CH(CH_3)CH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 551 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 41 | $NaOC_2H_5$ | Ethanol | 718, 748 |
| | $i$-$C_3H_7SCH(CH_3)Cl$ | $i$-$C_3H_7SCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 25 | $NaOC_2H_5$ | Ethanol | 223 |
| | Cyclopentyl halide‡ | Diethyl cyclopentyl-($n$-nropyl)malonate | — | — | — | 911 |
| | $C_6$ | | | | | |
| | $n$-$C_4H_9SCH(CH_3)Cl$ | $n$-$C_4H_9SCH(CH_3)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 12 | $NaOC_2H_5$ | Ethanol | 223 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 21 | $NaOC_2H_5$ | Ethanol | 223 |
| | 2,4-Dinitrochlorobenzene | Diethyl $n$-propyl-(2,4-dinitrophenyl)-<br>malonate | 54 | Na | Ether | 139 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

†† The lactone $CH_2CH_2CHCO_2C_2H_5$ was used as the ester to be alkylated.
    \|      \|
    O——CO

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R′CH(CO₂R)₂

#### (The diethyl ester was used unless otherwise indicated.)

| R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| n-C₃H₇ (Cont.) | C₇ | | | | | |
| | i-C₃H₇CHBrCO₂C₂H₅ | C₂H₅O₂CCH(C₃H₇-i)C(C₃H₇-n)(CO₂C₂H₅)₂ | Poor | NaOC₂H₅ | Ethanol | 223 |
| | β-Cyclopentylethyl bromide | Diethyl n-propyl-(β-cyclopentylethyl)-malonate | 50–60 | NaOC₂H₅ | Ethanol | 725 |
| | C₈ | | | | | |
| | β-Cyclohexylethyl bromide | Diethyl n-propyl-(β-cyclohexylethyl)-malonate | — | NaOC₂H₅ | Ethanol | 902 |
| | C₆H₅O(CH₂)₂Br | C₆H₅O(CH₂)₂C(C₃H₇-n)(CO₂C₂H₅)₂ | 48 | NaOC₂H₅ | Ethanol | 910 |
| | C₉ | | | | | |
| | γ-Cyclohexylpropyl bromide | Diethyl n-propyl-(γ-cyclohexylpropyl)-malonate | — | NaOC₂H₅ | Ethanol | 902 |
| | C₆H₅O(CH₂)₃Cl | C₆H₅O(CH₂)₃C(C₃H₇-n)(CO₂C₂H₅)₂ | 27 | NaOC₃H₇-n | n-C₃H₇OH | 774 |
| | C₁₀ | | | | | |
| | n-C₁₀H₂₁X‡ | n-C₁₀H₂₁C(C₃H₇-n)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 887 |
| | δ-Cyclohexylbutyl bromide | Diethyl n-propyl-(δ-cyclohexylbutyl)-malonate | — | NaOC₂H₅ | Ethanol | 902 |
| | C₁₁–C₁₆ | | | | | |
| | n-C₁₁H₂₃X‡ | n-C₁₁H₂₃C(C₃H₇-n)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 888 |
| | n-C₁₂H₂₅X‡ | n-C₁₂H₂₅C(C₃H₇-n)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 887 |
| | β-(1-Naphthyl)ethyl bromide | Diethyl n-propyl-[β-(1-naphthyl)ethyl]-malonate | 29 | K | C₆H₆ | 419 |
| | n-C₁₃H₂₇X‡ | n-C₁₃H₂₇C(C₃H₇-n)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 888 |
| | n-C₁₄H₂₉X‡ | n-C₁₄H₂₉C(C₃H₇-n)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 887 |
| | n-C₁₆H₃₃I | n-C₁₆H₃₃C(C₃H₇-n)(CO₂C₂H₅)₂ | 78 | NaOC₂H₅ | Ethanol | 135 |
| Cl(CH₂)₃ | None | Diethyl cyclobutane-1,1-dicarboxylate | 88 | NaOC₂H₅ | Ethanol | 622, 480, 490 |
| Br(CH₂)₃ | None | Diethyl cyclobutane-1,1-dicarboxylate | 74 | NaOC₂H₅ | Ethanol | 315 |
| I(CH₂)₃ | None | Diethyl cyclobutane-1,1-dicarboxylate | — | Na(C₆H₅CHCN) | Ether | 92 |
| | None | Diethyl cyclobutane-1,1-dicarboxylate | — | Na[C₆H₅-C(CO₂C₂H₅)₂] | Toluene | 92 |
| †† | n-C₁₄H₂₉Br | CH₃CHCH₂C(C₁₄H₂₉-n)CO₂C₂H₅ <br>    &#124;     &#124; <br>   O——CO | — | NaOC₂H₅ | Ethanol | 527 |
| †† | n-C₁₆H₃₃Br | CH₃CHCH₂C(C₁₆H₃₃-n)CO₂C₂H₅ <br>    &#124;     &#124; <br>   O——CO | — | NaOC₂H₅ | Ethanol | 527 |
| i-C₃H₇ | C₁ | | | | | |
| | CH₃I | i-C₃H₇C(CH₃)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 569 |
| | C₂ | | | | | |
| | C₂H₅X‡ | i-C₃H₇C(C₂H₅)(CO₂C₂H₅)₂ | Very low | NaOC₂H₅ | Ethanol | 145 |
| | (C₂H₅O)₂CO | i-C₃H₇C(C₂H₅)(CO₂C₂H₅)₂ | 10 | NaOC₂H₅ | (C₂H₅O)₂CO | 890 |
| | C₂H₅X‡ | i-C₃H₇C(C₂H₅)(CO₂C₂H₅)₂ | 65 | NaOC₄H₉-t | t-C₄H₉OH | 35 |
| | CH₃OCH₂Cl | CH₃OCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | — | Na | Ether | 204 |
| | Br(CH₂)₂Br | Br(CH₂)₂C(C₃H₇-i)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 172 |
| | C₃ | | | | | |
| | n-C₃H₇Br | n-C₃H₇C(C₃H₇-i)(CO₂C₂H₅)₂ | ca. 80 | NaOC₂H₅ | Ethanol | 536 |
| | C₂H₅SCH₂Cl | C₂H₅SCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | 33 | Na | Ether | 205 |
| | C₂H₅SCH₂Cl | C₂H₅SCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Toluene | 125 |
| | i-C₃H₇I | (i-C₃H₇)₂C(CO₂C₂H₅)₂ | 40 | Na | Ether | 52 |
| | CH₂=CHCH₂Br | CH₂=CHCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | 84 | NaOC₂H₅ | (C₂H₅O)₂CO | 44 |
| | CH₂=CHCH₂Br | CH₂=CHCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | 90 | Mg(OC₂H₅)₂ | Ethanol | 56 |
| | C₄ | | | | | |
| | n-C₄H₉Br | n-C₄H₉C(C₃H₇-i)(CO₂C₂H₅)₂ | ca. 80 | NaOC₂H₅ | Ethanol | 536, 770 |
| | C₂H₅CH(CH₃)Br | C₂H₅CH(CH₃)C(C₃H₇-i)(CO₂C₂H₅)₂ | 26 | NaOC₂H₅ | (C₂H₅O)₂CO | 44 |
| | i-C₄H₉Br | i-C₄H₉C(C₃H₇-i)(CO₂C₂H₅)₂ | 67 | NaOC₂H₅ | (C₂H₅O)₂CO | 44 |
| | i-C₃H₇SCH₂Cl | i-C₃H₇SCH₂C(C₃H₇-i)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Toluene | 125 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

†† The lactone CH₃CHCH₂CHCO₂C₂H₅ was used as the ester to be alkylated.
      &#124;    &#124;
    O——CO

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| i-C_3H_7 *(Cont.)* | $C_5$ | | | | | |
| | $n$-C_5H_{11}Br | $n$-C_5H_{11}C(C_3H_7-i)(CO_2C_2H_5)_2$ | 70–85 | NaOC_2H_5 | Ethanol | 545 |
| | $n$-C_4H_9SCH_2Cl | $n$-C_4H_9SCH_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Toluene | 125 |
| | $i$-C_5H_{11}Br | $i$-C_5H_{11}C(C_3H_7-i)(CO_2C_2H_5)_2$ | ca. 80 | NaOC_2H_5 | Ethanol | 536 |
| | $(CH_3)_2C=CHCH_2Br$ | $(CH_3)_2C=CHCH_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | Poor | NaOC_2H_5 | Ethanol | 912 |
| | $(CH_3)_2C=CHCH_2Br$ | $(CH_3)_2C=CHCH_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | 73 | NaOC_2H_5 | $(C_2H_5O)_2CO$ | 47 |
| | CH_3CHBrCO_2C_2H_5 | $C_2H_5O_2CCH(CH_3)C(C_3H_7-i)(CO_2C_2H_5)_2$ | Poor | NaOC_2H_5 | Ethanol | 223 |
| | $I(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Ethanol | 672 |
| | 2-Chloromethylthiophene | Diethyl isopropyl-(2-thenyl)malonate | — | Na | None | 897 |
| | $C_6$ | | | | | |
| | $n$-C_4H_9S(CH_2)_2Cl | $n$-C_4H_9S(CH_2)_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 553 |
| | $n$-C_4H_9SCH(CH_3)Cl | $n$-C_4H_9SCH(CH_3)C(C_3H_7-i)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 126 |
| | C_2H_5CHBrCO_2C_2H_5 | $C_2H_5O_2CCH(C_2H_5)C(C_3H_7-i)(CO_2C_2H_5)_2$ | Poor | NaOC_2H_5 | Ethanol | 223 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | Poor | NaOC_2H_5 | Ethanol | 223 |
| | $C_7$ | | | | | |
| | $i$-C_3H_7CHBrCO_2C_2H_5 | None | — | NaOC_2H_5 | Ethanol | 223 |
| | C_6H_5CH_2Cl | $C_6H_5CH_2C(C_3H_7-i)(CO_2C_2H_5)_2$ | 45 | NaOC_2H_5 | $(C_2H_5O)_2CO$ | 48 |
| | $C_8$-$C_{13}$ | | | | | |
| | C_6H_5COCH_2Br | (structure: $H_5C_6C$, $CO$ with O bridge; $HC——C(C_3H_7-i)CO_3C_2H_5$) | — | NaOC_2H_5 | Ethanol | 106 |
| | 2,5-Dimethylbenzyl chloride | Diethyl isopropyl-(2,5-dimethylbenzyl)-malonate | 67 | Na | Xylene | 158 |
| | $n$-C_{13}H_{27}X‡ | $n$-C_{13}H_{27}C(C_3H_7-i)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Ethanol | 888 |
| CH_2=CHCH_2 ( = C_3H_5) | $C_2$ | | | | | |
| | C_2H_5Br | $C_2H_5C(C_3H_5)(CO_2C_2H_5)_2$ | 70–85 | NaOC_2H_5 | Ethanol | 545 |
| | Br(CH_2)_2Br | $Br(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Ethanol | 172 |
| | BrCH=CHBr | $BrCH=CHC(C_3H_5)(CO_2C_2H_5)_2$ | 26 | NaNH_2 | Ether-ethanol | 277 |
| | $CH_2——CH_2$ over O | $(CH_2)_2C(C_3H_5)$, O——CO | ca. 70 | NaOC_2H_5 | Ethanol | 282 |
| | $C_3$ | | | | | |
| | C_2H_5SCH_2Cl | $C_2H_5SCH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Toluene | 125 |
| | $i$-C_3H_7Br | $i$-C_3H_7C(C_3H_5)(CO_2C_2H_5)_2$ | 49 | NaOC_2H_5 | Ethanol | 531 |
| | CH_3SCH(CH_3)Cl | $CH_3SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 126 |
| | CH_2=CHCH_2Br | $(C_3H_5)_2C(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Ethanol | 615 |
| | $(CH_3)_2CClNO_2$ | $(CH_3)_2C(NO_2)C(C_3H_5)(CO_2C_2H_5)_2$ | 46 | Na | Ether | 556 |
| | $C_4$ | | | | | |
| | $n$-C_4H_9Br | $n$-C_4H_9C(C_3H_5)(CO_2C_2H_5)_2$ | 87 | NaOC_2H_5 | $(C_2H_5O)_2CO$ | 44, 51 |
| | C_2H_5OCH(CH_3)Cl | $C_2H_5OCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 83 | NaNH_2 | C_6H_6-ether | 203 |
| | $n$-C_3H_7SCH_2Cl | $n$-C_3H_7SCH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Toluene | 125 |
| | $C_2H_5S(CH_2)_2Cl$ | $C_2H_5S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 553 |
| | C_2H_5SCH(CH_3)Cl | $C_2H_5SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 126 |
| | Cyclobutylmethyl tosylate | Diethyl allyl(cyclobutylmethyl)malonate | 86 | NaOC_2H_5 | Ethanol | 334 |
| | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | — | — | 561 |
| | $CH_2=CHCH——CH_2$ over O | $CH_2=CHCHCH_2C(C_3H_5)CO_2C_2H_5$, O——CO | 54 | NaOC_2H_5 | Ethanol | 11 |
| | $C_5$ | | | | | |
| | $n$-C_4H_9SCH_2Cl | $n$-C_4H_9SCH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Toluene | 125 |
| | $n$-C_3H_7S(CH_2)_2Cl | $n$-C_3H_7S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 553 |
| | $n$-C_3H_7CH(CH_3)Br | $n$-C_3H_7CH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | — | NaOC_2H_5 | Ethanol | 617 |
| | C_2H_5SCH_2CH(CH_3)Cl | $C_2H_5SCH_2CH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–75 | NaOC_2H_5 | Toluene | 554 |
| | $n$-C_3H_7OCH(CH_3)Cl | $n$-C_3H_7OCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 82 | NaNH_2 | C_6H_6-ether | 203 |
| | $n$-C_3H_7SCH(CH_3)Cl | $n$-C_3H_7SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 126 |
| | $i$-C_3H_7S(CH_2)_2Cl | $i$-C_3H_7S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 553 |
| | $CH_2=CHCH_2SCH(CH_3)Cl$ | $CH_2=CHCH_2SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | NaOC_2H_5 | Toluene | 126 |
| | $(CH_3)_2C=CHCH_2Br$ | $(CH_3)_2C=CHCH_2C(C_3H_5)(CO_2C_2H_5)_2$ | Poor | NaOC_2H_5 | Ethanol | 912 |
| | CH_3CHBrCO_2C_2H_5 | $C_2H_5O_2CCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 26 | NaOC_2H_5 | Ethanol | 223 |
| | 2-Chloromethylthiophene | Diethyl (2-thenyl)allylmalonate | 68 | NaOC_2H_5 | Ethanol | 913 |

*Note:* References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $CH_2=CHCH_2$ (*Cont.*) | $C_6$ | | | | | |
| | $n\text{-}C_4H_9S(CH_2)_2Cl$ | $n\text{-}C_4H_9S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $n\text{-}C_4H_9SCH(CH_3)Cl$ | $n\text{-}C_4H_9SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $i\text{-}C_4H_9SCH(CH_3)Cl$ | $i\text{-}C_4H_9SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $CH_2=C(CH_3)CH(C_2H_5)Cl$ | $CH_2=C(CH_3)CH(C_2H_5)C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 898 |
| | $Br(CH_2)_3CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_3C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 530 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 16 | $NaOC_2H_5$ | Ethanol | 223 |
| | $C_7$ | | | | | |
| | $n\text{-}C_4H_9SCH_2CH(CH_3)Cl$ | $n\text{-}C_4H_9SCH_2CH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$ | 70–75 | $NaOC_2H_5$ | Toluene | 554 |
| | $i\text{-}C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7\text{-}i)C(C_3H_5)(CO_2C_2H_5)_2$ | 5 | $NaOC_2H_5$ | Ethanol | 223 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | — | — | 506 |
| | $C_8$ | | | | | |
| | $n\text{-}C_4H_9CH(C_2H_5)CH_2Br$ | $n\text{-}C_4H_9CH(C_2H_5)CH_2C(C_3H_5)(CO_2C_2H_5)_2$ | — | Na | Xylene | 914 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl allyl-($\beta$-cyclohexylethyl)malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $o$-Methylbenzyl bromide | Diethyl allyl-($o$-methylbenzyl)malonate | 34 | $NaOC_2H_5$ | Ethanol | 516 |
| | $H_5C_6CH\text{—}CH_2$ | $H_5C_6CHCH_2C(C_3H_5)CO_2C_2H_5$ | 25 | $NaOC_2H_5$ | Ethanol | 11 |
| | $\quad\quad\diagdown O\diagup$ | $\quad\quad O\text{——}CO$ | | | | |
| | $C_9$ | | | | | |
| | $n\text{-}C_9H_{19}Br$ | $n\text{-}C_9H_{19}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $\gamma$-Cyclohexylpropyl bromide | Diethyl allyl-($\gamma$-cyclohexylpropyl)malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $C_{10}\text{–}C_{12}$ | | | | | |
| | $n\text{-}C_{10}H_{21}Br$ | $n\text{-}C_{10}H_{21}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $\delta$-Cyclohexylbutyl bromide | Diethyl allyl-($\delta$-cyclohexylbutyl)malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $p\text{-}i\text{-}C_3H_7C_6H_4CH_2Cl$ | $p\text{-}i\text{-}C_3H_7C_6H_4CH_2C(C_3H_5)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Toluene | 509 |
| | $n\text{-}C_{11}H_{23}Br$ | $n\text{-}C_{11}H_{23}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $p\text{-}t\text{-}C_4H_9C_6H_4CH_2Cl$ | $p\text{-}t\text{-}C_4H_9C_6H_4CH_2C(C_3H_5)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Toluene | 510 |
| | $n\text{-}C_{12}H_{25}Br$ | $n\text{-}C_{12}H_{25}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $\beta$-($p\text{-}t$-Butylphenyl)ethyl bromide | $p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$ | 58 | Na | Toluene | 321 |
| | $C_{13}\text{–}C_{16}$ | | | | | |
| | $n\text{-}C_{13}H_{27}Br$ | $n\text{-}C_{13}H_{27}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $o$-Phenylbenzyl bromide | Diethyl allyl-($o$-phenylbenzyl)malonate | 41 | $NaOC_2H_5$ | Ethanol | 516 |
| | $(C_6H_5)_2CHBr$ | $(C_6H_5)_2CHC(C_3H_5)(CO_2C_2H_5)_2$ | 37 | $NaOC_2H_5$ | Ethanol | 516 |
| | 9-Bromofluorene | Diethyl allyl-(9-fluorenyl)malonate | 62 | $NaOC_2H_5$ | Ethanol | 516 |
| | $n\text{-}C_{14}H_{29}Br$ | $n\text{-}C_{14}H_{29}C(C_3H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | Hydnocarpyl chloride | Diethyl allyl(hydnocarpyl)malonate | 50 | K | Toluene | 291 |
| $CH_2=CBrCH_2$ | $CH_3I$ | $HC\equiv CC(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 639 |
| $HC\equiv CCH_2$ | $CH_3I$ | $HC\equiv CCH_2C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 639 |
| $\begin{matrix}CH_2\diagdown\\ \quad\quad CH\text{—}\\ CH_2\diagup\end{matrix}$ | $C_2H_5I$ | $\begin{matrix}CH_2\diagdown\\ \quad\quad CHC(C_2H_5)(CO_2C_2H_5)_2\\ CH_2\diagup\end{matrix}$ | 75 | $NaOC_2H_5$ | Ethanol | 384 |
| $CH_3COCH_2\text{—}$ | $C_2H_5I$ | $CH_3COCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 593, 634 |
| | $CH_3COCH_2Br$ | $(CH_3COCH_2)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 593 |
| | $i\text{-}C_4H_9I$ | $CH_3COCH_2C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$ | 72 | $NaOC_2H_5$ | Ethanol | 593, 634 |
| $NC(CH_2)_2\text{—}$ | $\beta$-Cyanoethyl $p$-toluenesulfonate | $[NC(CH_2)_2]_2C(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 102 |
| $C_4$ | $C_2$ | | | | | |
| $n\text{-}C_4H_9$ | $C_2H_5Br$ | $n\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | — | 532 |
| | $C_2H_5I$ | $n\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 142 |
| | $(C_2H_5O)_2CO$ | $n\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$ | 34 (50)§ | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 890 |
| | $CH_3OCH_2Cl$ | $CH_3OCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 86 | Na | Ether | 489 |
| | $BrCH_2CH_2Br$ | $Br(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 79 (82)§ | Na | $C_6H_6$ | 316 |
| | $BrCH_2CH_2Br$ | $(CH_2)_2C(C_4H_9\text{-}n)CO_2C_2H_5$ | — | Na | $C_6H_6$ | 555 |
| | | $\quad O\text{——}CO$ | | | | |
| | $BrCH=CHBr$ | $BrCH=CHC(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 26 | Na | Ether | 277 |
| | $CH_2\text{—}CH_2$ | $(CH_2)_2CH(C_4H_9\text{-}n)$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $\quad\diagdown O\diagup$ | $\quad O\text{——}CO$ | | | | |

*Note:* References 577–1080 are on pp. 322–331.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| B' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $n$-$C_4H_9$ (*Cont.*) | $C_3$ | | | | | |
| | $C_6H_5SCH_2Cl$ | $C_6H_5SCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125, 893 |
| | $i$-$C_3H_7Br$ | $i$-$C_3H_7C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 915 |
| | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 148 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 47 | Na | None | 656, 129 |
| | $(CH_3)_2CClNO_2$ | $(CH_3)_2C(NO_2)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 39 | Na | Ether | 556 |
| | $C_4$ | | | | | |
| | $n$-$C_4H_9Br$ | $(n\text{-}C_4H_9)_2C(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 142 |
| | $n$-$C_4H_9I$ | $(n\text{-}C_4H_9)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 141 |
| | $sec$-$C_4H_9Br$ | $sec$-$C_4H_9C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $C_2H_5OCH(CH_3)Cl$ | $C_2H_5OCH(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 68 | $NaNH_2$ | $C_6H_5$-ether | 203 |
| | $CH_2$=$CHO(CH_2)_2Cl$ | $CH_2$=$CHO(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 40–50 | $NaOC_2H_5$ | Ethanol | 541 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_2H_5OCHClCH_2Cl$ | $C_2H_5OCH(CH_2Cl)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 68 | Na | Ether | 277 |
| | $C_2H_5OCHBrCH_2Br$ | $CH_2CH(OC_2H_5)C(C_4H_9\text{-}n)CO_2C_2H_5$ <br> $O$————$CO$ | 56 | Na | Ether | 277 |
| | $CH_2CCl$=$CHCH_2Cl$ | $CH_2CCl$=$CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 916, 917 |
| | $CH_2$=$CHCH$——$CH_2$ <br> $\diagdown O \diagup$ | $CH_2$=$CHCHCH_2C(C_4H_9\text{-}n)CO_2C_2H_5$ <br> $O$————$CO$ | 30 | $NaOC_2H_5$ | Ethanol | 11 |
| | $C_5$ | | | | | |
| | $n$-$C_4H_9SCH_2Cl$ | $n$-$C_4H_9SCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5CH(C_2H_5)Br$ | $C_2H_5CH(C_2H_5)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $C_2H_5CH(CH_3)CH_2Br$ | $C_2H_5CH(CH_3)CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 78 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $CH_2$=$CHCH_2S(CH_2)_2Cl$ | $CH_2$=$CHCH_2S(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | Cyclopentyl halide‡ | Diethyl cyclopentyl-($n$-butyl)malonate | — | — | — | 911 |

| | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | 2-Chloromethylthiophene | Diethyl $n$-butyl-(2-thenyl)malonate | — | Na | None | 897 |
| | $(CH_3)_2C(CH_2Br)_2$ | $n$-$C_4H_9C(CO_2C_2H_5)_2CH_2C(CH_3)_2$-$CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 13 | $NaOC_2H_5$ | Ethanol | 918 |
| | $C_6$-$C_7$ | | | | | |
| | $n$-$C_6H_{13}Br$ | $n$-$C_6H_{13}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethano | 641, 919 |
| | $n$-$C_7H_{15}Br$ | $n$-$C_7H_{15}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 641 |
| | $n$-$C_7H_{15}I$ | $n$-$C_7H_{15}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 399 |
| | $\beta$-Cyclopentylethyl bromide | Diethyl $n$-butyl-($\beta$-cyclopentylethyl)-malonate | 50–60 | $NaOC_2H_5$ | Ethanol | 725 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 121, 142, 143 |
| | $p$-$IC_6H_4CH_2Br$ | $p$-$IC_6H_4CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 67 | $NaOC_2H_5$ | Ethanol | 900 |
| | $C_8$-$C_{10}$ | | | | | |
| | $n$-$C_6H_{13}CH(CH_3)Br$ | $n$-$C_6H_{13}CH(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl $n$-butyl-($\beta$-cyclohexylethyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $C_6H_5(CH_2)_2Br$ | $C_6H_5(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 44 | $NaOC_2H_5$ | Ethanol | 142 |
| | $H_5C_6CH$——$CH_2$ <br> $\diagdown O \diagup$ | $H_5C_6CHCH_2C(C_4H_9\text{-}n)CO_2C_2H_5$ <br> $O$————$CO$ | 50 | $NaOC_2H_5$ | Ethanol | 11 |
| | $n$-$C_9H_{19}X$‡ | $n$-$C_9H_{19}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | $\gamma$-Cyclohexylpropyl bromide | Diethyl $n$-butyl-($\gamma$-cyclohexylpropyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $C_6H_5(CH_2)_3X$‡ | $C_6H_5(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 35 | $NaOC_2H_5$ | Ethanol | 142 |
| | $n$-$C_{10}H_{21}X$‡ | $n$-$C_{10}H_{21}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $\delta$-Cyclohexylbutyl bromide | Diethyl $n$-butyl-($\delta$-cyclohexylbutyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $C_{11}$-$C_{20}$ | | | | | |
| | $n$-$C_{11}H_{23}$-$X$‡ | $n$-$C_{11}H_{23}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | Undecenyl bromide | Diethyl undecenyl-($n$-butyl)malonate | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $n$-$C_{12}H_{25}I$ | $n$-$C_{12}H_{25}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 70 | Na | Toluene | 906, 888 |
| | $n$-$C_{16}H_{33}I$ | $n$-$C_{16}H_{33}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | Ethanol | 135 |
| | $n$-$C_{20}H_{41}I$ | $n$-$C_{20}H_{41}C(C_4H_9\text{-}n)(CO_2H)_2$ | 90 | $NaOC_4H_9$-$n$ | $n$-$C_4H_9OH$ | 684 |
| $i$-$C_4H_9$ | $C_2$ | | | | | |
| | $C_2H_5Br$ | $i$-$C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | None | 532 |
| | $C_2H_5I$ | $i$-$C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$ | 74 | $NaOC_2H_5$ | Ethanol | 657 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $i$-$C_4H_9$ *(Cont.)* | $CH_3SCH_2Cl$ | $CH_3SCH_2C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $BrCH_2CH_2Br$ | $(CH_2)_2C(C_4H_9$-$i)CO_2C_2H_5$ $\underset{O\!-\!\!-\!CO}{\overset{\mid\qquad\mid}{}}$ | 66 | Na | $C_6H_6$ | 555 |
| | $Br(CH_2)_2Br$ | $Br(CH_2)_2C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 172 |
| | $C_3$ | | | | | |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $(CH_3)_2CClNO_2$ | $(CH_3)_2C(NO_2)C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 45 | Na | Ether | 556 |
| | $C_4$ | | | | | |
| | $i$-$C_4H_9Br$ | $(i$-$C_4H_9)_2C(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 642 |
| | $i$-$C_4H_9Br$ | $(i$-$C_4H_9)_2C(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $C_5$ | | | | | |
| | $n$-$C_4H_9SCH_2Cl$ | $n$-$C_4H_9SCH_2C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125, 893 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 73 | $NaOC_2H_5$ | Ethanol | 657 |
| | $CH_2$=$CHCH_2SCH(CH_3)Cl$ | $CH_2$=$CHCH_2SCH(CH_3)$-$C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126, 899 |
| | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 21 | $NaOC_2H_5$ | Ethanol | 223 |
| | 2-Chloromethylthiophene | Diethyl $i$-butyl-(2-thenyl)malonate | — | Na | None | 897 |
| | $C_6$ | | | | | |
| | $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 10 | $NaOC_2H_5$ | Ethanol | 223 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 13 | $NaOC_2H_5$ | Ethanol | 223 |
| | $C_7$-$C_{12}$ | | | | | |
| | $i$-$C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7$-$i)C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 223 |
| | $n$-$C_{10}H_{21}X$‡ | $n$-$C_{10}H_{21}C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | $n$-$C_{12}H_{25}X$‡ | $n$-$C_{12}H_{25}C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| $ClCH_2C(CH_3)CH_2$ | None | Diethyl 3-methylcyclobutane-1,1-dicarboxylate | 83 | $NaOC_2H_5$ | Ethanol | 482, 481 |
| $sec$-$C_4H_9$ | $C_2$ | | | | | |
| | $C_2H_5Br$ | $C_2H_5C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 148 |
| | $C_2H_5Br$ | $C_2H_5C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 95 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44, 51 227 |
| | $C_2H_5I$ | $C_2H_5C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 146 |
| | $(C_2H_5O)_2CO$ | $C_2H_5C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 330 |
| | $CH_3SCH_2Cl$ | $CH_3SCH_2C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_3$ | | | | | |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44, 51 |
| | $C_2H_5OCH(CH_3)Cl$ | $C_2H_5OCH(CH_3)C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 84 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $C_4$ | | | | | |
| | $sec$-$C_4H_9Br$ | $(sec$-$C_4H_9)_2C(CO_2C_2H_5)_2$ | 15 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $sec$-$C_4H_9Br$ | $(sec$-$C_4H_9)_2C(CO_2C_4H_9$-$sec)_2$§§ | 25 (59)§ | $NaOC_4H_9$-$sec$ | $(sec$-$C_4H_9O)_2CO$ | 44 |
| | $(sec$-$C_4H_9O)_2CO$ | $(sec$-$C_4H_9)_2C(CO_2C_4H_9$-$sec)_2$§§ | Poor | $NaOC_4H_9$-$sec$ | $(sec$-$C_4H_9O)_2CO$ | 330 |
| | $C_5$ | | | | | |
| | $n$-$C_5H_{11}Br$ | $n$-$C_5H_{11}C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 84 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $n$-$C_4H_9SCH_2Cl$ | $n$-$C_4H_9SCH_2C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 447 |
| $t$-$C_4H_9$ | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2C(C_4H_9$-$t)(CO_2C_2H_5)_2$ | 36 (53)§ | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| $CH_3CCl$=$CHCH_2$ | $C_2H_5X$‡ | $CH_3CCl$=$CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 561 |
| | $CH_3CCl$=$CHCH_2Cl$ | $(CH_3CCl$=$CHCH_2)_2C(CO_2C_2H_5)_2$ | 80 | — | — | 561 |
| | $i$-$C_5H_{11}X$‡ | $CH_3CCl$=$CHCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | — | — | 561 |
| $CH_2$=$C(CH_3)CH_2$ | $CH_3SCH_2Cl$ | $CH_2$=$C(CH_3)CH_2C(CH_2SCH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5SCH_2Cl$ | $CH_2$=$C(CH_3)CH_2C(CH_2SC_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $n$-$C_3H_7X$‡ | $CH_2$=$C(CH_3)CH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 552 |
| | $i$-$C_3H_7X$‡ | $CH_2$=$C(CH_3)CH_2C(C_3H_7$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 552 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

§§ Di-*sec*-butyl *sec*-butylmalonate was used in this experiment.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO$_2$R)$_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| CH$_2$=C(CH$_3$)CH$_2$ (Cont.) | CH$_2$=CHCH$_2$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ \| CH$_2$CH=CH$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | *C$_4$* | | | | | |
| | n-C$_4$H$_9$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_4$H$_9$-n)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | sec-C$_4$H$_9$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_4$H$_9$-sec)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | i-C$_4$H$_9$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_4$H$_9$-i)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | CH$_2$=C(CH$_3$)CH$_2$X‡ | [CH$_2$=C(CH$_3$)CH$_2$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | *C$_5$* | | | | | |
| | n-C$_5$H$_{11}$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_5$H$_{11}$-n)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | n-C$_3$H$_7$CH(CH$_3$)X‡ | CH$_2$=C(CH$_3$)CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ \| CH(CH$_3$)C$_3$H$_7$-n | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | C$_2$H$_5$CH(CH$_3$)CH$_2$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ \| CH$_2$CH(CH$_3$)C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | i-C$_5$H$_{11}$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_5$H$_{11}$-i)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | CH$_2$=CHCH$_2$SCH(CH$_3$)Cl | CH$_2$=C(CH$_3$)CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ \| CH$_3$CHSCH$_2$CH=CH$_2$ | 70–90 | NaOC$_2$H$_5$ | Toluene | 126 |
| | 2-Chloromethylthiophene | CH$_2$=C(CH$_3$)CH$_2$C(CH$_2$C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 897 |
| | *C$_6$* | | | | | |
| | n-C$_6$H$_{13}$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(C$_6$H$_{13}$-n)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |
| | (C$_2$H$_5$)$_2$CHCH$_2$X‡ | CH$_2$=C(CH$_3$)CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ \| CH$_2$CH(C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 552 |

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| CH$_2$>CHCH$_2$ (cyclopropylmethyl) CH$_2$ (=C$_4$H$_7$) | *C$_5$–C$_{14}$* | | | | | |
| | n-C$_5$H$_{11}$Br | n-C$_5$H$_{11}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_6$H$_{13}$Br | n-C$_6$H$_{13}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_7$H$_{15}$Br | n-C$_7$H$_{15}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_8$H$_{17}$Br | n-C$_8$H$_{17}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_9$H$_{19}$Br | n-C$_9$H$_{19}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_{10}$H$_{21}$Br | n-C$_{10}$H$_{21}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_{11}$H$_{23}$Br | n-C$_{11}$H$_{23}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_{12}$H$_{25}$Br | n-C$_{12}$H$_{25}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| | n-C$_{14}$H$_{29}$Br | n-C$_{14}$H$_{29}$C(C$_4$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 60–66 | NaOC$_2$H$_5$ | Ethanol | 649 |
| C$_2$H$_5$O$_2$CCH$_2$ | *C$_1$–C$_7$* | | | | | |
| | CH$_3$I | C$_2$H$_5$O$_2$CCH$_2$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 161 |
| | C$_2$H$_5$I | C$_2$H$_5$O$_2$CCH$_2$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 161 |
| | n-C$_3$H$_7$I | C$_2$H$_5$O$_2$CCH$_2$C(C$_3$H$_7$-n)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 921 |
| | ClCH$_2$CO$_2$C$_2$H$_5$ | (C$_2$H$_5$O$_2$CCH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 922 |
| | C$_6$H$_5$CH$_2$Cl | C$_2$H$_5$O$_2$CCH$_2$C(CH$_2$C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 923 |
| 2-furyl (ring) | C$_2$H$_5$I | Dimethyl ethyl-(2-furyl)malonate* | 88 | NaOCH$_3$ | Methanol | 379 |
| 2-Thienyl (=C$_4$H$_3$S) | n-C$_3$H$_7$Br | n-C$_3$H$_7$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 74 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 78 | NaOC$_2$H$_5$ | Ethanol | 924 |
| | n-C$_4$H$_9$Br | n-C$_4$H$_9$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 70 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | i-C$_4$H$_9$Br | i-C$_4$H$_9$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 37 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | CH$_2$=C(CH$_3$)CH$_2$Cl | CH$_2$=C(CH$_3$)CH$_2$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 53 | NaOC$_2$H$_5$ | Ethanol | 924 |
| | n-C$_5$H$_{11}$Br | n-C$_5$H$_{11}$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 77 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | Cyclopentyl bromide | Diethyl cyclopentyl-(2-thienyl)malonate | 66 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenyl-(2-thienyl)-malonate | 76 | NaOC$_2$H$_5$ | Ethanol | 924 |
| | 2-Chloromethylthiophene | Diethyl 2-thienyl-(2-thenyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| | n-C$_6$H$_{13}$Br | n-C$_6$H$_{13}$C(C$_4$H$_3$S)(CO$_2$C$_2$H$_5$)$_2$ | 74 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | Cyclohexyl bromide | Diethyl cyclohexyl-(2-thienyl)malonate | 51 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 924 |
| | 2-Cyclohexenyl bromide | Diethyl 2-cyclohexenyl-(2-thienyl)malonate | 82 | NaOC$_2$H$_5$ | Ethanol | 924 |

*Note:* References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.
‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_5$ | $C_2$ | | | | | |
| $n$-$C_5H_{11}$ | $C_2H_5Br$ | $n$-$C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 40 | $NaOC_2H_5$ | Ethanol | 148 |
| | $BrCH_2CH_2Br$ | $(CH_2)_2C(C_5H_{11}$-$n)CO_2C_2H_5$ <br> $\|$ $\|$ <br> $O$——$CO$ | — | Na | $C_6H_5$ | 555 |
| | $C_3$ | | | | | |
| | $CH_3SCH(CH_3)Cl$ | $CH_3SCH(CH_3)C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545. 743 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | Na | — | 656 |
| | $C_4$ | | | | | |
| | $C_2H_5SCH(CH_3)Cl$ | $C_2H_5SCH(CH_3)C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 126 |
| | $i$-$C_4H_9Br$ | $n$-$C_5H_{11}C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $C_5$-$C_7$ | | | | | |
| | $n$-$C_5H_{11}Br$ | $(C_5H_{11}$-$n)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 641 |
| | $n$-$C_6H_{13}Br$ | $n$-$C_6H_{13}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 641 |
| | $n$-$C_7H_{15}Br$ | $n$-$C_7H_{15}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 641 |
| | $CH_3CHBr(CH_2)_2CO_2C_2H_5$ | None | — | $NaOC_2H_5$ | Ethanol | 720 |
| | $C_8$-$C_{16}$ | | | | | |
| | $n$-$C_8H_{17}X\ddagger$ | $n$-$C_8H_{17}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl $n$-amyl-($\beta$-cyclohexylethyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $\gamma$-Cyclohexylpropyl bromide | Diethyl $n$-amyl-($\gamma$-cyclohexylpropyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $n$-$C_9H_{19}Br$ | $n$-$C_9H_{19}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $\delta$-Cyclohexylbutyl bromide | Diethyl $n$-amyl-($\delta$-cyclohexylbutyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 902 |
| | $n$-$C_{10}H_{21}X\ddagger$ | $n$-$C_{10}H_{21}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | $n$-$C_{11}H_{23}X\ddagger$ | $n$-$C_{11}H_{23}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $n$-Undecenyl bromide | Diethyl $n$-amyl-($n$-undeceuyl)malonate | — | $NaOC_2H_5$ | Ethanol | 920 |
| | $n$-$C_{12}H_{25}X\ddagger$ | $n$-$C_{12}H_{25}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 887 |
| | $n$-$C_{16}H_{33}I$ | $n$-$C_{16}H_{33}C(C_5H_{11}$-$n)(CO_2C_2H_5)_2$ | 81 | $NaOC_2H_5$ | Ethanol | 135 |
| $i$-$C_5H_{11}$ | $C_2$ | | | | | |
| | $C_2H_5Br$ | $i$-$C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 532 |
| | $C_2H_5X\ddagger$ | $i$-$C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 78 | $NaOC_4H_9$-$t$ | $t$-$C_4H_9OH$ | 35 |
| | $(C_2H_5O)_2CO$ | $i$-$C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 45 (60) § | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 890 |
| | $Cl(CH_2)_2I$ | $Cl(CH_2)_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 316 |
| | $Br(CH_2)_2Br$ | $(CH_2)_2C(C_5H_{11}$-$i)CO_2C_2H_5$ <br> $\|$ $\|$ <br> $O$——$CO$ | 85–90 | Na | $C_6H_6$ | 555, 316 |
| | $Br(CH_2)_2Br$ | $Br(CH_2)_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 172 |
| | $BrCH{=}CHBr$ | $BrCH{=}CHC(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 38 | $NaNH_2$ | Ether-ethanol | 277 |
| | $CH_2$——$CH_2$ <br> $\diagdown O \diagup$ | $(CH_2)_2C(C_5H_{11}$-$i)$ <br> $\|$ $\|$ <br> $O$——$CO$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $C_3$ | | | | | |
| | $n$-$C_3H_7Br$ | $i$-$C_5H_{11}C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 718 |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $(CH_3)_2CClNO_2$ | $(CH_3)_2C(NO_2)C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 48 | Na | Ether | 556 |
| | $HC{\equiv}CCH_2Br$ | $HC{\equiv}CCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 547 |
| | $Br(CH_2)_3Br$ | $Br(CH_2)_3C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 43 | Na | $C_6H_6$ | 537 |
| | $C_4$ | | | | | |
| | $C_2H_5S(CH_2)_2Cl$ | $C_2H_5S(CH_2)_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 70–90 | $NaOC_2H_5$ | Toluene | 553 |
| | $C_2H_5OCH(CH_3)Cl$ | $C_2H_5OCH(CH_3)C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 63 | $NaNH_2$ | $C_6H_6$-ether | 203 |
| | $i$-$C_4H_9Br$ | $i$-$C_5H_{11}C(C_4H_9$-$i)(CO_2C_2H_5)_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $CH_3CCl{=}CHCH_2Cl$ | $CH_3CCl{=}CHCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 916 |
| | $CH_2{=}CHCH$——$CH_2$ <br> $\diagdown O \diagup$ | $CH_2{=}CHCHCH_2C(C_5H_{11}$-$i)CO_2C_2H_5$ <br> $\|$ $\|$ <br> $O$——$CO$ | 72 | $NaOC_2H_5$ | Ethanol | 11 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | $C_5$–$C_8$ | | | | | |
| $i$-$C_5H_{11}$ (*Cont.*) | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 24 | $NaOC_2H_5$ | Ethanol | 223 |
| | 2-Chloromethylthiophene | $C_4H_3SCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | Na | None | 897 |
| | $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 9 | $NaOC_2H_5$ | Ethanol | 223 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | 14 | $NaOC_2H_5$ | Ethanol | 223 |
| | $i$-$C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7$-$i)C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 223 |
| | $H_5C_6CH\!\!-\!\!CH_2$ $\diagdown O \diagup$ | $C_6H_5CHCH_2C(C_5H_{11}$-$i)CO_2C_2H_5$ $O\!\!-\!\!-\!\!CO$ | 65 | $NaOC_2H_5$ | Ethanol | 11 |
| $n$-$C_3H_7CH(CH_3)$ | $C_6H_5COCH_2Br$ | $C_6H_5COCH_2C(C_5H_{11}$-$i)(CO_2C_2H_5)_2$ | — | Na | Ether | 658 |
| | $CH_3SCH_2Cl$ | $CH_3SCH_2C[CH(CH_3)C_3H_7$-$n](CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C[CH(CH_3)C_3H_7$-$n](CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | $CH_2\!=\!CHCH_2SCH_2Cl$ | $CH_2\!=\!CHCH_2SCH_2C(CO_2C_2H_5)_2$ $CH(CH_3)C_3H_7$-$n$ | — | $NaOC_2H_5$ | Toluene | 125 |
| | 2-Chloromethylthiophene | $C_4H_3SCH_2C[CH(CH_3)C_3H_7$-$n](CO_2C_2H_5)_2$ | — | Na | None | 897 |
| | 2-Chlorotetrahydropyran | Diethyl 2-tetrahydropyranyl-(1-methylbutyl)malonate | — | NaH | Toluene | 683 |
| | $C_3$–$C_{12}$ | | | | | |
| $C_2H_5CH(CH_3)CH_2$ | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(CO_2C_2H_5)_2$ $CH_2CH(CH_3)C_2H_5$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $n$-$C_{10}H_{21}X\ddagger$ | $C_2H_5CH(CH_3)CH_2C(C_{10}H_{21}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $n$-$C_{12}H_{25}X\ddagger$ | $C_2H_5CH(CH_3)CH_2C(CO_2C_2H_5)_2$ $C_{12}H_{25}$-$n$ | — | $NaOC_2H_5$ | Ethanol | 888 |
| | $C_2$–$C_7$ | | | | | |
| $(CH_3)_2C\!=\!CHCH_2$ | $C_2H_5X\ddagger$ | $(CH_3)_2C\!=\!CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $n$-$C_3H_7X\ddagger$ | $(CH_3)_2C\!=\!CHCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $i$-$C_3H_7Br$ | $(CH_3)_2C\!=\!CHCH_2C(C_3H_7$-$i)(CO_2C_2H_5)_2$ | Poor | $NaOC_2H_5$ | Ethanol | 912 |
| | $CH_2\!=\!CHCH_2Br$ | $(CH_3)_2C\!=\!CHCH_2C(CO_2C_2H_5)_2$ $CH_2CH\!=\!CH_2$ | 71 | $NaOC_2H_5$ | Ethanol | 912 |
| | $n$-$C_4H_9X\ddagger$ | $(CH_3)_2C\!=\!CHCH_2C(C_4H_9$-$n)(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $sec$-$C_4H_9X\ddagger$ | $(CH_3)_2C\!=\!CHCH_2C(C_4H_9$-$sec)(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $(CH_3)_2C\!=\!CHCH_2Br$ | $[(CH_3)_2C\!=\!CHCH_2]_2C(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | Not stated | $(CH_3)_2C\!=\!CHCH_2(C_6H_{11}$-$cyclo)(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $C_6H_5CH_2X\ddagger$ | $(CH_3)_2C\!=\!CHCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| $(CH_2)_2CO_2C_2H_5$ | $Br(CH_2)_2CO_2C_2H_5$ | $(C_2H_5O_2CCH_2CH_2)_2C(CO_2C_2H_5)_2$ | 14 | $NaOC_2H_5$ | Ethanol | 670 |
| | $BrCH_2CHCH_2CO_2C_2H_5$ $CO_2C_2H_5$ | $C_2H_5O_2CCH_2CH(CO_2C_2H_5)CH_2C$-$(CO_2C_2H_5)_2(CH_2)_2CO_2C_2H_5$ | 55 | $NaOC_2H_5$ | Ethanol | 671 |
| $CH(CH_3)CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | — | Na | None | 161 |
| | $C_2H_5I$ | $C_2H_5O_2CCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | None | 162 |
| | $C_6H_5CH_2Cl$ | $C_2H_5O_2CCH(CH_3)C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | Na | None | 923 |
| | $C_5$–$C_{11}$ | | | | | |
| Cyclopentyl(=$C_5H_9$) | $C_2H_5Br$ | $C_5H_9C(C_2H_5)(CO_2C_2H_5)_2$ | 48 | $NaOC_2H_5$ | Ethanol | 148 |
| | $n$-$C_7H_{15}Br$ | $n$-$C_7H_{15}C(C_5H_9)(CO_2C_2H_5)_2$ | 50–60 | Na | $C_6H_6$ | 725 |
| | $n$-$C_8H_{17}Br$ | $n$-$C_8H_{17}C(C_5H_9)(CO_2C_2H_5)_2$ | 50–60 | Na | $C_6H_6$ | 725 |
| | $n$-$C_9H_{19}Br$ | $n$-$C_9H_{19}C(C_5H_9)(CO_2C_2H_5)_2$ | 50–60 | Na | $C_6H_6$ | 725 |
| | $n$-$C_{10}H_{21}Br$ | $n$-$C_{10}H_{21}C(C_5H_9)(CO_2C_2H_5)_2$ | 50–60 | Na | $C_6H_6$ | 725 |
| | Geranyl bromide | Diethyl cyclopentyl(geranyl)malonate | 25 | $NaOC_2H_5$ | Ethanol | 31 |
| | $n$-$C_{11}H_{23}Br$ | $n$-$C_{11}H_{23}C(C_5H_9)(CO_2C_2H_5)_2$ | 50–60 | Na | $C_6H_6$ | 725 |
| | $C_2$–$C_5$ | | | | | |
| 2-Cyclopentenyl (=$C_5H_7$) | $C_2H_5Br$ | $C_5H_7C(C_2H_5)(CO_2H)_2$ | 30 | Na | Toluene | 151 |
| | $n$-$C_3H_7Br$ | $C_5H_7C(C_3H_7$-$n)(CO_2H)_2$ | 26 | Na | Toluene | 151 |
| | $i$-$C_3H_7Br$ | $C_5H_7C(C_3H_7$-$i)(CO_2H)_2$ | 8 | Na | Toluene | 151 |
| | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(C_5H_7)(CO_2H)_2$ | 32 | Na | Toluene | 151 |
| | $n$-$C_4H_9Br$ | $n$-$C_4H_9C(C_5H_7)(CO_2H)_2$ | 35 | Na | Toluene | 151 |
| | $n$-$C_5H_{11}Br$ | $n$-$C_5H_{11}C(C_5H_7)(CO_2C_2H_5)_2$ | 37 | $NaOC_2H_5$ | Ethanol | 680 |
| | 2-Cyclopentenyl chloride | $(C_5H_7)_2C(CO_2C_2H_5)_2$ | 50 | Na | Toluene | 151, 925, 926 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO$_2$R)$_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | $C_6$–$C_8$ | | | | | |
| 2-Cyclopentenyl | $n$-C$_6$H$_{13}$Br | $n$-C$_6$H$_{13}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 39 | NaOC$_2$H$_5$ | Ethanol | 680 |
| (=C$_5$H$_7$) (*Cont.*) | Br(CH$_2$)$_6$Br | {Br(CH$_2$)$_6$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 10 | Na | Xylene | 679 |
| | | (C$_2$H$_5$O$_2$C)$_2$C(CH$_2$)$_6$C(CO$_2$C$_2$H$_5$)$_2$ | 22 | | | |
| | | $\quad\quad\quad$ | $\quad\quad\quad$ | C$_5$H$_7$$\quad$C$_5$H$_7$ | | |
| | 1,2-Dibromocyclohexane | Diethyl 2-cyclohexenyl-(2-cyclopentenyl)-malonate | 53 | NaOC$_2$H$_5$ | Toluene | 927 |
| | $n$-C$_7$H$_{15}$Br | $n$-C$_7$H$_{15}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 35 | NaOC$_2$H$_5$ | Ethanol | 680 |
| | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 67 | Na | Toluene | 927 |
| | $n$-C$_8$H$_{17}$Br | $n$-C$_8$H$_{17}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 34 | NaOC$_2$H$_5$ | Ethanol | 680 |
| | $n$-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$Br | $n$-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 56 | Na | Xylene | 914 |
| | $C_9$–$C_{16}$ | | | | | |
| | $n$-C$_9$H$_{19}$Br | $n$-C$_9$H$_{19}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 42 | NaOC$_2$H$_5$ | Ethanol | 680 |
| | $n$-C$_{10}$H$_{21}$Br | $n$-C$_{10}$H$_{21}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 66–69 | NaOC$_2$H$_5$ | Ethanol | 928 |
| | Geranyl chloride | Diethyl geranyl-(2-cyclopentenyl)malonate | 30 | NaOC$_2$H$_5$ | Ethanol | 31 |
| | $n$-C$_{11}$H$_{23}$Br | $n$-C$_{11}$H$_{23}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 66–69 | NaOC$_2$H$_5$ | Ethanol | 928 |
| | $n$-C$_{12}$H$_{25}$Br | $n$-C$_{12}$H$_{25}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 66–69 | NaOC$_2$H$_5$ | Ethanol | 928 |
| | $n$-C$_{16}$H$_{33}$Br | $n$-C$_{16}$H$_{33}$C(C$_5$H$_7$)(CO$_2$C$_2$H$_5$)$_2$ | 64 | Na | Xylene | 679 |
| | Hydnocarpyl bromide-KI | Diethyl hydnocarpyl-(2-cyclopentenyl)-malonate | 36 | K | Toluene | 287 |
|  |  |  | 36 | NaOC$_2$H$_5$ | Ethanol | 682 |
|  | ClCH$_2$CO$_2$C$_2$H$_5$ |  | 40 | NaOC$_2$H$_5$ | Ethanol | 356 |

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| (=C$_5$H$_5$S) | $C_2$–$C_8$ | | | | | |
| | C$_2$H$_5$Br | C$_5$H$_5$SC(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 72 | NaOC$_2$H$_5$ | Ethanol | 358 |
| | 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenyl-(2-thenyl)-malonate | 54 | NaOC$_2$H$_5$ | Ethanol | 924 |
| | 2-Chloromethylthiophene | (C$_5$H$_5$S)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| | 2-Cyclohexenyl bromide | Diethyl 2-cyclohexenyl-(2-thenyl)malonate | 79 | NaOC$_2$H$_5$ | Ethanol | 924 |
| | $\beta$-2-(Thienyl)ethyl chloride | Diethyl[$\beta$-(2-thienyl)ethyl]-2-thenyl-malonate | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_5$H$_5$S)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl ($\beta$-cyclohexylethyl)-2-thenyl-malonate | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| $C_6$ $n$-C$_6$H$_{13}$ | $C_2$–$C_6$ | | | | | |
| | CH$_2$—CH$_2$ \ O / | (CH$_2$)$_2$C(C$_6$H$_{13}$-$n$)CO$_2$C$_2$H$_5$ \| \| O——CO | ca. 70 | NaOC$_2$H$_5$ | Ethanol | 282 |
| | C$_2$H$_5$SCH$_2$Cl | C$_2$H$_5$SCH$_2$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Toluene | 125 |
| | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 743 |
| | C$_6$H$_5$SCH(CH$_3$)Cl | C$_6$H$_5$SCH(CH$_3$)C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | 70–90 | NaOC$_2$H$_5$ | Toluene | 126 |
| | 2-Chloromethylthiophene | C$_4$H$_3$SCH$_2$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 897 |
| | $n$-C$_6$H$_{13}$Br | (C$_6$H$_{13}$-$n$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 641 |
| | $C_7$–$C_9$ | | | | | |
| | $n$-C$_7$H$_{15}$X‡ | $n$-C$_7$H$_{15}$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 887 |
| | $\beta$-Cyclopentylethyl bromide | Diethyl $n$-hexyl-($\beta$-cyclopentylethyl)-malonate | 50–60 | NaOC$_2$H$_5$ | Ethanol | 725 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl $n$-hexyl-[$\beta$-(2-cyclopentenyl)ethyl]-malonate | — | NaOC$_2$H$_5$ | Ethanol | 928 |
| | $n$-C$_8$H$_{17}$Br | $n$-C$_8$H$_{17}$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 888 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl $n$-hexyl-($\beta$-cyclohexylethyl)-malonate | — | NaOC$_2$H$_5$ | Ethanol | 902 |
| | $n$-C$_9$H$_{19}$X‡ | $n$-C$_9$H$_{19}$C(C$_6$H$_{13}$-$n$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 887 |
| | $\gamma$-Cyclohexylpropyl bromide | Diethyl $n$-hexyl-($\gamma$-cyclohexylpropyl)-malonate | — | NaOC$_2$H$_5$ | Ethanol | 902 |

*Note:* References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | $C_{10}-C_{18}$ | | | | | |
| $n$-C₆H₁₃ (*Cont.*) | $n$-C₁₀H₂₁I | $n$-C₁₀H₂₁C(C₆H₁₃-$n$)(CO₂C₂H₅)₂ | 70 | Na | Toluene | 906, 888 |
| | δ-Cyclohexylbutyl bromide | Diethyl $n$-hexyl-(δ-cyclohexylbutyl)-malonate | — | NaOC₂H₅ | Ethanol | 902 |
| | $n$-Undecenyl bromide | Diethyl $n$-hexyl-($n$-undecenyl)malonate | — | NaOC₂H₅ | Ethanol | 920 |
| | $n$-C₁₆H₃₃I | $n$-C₁₆H₃₃C(C₆H₁₃-$n$)(CO₂C₂H₅)₂ | 84 | NaOC₂H₅ | Ethanol | 135 |
| | $n$-C₁₈H₃₇I | $n$-C₁₈H₃₇C(C₆H₁₃-$n$)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 684 |
| CH₃CHBr(CH₂)₄ | None | Diethyl 2-methylcyclohexane-1,1-dicarboxylate | 45 | NaOC₂H₅ | Ethanol | 210 |
| C₂H₅O(CH₂)₄ | C₂H₅O(CH₂)₄Br | [C₂H₅O(CH₂)₄]₂C(CO₂C₂H₅)₂ | 78 | NaOC₂H₅ | Ethanol | 646 |
| $n$-C₃H₇CH(CH₃) | CH₂=CHCH₂Br | $n$-C₃H₇CH(CH₃)C(CH₂CH=CH₂)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 551 |
| Br(CH₂)₄CH(CH₃) | None | Diethyl 2-methylcyclohexane-1,1-dicarboxylate | 72 | NaOC₂H₅ | Ethanol | 210 |
| 3-Hexyl | CH₃X‡ | Diethyl methyl-(3-hexyl)malonate | 62 | NaOC₄H₉-$t$ | $t$-C₄H₉OH | 35 |
| | C₂H₅X‡ | Diethyl ethyl-(3-hexyl)malonate | 76 | NaOC₄H₉-$t$ | $t$-C₄H₉OH | 35 |
| $n$-C₃H₇CH(CH₃)CH₂ | Br(CH₂)₃Br | CH₂CH₂C[CH₂CH(CH₃)C₃H₇-$n$]CO₂C₂H₅  \|       \|  O———CO | 85 | Na | C₆H₆ | 555 |
| $i$-C₄H₉CH(CH₃) | 2-Chloromethylthiophene | $i$-C₄H₉CH(CH₃)C(CH₂C₄H₃S)(CO₂C₂H₅)₂ | — | Na | None | 897 |
| | $C_1-C_3$ | | | | | |
| (C₂H₅)₂CHCH₂ | CH₃Br | (C₂H₅)₂CHCH₂C(CH₃)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | C₂H₅Br | (C₂H₅)₂CHCH₂C(C₂H₅)(CO₂C₂H₅)₂ | 77 | NaOC₂H₅ | Ethanol | 688, 687 |
| | Br(CH₂)₃Br | CH₂CH₂C[CH₂CH(C₂H₅)₂]CO₂C₂H₅  \|       \|  O———CO | 91 | Na | C₆H₆ | 555 |
| | CH₂—CH₂ (epoxide, O) | CH₂CH₂C[CH₂CH(C₂H₅)₂]CO₂C₂H₅  \|       \|  O———CO | ca. 70 | NaOC₂H₅ | Ethanol | 282 |
| | $n$-C₃H₇Br | (C₂H₅)₂CHCH₂C(C₃H₇-$n$)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | $i$-C₃H₇Br | (C₂H₅)₂CHCH₂C(C₃H₇-$i$)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | CH₂=CHCH₂Br | (C₂H₅)₂CHCH₂C(CH₂CH=CH₂)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | HC≡CCH₂Br | (C₂H₅)₂CHCH₂C(CH₂C≡CH)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | CH₂=CBrCH₂Br | (C₂H₅)₂CHCH₂C(CH₂CBr=CH₂)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | $C_4-C_6$ | | | | | |
| | $n$-C₄H₉Br | (C₂H₅)₂CHCH₂C(C₄H₉-$n$)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | $i$-C₄H₉Br | (C₂H₅)₂CHCH₂C(C₄H₉-$i$)(CO₂C₂H₅)₂ | — | — | — | 687 |
| | (C₂H₅)₂CHCH₂Br | [(C₂H₅)₂CHCH₂]₂C(CO₂C₂H₅)₂ | — | — | — | 687 |
| | 1,2-Dibromocyclohexane | Diethyl 2-cyclohexenyl-(2-ethylbutyl)-malonate | — | — | — | 687 |
| *cis*-C₂H₅CH=CHCH(CH₃) | CH₂=CHCH₂Br | *cis*-C₂H₅CH=CHCH(CH₃)-C(CH₂CH=CH₂)(CO₂C₂H₅)₂ | 77 | Na | — | 693 |
| | $C_1-C_7$ | | | | | |
| C₂H₅O₂CCH(C₂H₅) | CH₃I | C₂H₅O₂CCH(C₂H₅)C(CH₃)(CO₂C₂H₅)₂ | — | Na | None | 162 |
| | C₂H₅I | C₂H₅O₂CCH(C₂H₅)C(C₂H₅)(CO₂C₂H₅)₂ | — | Na | None | 162 |
| | C₆H₅CH₂Cl | C₆H₅O₂CCH(C₂H₅)C(CH₂C₆H₅)(CO₂C₂H₅)₂ | — | Na | None | 162 |
| | $C_1-C_7$ | | | | | |
| C₂H₅O₂CC(CH₃)₂ | CH₃I | C₂H₅O₂CC(CH₃)₂C(CH₃)(CO₂C₂H₅)₂ | — | Na | None | 162 |
| | C₆H₅CH₂Cl | C₂H₅O₂CC(CH₃)₂C(CH₂C₆H₅)(CO₂C₂H₅)₂ | — | Na | None | 162 |
| (thiophene)(CH₂)₂ | (thiophene)CH₂Cl | C₄H₃S(CH₂)₂C(CH₂SC₄H₃)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 50, 708 |
| | $C_2-C_6$ | | | | | |
| Cyclohexyl(=C₆H₁₁) | C₂H₅X‡ | C₆H₁₁C(C₂H₅)(CO₂C₂H₅)₂ | 58 | NaOC₄H₉-$t$ | $t$-C₄H₉OH | 35 |
| | CH₂=CHCH₂Br | CH₂=CHCH₂C(C₆H₁₁)(CO₂C₂H₅)₂ | — | — | — | 743 |
| | $n$-C₄H₉Br | $n$-C₄H₉C(C₆H₁₁)(CO₂C₂H₅)₂ | Poor | — | — | 926 |
| | $n$-C₅H₁₁Br | $n$-C₅H₁₁C(C₆H₁₁)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 32 |
| | 2-Chloromethylthiophene | C₄H₃SCH₂C(C₆H₁₁)(CO₂C₂H₅)₂ | 68 | NaOC₂H₅ | (C₂H₅O)₂CO | 50, 709 |
| | $n$-C₆H₁₃Br | $n$-C₆H₁₃C(C₆H₁₁)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 32 |
| | Cyclohexyl bromide | (C₆H₁₁)₂C(CO₂C₂H₅)₂ | — | Na | Toluene | 147 |
| | Cyclohexyl bromide | None | — | NaOC₂H₅ | Ethanol | 149 |
| | $C_7-C_{12}$ | | | | | |
| | $n$-C₇H₁₅Br | $n$-C₇H₁₅C(C₆H₁₁)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 32 |
| | (CH₃)₃CC(CH₃)₂Cl | (C₂H₅O₂C)C(C₆H₁₁)C(C₆H₁₁)(CO₂C₂H₅)₂ | 15 | NaOC₂H₅ | Ethanol | 719 |
| | $n$-C₈H₁₇Br | $n$-C₈H₁₇C(C₆H₁₁)(CO₂C₂H₅)₂ | — | NaOC₂H₅ | Ethanol | 32 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

# TABLE III—*Continued*

## ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO$_2$R)$_2$

### (The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Cyclohexyl(=C$_6$H$_{11}$) (*Cont.*) | β-Cyclohexylethyl bromide | Diethyl cyclohexyl-(β-cyclohexylethyl)-malonate | — | NaOC$_2$H$_5$ | Ethanol | 929 |
| | n-C$_9$H$_{19}$Br | n-C$_9$H$_{19}$C(C$_6$H$_{11}$)(CO$_2$C$_2$H$_5$)$_2$ | 45 | Na | Xylene | 31 |
| | n-C$_9$H$_{19}$Br | n-C$_9$H$_{19}$C(C$_6$H$_{11}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
| | n-C$_{10}$H$_{21}$Br | n-C$_{10}$H$_{21}$C(C$_6$H$_{11}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
| | Geranyl chloride | Diethyl cyclohexyl(geranyl)malonate | — | Na | Toluene | 930 |
| | n-C$_{11}$H$_{23}$Br | n-C$_{11}$H$_{23}$C(C$_6$H$_{11}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
| | n-C$_{12}$H$_{25}$Br | n-C$_{12}$H$_{25}$C(C$_6$H$_{11}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
| 1-Cyclohexenyl (=C$_6$H$_9$) | C$_2$H$_5$SCH$_2$Cl | C$_2$H$_5$SCH$_2$C(C$_6$H$_9$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Toluene | 125 |
| | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_6$H$_9$)(CO$_2$C$_2$H$_5$)$_2$ | 46 | NaOC$_2$H$_5$ | Ethanol | 215 |
| | 2-Chloromethylthiophene | C$_4$H$_3$SCH$_2$C(C$_6$H$_9$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 897 |
| 2-Cyclohexenyl | Hydnocarpyl bromide-KI | Diethyl hydnocarpyl-(2-cyclohexenyl)-malonate | 58 | K | Toluene | 287 |
| Phenyl | C$_1$ | | | | | |
| | CH$_3$I | C$_6$H$_5$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 96‖‖ | NaOC$_2$H$_5$ | Ethanol | 169 |
| | CH$_3$I | C$_6$H$_5$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Ethanol | 182 |
| | C$_2$ | | | | | |
| | C$_2$H$_5$Cl | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 81 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 51 |
| | C$_2$H$_5$Br | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 97‖‖ | NaOC$_2$H$_5$ | Ethanol | 42, 755 |
| | C$_2$H$_5$Br | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 84 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 51, 44, 227 |
| | C$_2$H$_5$I | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$CH$_3$)$_2$* | 76 | NaOCH$_3$ | CH$_3$OH | 375 |
| | C$_2$H$_5$I | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 61 | NaOC$_2$H$_5$ | Ethanol | 331, 571 |
| | C$_2$H$_5$I | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | ·90 | Mg(OC$_2$H$_5$)$_2$ | (C$_2$H$_5$O)$_2$CO | 51, 44 |
| | (C$_2$H$_5$O)$_2$CO | C$_6$H$_5$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 30 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 330, 890 |
| | Br(CH$_2$)$_2$Br | Br(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 59 | NaH | Toluene | 931 |
| | Br(CH$_2$)$_2$Br | None | 0 | NaOC$_2$H$_5$ | Ethanol | 92 |
| | I(CH$_2$)$_2$I | (C$_2$H$_5$O$_2$)$_2$C(C$_6$H$_5$)C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 26 | NaOC$_2$H$_5$ | Ethanol | 92 |
| | CH$_2$——CH$_2$   O | CH$_2$CH$_2$C(C$_6$H$_5$)CO$_2$C$_2$H$_5$   O———CO | ca. 70 | NaOC$_2$H$_5$ | Ethanol | 282 |

| | C$_3$ | | | | | |
|---|---|---|---|---|---|---|
| | C$_2$H$_5$SCH$_2$Cl | C$_2$H$_5$SCH$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 48 | Na | Ether | 205 |
| | C$_2$H$_5$SCH$_2$Cl | C$_2$H$_5$SCH$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Toluene | 125 |
| | CH$_2$=CHCH$_2$I | CH$_2$=CHCH$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 79 |
| | Cl(CH$_2$)$_2$CN | NC(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 32 | NaOC$_2$H$_5$ | Ethanol | 932 |
| | Br(CH$_2$)$_3$Br | Br(CH$_2$)$_3$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 129 |
| | I(CH$_2$)$_3$I | None | — | NaOC$_2$H$_5$ | Ethanol | 92 |
| | C$_4$ | | | | | |
| | n-C$_4$H$_9$Br | n-C$_4$H$_9$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 58 | NaOC$_2$H$_5$ | Ethanol | 142 |
| | CH$_2$=CHO(CH$_2$)$_2$Cl | CH$_2$=CHO(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 52 | Na | Ether | 331 |
| | C$_2$H$_5$S(CH$_2$)$_2$Cl | C$_2$H$_5$S(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 70–90 | NaOC$_2$H$_5$ | Toluene | 553 |
| | I(CH$_2$)$_3$CN | NC(CH$_2$)$_3$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | >43 | Na | Toluene | 92 |
| | C$_5$–C$_8$ | | | | | |
| | 2-Chloromethylthiophene | Diethyl phenyl-(2-thenyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 50 |
| | 2-Chlorotetrahydropyran | Diethyl phenyl-(2-tetrahydropyranyl)malonate | — | NaH | Toluene | 683 |
| | Br(CH$_2$)$_6$Br | (C$_2$H$_5$O$_2$C)$_2$C(CH$_2$)$_6$C(CO$_2$C$_2$H$_5$)$_2$    C$_6$H$_5$   C$_6$H$_5$ | — | Na | Xylene | 679 |
| | 2-Cyclohexenyl bromide | Diethyl phenyl-(2-cyclohexenyl)malonate | 55 | KOCH$_3$ | C$_6$H$_6$ | 534 |
| | 1,2-Dibromocyclohexane | Diethyl phenyl-(2-cyclohexenyl)malonate | 55 | NaOC$_2$H$_5$ | Ethanol | 911, 933 |
| | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 55 | NaOC$_2$H$_5$ | Ethanol | 182 |
| | C$_6$H$_5$CH(CH$_3$)I | C$_6$H$_5$CH(CH$_3$)C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 934 |
| | C$_6$H$_5$O(CH$_2$)$_2$Cl | C$_6$H$_5$O(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 374 |
| | C$_9$–C$_{16}$ | | | | | |
| | C$_6$H$_5$CH(C$_2$H$_5$)I | C$_6$H$_5$CH(C$_2$H$_5$)C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 934 |
| | I(CH$_2$)$_3$CH(CO$_2$C$_2$H$_5$)$_2$ | (C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_3$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 91 | Na | Toluene | 92 |
| | p-t-C$_4$H$_9$C$_6$H$_4$(CH$_2$)$_2$Br | p-t-C$_4$H$_9$C$_6$H$_4$(CH$_2$)$_2$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 46 | Na | Toluene | 321 |
| | I(CH$_2$)$_{10}$CO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$C(CH$_2$)$_{10}$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | Toluene | 92 |
| | β-(p-Cyclohexylphenyl)ethyl bromide | Diethyl phenyl-[β-(p-cyclohexylphenyl)ethyl]malonate | 44 | Na | Xylene | 935 |
| | n-C$_{16}$H$_{33}$Br | n-C$_{16}$H$_{33}$C(C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 42 | Na | Xylene | 679 |

*Note:* References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

‖‖ The reactants were added in inverse order.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO$_2$R)$_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| *m*-Bromophenyl | C$_2$H$_5$I | *m*-BrC$_6$H$_4$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 036 |
| 2,4-Dinitrophenyl | *n*-C$_3$H$_7$Br | Diethyl *n*-propyl-(2,4-dinitrophenyl)-malonate | 20 | NaOC$_2$H$_5$ | Ethanol | 139 |
|  | 2,4-Dinitrobromobenzene | Ethyl bis-(2,4-dinitrophenyl)acetate | — | NaOC$_2$H$_5$ | Ethanol | 184 |
| C$_7$ | C$_2$–C$_3$ |  |  |  |  |  |
| *n*-C$_7$H$_{15}$ | C$_2$H$_5$Br | *n*-C$_7$H$_{15}$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 62 | NaOC$_2$H$_5$ | Ethanol | 148 |
|  | CH$_2$—CH$_2$ (O) | CH$_2$CH$_2$C(C$_7$H$_{15}$-*n*)CO$_2$C$_2$H$_5$ (O——CO) | ca. 70 | NaOC$_2$H$_5$ | Ethanol | 282 |
|  | *i*-C$_3$H$_7$Br | *n*-C$_7$H$_{15}$C(C$_3$H$_7$-*i*)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 641 |
|  | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 743 |
|  | Br(CH$_2$)$_3$Br | Br(CH$_2$)$_3$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 656 |
|  | C$_5$–C$_8$ |  |  |  |  |  |
|  | *n*-C$_7$H$_{15}$X‡ | (*n*-C$_7$H$_{15}$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 888 |
|  | β-Cyclopentylethyl bromide | Diethyl *n*-heptyl-(β-cyclopentylethyl)-malonate | 50–60 | NaOC$_2$H$_5$ | Ethanol | 725 |
|  | 2-Chloromethylthiophene | C$_4$H$_3$SCH$_2$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 897 |
|  | β-(2-Cyclopentenyl)ethyl bromide | Diethyl *n*-heptyl-[β-(2-cyclopentenyl)-ethyl]malonate | — | NaOC$_2$H$_5$ | Ethanol | 928 |
|  | *n*-C$_8$H$_{17}$X‡ | *n*-C$_8$H$_{17}$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 887 |
|  | β-Cyclohexylethyl bromide | Diethyl *n*-heptyl-(β-cyclohexylethyl)-malonate | — | NaOC$_2$H$_5$ | Ethanol | 902 |
|  | C$_9$–C$_{16}$ |  |  |  |  |  |
|  | *n*-C$_9$H$_{19}$X‡ | *n*-C$_9$H$_{19}$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 888 |
|  | γ-Cyclohexylpropyl bromide | Diethyl *n*-heptyl-(γ-cyclohexylpropyl)-malonate | — | NaOC$_2$H$_5$ | Ethanol | 902 |
|  | *n*-C$_{10}$H$_{21}$X‡ | *n*-C$_{10}$H$_{21}$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 887 |
|  | *n*-Undecenyl bromide | Diethyl *n*-heptyl-(*n*-undecenyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 920 |
|  | *n*-C$_{16}$H$_{33}$I | *n*-C$_{16}$H$_{33}$C(C$_7$H$_{15}$-*n*)(CO$_2$C$_2$H$_5$)$_2$ | 83 | NaOC$_2$H$_5$ | Ethanol | 135 |
|  | Hydnocarpyl chloride | Diethyl *n*-heptyl-(hydnocarpyl)malonate | 60 | K | Toluene | 291 |
| *i*-C$_7$H$_{15}$ | CH$_3$I | *i*-C$_7$H$_{15}$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 72 | NaOC$_2$H$_5$ | Ethanol | 718, 748 |
| *i*-C$_5$H$_{11}$CH(CH$_3$) | CH$_3$I | *i*-C$_5$H$_{11}$CH(CH$_3$)C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 50 | NaOC$_2$H$_5$ | Ethanol | 718 |
| *n*-C$_4$H$_9$CH(C$_2$H$_5$) | 2-Chloromethylthiophene | *n*-C$_4$H$_9$CH(C$_2$H$_5$)C(CH$_2$C$_4$H$_5$S)(CO$_2$C$_2$H$_5$)$_2$ | — | Na | None | 897 |
| C$_2$H$_5$O$_2$C(CH$_2$)$_2$CH(CH$_3$) | *n*-C$_5$H$_{11}$Br | C$_2$H$_5$O$_2$C(CH$_2$)$_2$CH(CH$_3$)C(CO$_2$C$_2$H$_5$)$_2$ (C$_5$H$_{11}$-*n*) | 20 | NaOC$_2$H$_5$ | Ethanol | 720 |
| C$_2$H$_5$O$_2$CCH$_2$C(CH$_3$)$_2$ | C$_6$H$_5$O(CH$_2$)$_3$Br | [C$_6$H$_5$O(CH$_2$)$_3$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 206 |
| β-Cyclopentylidene-ethyl | Not stated | Diethyl ethyl-[β-(cyclopentylidene)ethyl]-malonate | 70 | NaOC$_2$H$_5$ | (C$_2$H$_5$O)$_2$CO | 663 |
|  | C$_3$–C$_8$ |  |  |  |  |  |
| Cyclohexylmethyl (=C$_7$H$_{13}$) | C$_2$H$_5$Br | C$_2$H$_5$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | *n*-C$_3$H$_7$Br | *n*-C$_3$H$_7$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | *n*-C$_4$H$_9$Br | *n*-C$_4$H$_9$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | *n*-C$_5$H$_{11}$Br | *n*-C$_5$H$_{11}$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | 2-Chloromethylthiophene | Diethyl (cyclohexylmethyl)-2-thenylmalonate | — | NaOC$_2$H$_5$ | Ethanol | 50, 709 |
|  | *n*-C$_6$H$_{13}$Br | *n*-C$_6$H$_{13}$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | *n*-C$_7$H$_{15}$Br | *n*-C$_7$H$_{15}$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | *n*-C$_8$H$_{17}$Br | *n*-C$_8$H$_{17}$C(C$_7$H$_{13}$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 32 |
|  | β-Cyclohexylethyl bromide | Diethyl (cyclohexylmethyl)-(β-cyclohexylethyl)malonate | — | NaOC$_2$H$_2$ | Ethanol | 929 |
| 2-Methylcyclohexyl | 2-Methylcyclohexyl bromide | Diethyl di-(2-methylcyclohexyl)malonate | 10 | Na | Toluene | 147 |
|  | Oeranyl chloride | Diethyl geranyl-(2-methylcyclohexyl)-malonate | — | Na | Toluene | 147 |
| C$_2$H$_5$O$_2$CC(CH$_3$)=C(CH$_3$) | CH$_3$I | C$_2$H$_5$O$_2$CC(CH$_3$)=C(CH$_3$)C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 60 | NaOC$_2$H$_5$ | Ethanol | 937 |
|  | C$_1$ |  |  |  |  |  |
| C$_6$H$_5$CH$_2$ | CH$_3$I | C$_6$H$_5$CH$_2$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 80 | NaOC$_2$H$_5$ | C$_6$H$_6$ | 938 |
|  | CH$_3$I | C$_6$H$_5$CH$_2$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 63 | NaOC$_2$H$_5$ | Ethanol | 144, 615 939 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_6H_5CH_2$ (*Cont.*) | $CHCl_3$ | $(C_2H_5O_2C)_2C(CH_2C_6H_5)CHClC(CO_2C_2H_5)_2$ <br> $\|$ <br> $CH_2C_6H_5$ | — | Na | — | 231 |
| | $C_2$ | | | | | |
| | $C_2H_5Br$ | $C_6H_5CH_2C(C_2H_5)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 121, 144 411 |
| | $CH_3OCH_2Cl$ | $CH_3OCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 78 | Na | Ether | 940 |
| | $CH_3SCH_2Cl$ | $CH_3SCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 71 | $NaOC_3H_7$-$i$ | $i$-$C_3H_7OH$ | 205 |
| | $BrCH=CHBr$ | $BrCH=CHC(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 7 | K | Ether | 941 |
| | $CH_2{-}CH_2$ <br> $\diagdown O$ | $CH_2CH_2C(CH_2C_6H_5)CO_2C_2H_5$ <br> $\| \quad \|$ <br> $O{-}CO$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $C_3$ | | | | | |
| | $C_2H_5SCH_2Cl$ | $C_2H_5SCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 74 | Na | Ether | 205 |
| | $i$-$C_3H_7Br$ | $i$-$C_3H_7C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 23 | $NaOC_2H_5$ | Ethanol | 144 |
| | $Cl(CH_2)_3Br$ | $(C_2H_5O_2C)_2C(CH_2C_6H_5)(CH_2)_3C(CO_2C_2H_5)_2$ <br> $\|$ <br> $CH_2C_6H_5$ | — | $NaOC_2H_5$ | Ethanol | 530 |
| | $C_4$ | | | | | |
| | $n$-$C_4H_9Br$ | $n$-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 144 |
| | $n$-$C_4H_9I$ | $n$-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 142, 143 |
| | $(n$-$C_4H_9O)_2CO$ | $n$-$C_4H_9C(CH_2C_6H_5)(CO_2C_4H_9$-$n)_2$¶ | 80 | $KOC_4H_9$-$n$ | $(n$-$C_4H_9O)_2CO$ | 330, 890 |
| | $i$-$C_4H_9Br$ | $i$-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 47 | $NaOC_2H_5$ | Ethanol | 144 |
| | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 108 |
| | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 90 | $NaOC_2H_5$ | Ethanol | 916 |
| | $C_5$-$C_7$ | | | | | |
| | $n$-$C_5H_{11}X$‡ | $n$-$C_5H_{11}C(CH_2C_6H_5)(CO_2C_2H_6)_2$ | — | — | — | 942 |
| | $i$-$C_5H_{11}Br$ | $i$-$C_5H_{11}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 144 |
| | $Cl(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 85 | Na | None | 830 |
| | $n$-$C_6H_{13}Br$ | $n$-$C_6H_{13}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 942 |
| | $Br(CH_2)_3CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_3C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 530 |
| | $n$-$C_7H_{15}X$‡ | $n$-$C_7H_{15}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 942 |
| | $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 121, 142, 733 |
| | $m$-$FC_6H_4CH_2Br$ | $m$-$FC_6H_4CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 402 |
| | $m$-$ClC_6H_4CH_2Br$ | $m$-$ClC_6H_4CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 943 |
| | $p$-$ClC_6H_4CH_2Br$ | $p$-$ClC_6H_4CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 943 |
| | $m$-$BrC_6H_4CH_2Br$ | $m$-$BrC_6H_4CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 402 |
| | $C_8$-$C_{16}$ | | | | | |
| | $n$-$C_8H_{17}X$‡ | $n$-$C_8H_{17}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 942 |
| | Diethyl α-bromosuccinate | Tetraethyl δ-phenyl-butane-α,β,γ,γ-tetracarboxylate | 45 | $NaOC_2H_5$ | Ethanol | 207, 735, 944 |
| | $p$-$CH_3C_6H_4CH_2Br$ | $p$-$CH_3C_6H_4CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 80 | — | — | 945 |
| | $C_6H_5COCH_2Br$ | $C_6H_5COCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 106 |
| | $C_6H_5(CH_2)_3Br$ | $C_6H_5(CH_2)_3C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 70 | — | — | 830 |
| | $n$-$C_{12}H_{25}X$‡ | $n$-$C_{12}H_{25}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | — | — | 942 |
| | α-Naphthyimethyl bromide | Diethyl benzyl-(α-naphthylmethyl)-malonate | — | — | — | 945 |
| | β-Naphthylmethyl bromide | Diethyl benzyl-(β-naphthylmethyl)-malonate | 60 | — | — | 945 |
| | $(C_6H_5)_2CHBr$ | $(C_6H_5)_2CHC(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | Na | $C_6H_6$ | 946 |
| | Hydnocarpyl chloride-KI | Diethyl hydnocarpyl(benzyl)malonate | 30 | K | Toluene | 291 |
| $m$-$ClC_6H_4CH_2$ | $m$-$BrC_6H_4CH_2Br$ | $m$-$BrC_6H_4CH_2C(CH_2C_6H_4Cl$-$m)(CO_2C_2H_5)_2$ | — | — | — | 402 |
| | $p$-$CH_3C_6H_4CH_2Br$ | $p$-$CH_3C_6H_4CH_2C(CH_2C_6H_4Cl$-$m)(CO_2C_2H_5)_2$ | — | — | — | 402 |
| $o$-$O_2NC_6H_4CH_2$ | $o$-$O_2NC_6H_4CH_2Cl$ | $(o$-$O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 741, 740 |
| $p$-$O_2NC_6H_4CH_2$ | $o$-$O_2NC_6H_4CH_2Cl$ | $o$-$O_2NC_6H_4CH_2C(CO_2C_2H_5)_2$ <br> $\|$ <br> $CH_2C_6H_4NO_2$-$p$ | 100 | $NaOC_2H_5$ | Ethanol | 112 |
| | $p$-$O_2NC_6H_4CH_2Cl$ | $(p$-$O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 741 |
| $p$-$CH_3C_6H_4$ | $C_2H_5Br$ | $p$-$CH_3C_6H_4C(C_2H_5)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 44, 227 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

¶ The di-$n$-butyl ester was used in this experiment.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R′CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

| R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_8$ | $C_2$–$C_{13}$ | | | | | |
| $n$-$C_8H_{17}$ | $(C_2H_5O)_2CO$ | $n$-$C_8H_{17}C(C_2H_5)(CO_2C_2H_5)_2$ | 33 (50)§ | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 890, 330 |
| | CH₂—CH₂ (O) | CH₂CH₂C(C₈H₁₇-$n$)CO₂C₂H₅ (O——CO) | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2C(C_8H_{17}\text{-}n)(CO_2C_2H_5)_2$ | — | — | — | 743 |
| | Cyclobutylmethyl bromide | Diethyl $n$-octyl(cyclobutylmethyl)-malonate | — | $NaOC_2H_5$ | Ethanol | 947 |
| | 2-Chloromethylthiophene | $C_4H_3SCH_2C(C_8H_{17}\text{-}n)(CO_2C_2H_5)_2$ | — | Na | None | 897 |
| | $\beta$-Cyclopentylethyl bromide | Diethyl $n$-octyl-($\beta$-cyclopentylethyl)-malonate | 50–60 | $NaOC_2H_5$ | Ethanol | 725 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl $n$-octyl-[$\beta$-(2-cyclopentenyl)-ethyl]malonate | — | $NaOC_2H_5$ | Ethanol | 928 |
| | $n$-$C_8H_{17}I$ | $(n\text{-}C_8H_{17})_2C(CO_2C_2H_5)_2$ | 60 | Na | Toluene | 906, 888 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl $n$-octyl-($\beta$-cyclohexylethyl)-malonate | 52 | Na | Xylene | 31, 902 |
| | $n$-$C_{16}H_{33}I$ | $n$-$C_{16}H_{33}C(C_8H_{17}\text{-}n)(CO_2C_2H_5)_2$ | 84 | $NaOC_2H_5$ | Ethanol | 135 |
| $n$-$C_6H_{13}CH(CH_3)$ | $C_1$–$C_7$ | | | | | |
| | $CH_3Br$ | $n$-$C_6H_{13}CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 96 | — | — | 746 |
| | $n$-$C_3H_7Br$ | $n$-$C_6H_{13}CH(CH_3)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 85 | — | — | 746 |
| | $CH_2{=}CHCH_2Br$ | $n$-$C_6H_{13}CH(CH_3)C(CO_2C_2H_5)_2$ \| $CH_2CH{=}CH_2$ | 70–85 | $NaOC_2H_5$ | Ethanol | 545 |
| | $C_2H_5CH(CH_3)CH_2Br$ | $n$-$C_6H_{13}CH(CH_3)C(CO_2C_2H_5)_2$ \| $CH_2CH(CH_3)C_2H_5$ | 60 | — | — | 746 |
| | $i$-$C_5H_{11}Br$ | $n$-$C_6H_{13}CH(CH_3)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$ | 60 | — | — | 746 |
| | 2-Chloromethylthiophene | $n$-$C_6H_{13}CH(CH_3)C(CH_2C_4H_3S)(CO_2C_2H_5)_2$ | — | Na | None | 897 |
| | $n$-$C_7H_{15}Br$ | $n$-$C_6H_{13}CH(CH_3)C(C_7H_{15}\text{-}n)(CO_2C_2H_5)_2$ | 56 | — | — | 746 |
| $i$-$C_8H_{13}CH(CH_3)$ | $C_2H_5O(CH_2)_2I$ | $i$-$C_8H_{13}CH(CH_3)C(CO_2C_2H_5)_2$ \| $(CH_2)_2OC_2H_5$ | 47 | K | Xylene | 750 |
| $n$-$C_4H_9CH(C_2H_5)CH_2$ | $CH_2{=}CHCH_2Br$ | $n$-$C_4H_9CH(C_2H_5)CH_2C(CO_2C_2H_5)_2$ \| $CH_2CH{=}CH_2$ | — | $NaOC_2H_5$ | Ethanol | 749 |
| | 2-Chloromethylthiophene | $n$-$C_4H_9CH(C_2H_5)CH_2C(CO_2C_2H_5)_2$ \| $CH_2C_4H_3S$ | — | Na | None | 897 |
| $\beta$-Cyclohexylethyl | 2-Chloromethylthiophene | Diethyl ($\beta$-cyclohexylethyl)-2-thenylmalonate | — | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 50 |
| | $\beta$-Cyclohexylethylbromide | Diethyl di-($\beta$-cyclohexylethyl)malonate | — | $NaOC_2H_5$ | Ethanol | 929 |
| $\beta$-Cyclohexylideneëthyl | $CH_3X‡$ | Diethyl methyl($\beta$-cyclohexylideneëthyl)-malonate | 60 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $C_2H_5X‡$ | Diethyl ethyl($\beta$-cyclohexylideneëthyl)-malonate | 75 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| | $\beta$-Cyclohexylideneëthyl halide‡ | Diethyl di-($\beta$-cyclohexylideneëthyl)-malonate | 65 | $NaOC_2H_5$ | $(C_2H_5O)_2CO$ | 663 |
| $C_6H_5(CH_2)_2$ | $C_2$–$C_3$ | | | | | |
| | $C_2H_5Br$ | $C_6H_5(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 85 | Na | Toluene | 411 |
| | $C_2H_5Br$ | $C_6H_5(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$ | 89 | $NaOC_2H_5$ | Ethanol | 539, 148 |
| | $n$-$C_3H_7Br$ | $C_6H_5(CH_2)_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| | $CH_3O(CH_2)_2Cl$ | $CH_3O(CH_2)_2C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $i$-$C_3H_7Br$ | $C_6H_5(CH_2)_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| | $CH_2{=}CHCH_2Br$ | $C_6H_5(CH_2)_2C(CH_2CH{=}CH_2)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 755, 508 |
| | $C_4$–$C_5$ | | | | | |
| | $n$-$C_4H_9I$ | $C_6H_5(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 53 | $NaOC_2H_5$ | Ethanol | 142 |
| | $C_2H_5O(CH_2)_2Cl$ | $C_2H_5O(CH_2)_2C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$ | — | — | — | 374 |
| | $sec$-$C_4H_9X‡$ | $C_6H_5(CH_2)_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| | $i$-$C_4H_9Br$ | $C_6H_5(CH_2)_2C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| | $CH_3CCl{=}CHCH_2Cl$ | $CH_3CCl{=}CHCH_2C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$ | 79 | $NaOC_2H_5$ | Ethanol | 948 |
| | Cyclopentyl bromide | Diethyl cyclopentyl-($\beta$-phenylethyl)-malonate | 66 | K | Toluene | 949 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO$_2$R)$_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| C$_6$H$_5$(CH$_2$)$_2$ *(Cont.)* | Cyclopentyl bromide | Diethyl cyclopentyl-($\beta$-phenylethyl)malonate | 75 | NaOC$_2$H$_5$ | Ethanol | 949 |
| | 2-Cyclopentenyl chloride | Diethyl ($\beta$-phenylethyl)-2-cyclopentenyl-malonate | 61 | NaOC$_2$H$_5$ | Ethanol | 949 |
| | *C$_6$–C$_9$* | | | | | |
| | n-C$_4$H$_9$O(CH$_2$)$_2$Cl | n-C$_4$H$_9$O(CH$_2$)$_2$C[(CH$_2$)$_2$C$_6$H$_5$](CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 374 |
| | 2-Methylcyclopentyl bromide | Diethyl ($\beta$-phenylethyl)-(2-methylcyclopentyl)malonate | 54 | NaOC$_2$H$_5$ | Ethanol | 949 |
| | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$(CH$_2$)$_2$C(CH$_2$C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 64 | NaOC$_2$H$_5$ | Ethanol | 757 |
| | C$_6$H$_5$CH$_2$Br | C$_6$H$_5$(CH$_2$)$_2$C(CH$_2$C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 756 |
| | $\beta$-Cyclohexylethyl bromide | Diethyl ($\beta$-phenylethyl)-($\beta$-cyclohexylethyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 755 |
| | C$_6$H$_5$(CH$_2$)$_2$Br | [C$_6$H$_5$(CH$_2$)$_2$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 62 | Na | Toluene | 757 |
| | C$_6$H$_5$O(CH$_2$)$_2$Cl | C$_6$H$_5$O(CH$_2$)$_2$C[(CH$_2$)$_2$C$_6$H$_5$](CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 374 |
| | C$_6$H$_5$O(CH$_2$)$_3$Cl | C$_6$H$_5$O(CH$_2$)$_3$C[(CH$_2$)$_2$C$_6$H$_5$](CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 374 |
| C$_6$H$_5$O(CH$_2$)$_2$ | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$O(CH$_2$)$_2$C(CH$_2$C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 75 | NaOC$_2$H$_5$ | Ethanol | 757 |
| | C$_6$H$_5$O(CH$_2$)$_2$X‡ | [C$_6$H$_5$O(CH$_2$)$_2$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 50 | NaOC$_2$H$_5$ | Ethanol | 757 |
| o-CH$_3$C$_6$H$_4$CH$_2$ | BrCH$_2$CO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCH$_2$C(CH$_2$C$_6$H$_4$CH$_3$-o)(CO$_2$C$_2$H$_5$)$_2$ | 92 | NaOC$_2$H$_5$ | Ethanol | 421 |
| m-CH$_3$C$_6$H$_4$CH$_2$ | C$_6$H$_5$CH$_2$Cl | m-CH$_3$C$_6$H$_4$CH$_2$C(CH$_2$C$_6$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 70 | — | — | 945 |
| p-CH$_3$C$_6$H$_4$CH$_2$ | CH$_2$=CHCH$_2$Br | p-CH$_3$C$_6$H$_4$CH$_2$C(CH$_2$CH=CH$_2$)(CO$_2$C$_2$H$_5$)$_2$ | 78 | NaOC$_2$H$_5$ | Toluene | 507 |
| 2-Methoxy-5-nitrobenzyl | CH$_3$I | Diethyl methyl-(2-methoxy-5-nitrobenzyl)malonate | — | — | — | 763 |
| | C$_2$H$_5$I | Diethyl ethyl-(2-methoxy-5-nitrobenzyl)malonate | — | — | — | 763 |
| p-CH$_3$OC$_6$H$_4$CH$_2$ | CH$_2$=CHCH$_2$Br | p-CH$_3$OC$_6$H$_4$CH$_2$C(CO$_2$C$_2$H$_5$)$_2$ &#124; CH$_2$CH=CH$_2$ | 100 | NaOC$_2$H$_5$ | Toluene | 511 |
| | BrCH$_2$CO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCH$_2$C(CO$_2$C$_2$H$_5$)$_2$ &#124; CH$_2$C$_6$H$_4$OCH$_3$-p | — | — | — | 950 |

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Piperonyl | C$_2$H$_5$Br | Diethyl ethyl(piperonyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 560 |
| | CH$_2$=CHCH$_2$Br | Diethyl allyl(piperonyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 560 |
| *C$_9$* | *C$_2$–C$_{16}$* | | | | | |
| n-C$_9$H$_{19}$ | CH$_2$—CH$_2$ (over O) | CH$_2$CH$_2$C(C$_9$H$_{19}$-n)CO$_2$C$_2$H$_5$ (O—CO) | ca. 70 | NaOC$_2$H$_5$ | Ethanol | 282 |
| | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_9$H$_{19}$-n)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 920 |
| | Cyclobutylmethyl bromide | Diethyl (cyclobutylmethyl)-n-nonylmalonate | — | NaOC$_2$H$_5$ | Ethanol | 947 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl n-nonyl-[$\beta$-(2-cyclopentenyl)ethyl]malonate | — | NaOC$_2$H$_5$ | Ethanol | 928 |
| | n-C$_{16}$H$_{33}$I | n-C$_{16}$H$_{33}$C(C$_9$H$_{19}$-n)(CO$_2$C$_2$H$_5$)$_2$ | 84 | NaOC$_2$H$_5$ | Ethanol | 135 |
| $\gamma$-Cyclohexylpropyl | $\gamma$-Cyclohexylpropyl bromide | Diethyl di-($\gamma$-cyclohexylpropyl)malonate | — | NaOC$_2$H$_5$ | Ethanol | 929 |
| C$_6$H$_5$(CH$_2$)$_3$ | n-C$_4$H$_9$Br | C$_6$H$_5$(CH$_2$)$_3$C(C$_4$H$_9$-n)(CO$_2$C$_2$H$_5$)$_2$ | 63 | NaOC$_2$H$_5$ | Ethanol | 142 |
| | C$_6$H$_5$(CH$_2$)$_2$Br | C$_6$H$_5$(CH$_2$)$_3$C[(CH$_2$)$_2$C$_6$H$_5$](CO$_2$C$_2$H$_5$)$_2$ | 45 | NaOC$_2$H$_5$ | Ethanol | 769 |
| | C$_6$H$_5$(CH$_2$)$_3$Br | [C$_6$H$_5$(CH$_2$)$_3$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 62 | Na | Toluene | 768 |
| | *C$_1$–C$_9$* | | | | | |
| C$_6$H$_5$O(CH$_2$)$_3$ | CH$_3$I | C$_6$H$_5$O(CH$_2$)$_3$C(CH$_3$)(CO$_2$C$_2$H$_5$)$_2$ | 73 | NaOCH$_3$ | CH$_3$OH | 581 |
| | C$_2$H$_5$I | C$_6$H$_5$O(CH$_2$)$_3$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | 69 | NaOC$_2$H$_5$ | Ethanol | 772 |
| | n-C$_3$H$_7$I | C$_6$H$_5$O(CH$_2$)$_3$C(C$_3$H$_7$-n)(CO$_2$C$_2$H$_5$)$_2$ | 67 | NaOC$_3$H$_7$-n | n-C$_3$H$_7$OH | 774 |
| | C$_6$H$_5$O(CH$_2$)$_3$Br | [C$_6$H$_5$O(CH$_2$)$_3$]$_2$C(CO$_2$C$_2$H$_5$)$_2$ | 66 | NaOC$_2$H$_5$ | Ethanol | 775, 374 |
| C$_6$H$_5$CH$_2$O(CH$_2$)$_2$ | C$_2$H$_5$I | C$_6$H$_5$CH$_2$O(CH$_2$)$_2$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | — | — | 374 |
| C$_6$H$_5$CH=CHCH$_2$ | C$_2$H$_5$Br | C$_6$H$_5$CH=CHCH$_2$C(C$_2$H$_5$)(CO$_2$C$_2$H$_5$)$_2$ | — | NaOC$_2$H$_5$ | Ethanol | 755 |
| m-CH$_3$C$_6$H$_4$(CH$_2$)$_2$ | CH$_3$CCl=CHCH$_2$Cl | m-CH$_3$C$_6$H$_4$(CH$_2$)$_2$C(CO$_2$C$_2$H$_5$)$_2$ &#124; CH$_2$CH=CClCH$_3$ | 93 | NaOC$_2$H$_5$ | Ethanol | 517 |
| m-CH$_3$OC$_6$H$_4$(CH$_2$)$_2$ | Cyclopentyl bromide | Diethyl cyclopentyl-[$\beta$-(m-methoxyphenyl)ethyl]malonate | 75 | K | Toluene | 412 |
| | 2-Cyclopentenyl chloride | Diethyl 2-cyclopentenyl-[$\beta$-(m-methoxyphenyl)ethyl]malonate | 68–70 | K | Toluene | 412 |
| p-CH$_3$C$_6$H$_4$(CH$_2$)$_2$ | CH$_3$CCl=CHCH$_2$Cl | CH$_3$CCl=CHCH$_2$C(CO$_2$C$_2$H$_5$)$_2$ &#124; (CH$_2$)$_2$C$_6$H$_4$CH$_3$-p | 86 | NaOC$_2$H$_5$ | Ethanol | 519 |

*Note:* References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

ORGANIC REACTIONS

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$
#### (The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| **$C_{10}$** | **$C_2$–$C_{15}$** | | | | | |
| $n\text{-}C_{10}H_{21}$ | $CH_2\!-\!CH_2$ (epoxide, O) | $CH_2CH_2C(C_{10}H_{21}\text{-}n)CO_2C_2H_5$, $O\!-\!CO$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(C_{10}H_{21}\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920, 743 |
| | Cyclobutylmethyl bromide | Diethyl (cyclobutylmethyl)-n-decylmalonate | — | $NaOC_2H_5$ | Ethanol | 947 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl n-decyl-[$\beta$-(2-cyclopentenyl)ethyl]malonate | — | $NaOC_2H_5$ | Ethanol | 928 |
| | $n\text{-}C_{10}H_{21}Br$ | $(n\text{-}C_{10}H_{21})_2C(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 951 |
| | $n\text{-}C_{12}H_{25}Br\text{-}KI$ | $n\text{-}C_{12}H_{25}C(C_{10}H_{21}\text{-}n)(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 70 |
| | $n\text{-}C_{14}H_{29}I$ | $n\text{-}C_{14}H_{29}C(C_{10}H_{21}\text{-}n)(CO_2H)_2$ | 79 | $NaOC_2H_5$ | Ethanol | 684 |
| | $n\text{-}C_{14}H_{29}I$ | $n\text{-}C_{16}H_{33}C(C_{10}H_{21}\text{-}n)(CO_2C_2H_5)_2$ | 84 | $NaOC_2H_5$ | Ethanol | 135 |
| $Br(CH_2)_{10}$ | $CH_3I$ | $Br(CH_2)_{10}C(CH_3)(CO_2C_2H_5)_2$ | 100 | $NaOC_2H_5$ | Ethanol | 788 |
| 3,7-Dimethyloctyl | $CH_2\!=\!CHCH_2Br$ | Diethyl allyl-(3,7-dimethyloctyl)malonate | — | — | — | 743 |
| Citronellyl($=C_{10}H_{19}$) | Cyclopentyl bromide | Diethyl cyclopentyl(citronellyl)malonate | 46 | Na | Xylene | 31 |
| | $n\text{-}C_6H_{13}Br$ | $n\text{-}C_6H_{13}C(C_{10}H_{19})(CO_2C_2H_5)_2$ | 67 | Na | Xylene | 31 |
| Geranyl($=C_{10}H_{17}$) | $CH_2\!-\!CH_2$ (epoxide, O) | $CH_2CH_2C(C_{10}H_{17})CO_2C_2H_5$, $O\!-\!CO$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | Cyclopentyl bromide | Diethyl cyclopentyl(geranyl)malonate | 52 | Na | Xylene | 31 |
| $C_6H_5(CH_2)_4$ | $C_2H_5Br$ | $C_6H_5(CH_2)_4C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| $C_6H_5CH_2SCH_2CH(CH_3)$ | $CH_3I$ | $C_6H_5CH_2SCH_2CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 794 |
| $\alpha$-Naphthyl | $C_2H_5I$ | Dimethyl ethyl-($\alpha$-naphthyl)malonate* | 49 | $NaOCH_3$ | $CH_3OH$ | 376 |
| $\beta$-Naphthyl | $CH_2\!=\!CHCH_2Br$ | Diethyl allyl-($\beta$-naphthyl)malonate | 88 | $NaOC_2H_5$ | Ethanol | 952 |
| **$C_{11}$** | **$C_2$–$C_7$** | | | | | |
| $n\text{-}C_{11}H_{23}$ | $CH_2\!-\!CH_2$ (epoxide, O) | $CH_2CH_2C(C_{11}H_{23}\text{-}n)CO_2C_2H_5$, $O\!-\!CO$ | ca. 70 | $NaOC_2H_5$ | Ethanol | 282 |
| | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(C_{11}H_{23}\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | Cyclobutylmethyl bromide | Diethyl (cyclobutylmethyl)-n-undecylmalonate | — | $NaOC_2H_5$ | Ethanol | 947 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl n-undecyl-[$\beta$-(2-cyclopentenyl)ethyl]malonate | — | $NaOC_2H_5$ | Ethanol | 928 |
| | $n\text{-}C_{16}H_{33}I$ | $n\text{-}C_{16}H_{33}C(C_{11}H_{23}\text{-}n)(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 135 |
| $n\text{-}C_8H_{19}CH(CH_3)$ | $n\text{-}C_{12}H_{25}Br\text{-}NaI$ | $n\text{-}C_8H_{19}CH(CH_3)C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$ | 50 | Na | Xylene | 70 |
| $C_6H_5(CH_2)_5$ | $C_2H_5Br$ | $C_6H_5(CH_2)_5C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |
| 2-p-Cymylmethyl | $CH_3I$ | Diethyl methyl-(2-methyl-5-isopropylbenzyl)malonate | 76 | Na | $C_6H_6$ | 808 |
| | $CH_3I$ | Diethyl methyl-(2-methyl-5-isopropylbenzyl)malonate | 76 | $NaOC_2H_5$ | Ethanol | 418 |
| 1-Naphthylmethyl ($=C_{11}H_{15}$) | $CH_2\!=\!CHCH_2X$‡ | Diethyl allyl-(1-naphthylmethyl)malonate | — | $NaOC_2H_5$ | Toluene | 512 |
| | $\beta$-Bromomethylnaphthalene | Diethyl (1-naphthylmethyl)-(2-naphthylmethyl)malonate | — | — | — | 945 |
| 2-Naphthylmethyl ($=C_{11}H_{13}$) | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(C_{11}H_{13})(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Toluene | 513 |
| **$C_{12}$** | | | | | | |
| $n\text{-}C_{12}H_{25}$¶¶ | $C_2H_5X$¶¶ | $n\text{-}C_{12}H_{25}C(C_2H_5)(CO_2C_2H_5)_2$ | — | — | — | 783 |
| | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| | Cyclobutylmethyl bromide | Diethyl (cyclobutylmethyl)-n-dodecylmalonate | — | $NaOC_2H_5$ | Ethanol | 947 |
| | $\beta$-(2-Cyclopentenyl)ethyl bromide | Diethyl n-dodecyl-[$\beta$-(2-cyclopentenyl)ethyl]malonate | — | $NaOC_2H_5$ | Ethanol | 928 |
| | $n\text{-}C_{16}H_{33}I$ | $n\text{-}C_{16}H_{33}C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 135 |
| $C_6H_5(CH_2)_6$ | $C_2H_5Br$ | $C_6H_5(CH_2)_6C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 755 |

*Note:* References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.
‡ The halogen was not specified.
¶¶ The order of introduction of the alkyl groups was not stated.

THE ALKYLATION OF ESTERS AND NITRILES

## TABLE III—Continued

### ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

| R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $\beta$-1-Naphthylethyl ($=C_{12}H_{11}$) | $CH_3Br$ | $C_{12}H_{11}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 839 |
| | $CH_3I$ | $C_{12}H_{11}C(CH_3)(CO_2C_2H_5)_2$ | 96 | $NaOC_2H_5$ | Ethanol | 953 |
| | $C_2H_5Br$ | $C_{12}H_{11}C(C_2H_5)(CO_2C_2H_5)_2$ | 67 | $NaOC_2H_5$ | Ethanol | 546 |
| | $CH_2=CHCH_2Br$ | $C_{12}H_{11}C(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 47 | $NaOC_2H_5$ | Ethanol | 546 |
| | $n\text{-}C_4H_9Br$ | $C_{12}H_{11}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 81 | $NaOC_2H_5$ | Ethanol | 546 |
| | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(C_{12}H_{11})(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 517 |
| $\beta$-2-Naphthylethyl ($=C_{12}H_{11}$) | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(C_{12}H_{11})(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 817 |
| 2-Methyl-1-naphthyl-methyl | $CH_3I$ | Diethyl methyl-(2-methyl-1-naphthylmethyl)malonate | — | Na | Xylene | 821 |
| 4-Methyl-1-naphthyl-methyl | $CH_2=CHCH_2Br$ | Diethyl allyl-(4-methyl-1-naphthylmethyl)malonate | — | $NaOC_2H_5$ | Toluene | 514 |
| $C_{13}$ | | | | | | |
| $n\text{-}C_{13}H_{27}$ | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_{13}H_{27}\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| $(C_6H_5)_2CH$ | $CH_3I$ | $(C_6H_5)_2CHC(CH_3)(CO_2C_2H_5)_2$ | >45 | Na | Ether | 938 |
| | $CH_2=CHCH_2Br$ | $(C_6H_5)_2CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 39 | $NaOC_2H_5$ | Ethanol | 516 |
| | $(C_6H_5)_2CHBr$ | $[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$ | 77 | Na | $C_6H_6$ | 156 |
| | $(C_6H_5)_2CHBr$ | $[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$ | 22 | Na | Toluene | 224 |
| | $(C_6H_5)_2CHBr$ | $[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$ | 89 | BrMg salt*** of enolate | Ether | 156, 954 |
| | $(C_6H_5)_2CHBr$ | $[(C_6H_5)_2CH]_2C(CO_2C_2H_5)[CO_2CH(C_6H_5)_2]$††† | 25 | Na | $C_6H_6$ | 224 |
| | $(p\text{-}CH_3C_6H_4)_2CHCl$ | $(p\text{-}CH_3C_6H_4)_2CHC[CH(C_6H_5)_2](CO_2C_2H_5)_2$ | 63 | Na | $C_6H_6$ | 156 |
| 9-Fluorenyl | $CH_2=CHCH_2Br$ | Diethyl allyl-(9-fluorenyl)malonate | — | — | — | 516 |
| $\beta$-(5-Methoxy-1-naphthyl)ethyl ($=C_{13}H_{13}O$) | $CH_3CCl=CHCH_2Cl$ | $CH_3CCl=CHCH_2C(C_{13}H_{13}O)(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 520 |
| $C_{14}$ | | | | | | |
| $n\text{-}C_{14}H_{29}$ | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_{14}H_{29}\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 920 |
| 4-Isopropyl-1-naphthylmethyl | $CH_2=CHCH_2Br$ | Diethyl allyl-(4-isopropyl-1-naphthylmethyl)malonate | — | $NaOC_2H_5$ | Toluene | 515 |
| 9-Phenanthryl ($=C_{14}H_9$) | $n\text{-}C_3H_7I$ | $C_{14}H_9C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 61 | $NaOC_2H_5$ | Ethanol | 955 |
| | $CH_2=CHCH_2Br$ | $C_{14}H_9C(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 955 |
| $C_{15}$ | | | | | | |
| $C_6H_5CH_2CH\text{-}(CO_2C_2H_5)CH\text{-}(CO_2C_2H_5)$ | $CH_3I$ | Tetraethyl $\alpha$-methyl-$\delta$-phenyl-butane-$\alpha,\alpha,\beta,\gamma$-tetracarboxylate | 75 | Na | $C_6H_6$ | 207 |
| | $CH_3I$ | Tetraethyl $\alpha$-methyl-$\delta$-phenyl-butane-$\alpha,\alpha,\beta,\gamma$-tetracarboxylate | 75 | $NaOC_2H_5$ | Ethanol | 207 |
| †† | $CH_3I$ | $C_6H_5CH_2CH(CH_3)CONH_2$ | — | Na | $C_6H_6$ | 207 |
| †† | $CH_3I$ | $\begin{cases} C_6H_5CH_2C(CH_3)(CO_2C_2H_5)_2 \\ C_6H_5CH_2CH\text{——}CHC(CH_3)(CO_2C_2H_5)_2 \\ \qquad\quad| \qquad\qquad | \\ \qquad CO_2C_2H_5 \ \ CO_2C_2H_5 \end{cases}$ | — / 68 | $NaOC_2H_5$ | Ethanol | 207 |
| $(p\text{-}CH_3C_6H_4)_2CH$ | $(C_6H_5)_2CHBr$ | $(p\text{-}CH_3C_6H_4)_2CHC[CH(C_6H_5)_2](CO_2C_2H_5)_2$ | 40 | Na | $C_6H_6$ | 156 |
| | $(C_6H_5)_2CHBr$ | $(p\text{-}CH_3C_6H_4)_2CHC[CH(C_6H_5)_2](CO_2C_2H_5)_2$ | 4 | BrMg salt‡‡‡ of enolate | Ether | 156 |
| | $(p\text{-}CH_3C_6H_4)_2CHCl$ | $[(p\text{-}CH_3C_6H_4)_2CH]_2C(CO_2C_2H_5)_2$ | 80 | Na | $C_6H_6$ | 156 |
| | $(p\text{-}CH_3C_6H_4)_2CHCl$ | $[(p\text{-}CH_3C_6H_4)_2CH]_2C(CO_2C_2H_5)_2$ | 88 | BrMg salt‡‡‡ of enolate | Ether | 156 |
| $C_6H_5COCH_2CH(C_6H_5)$ | $CH_3I$ | $C_6H_5COCH_2CH(C_6H_5)C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 154 |
| $C_6H_5COCHBrCH(C_6H_5)$ low and high melting isomers | None | $\begin{array}{c} H_5C_6CH\text{——}CHCOC_6H_5 \\ \diagdown\quad\diagdown \\ C(CO_2CH_3)_2* \\ \text{(both isomers)} \end{array}$ | — | $Mg(OCH_3)_2$ | $CH_3OH$ | 86, 956 |

*Note:* References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

†† The ester alkylated in this experiment was $C_6H_5CH_2CH(CO_2C_2H_5)CH(CO_2C_2H_5)CH_2CO_2C_2H_5$.

*** The bromomagnesium salt of the enolate was derived from the addition of phenylmagnesium bromide to diethyl benzylidenemalonate.

††† Benzhydryl ethyl benzhydrylmalonate was used in this experiment.

‡‡‡ The bromomagnesium salt of the enolate was derived from addition of $p$-tolylmagnesium bromide to $p$-methylbenzylidenemalonate.

## TABLE III—*Continued*

### ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂
### (The diethyl ester was used unless otherwise indicated.)

Alkylation of Monoalkylmalonic Esters, $R'CH(CO_2R)_2$

| R | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $p$-$BrC_6H_4COCHBr$-$CH(C_6H_5)$ (both isomers) | None | $H_5C_6CH$——$CHCOC_6H_4Br$-$p$ / $C(CO_2CH_3)_2$* (both isomers) | — | $KOCOCH_3$ | $CH_3OH$ | 85 |
| | None | $H_5C_6CH$——$CHCOC_6H_4Br$-$p$ / $C(CO_2CH_3)_2$* (both isomers) | — | $Mg(OCH_3)_2$ | $CH_3OH$ | 85 |
| $C_6H_5COCHBrCH$-$(C_6H_4NO_2$-$m)$ (both isomers) | None | $m$-$O_2NH_4C_6CH$——$CHCOC_6H_5$ / $C(CO_2CH_3)_2$* (both isomers) | 100 | $KOCOCH_3$ | $CH_3OH$ | 85 |
| | None | $m$-$O_2NH_4C_6CH$——$CHCOC_6H_5$ / $C(CO_2CH_3)_2$* (both isomers) | 100 | $Mg(OCH_3)_2$ | $CH_3OH$ | 85 |
| $C_{16}$ | $C_1$-$C_{16}$ | | | | | |
| $n$-$C_{16}H_{33}$ | $CH_3I$ | $n$-$C_{16}H_{33}C(CH_3)(CO_2C_2H_5)_2$ | — | Na | Xylene | 679 |
| | $(n$-$C_4H_9O)_2CO$ | $n$-$C_{16}H_{33}C(C_4H_9$-$n)(CO_2C_4H_9)_2$§§§ | 83 | $NaOC_4H_9$-$n$ | $(n$-$C_4H_9O)_2CO$ | 330, 890 |
| | $C_6H_5CH_2Cl$ | $n$-$C_{16}H_{33}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | 67 | $KOC_2H_5$ | $(C_2H_5O)_2CO$ | 44 |
| | $C_6H_5CH_2Ci$ | $n$-$C_{16}H_{33}C(CH_2C_6H_5)(CO_2C_4H_9)_2$§§§ | 67 | $KOC_4H_9$-$n$ | $(n$-$C_4H_9O)_2CO$ | 51, 227 |
| | $n$-$C_8H_{17}I$ | $n$-$C_{16}H_{33}C(C_8H_{17}$-$n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 134 |
| | $n$-$C_{16}H_{33}Br$ | $(n$-$C_{16}H_{33})_2C(CO_2C_2H_5)_2$ | 64 | Na | Xylene | 679, 957 |
| | $n$-$C_{16}H_{33}Br$ | $(n$-$C_{16}H_{33})_2C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 841 |
| $C_6H_5COCHBrCH$ (Br, OCH₃ substituted ring) | None | $C_6H_5COCH$—$CH$—(ring OCH₃, Br) / $C(CO_2CH_3)_2$* | 53 | $KOCOCH_3$ | $CH_3OH$ | 958 |
| $C_{17}$ | | | | | | |
| $n$-$C_{17}H_{35}$ | $CH_3I$ | $n$-$C_{17}H_{35}C(CH_3)(CO_2C_2H_5)_2$ | — | Na | Toluene | 400 |
| $C_{23}$ | | | | | | |
| 3-Decyltridecyl | $CH_3I$ | Diethyl (3-decyltridecyl) methylmalonate | — | $NaOC_2H_5$ | Ethanol | 70 |

*Note:* References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

§§§ The di-$n$-butyl ester was used in this experiment.

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# TABLE IV

## ALKYLATION OF POLYMETHYLENE-$\alpha,\omega$-DIMALONIC ESTERS

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $(C_2H_5O_2C)_2CH\text{-}$ $CH(CO_2C_2H_5)_2$ | $CH_3I$ | $\{(C_2H_5O_2C)_2CHC(CH_3)(CO_2C_2H_5)_2$ $(C_2H_5O_2C)_2C(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 39 10 | $NaOC_2H_5$ | Ethanol | 578 |
| | $CH_2Cl_2$ | None | — | $NaOC_2H_5$ | Ethanol | 300 |
| | $CH_2I_2$ | Tetraethyl cyclopropane-1,1,2,2-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 300 |
| | $Br(CH_2)_2O(CH_2)_2Br$ | Tetraethyl hexamethylene-oxide-4,4,5,5-tetracarboxylate | 44 | $NaOC_2H_5$ | Ethanol | 219 |
| | $Br_2C(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 261 |
| (biphenyl-2,2′-diylbis(methylene) dibromide) | | (biphenyl product) * | 24 | $NaOC_2H_5$ | Ethanol-ether | 492 |
| | $(C_2H_5O_2C)_2CBrCH_2CBr(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ and tetraethyl cyclopropane-1,1,2,2-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 261 |
| | $(C_2H_5O_2C)_2CBr(CH_2)_2CBr(CO_2C_2H_5)_2$ | $(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ and cyclobutane-cis-1,2-dicarboxylic acid | — | $NaOC_2H_5$ | Ethanol | 261 |
| $CH_2[CH(CO_2C_2H_5)_2]_2$ | $CH_3I$ | $(C_2H_5O_2C)_2C(CH_3)CH_2\text{-}CH(CH_3)CO_2H$ | 74 | $NaOC_2H_5$ | Ethanol | 872, 296 |
| | $CH_2I_2$ | Tetraethyl cyclobutane-1,1,3,3-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 296 |
| | $C_2H_5I$ | $(C_2H_5O_2C)_2C(C_2H_5)CH_2\text{-}C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 296 |
| | $n\text{-}C_3H_7I$ | $(C_2H_5O_2C)_2C(C_3H_7\text{-}n)CH_2\text{-}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 296 |
| | $Br(CH_2)_3Br$ | Cyclohexane-1,1,3,3-tetracarboxylic acid | — | $NaOC_2H_5$ | Ethanol | 293 |
| | $(C_2H_5O_2C)_2CBrCH_2CBr(CO_2C_2H_5)_2$ | Tetraethyl cyclopropane-1,1,2,2-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 959, 960 |
| $(C_2H_5O_2C)_2CBr\text{-}CH_2CH(CO_2C_2H_5)_2$ | None | Tetraethyl cyclopropane-1,1,2,2-tetracarboxylate | — | $NH_3$ | $CH_3OH$ | 87 |
| $(C_2H_5O_2C)_2CH\text{-}CH(C_2H_5)CH(CO_2C_2H_5)_2$ | $Br_2$ or $I_2$ | Tetraethyl 3-ethylcyclopropane-1,1,2,2-tetracarboxylate | — | Na | Ether | 87 |
| | $C_2H_5I$ | $(C_2H_5O_2C)_2C(C_2H_5)CH(C_2H_5)\text{-}C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 87 |
| $(C_2H_5O_2C)_2CHC(CH_3)_2\text{-}CH(CO_2C_2H_5)_2$ | $Br_2$ | None | — | Na | Ether | 87 |
| $(C_2H_5O_2C)_2CBrC(CH_3)_2\text{-}CH(CO_2C_2H_5)_2$ | None | Tetraethyl 3,3-dimethylcyclopropane-1,1,2,2-tetracarboxylate | — | $NH_3$ | $CH_3OH$ | 87 |
| $(C_2H_5O_2C)_2CH\text{-}CH{=}C(CO_2C_2H_5)_2$ | $CH_3I$ | $(C_2H_5O_2C)_2C(CH_3)CH{=}C(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 221 |
| | $C_6H_5CH_2Cl$ | $(C_2H_5O_2C)_2C(CH_2C_6H_5)\text{-}CH{=}C(CO_2C_2H_5)_2$ | 72–84 | $NaOC_2H_5$ | Ethanol | 221, 231 |
| $(C_2H_5O_2C)_2CBr\text{-}CH(C_6H_5)CH(CO_2C_2H_5)_2$ | None | Tetraethyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate | — | $NH_3$ | $CH_3OH$ | 87 |
| $(C_2H_5O_2C)_2CH(CH_2)_2\text{-}CH(CO_2C_2H_5)_2$ | $CH_3I$ | $(C_2H_5O_2C)_2C(CH_3)(CH_2)_2\text{-}C(CH_3)(CO_2C_2H_5)_2$ | 85 | $NaOC_2H_5$ | Ethanol | 602 |
| | $CH_2I_2$ | Tetraethyl cyclopentane-1,1,3,3-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 301, 302 |
| | $C_2H_5I$ | $(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_2\text{-}CH(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 600 |
| | $Br(CH_2)_2O(CH_2)_2Br$ | Tetraethyl octamethylene-oxide-4,4,7,7-tetracarboxylate | 17 | $Mg(OC_2H_5)_2$ | Ethanol | 219 |
| | $(C_2H_5O_2C)_2CBr(CH_2)_2CBr(CO_2C_2H_5)_2$ | Cyclobutane-cis-1,2-dicarboxylic acid | — | $NaOC_2H_5$ | Ethanol | 261 |
| $(C_2H_5O_2C)_2CH(CH_2)_3\text{-}CH(CO_2C_2H_5)_2$ | $CH_3I$ | $(C_2H_5O_2C)_2C(CH_3)(CH_2)_3\text{-}C(CH_3)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |
| | $CH_2I_2$ | Tetraethyl cyclohexane-1,1,3,3-tetracarboxylate | — | $NaOC_2H_5$ | Ethanol | 299 |
| | $C_2H_5I$ | $(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_3\text{-}C(C_2H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |
| | $n\text{-}C_3H_7I$ | $(C_2H_5O_2C)_2C(C_3H_7\text{-}n)(CH_2)_3\text{-}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |
| | $i\text{-}C_3H_7I$ | $(C_2H_5O_2C)_2C(C_3H_7\text{-}i)(CH_2)_3\text{-}C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |
| | $i\text{-}C_4H_9I$ | $(C_2H_5O_2C)_2C(C_4H_9\text{-}i)(CH_2)_3\text{-}C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |
| | $C_6H_5CH_2Cl$ | $(C_2H_5O_2C)_2C(CH_2C_6H_5)(CH_2)_3\text{-}C(CH_2C_6H_5)(CO_2C_2H_5)_2$ | — | $NaOC_2H_5$ | Ethanol | 303 |

*Note:* References 577–1080 are on pp. 322–331.
* The structure of the product is uncertain.

## TABLE V

### ALKYLATION OF ALKYLIDENEMALONIC ESTERS, $R=C(CO_2C_2H_5)_2$

| R= | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_2H_5CH=$ | $n\text{-}C_3H_7I$ | $CH_3CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 51 | $NaOC_2H_5$ | Ethanol | 28 |
| | $i\text{-}C_3H_7I$ | $CH_3CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | 35 | $NaOC_2H_5$ | Ethanol | 28 |
| | $CH_2=CHCH_2Br$ | $CH_3CH=CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 76 | $NaOC_2H_5$ | Ethanol | 215 |
| | $n\text{-}C_4H_9I$ | $CH_3CH=CHC(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 50 | $NaOC_2H_5$ | Ethanol | 28 |
| $(CH_3)_2C=$ | $(CH_3)_2SO_4$ | $CH_2=C(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 88 | $NaNH_2$ | Toluene | 63 |
| | $(C_2H_5)_2SO_4$ | $CH_2=C(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 81 | $NaNH_2$ | Toluene | 63 |
| | $n\text{-}C_3H_7Br$ | $CH_2=C(CH_3)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 50 | $NaNH_2$ | Toluene | 63 |
| | $i\text{-}C_3H_7I$ | $CH_2=C(CH_3)C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | 10 | $NaNH_2$ | Toluene | 63 |
| | $CH_2=CHCH_2Br$ | $CH_2=C(CH_3)C(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 82 | $NaNH_2$ | Toluene | 63, 213 |
| | $CH_2=CClCH_2Cl$ | Structure not determined | Poor | $NaNH_2$ | Toluene | 64 |
| | $CH_2=CBrCH_2Br$ | Structure not determined | Poor | $NaNH_2$ | Toluene | 64 |
| | $n\text{-}C_4H_9I$ | $CH_2=C(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 59 | $NaNH_2$ | Toluene | 63 |
| | $i\text{-}C_4H_9Br$ | $CH_2=C(CH_3)C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$ | 40 | $NaNH_2$ | Toluene | 63 |
| | $CH_3CH=CHCH_2Br$ | $CH_2=C(CH_3)C(CH_2CH=CHCH_3)(CO_2C_2H_5)_2$ | 61 | $NaNH_2$ | Toluene | 64 |
| | $n\text{-}C_5H_{11}Br$ | $CH_2=C(CH_3)C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$ | 50 | $NaNH_2$ | Toluene | 63 |
| | $i\text{-}C_5H_{11}Br$ | $CH_2=C(CH_3)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$ | 36 | $NaNH_2$ | Toluene | 63 |
| | $C_6H_5CH=CHCH_2Br$ | $CH_2=C(CH_3)C(CH_2CH=CHC_6H_5)(CO_2C_2H_5)_2$ | Poor | $NaNH_2$ | Toluene | 64 |
| $n\text{-}C_3H_7CH=$ | $CH_3I$ | $C_2H_5CH=CHC(CH_3)(CO_2C_2H_5)_2$ | 80 | $NaOC_2H_5$ | Ethanol | 961 |
| | $C_2H_5I$ | $C_2H_5CH=CHC(C_2H_5)(CO_2C_2H_5)_2$ | 75 | $NaOC_2H_5$ | Ethanol | 28 |
| | $(C_2H_5)_2SO_4$ | $C_2H_5CH=CHC(C_2H_5)(CO_2C_2H_5)_2$ | — | Na | Ether | 212 |
| | $n\text{-}C_3H_7Br$ | $C_2H_5CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 55 | $NaOC_2H_5$ | Ethanol | 28 |
| | $i\text{-}C_3H_7Br$ | $C_2H_5CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | 67 | $NaOC_2H_5$ | Ethanol | 28 |
| | $CH_2=CHCH_2Br$ | $C_2H_5CH=CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 79 | $NaOC_2H_5$ | Ethanol | 28 |
| | $n\text{-}C_4H_9Br$ | $C_2H_5CH=CHC(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 59 | $NaOC_2H_5$ | Ethanol | 28 |
| | $sec\text{-}C_4H_9Br$ | $C_2H_5CH=CHC(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$ | 21 | $NaOC_2H_5$ | Ethanol | 28 |
| $CH_3C(OC_2H_5)=$ | $C_2H_5X*$ | $CH_2=C(OC_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 20 | $NaOC_2H_5$ | Ethanol | 203 |
| | $C_2H_5X*$ | $CH_2=C(OC_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$ | 60 | $NaOC_4H_9\text{-}t$ | $t\text{-}C_4H_9OH$ | 203 |
| | $n\text{-}C_3H_7X*$ | $CH_2=C(OC_2H_5)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 72 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| | $CH_2=CHCH_2X*$ | $CH_2=C(OC_2H_5)C(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 59 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| | $n\text{-}C_4H_9X*$ | $CH_2=C(OC_2H_5)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 85 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| | $i\text{-}C_5H_{11}X*$ | $CH_2=C(OC_2H_5)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$ | 79 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| $C_2H_5C(CH_3)=$ | $(CH_3)_2SO_4$ | $CH_3CH=C(CH_3)C(CH_3)(CO_2C_2H_5)_2$ | 76 | $NaNH_2$ | Toluene | 237 |
| | $(C_2H_5)_2SO_4$ | $CH_3CH=C(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$ | 70 | $NaNH_2$ | Toluene | 237 |
| | $n\text{-}C_3H_7Br$ | $CH_3CH=C(CH_3)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 65 | $NaNH_2$ | Toluene | 237 |
| | $CH_2=CHCH_2Br$ | $CH_3CH=C(CH_3)C(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 60 | $NaNH_2$ | Toluene | 237 |
| | $n\text{-}C_4H_9Br$ | $CH_3CH=C(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$ | 67 | $NaNH_2$ | Toluene | 237 |
| $i\text{-}C_3H_7CH=$ | $C_2H_5I$ | $(CH_3)_2C=CHC(C_2H_5)(CO_2C_2H_5)_2$ | 40 | $NaOC_2H_5$ | Ethanol | 28 |
| $n\text{-}C_4H_9CH=$ | $C_2H_5Br$ | $n\text{-}C_3H_7CH=CHC(C_2H_5)(CO_2C_2H_5)_2$ | 60 | $NaOC_2H_5$ | Ethanol | 28 |
| | $n\text{-}C_3H_7Br$ | $n\text{-}C_3H_7CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 65 | $NaOC_2H_5$ | Ethanol | 28 |
| | $i\text{-}C_3H_7I$ | $n\text{-}C_3H_7CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | 70 | $NaOC_2H_5$ | Ethanol | 28 |
| $CH_3C(OC_3H_7\text{-}n)=$ | $C_2H_5X*$ | $CH_2=C(OC_3H_7\text{-}n)C(C_2H_5)(CO_2C_2H_5)_2$ | 39 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| $i\text{-}C_4H_9CH=$ | $CH_3I$ | $i\text{-}C_3H_7CH=CHC(CH_3)(CO_2C_2H_5)_2$ | 93 | $NaOC_2H_5$ | Ethanol | 28 |
| | $C_2H_5I$ | $i\text{-}C_3H_7CH=CHC(C_2H_5)(CO_2C_2H_5)_2$ | 88 | $NaOC_2H_5$ | Ethanol | 28 |
| | $n\text{-}C_3H_7Br$ | $i\text{-}C_3H_7CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 28 |
| | $i\text{-}C_3H_7Br$ | $i\text{-}C_3H_7CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$ | 86 | $NaOC_2H_5$ | Ethanol | 28 |
| | $CH_2=CHCH_2Br$ | $i\text{-}C_3H_7CH=CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$ | 92 | $NaOC_2H_5$ | Ethanol | 215 |
| $n\text{-}C_5H_{11}CH=$ | $CH_3I$ | $n\text{-}C_4H_9CH=CHC(CH_3)(CO_2C_2H_5)_2$ | 82 | $NaOC_2H_5$ | Ethanol | 28 |
| | $C_2H_5Br$ | $n\text{-}C_4H_9CH=CHC(C_2H_5)(CO_2C_2H_5)_2$ | 58 | $NaOC_2H_5$ | Ethanol | 28 |
| $CH_3C(OC_4H_9\text{-}n)=$ | $C_2H_5X*$ | $CH_2=C(OC_4H_9\text{-}n)C(C_2H_5)(CO_2C_2H_5)_2$ | 24 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 203 |
| $CH_3C(OC_5H_{11}\text{-}i)=$ | $C_2H_5X*$ | $CH_2=C(OC_5H_{11}\text{-}i)C(C_2H_5)(CO_2C_2H_5)_2$ | 55 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 208 |

*Note:* References 577–1080 are on pp. 322–331.

\* The halogen was not specified.

# TABLE VI

## ALKYLATION OF CYANOACETIC ESTERS, CH$_2$(CN)CO$_2$R

(The ethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| I$_2$ | Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate | — | Na | Ether | 270 |
| I$_2$ | C$_2$H$_5$O$_2$CCH(CN)CH(CN)CO$_2$C$_2$H$_5$ | — | Na | Ether | 271, 272 |
| **C$_1$** | | | | | |
| CH$_3$I | CH$_3$CH(CN)CO$_2$C$_2$H$_5$ | — | Na | Ether | 962 |
| CH$_3$I | { CH$_3$CH(CN)CO$_2$C$_2$H$_5$ | 72 | NaOC$_2$H$_5$ | Ethanol | 568, 963 |
| | { (CH$_3$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 12 | | | |
| CH$_3$I | CH$_3$CH(CN)CO$_2$C$_2$H$_5$ | 80 | NaOC$_2$H$_5$ | Ether | 185 |
| CHCl$_3$ | CH$_3$O$_2$CCH(CN)CH=C(CN)CO$_2$CH$_3$* | — | NaOCH$_3$ | CH$_3$OH | 964 |
| CHCl$_3$ | C$_2$H$_5$O$_2$CCH(CN)CH=C(CN)CO$_2$C$_2$H$_5$ | 70 | NaOC$_2$H$_5$ | Ethanol | 964, 586 965, 966, 967 |
| CHI$_3$ | C$_2$H$_5$O$_2$CCH(CN)CH=C(CN)CO$_2$C$_2$H$_5$ | 60 | NaOC$_2$H$_5$ | Ethanol | 964 |
| CCl$_4$ | C$_2$H$_5$O$_2$CC(Na)(CN)CH=C(CN)CO$_2$C$_2$H$_5$ | 41 | NaOC$_2$H$_5$ | Ethanol | 589, 590, 591 |
| CBr$_4$ | C$_2$H$_5$O$_2$CCH(CN)CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 590, 591 |
| CCl$_3$NO$_2$ | C$_2$H$_5$O$_2$CCH(CN)CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 590, 591 |
| **C$_2$** | | | | | |
| C$_2$H$_5$Br | { C$_2$H$_5$CH(CN)CO$_2$H | 28 | NaOC$_2$H$_5$ | Ethanol | 39 |
| | { (C$_2$H$_5$)$_2$C(CN)CO$_2$CH$_3$* | 23 | | | |
| C$_2$H$_5$Br | C$_2$H$_5$CH(CN)CO$_2$C$_2$H$_5$ and (C$_2$H$_5$)$_2$C(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 968 |
| C$_2$H$_5$Br | (C$_2$H$_5$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 93† | NaOC$_2$H$_5$ | Ethanol | 169 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CN)CO$_2$C$_2$H$_5$ | — | Na | Ether | 962 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CN)CO$_2$C$_2$H$_5$ | 89 | NaOC$_2$H$_5$ | Ether | 185 |
| C$_2$H$_5$I | C$_2$H$_5$CH(CN)CO$_2$C$_2$H$_5$ | 74 | NaOC$_2$H$_5$ | Ethanol | 95, 963 |
| C$_2$H$_5$I | (C$_2$H$_5$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 30 | NaOC$_2$H$_5$ | Ethanol | 95 |
| (C$_2$H$_5$)$_2$SO$_4$ | C$_2$H$_5$CH(CN)CO$_2$C$_2$H$_5$ | 75 | NaOC$_2$H$_5$ | Ethanol | 249 |
| (C$_2$H$_5$)$_2$SO$_4$ | (C$_2$H$_5$)$_2$CH(CN) | 60 | NaOC$_2$H$_5$ | Ethanol | 249 |
| CH$_3$OCH$_2$Cl | CH$_3$OCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | Na | Ether | 969 |
| CH$_2$ClCH$_2$Cl | C$_2$H$_5$O$_2$CCH(CN)(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | — | — | 970 |
| CH$_2$BrCH$_2$Br | { Ethyl 1-cyanocyclopropane-1-carboxylate | >50 | NaOC$_2$H$_5$ | Ethanol | 309, 479 |
| | { Ethyl 2-imino-3-cyanocyclopentane-1-carboxylate‡ | — | | | |
| CH$_2$BrCH$_2$Br | Ethyl 1-cyanocyclopropane-1-carboxylate, diethyl α,α'-dicyanoadipate, and ethyl 2-imino-3-cyanocyclopentane-1-carboxylate | — | NaOC$_2$H$_5$ | Ethanol | 310 |
| **C$_3$** | | | | | |
| n-C$_3$H$_7$Br | { n-C$_3$H$_7$CH(CN)CO$_2$C$_2$H$_5$ | ca. 63 | NaOC$_2$H$_5$ | Ethanol | 971, 972, 973 |
| | { (n-C$_3$H$_7$)$_2$C(CN)CO$_2$C$_2$H$_5$ | ca. 27 | | | |
| n-C$_3$H$_7$I | { n-C$_3$H$_7$CH(CN)CO$_2$C$_2$H$_5$ | 49 | NaOC$_2$H$_5$ | Ethanol | 38, 963 |
| | { (n-C$_3$H$_7$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 20 | | | |
| n-C$_3$H$_7$I | (n-C$_3$H$_7$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 70 | NaOC$_2$H$_5$ | Ethanol | 562 |
| CH$_3$SCH$_2$CH$_2$Cl-KI | CH$_3$S(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 54 | NaOC$_2$H$_5$ | Ethanol | 288 |
| i-C$_3$H$_7$Br | i-C$_3$H$_7$CH(CN)CO$_2$C$_2$H$_5$ | 65 | NaOC$_2$H$_5$ | Ethanol | 240 |
| i-C$_3$H$_7$I | { i-C$_3$H$_7$CH(CN)CO$_2$C$_2$H$_5$ | 63 | NaOC$_2$H$_5$ | Ethanol | 568, 225, 963 |
| | { (i-C$_3$H$_7$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 5 | | | |
| CH$_2$=CHCH$_2$I | CH$_2$=CHCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | Na | Ether | 962, 963 |

*Note:* References 577–1080 are on pp. 322–331.

\* The methyl ester was used in this experiment.

† The reactants were added in inverse order.

‡ When originally isolated this product was formulated as ethyl α,δ-dicyanovalerate (ref. 697). It was later identified as the cyclopentane derivative indicated (ref. 712).

TABLE VI—*Continued*

ALKYLATION OF CYANOACETIC ESTERS, CH$_2$(CN)CO$_2$R

(The ethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| CH$_3$COCH$_2$Cl | CH$_3$COCH$_2$CH(CN)CO$_2$CH$_3$* | — | NaOCH$_3$ | CH$_3$OH | 123 |
| CH$_3$COCH$_2$Cl | CH$_3$COCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ether | 123 |
| NC(CH$_2$)$_2$OSO$_2$C$_6$H$_4$CH$_3$-$p$ | [NC(CH$_2$)$_2$]$_2$C(CN)CO$_2$C$_2$H$_5$ | 86 | NaOC$_2$H$_5$ | Ethanol | 102 |
| ClCH$_2$CO$_2$CH$_3$ | CH$_3$O$_2$CCH$_2$CH(CN)CO$_2$CH$_3$* and (CH$_3$O$_2$CCH$_2$)$_2$C(CN)CO$_2$CH$_3$* | — | NaOCH$_3$ | CH$_3$OH | 974 |
| Cl(CH$_2$)$_3$Br | Cl(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 60 | NaOC$_2$H$_5$ | Ethanol | 127 |
| Br(CH$_2$)$_3$Br | Br(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 18 | NaOC$_2$H$_5$ | Ethanol | 185 |
| Br(CH$_2$)$_3$Br | C$_2$H$_5$O$_2$CCH(CN)(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ and ethyl 1-cyanocyclobutane-1-carboxylate | — | NaOC$_2$H$_5$ | Ethanol | 309 |
| H$_3$CCH——CH$_2$ \ O / | H$_3$CCHCH$_2$CHCN \| \| O——CO | 61 | NaOC$_2$H$_5$ | Ethanol | 528 |
| $C_4$ | | | | | |
| $n$-C$_4$H$_9$Br | $n$-C$_4$H$_9$CH(CN)CO$_2$C$_2$H$_5$ | 76 | NaOC$_2$H$_5$ | Ethanol | 288, 40 |
| C$_2$H$_5$O(CH$_2$)$_2$Br | C$_2$H$_5$O(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 65 | NaOC$_2$H$_5$ | Ethanol | 128 |
| $i$-C$_4$H$_9$Br | $i$-C$_4$H$_9$CH(CN)CO$_2$C$_2$H$_5$ | 34 | NaOC$_2$H$_5$ | Ethanol | 973, 975 |
| $i$-C$_4$H$_9$Br | $i$-C$_4$H$_9$CH(CN)CO$_2$C$_2$H$_5$ and ($i$-C$_4$H$_9$)$_2$C(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 472 |
| $i$-C$_4$H$_9$I | {$i$-C$_4$H$_9$CH(CN)CO$_2$C$_2$H$_5$ {($i$-C$_4$H$_9$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 47 — | NaOC$_2$H$_5$ | Ethanol | 38, 963 |
| $i$-C$_4$H$_9$I | {$i$-C$_4$H$_9$CH(CN)CO$_2$H {($i$-C$_4$H$_9$)$_2$C(CN)CO$_2$C$_4$H$_9$-$i$§ | 14 50 | NaOC$_4$H$_9$-$i$ | $i$-C$_4$H$_9$OH | 40 |
| C$_2$H$_5$CH(CH$_3$)Br | C$_2$H$_5$CH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$ | 59 | NaOC$_2$H$_5$ | Ethanol | 288 |
| CH$_3$CH=CHCH$_2$Br | CH$_3$CH=CHCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 976 |
| (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 39 | Na | CH$_2$(CN)CO$_2$C$_2$H$_5$–C$_6$H$_6$ | 130 |
| Cl(CH$_2$)$_2$O(CH$_2$)$_2$Cl | Ethyl 4-cyanotetrahydropyran-4-carboxylate | 33 | NaOC$_2$H$_5$ | Ethanol | 498, 497 |
| (CH$_3$)$_2$C——CH$_2$ \ O / | (CH$_3$)$_2$CCH$_2$CHCN \| \| O——CO | 82 | NaOC$_2$H$_5$ | Ethanol | 528 |
| BrCH$_2$CH=CHCH$_2$Br | Ethyl 1-cyano-2-vinylcyclopropane-1-carboxylate, ethyl 2-imino-3-cyano-4-vinylcyclopentane-1-carboxylate and ethyl 2-imino-3-cyano-5-vinylcyclopentane-1-carboxylate | 40 | NaOC$_2$H$_5$ | Ethanol | 201 |
| ClCH$_2$CO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 731, 974, 977 |
| Cl$_3$CCO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCNa(CN)CH=C(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 964 |
| $C_5$ | | | | | |
| $n$-C$_5$H$_{11}$Br | $n$-C$_5$H$_{11}$CH(CN)CO$_2$C$_2$H$_5$ | 82 | NaOC$_2$H$_5$ | Ethanol | 185 |
| $n$-C$_3$H$_7$CH(CH$_3$)Br | $n$-C$_3$H$_7$CH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$ | 63 | NaOC$_2$H$_5$ | Ethanol | 127 |
| (C$_2$H$_5$)$_2$CHBr | (C$_2$H$_5$)$_2$CHCH(CN)CO$_2$C$_2$H$_5$ | 62 | NaOC$_2$H$_5$ | Ethanol | 127, 238 |
| $i$-C$_5$H$_{11}$Br | $i$-C$_5$H$_{11}$CH(CN)CO$_2$C$_2$H$_5$ | 76 | NaOC$_2$H$_5$ | Ethanol | 973, 978 |
| $i$-C$_5$H$_{11}$I | {$i$-C$_5$H$_{11}$CH(CN)CO$_2$C$_2$H$_5$ {($i$-C$_5$H$_{11}$)$_2$C(CN)CO$_2$C$_2$H$_5$ | — 28 | NaOC$_2$H$_5$ | Ethanol | 568 |
| $i$-C$_5$H$_{11}$I | {$i$-C$_5$H$_{11}$CH(CN)CO$_2$C$_5$H$_{11}$-$i$∥ and {($i$-C$_5$H$_{11}$)$_2$C(CN)CO$_2$C$_5$H$_{11}$-$i$ | — | NaOC$_5$H$_{11}$-$i$ | $i$-C$_5$H$_{11}$OH | 39 |
| $i$-C$_3$H$_7$CH(CH$_3$)Br | $i$-C$_3$H$_7$CH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$ | 45 | NaOC$_2$H$_5$ | Ethanol | 470 |
| CH$_3$CHBrCO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$ | 70 | NaOC$_2$H$_5$ | Ethanol | 167, 974 |
| I(CH$_2$)$_2$CO$_2$C$_2$H$_5$ | [C$_2$H$_5$O$_2$C(CH$_2$)$_2$]$_2$C(CN)CO$_2$C$_2$H$_5$ | 100 | NaOC$_2$H$_5$ | Ethanol | 979 |

*Note:* References 577–1080 are on pp. 322–331.

\* The methyl ester was used in this experiment.

§ The isobutyl ester was used in this experiment.

∥ The product also contained some of the ethyl ester.

TABLE VI—*Continued*

ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| | $\overset{\displaystyle C(CN)CO_2C_2H_5}{\diagup\diagdown}$ | | | | |
| $BrCH(CN)CO_2C_2H_5$ | $C_2H_5O_2C(NC)C\!\!-\!\!\!-\!\!C(CN)CO_2C_2H_5$ | 67 | Na | Ether | 273 |
| $C_6$ | | | | | |
| $n\text{-}C_6H_{13}Br$ | $n\text{-}C_6H_{13}CH(CN)CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 469 |
| $n\text{-}C_4H_9CH(CH_3)Br$ | $n\text{-}C_4H_9CH(CH_3)CH(CN)CO_2C_2H_5$ | 50 | $NaOC_2H_5$ | Ethanol | 127 |
| $i\text{-}C_4H_9CH(CH_3)Br$ | $i\text{-}C_4H_9CH(CH_3)CH(CN)CO_2C_2H_5$ | 60 | $NaOC_2H_5$ | Ethanol | 470 |
| $(C_2H_5)_2CHCH_2Br$ | $(C_2H_5)_2CHCH_2CH(CN)CO_2C_2H_5$ | 50 | $NaOC_2H_5$ | Ethanol | 469 |
| $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2CH(CN)CO_2C_2H_5$ | 69 | Na | $CH_2(CN)CO_2C_2H_5 \cdot C_6H_6$ | 130 |
| $C_2H_5CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_2H_5)CH(CN)CO_2C_2H_5$ | 67 | $NaOC_2H_5$ | Ethanol | 980 |
| $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2CH(CN)CO_2C_2H_5$ | 58 | $NaOC_2H_5$ | Ethanol | 167, 981 |
| $Br(CH_2)_3CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_3CH(CN)CO_2C_2H_5$ | 62 | $NaOC_2H_5$ | Ethanol | 185, 982 |
| Cyclohexyl bromide | Ethyl cyclohexylcyanoacetate | 23 | $NaOC_2H_5$ | Ethanol | 469 |
| Cyclohexyl iodide | Ethyl cyclohexylmalonamic acid | 62 | $K_2CO_3$ | None | 89 |
| 1,2-Dibromocyclohexane | {Ethyl 2-cyclohexenylcyanoacetate | 40 | — | — | 150, 322 |
| | {Ethyl di-(2-cyclohexenyl)cyanoacetate | — | | | |
| Cyclohexene oxide | 3-Cyanohexahydro-2-benzofuranone | 17 | $NaOC_2H_5$ | Ethanol | 528 |
| $p\text{-}O_2NC_6H_4Cl$ | $p\text{-}O_2NC_6H_4CH(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 325 |
| 2,4-Dinitrochlorobenzene | Ethyl (2,4-dinitrophenyl)cyanoacetate | 90 | $NaOC_2H_5$ | Ethanol | 325 |
| Picryl chloride | Ethyl (2,4,6-trinitrophenyl)cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 325 |
| $C_7$ | | | | | |
| $n\text{-}C_7H_{15}Br$ | $n\text{-}C_7H_{15}CH(CO_2H)_2$ | 84 | $K_2CO_3$ | None | 89 |
| $n\text{-}C_7H_{15}Br$ | $n\text{-}C_7H_{15}CH(CN)CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 469 |
| $n\text{-}C_5H_{11}CH(CH_3)Br$ | $n\text{-}C_5H_{11}CH(CH_3)CH(CN)CO_2C_2H_5$ | 71 | $NaOC_2H_5$ | Ethanol | 128 |
| $n\text{-}C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7\text{-}n)CH(CN)CO_2C_2H_5$ | 44–50 | $NaOC_2H_5$ | Ethanol | 984 |
| $CH_3CHBr(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2CH(CH_3)CH(CN)CO_2C_2H_5$ | — | — | — | 283 |
| $Br(CH_2)_4CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_4CH(CN)CO_2C_2H_5$ | 30 | $NaOC_2H_5$ | Ethanol | 982 |
| $I(CH_2)_4CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_4CH(CN)CO_2C_2H_5$ | 85 | $NaOC_2H_5$ | Ethanol | 185 |
| $Br(CH_2)_3CHBrCO_2C_2H_5$ | Diethyl 1-cyanocyclopentane-1,2-dicarboxylate | 89 | $NaOC_2H_5$ | Ethanol | 629 |
| $i\text{-}C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7\text{-}i)CH(CN)CO_2C_2H_5$ | 44–50 | $NaOC_2H_5$ | Ethanol | 984 |
| $C_2H_5OCH_2CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_2OC_2H_5)CH(CN)CO_2C_2H_5$ | 28 | Na | None | 721 |
| Cyclohexylmethyl iodide | Ethyl (cyclohexylmethyl)cyanoacetate | 51 | $NaOC_2H_5$ | Ethanol | 470 |
| 2-Methylcyclohexyl bromide | Ethyl (2-methylcyclohexyl)cyanoacetate | 18 | $NaOC_2H_5$ | Ethanol | 470 |
| 3-Methylcyclohexyl bromide | Ethyl (3-methylcyclohexyl)cyanoacetate | 32 | $NaOC_2H_5$ | Ethanol | 470 |
| 4-Methylcyclohexyl bromide | Ethyl (4-methylcyclohexyl)cyanoacetate | 32 | $NaOC_2H_5$ | Ethanol | 470 |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ and $(C_6H_5CH_2)_2C(CN)CO_2C_2H_5$ | — | Na | None | 95 |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 40 | KOH | $(n\text{-}C_3H_7O)_2CHCH_3$ | 83 |
| $C_6H_5CH_2Cl$ | {$C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 30 | KOH | $(n\text{-}C_4H_9O)_2CHCH_3$ | 83 |
| | {$(C_6H_5CH_2)_2C(CN)CO_2C_2H_5$ | 14 | | | |
| $C_6H_5CH_2Cl$ | {$C_6H_5CH_2CH(CN)CO_2H$ | Poor | $NaOCH_3$ | $CH_3OH$ | 38 |
| | {$(C_6H_5CH_2)_2C(CN)CO_2CH_3$* | Poor | | | |
| $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 60 | $NaOC_2H_5$ | Ethanol | 116, 95 |
| $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CN)CO_2C_2H_5$ | Good | $NaOC_2H_5$ | Ethanol | 562 |
| $o\text{-}ClC_6H_4CH_2Cl$ | $o\text{-}ClC_6H_4CH_2CH(CN)CO_2C_2H_5$ | 42 | $NaOC_2H_5$ | Ethanol | 128 |
| $o\text{-}O_2NC_6H_4CH_2Cl$ | $o\text{-}O_2NC_6H_4CH_2CH(CN)CO_2C_2H_5$ and $(o\text{-}O_2NC_6H_4CH_2)_2C(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 112 |
| $C_6H_5CH_2Br$ | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 44 | $NaOC_2H_5$ | Ethanol | 982 |
| $C_8$ | | | | | |
| $n\text{-}C_8H_{17}Br$ | $n\text{-}C_8H_{17}CH(CN)CO_2C_2H_5$ | 75 | $NaOC_2H_5$ | Ethanol | 469 |
| $n\text{-}C_8H_{17}I$ | $n\text{-}C_8H_{17}CH(CO_2H)_2$ | 95 | $K_2CO_3$ | None | 89 |
| $n\text{-}C_6H_{13}CH(CH_3)Br$ | $n\text{-}C_6H_{13}CH(CH_3)CH(CN)CO_2C_2H_5$ | 63 | $NaOC_2H_5$ | Ethanol | 128 |

*Note:* References 577–1080 are on pp. 322–331.

* The methyl ester was used in this experiment.

## TABLE VI—*Continued*

### ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| $n$-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$Br | $n$-C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 50 | NaOC$_2$H$_5$ | Ethanol | 469 |
| $i$-C$_6$H$_{13}$CH(CH$_3$)I | $i$-C$_6$H$_{13}$CH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$ | 81 | NaOC$_2$H$_5$ | Ethanol | 750 |
| $i$-C$_4$H$_9$CHBrCO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CCH(C$_4$H$_9$-$i$)CH(CN)CO$_2$C$_2$H$_5$ | 65 | NaOC$_2$H$_5$ | Ethanol | 985 |
| Br(CH$_2$)$_3$CBr(CH$_3$)CO$_2$C$_2$H$_5$ | Diethyl 2-cyano-1-methylcyclopentane-1,2-dicarboxylate | — | NaOC$_2$H$_5$ | Ethanol | 629 |
| C$_2$H$_5$O$_2$CCH$_2$CHBrCO$_2$C$_2$H$_5$ | Triethyl α-cyanotricarballylate | — | NaOC$_2$H$_5$ | Ethanol | 974 |
| CH$_3$O$_2$CCHBr(CH$_2$)$_2$CHBr-CO$_2$CH$_3$ (low-melting form) | Trimethyl 2-cyanocyclo-pentane-1,2,3-tricarboxylate* | — | NaOCH$_3$ | CH$_3$OH | 753 |
| CH$_3$O$_2$CCHBr(CH$_2$)$_2$CHBr-CO$_2$CH$_3$ (high-melting form) | Trimethyl 2-cyanocyclo-pentane-1,2,3-tricarboxylate* | — | NaOCH$_3$ | CH$_3$OH | 753 |
| C$_2$H$_5$O$_2$CCHBrCHBr-CO$_2$C$_2$H$_5$ (*meso* form) | Triethyl 1-cyanocyclo-propane-1,2,3-tricarboxylate | — | NaOC$_2$H$_5$ | Ethanol | 175 |
| C$_2$H$_5$O$_2$CCHBrCHBr-CO$_2$C$_2$H$_5$ (+,— form) | Triethyl 1-cyanocyclo-propane-1,2,3-tricarboxylate | 85 | NaOC$_2$H$_5$ | Ethanol | 175 |
| β-Cyclohexylethyl bromide | Ethyl (β-cyclohexylethyl)cyanoacetate | 70 | NaOC$_2$H$_5$ | Ethanol | 127 |
| C$_6$H$_5$(CH$_2$)$_2$Br | C$_6$H$_5$(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 78 | NaOC$_2$H$_5$ | Ethanol | 469 |
| C$_6$H$_5$(CH$_2$)$_2$Br | [C$_6$H$_5$(CH$_2$)$_2$]$_2$C(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 105 |
| C$_6$H$_5$O(CH$_2$)$_2$Br | {C$_6$H$_5$O(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ <br> {[C$_6$H$_5$O(CH$_2$)$_2$]$_2$C(CN)CO$_2$C$_2$H$_5$ | 62 <br> 32 | NaOC$_2$H$_5$ | Ethanol | 185 |
| $p$-ClC$_6$H$_4$O(CH$_2$)$_2$Br | $p$-ClC$_6$H$_4$O(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 52 | NaOC$_2$H$_5$ | Ethanol | 128 |
| $o$-CH$_3$C$_6$H$_4$CH$_2$Br | $o$-CH$_3$C$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 55 | NaOC$_2$H$_5$ | Ethanol | 470 |
| $m$-CH$_3$C$_6$H$_4$CH$_2$Br | $m$-CH$_3$C$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 55 | NaOC$_2$H$_5$ | Ethanol | 470 |
| $p$-CH$_3$C$_6$H$_4$CH$_2$Cl | $p$-CH$_3$C$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 48 | NaOC$_2$H$_5$ | Ethanol | 470 |
| $p$-CH$_3$OC$_6$H$_4$CH$_2$Cl | $p$-CH$_3$OC$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 48 | NaOC$_2$H$_5$ | Ethanol | 982 |
| C$_6$H$_5$COCH$_2$Br | C$_6$H$_5$COCH$_2$CH(CN)CO$_2$CH$_3$* and (C$_6$H$_5$COCH$_2$)$_2$C(CN)CO$_2$CH$_3$* | — | NaOCH$_3$ | CH$_3$OH | 123 |
| C$_6$H$_5$COCH$_2$Br | C$_6$H$_5$COCH$_2$CH(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 123, 124 |
| C$_6$H$_5$COCH$_2$Br | (C$_6$H$_5$COCH$_2$)$_2$C(CN)CO$_2$C$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 106 |
| C$_6$H$_5$COCH$_2$Br | C$_6$H$_5$COCH$_2$CH(CN)CO$_2$C$_3$H$_7$-$n$¶ | — | — | — | 123 |
| $o$-NCC$_6$H$_4$CH$_2$Cl | $o$-NCC$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | Good | NaOC$_2$H$_5$ | Ethanol | 198 |
| $o$-NCC$_6$H$_4$CH$_2$Cl | ($o$-NCC$_6$H$_4$CH$_2$)$_2$C(CN)CO$_2$C$_2$H$_5$ | 80 | NaOC$_2$H$_5$ | Ethanol | 198, 111 |
| (structure) CH$_2$Br / CH$_2$Br | (structure) C(CN)CO$_2$C$_2$H$_5$ | 95 | NaOC$_2$H$_5$ | Ethanol-ether | 185 |
| **C$_9$** | | | | | |
| $n$-C$_9$H$_{19}$Br | $n$-C$_9$H$_{19}$CH(CN)CO$_2$C$_2$H$_5$ | 70 | NaOC$_2$H$_5$ | Ethanol | 127 |
| C$_2$H$_5$O$_2$CCHBrCH$_2$-CHBrCO$_2$C$_2$H$_5$ | Triethyl 2-cyanocyclobutane-1,2,3-tricarboxylate | 70 | NaOC$_2$H$_5$ | Ethanol | 176 |
| C$_6$H$_5$(CH$_2$)$_3$Br | C$_6$H$_5$(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 68 | NaOC$_2$H$_5$ | Ethanol | 469 |
| C$_6$H$_5$O(CH$_2$)$_3$Br | C$_6$H$_5$O(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 40 | NaOC$_2$H$_5$ | Ethanol | 982 |
| $o$-BrC$_6$H$_4$O(CH$_2$)$_3$Br | $o$-BrC$_6$H$_4$O(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 45 | NaOC$_2$H$_5$ | Ethanol | 471 |
| 2,4-Cl$_2$C$_6$H$_3$O(CH$_2$)$_3$Br | 2,4-Cl$_2$C$_6$H$_3$O(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 38 | NaOC$_2$H$_5$ | Ethanol | 471 |
| $p$-BrC$_6$H$_4$O(CH$_2$)$_3$Br | $p$-BrC$_6$H$_4$O(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$ | 65 | NaOC$_2$H$_5$ | Ethanol | 128 |
| C$_6$H$_5$CH$_2$S(CH$_2$)$_2$Cl·KI | C$_6$H$_5$CH$_2$S(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 49 | NaOC$_2$H$_5$ | Ethanol | 288 |
| $p$-C$_2$H$_5$C$_6$H$_4$CH$_2$Cl | $p$-C$_2$H$_5$C$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$ | 50 | NaOC$_2$H$_5$ | Ethanol | 470 |
| $p$-CH$_3$C$_6$H$_4$O(CH$_2$)$_2$Cl | $p$-CH$_3$C$_6$H$_4$O(CH$_2$)$_2$CH(CN)CO$_2$C$_2$H$_5$ | 62 | NaOC$_2$H$_5$ | Ethanol | 128 |
| 1-Bromoindane | Ethyl 1-indanylcyanoacetate | 20 | NaOC$_2$H$_5$ | Ethanol | 127 |

*Note:* References 577–1080 are on pp. 322—331.

* The methyl ester was used in this experiment.

¶ The *n*-propyl ester was used in this experiment.

## TABLE VI—*Continued*

### ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

| Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|
| 2,3-Dichloroindenone | Ethyl chloroindenonylcyanoacetate** | — | — | — | 986 |
| 2,3-Dibromoindenone | Ethyl bromoindenonylcyanoacetate** and diethyl indenone-2,3-dicyanoacetate | — | — | — | 986 |
| $C_{10}$ | | | | | |
| $n$-$C_{10}H_{21}Br$ | $n$-$C_{10}H_{21}CH(CN)CO_2C_2H_5$ | 65 | $NaOC_2H_5$ | Ethanol | 469 |
| $C_2H_5O_2CCHBr(CH_2)_3$-$CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_3CH(CO_2C_2H_5)$-$CH(CN)CO_2C_2H_5$ | 55 | $NaOC_2H_5$ | Ethanol | 787 |
| $m$-$CH_3C_6H_4O(CH_2)_3Br$ | $[m$-$CH_3C_6H_4O(CH_2)_3]_2C(CN)CO_2C_2H_5$ | 57 | $NaOC_2H_5$ | Ethanol | 471 |
| $p$-$CH_3C_6H_4O(CH_2)_3Br$ | $p$-$CH_3C_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$ | 74 | $NaOC_2H_5$ | Ethanol | 128 |
| $p$-$C_2H_5C_6H_4O(CH_2)_2Br$ | $p$-$C_2H_5C_6H_4O(CH_2)_2CH(CN)CO_2C_2H_5$ | 60 | $NaOC_2H_5$ | Ethanol | 128 |



| | $CH(CN)CO_2C_2H_5$†† | — | — | — | 150 |
|---|---|---|---|---|---|



| | | — | — | — | 986 |
|---|---|---|---|---|---|

| $C_{11}$ | | | | | |
|---|---|---|---|---|---|
| $n$-$C_{11}H_{23}I$ | $n$-$C_{11}H_{23}CH(CO_2H)_2$ | 81 | $K_2CO_3$ | None | 89 |
| $m$-$C_2H_5C_6H_4O(CH_2)_3Br$ | $[m$-$C_2H_5C_6H_4O(CH_2)_3]_2C(CN)CO_2C_2H_5$ | 40 | $NaOC_2H_5$ | Ethanol | 471 |
| $p$-$C_2H_5C_6H_4O(CH_2)_3Br$ | $p$-$C_2H_5C_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 128 |
| 1-Chloromethylnaphthalene | Ethyl (1-naphthylmethyl)cyanoacetate | 45 | $NaOC_2H_5$ | Ethanol | 469 |
| $C_{12}$ | | | | | |
| $n$-$C_{12}H_{25}Br$ | $n$-$C_{12}H_{25}CH(CN)CO_2C_2H_5$ | 75 | $NaOC_2H_5$ | Ethanol | 128 |
| $C_{16}$–$C_{19}$ | | | | | |
| $n$-$C_{16}H_{33}I$ | $n$-$C_{16}H_{33}CH(CO_2H)_2$ | 90 | $K_2CO_3$ | None | 89 |
| $n$-$C_{16}H_{33}Br$ | $n$-$C_{16}H_{33}CH(CN)CO_2C_2H_5$ | 75 | $NaOC_2H_5$ | Ethanol | 127 |
| $(C_6H_5)_3CBr$ | $(C_6H_5)_3CCH(CN)CO_2C_2H_5$ | Poor | $NaOC_2H_5$ | Ethanol | 987 |

*Note:* References 577–1080 are on pp. 322–331.

** The structure of the product was not determined.

†† The position of the double bond was not stated.

TABLE VII

ALKYLATION OF BROMO-, ACETAMIDO-, AND PHENYLACETAMIDO-CYANOACETIC ESTERS, $XCH(CN)CO_2R$

(The ethyl ester was used unless otherwise indicated.)

| X | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Br | None | Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate | 25 | Aniline | Ether | 273 |
| | None | Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate | 60 | Na | Ether | 273 |
| $CH_3CONH$ | $CH_3I$ | $CH_3CONHC(CH_3)(CN)CO_2C_2H_5$ | 71 | $NaOC_2H_5$ | Ethanol | 232 |
| | $C_2H_5Br$ | $CH_3CONHC(C_2H_5)(CN)CO_2C_2H_5$ | 85 | $NaOC_2H_5$ | Ethanol | 232 |
| | $n$-$C_3H_7Br$ | $CH_3CONHC(C_3H_7$-$n)(CN)CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 232 |
| | $CH_3S(CH_2)_2Cl$ | $CH_3S(CH_2)_2C(NHCOCH_3)(CN)CO_2C_2H_5$ | 60 | $NaOC_2H_5$ | Ethanol | 241 |
| | $i$-$C_3H_7Br$ | $CH_3CONHC(C_3H_7$-$i)(CN)CO_2C_2H_5$ | 66 | $NaOC_2H_5$ | Ethanol | 241 |
| | $CH_2$=$CHCH_2Br$ | $CH_3CONHC(CH_2CH$=$CH_2)(CN)CO_2C_2H_5$ | 82 | $NaOC_2H_5$ | Ethanol | 232 |
| | $n$-$C_4H_9I$ | $CH_3CONHC(C_4H_9$-$n)(CN)CO_2C_2H_5$ | 78 | $NaOC_2H_5$ | Ethanol | 232 |
| | $i$-$C_4H_9Br$ | $CH_3CONHC(C_4H_9$-$i)(CN)CO_2C_2H_5$ | 65 | $NaOC_2H_5$ | Ethanol | 241, 232 |
| | $CH_2$=$C(CH_3)CH_2Cl$ | $CH_3CONHC[CH_2C(CH_3)$=$CH_2](CN)CO_2C_2H_5$ | 82 | $NaOC_2H_5$ | Ethanol | 232 |
| | 4-Chloro-methylimidazole hydrochloride | Ethyl $\alpha$-acetamido-$\alpha$-cyano-$\beta$-(4-imidazolyl)propionate | 66 | $NaOC_2H_5$ | Ethanol | 241 |
| | $n$-$C_5H_{11}Br$ | $CH_3CONHC(C_5H_{11}$-$n)(CN)CO_2C_2H_5$ | 57 | $NaOC_2H_5$ | Ethanol | 232 |
| | $n$-$C_6H_{13}I$ | $CH_3CONHC(C_6H_{13}$-$n)(CN)CO_2C_2H_5$ | 81 | $NaOC_2H_5$ | Ethanol | 232 |
| | $n$-$C_7H_{15}Br$ | $CH_3CONHC(C_7H_{15}$-$n)(CN)CO_2C_2H_5$ | 65 | $NaOC_2H_5$ | Ethanol | 232 |
| | $C_6H_5CH_2Cl$ | $CH_3CONHC(CH_2C_6H_5)(CN)CO_2C_2H_5$ | 83 | $NaOC_2H_5$ | Ethanol | 241 |
| | $n$-$C_8H_{17}I$ | $CH_3CONHC(C_8H_{17}$-$n)(CN)CO_2C_2H_5$ | 81 | $NaOC_2H_5$ | Ethanol | 232 |
| | $p$-$CH_3OC_6H_4CH_2Br$ | $p$-$CH_3OC_6H_4CH_2C(NHCOCH_3)(CN)CO_2C_2H_5$ * | 96 | $NaOC_2H_5$ | Ethanol | 242 |
| | $n$-$C_9H_{19}Br$ | $CH_3CONHC(C_9H_{19}$-$n)(CN)CO_2C_2H_5$ | 32 | $NaOC_2H_5$ | Ethanol | 232 |
| | $\gamma$-Phthalimidopropyl bromide | $C_8H_4O_2N(CH_2)_3C(NHCOCH_3)(CN)CO_2C_2H_5$ * | 75 | $NaOC_2H_5$ | Ethanol | 242 |
| | $\delta$-Phthalimidobutyl iodide | $C_8H_4O_2N(CH_2)_4C(NHCOCH_3)(CN)CO_2C_2H_5$ * | 80 | $NaOC_2H_5$ | Ethanol | 242 |
| $C_6H_5CH_2CONH$ ($=C_8H_8ON$) | $CH_3S(CH_2)_2Cl$ | $CH_3S(CH_2)_2C(C_8H_8ON)(CN)CO_2CH_3$† | ca. 76 | $NaOC_2H_5$ | Ethanol | 243 |
| | $i$-$C_3H_7I$ | $i$-$C_3H_7C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOC_2H_5$ | Ethanol | 243 |
| | $i$-$C_4H_9I$ | $i$-$C_4H_9C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOC_2H_5$ | Ethanol | 243 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOCH_3$ | $CH_3OH$ | 244 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOC_2H_5$ | Ethanol | 243 |
| | $p$-$CH_3OC_6H_4CH_2Cl$ | $p$-$CH_3OC_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOCH_3$ | $CH_3OH$ | 244 |
| | $p$-$CH_3OC_6H_4CH_2Cl$ | $p$-$CH_3OC_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$† | — | $NaOC_2H_5$ | Ethanol | 243 |
| | $p$-$CH_3C_6H_4SO_2$-$C_6H_4CH_2Br$-$p$ | $p$-$CH_3C_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$† | 50 | $NaOC_2H_5$ | Ethanol | 245 |
| | $p$-$CH_3OC_6H_4SO_2$-$C_6H_4CH_2Br$-$p$ | $p$-$CH_3OC_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$† | poor | Na | $C_6H_6$ | 245 |
| | $p$-$CH_3OC_6H_4SO_2$-$C_6H_4CH_2Br$-$p$ | $p$-$CH_3OC_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$† | 80 | $NaOC_2H_5$ | Ethanol | 245 |
| | $p$-$BrCH_2C_6H_4SO_2$-$C_6H_4CH_2Br$-$p$ | $O_2S[C_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$-$p]_2$† | 50 | $NaOC_2H_5$ | Ethanol | 245 |
| | $p$-$CH_3OC_6H_4COC_6H_4$-$CH_2Br$-$p$ | $p$-$CH_3OC_6H_4COC_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$† | 78 | $NaOC_2H_5$ | Ethanol | 245 |

* The ethyl acetamidocyanoacetate used contained radioactive carbon.
† The methyl ester was used in this experiment.

# TABLE VIII

ALKYLATION OF MONOALKYLCYANOACETIC ESTERS, $RCH(CN)CO_2R'$

(The ethyl ester was used unless otherwise indicated.)

| R | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_1$ | | | | | | |
| $CH_3$ | $CH_2I_2$ | $C_2H_5O_2CC(CH_3)(CN)CH_2$-$C(CH_3)(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 988 |
| | $(CH_3)_2CBrCO_2C_2H_5$ | $C_2H_5O_2CC(CH_3)_2C(CH_3)(CN)$-$CO_2C_2H_5$ | ca. 100 | $NaOC_2H_5$ | Ethanol | 989, 164 |
| $C_2$ | | | | | | |
| $C_2H_5$ | $i$-$C_3H_7I$ | $i$-$C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$ | 20 | $NaOC_2H_5$ | Ethanol | 145 |
| $C_3$ | | | | | | |
| $n$-$C_3H_7$ | $C_2H_5I$ | $n$-$C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 562 |
| | $CH_2$=$CHCH_2I$ | $CH_2$=$CHCH_2C(C_3H_7$-$n)(CN)$-$CO_2C_2H_5$ | 83 | $NaOC_2H_5$ | Ethanol | 971, 972 |
| $i$-$C_3H_7$ | $C_2H_5I$ | $i$-$C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$ | 86 | $NaOC_2H_5$ | Ethanol | 239 |
| | $n$-$C_3H_7Br$ | $i$-$C_3H_7C(C_3H_7$-$n)(CN)CO_2C_2H_5$ | 76 | $NaOC_2H_5$ | Ethanol | 240 |
| | $i$-$C_3H_7I$ | $(i$-$C_3H_7)_2C(CN)CO_2C_2H_5$ | 95 | $NaOC_2H_5$ | Ethanol | 225 |
| $C_4$ | | | | | | |
| $n$-$C_4H_9$ | $i$-$C_3H_7Br$ | $n$-$C_4H_9C(C_3H_7$-$i)(CN)CO_2C_2H_5$ | 87 | $NaOC_2H_5$ | Ethanol | 575 |
| $i$-$C_4H_9$ | $C_2H_5Br$ | $i$-$C_4H_9C(C_2H_5)(CN)CO_2C_3H_7$-$n$* | 78 | $NaOC_3H_7$-$n$ | $(n$-$C_3H_7O)_2CO$ | 44, 51, 227 |
| | $i$-$C_4H_9I$ | $(i$-$C_4H_9)_2C(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 975 |
| $sec$-$C_4H_9$ | $n$-$C_3H_7Br$ | $sec$-$C_4H_9C(C_3H_7$-$n)(CN)CO_2C_2H_5$ | 73 | $NaOC_2H_5$ | Ethanol | 214 |
| | $sec$-$C_4H_9Br$ | $(sec$-$C_4H_9)_2C(CN)CO_2C_2H_5$ | 50 | $NaOC_2H_5$ | Ethanol | 575 |
| $CH_3CH$=$CHCH_2$ | $CH_2$=$CHCH_2Br$ | $CH_3CH$=$CHCH_2$-$C(CH_2CH$=$CH_2)(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 976 |
| $CH_3O_2CCH_2$ | $CH_3I$ | $CH_3O_2CCH_2C(CH_3)(CN)CO_2CH_3$† | — | $NaOCH_3$ | $CH_3OH$ | 974 |
| $C_2H_5O_2CCH_2$ | $C_2H_5I$ | $C_2H_5O_2CCH_2C(C_2H_5)(CN)CO_2C_2H_5$ | 79 | $NaOC_2H_5$ | Ethanol | 980, 974 |
| | $n$-$C_3H_7I$ | $C_2H_5O_2CCH_2C(C_3H_7$-$n)(CN)$-$CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 974 |
| | $CH_2$=$CHCH_2I$ | $C_2H_5O_2CCH_2C(CN)CO_2C_2H_5$ <br> $\vert$ <br> $CH_2$=$CHCH_2$ | — | $NaOC_2H_5$ | Ethanol | 974 |
| | $ClCH_2CO_2C_2H_5$ | $(C_2H_5O_2CCH_2)_2C(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 977 |
| | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)C(CN)CO_2C_2H_5$ <br> $\vert$ <br> $CH_2CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 974 |
| | $C_6H_5CH_2Cl$ | $C_2H_5O_2CCH_2C(CH_2C_6H_5)(CN)$-$CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 974 |
| (=$C_4H_3S$) | $ClCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_4H_3S)(CN)$-$CO_2C_2H_5$ | 60 | $K_2CO_3$ | $(CH_3)_2CO$ | 88 |
| | 2-Cyclohexenyl bromide | Ethyl 2-thienyl-(2-cyclohexenyl)-cyanoacetate | 67 | $NaOC_2H_5$ | Ethanol | 187 |
| $C_5$ | | | | | | |
| $(C_2H_5)_2CH$ | $C_2H_5Br$ | $(C_2H_5)_2CHC(C_2H_5)(CN)CO_2C_2H_5$ | Good | $NaOC_2H_5$ | Ethanol | 238, 983 |
| $C_2H_5O_2CCH_2C($=$NH)$ | $ICH_2CN$ | $HN$=$C$⟨$\overset{NH—C=C(CN)CO_2C_2H_5}{\underset{CH_2—CHCO_2C_2H_5}{\vert}}$⟩ | — | $NaOC_2H_5$ | Ethanol | 990 |
| $CH_3CH(CO_2C_2H_5)$ | $CH_3I$ | $C_2H_5O_2CCH(CH_3)$-$C(CH_3)(CN)CO_2C_2H_5$ | 75 | $NaOC_2H_5$ | Ethanol | 167, 981 |
| | $n$-$C_3H_7I$ | $C_2H_5O_2CCH(CH_3)$-$C(C_3H_7$-$n)(CN)CO_2C_2H_5$ | 81 | $NaOC_2H_5$ | Ethanol | 985 |
| | $i$-$C_4H_9X$‡ | $C_2H_5O_2CCH(CH_3)$-$C(C_4H_9$-$i)(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 985 |
| $C_6$ | | | | | | |
| $(CH_3)_2C(CO_2C_2H_5)$ | $CH_3I$ | $C_2H_5O_2CC(CH_3)_2$-$C(CH_3)(CN)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 981 |
| 2-Cyclohexenyl (=$C_6H_9$) | $CH_3I$ | $C_6H_9C(CH_3)(CN)CO_2C_2H_5$ | 85 | $NaOC_2H_5$ | Ethanol | 290 |

*Note:* References 577–1080 are on pp. 322–331.

* The $n$-propyl ester was used in this experiment.

† The methyl ester was used in this experiment.

‡ The halogen was not specified.

## TABLE VIII—*Continued*

### ALKYLATION OF MONOALKYLCYANOACETIC ESTERS, RCH(CN)CO₂R'

(The ethyl ester was used unless otherwise indicated.)

| R | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| 2-Cyclohexenyl (=C₆H₉) (*Cont.*) | C₂H₅Br-KI | C₆H₉C(C₂H₅)(CN)CO₂C₂H₅ | 83–87 | NaOC₂H₅ | Ethanol | 290, 991 |
| | C₂H₅Br | C₂H₅C(C₂H₅)(CN)CO₂C₂H₅ | 90§ | NaOC₂H₅ | Ethanol | 169 |
| | n-C₃H₇Br-KI | C₆H₉C(C₃H₇-n)(CN)CO₂C₂H₅ | 62 | NaOC₂H₅ | Ethanol | 290 |
| | n-C₄H₉Br-KI | C₆H₉C(C₄H₉-n)(CN)CO₂C₂H₅ | 73 | NaOC₂H₅ | Ethanol | 290, 226 |
| | n-C₆H₁₃Br-KI | C₆H₉C(C₆H₁₃-n)(CN)CO₂C₂H₅ | 49 | NaOC₂H₅ | Ethanol | 290 |
| | C₆H₅CH₂Cl | C₆H₉C(CH₂C₆H₅)(CN)CO₂C₂H₅ | 54 | KOH | CH₃CH(OC₃H₇-n)₂ | 81, 83 |
| C₆H₅ | CH₃I | C₆H₅C(CH₃)(CN)CO₂C₂H₅ | 77 | NaOC₂H₅ | Ethanol | 992 |
| | ClCH₂CN | NCCH₂C(C₆H₅)(CN)CO₂C₂H₅ | 88 | KOH | 1-Butoxy-2-ethoxyethane | 81 |
| | ClCH₂CN | NCCH₂C(C₆H₅)(CN)CO₂C₂H₅ | 88 | KOH | CH₃CH(OC₄H₉-n)₂ | 83 |
| | ClCH₂CN | NCCH₂C(C₆H₅)(CN)CO₂C₂H₅ | 61 | NaNH₂ | Toluene | 188 |
| | CH₂BrCH₂Br | Br(CH₂)₂C(C₆H₅)(CN)CO₂C₂H₅ | — | NaOC₂H₅ | Ethanol | 188 |
| | Cl(CH₂)₂CN | NC(CH₂)₂C(C₆H₅)(CN)CO₂C₂H₅ | 63 | NaNH₂ | Toluene | 188 |
| | Cl(CH₂)₃Br | Cl(CH₂)₃C(C₆H₅)(CN)CO₂C₂H₅ | 78 | NaOC₂H₅ | Ethanol | 502, 188 |
| | ClCH₂CO₂C₂H₅ | C₂H₅O₂CCH₂C(C₆H₅)(CN)CO₂C₂H₅ | 81 | NaOC₂H₅ | Ethanol | 993 |
| | CH₃CHBrCO₂C₂H₅ | C₂H₅O₂CCH(CH₃)-C(C₆H₅)(CN)CO₂C₂H₅ | 60 | NaOC₂H₅ | Ethanol | 993 |
| | Cl(CH₂)₂CO₂C₂H₅ | C₂H₅O₂C(CH₂)₂-C(C₆H₅)(CN)CO₂C₂H₅ | 82 | NaOC₂H₅ | Ethanol | 993 |
| | (CH₃)₂CBrCO₂C₂H₅ | C₂H₅O₂CC(CH₃)₂-C(C₆H₅)(CN)CO₂C₂H₅ | 53 | NaOC₂H₅ | Ethanol | 993 |
| | C₆H₅CH₂Cl | C₆H₅CH₂C(C₆H₅)(CN)CO₂C₂H₅ | 88 | NaOC₂H₅ | Ethanol | 333 |
| | C₆H₄CH₂N(CH₃)-(CH₂)₂Cl | C₆H₅CH₂N(CH₃)(CH₂)₂-C(C₆H₅)(CN)CO₂C₂H₅ | 87 | Na | Ether-toluene | 188 |
| | C₆H₅CH₂N(CH₃)-(CH₂)₃Cl | C₆H₅CH₂N(CH₃)(CH₂)₃-C(C₆H₅)(CN)CO₂C₂H₅ | 76 | NaNH₂ | Toluene | 188 |
| **C₇** | | | | | | |
| C₂H₅O₂C(CH₂)₂CH(CH₃) | CH₃I | C₂H₅O₂C(CH₂)₂CH(CH₃)-C(CH₃)(CN)CO₂C₂H₅ | — | NaOC₂H₅ | Ethanol | 283 |
| n-C₃H₇CH(CO₂C₂H₅) | n-C₃H₇I | C₂H₅O₂CCH(C₃H₇-n)-C(C₃H₇-n)(CN)CO₂C₂H₅ | 78 | NaOC₂H₅ | Ethanol | 984 |
| i-C₃H₇CH(CO₂C₂H₅) | n-C₃H₇I | C₂H₅O₂CCH(C₃H₇-i)-C(C₃H₇-n)(CN)CO₂C₂H₅ | 82 | NaOC₂H₅ | Ethanol | 984 |
| | i-C₃H₇I | C₂H₅O₂CCH(C₃H₇-i)-C(C₃H₇-i)(CN)CO₂C₂H₅ | 70 | NaOC₂H₅ | Ethanol | 984 |
| C₆H₅CH₂ | C₆H₅CH₂N(CH₃)-(CH₂)₃Cl | C₆H₅CH₂N(CH₃)(CH₂)₃-C(CH₂C₆H₅)(CN)CO₂C₂H₅ | — | NaNH₂ | Toluene | 188 |
| o-CH₃C₆H₄ | C₆H₅CH₂N(CH₃)-(CH₂)₃Cl | C₆H₅CH₂N(CH₃)(CH₂)₃-C(CH₃C₆H₄-o)(CN)CO₂C₂H₅ | 65 | NaNH₂ | Toluene | 188 |
| p-CH₃C₆H₄ | C₂H₅Br | p-CH₃C₆H₄C(C₂H₅)(CN)CO₂C₂H₅ | 60 | NaOC₂H₅ | (C₂H₅O)₂CO | 44, 227 |
| **C₈** | | | | | | |
| i-C₆H₁₃CH(CH₃) | C₂H₅O(CH₂)₂I | C₂H₅O(CH₂)₂C(CN)CO₂C₂H₅ &#124; i-C₆H₁₃CHCH₃ | 80 | K | Xylene | 750 |
| i-C₄H₉CH(CO₂C₂H₅) | i-C₄H₉Br | C₂H₅O₂CCH(C₄H₉-i)-C(C₄H₉-i)(CN)CO₂C₂H₅ | — | NaOC₂H₅ | Ethanol | 985 |
| C₆H₅COCH₂ | CH₃I | C₆H₅COCH₂C(CH₃)(CN)CO₂CH₃* | — | NaOCH₃ | CH₃OH | 123 |
| | C₂H₅I | C₆H₅COCH₂C(C₂H₅)(CN)CO₂C₂H₅ | — | NaOC₂H₅ | Ethanol | 123 |
| | C₆H₅CH₂Cl | C₆H₅COCH₂C(CH₂C₆H₅)(CN)-CO₂CH₃* | — | NaOCH₃ | CH₃OH | 123 |
| **C₉** | | | | | | |
| 1-Indanyl | n-C₃H₇I | Ethyl 1-indanyl-(n-propyl)cyanoacetate | 41 | NaOC₂H₅ | Ethanol | 217 |
| **C₁₃** | | | | | | |
| (C₆H₅)₂CH | (C₆H₅)₂CHCl | [(C₆H₅)₂CH]₂C(CN)CO₂C₂H₅ | — | BrMg enolate‖ | Ether | 994 |

*Note:* References 577–1080 are on pp. 322–331.

\* The methyl ester was used in this experiment.

‖ The bromomagnesium enolate was obtained by the addition of phenylmagnesium bromide to ethyl benzylidenecyanoacetate.

§ The reactants were added in inverse order.

## TABLE IX

### ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $(C_2H_5)_2C{=}C(CN)_2$ | $CH_3I$ | $CH_3CH{=}C(C_2H_5)C(CH_3)(CN)_2$ | 93 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 41 |
| | $C_2H_5I$ | $CH_3CH{=}C(C_2H_5)C(C_2H_5)(CN)_2$ | 67 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 211 |
| | $CH_2{=}CHCH_2Br$ | $CH_3CH{=}C(C_2H_5)C(CH_2CH{=}CH_2)(CN)_2$ | 81 | $NaOC_2H_5$ | Ethanol | 215 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)_2$ | $C_2H_5Br$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)_2$ | — | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 211 |
| | $C_2H_5I$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)_2$ | — | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 211 |
| | $(C_2H_5)_2SO_4$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)_2$ | — | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 211 |
| [cyclohexylidene]${=}C(CN)_2$ | $C_2H_5I$ | (1-Cyclohexenyl)ethylmalononitrile | 63 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 211 |
| | $CH_2{=}CHCH_2Br$ | (1-Cyclohexenyl)allylmalononitrile | 93 | $NaOC_2H_5$ | Ethanol | 215 |
| $C_2H_5C(CH_3){=}C(CN)\text{-}CO_2C_2H_5$ | $CH_3I$ | $CH_3CH{=}C(CH_3)C(CH_3)(CN)CO_2C_2H_5$ | 65 | $NaOC_2H_5$ | Ethanol | 41 |
| | $C_2H_5I$ | $CH_3CH{=}C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$ | 55 | $NaOC_2H_5$ | Ethanol | 37 |
| | $n\text{-}C_3H_7I$ | $CH_3CH{=}C(CH_3)C(C_3H_7\text{-}n)(CN)CO_2C_2H_5$ | 42 | $NaOC_2H_5$ | Ethanol | 37 |
| | $CH_2{=}CHCH_2Br$ | $CH_3CH{=}C(CH_3)C(CH_2CH{=}CH_2)(CN)CO_2C_2H_5$ | 34 | $NaOC_2H_5$ | Ethanol | 214 |
| | $CH_2{=}CClCH_2Cl$ | Structure not determined* | Poor | $NaOC_2H_5$ | Ethanol | 64 |
| | $CH_2{=}CBrCH_2Br$ | Structure not determined* | Poor | $NaOC_2H_5$ | Ethanol | 64 |
| | $n\text{-}C_4H_9I$ | $CH_3CH{=}C(CH_3)C(C_4H_9\text{-}n)(CN)CO_2C_2H_5$ | 40 | $NaOC_2H_5$ | Ethanol | 37 |
| | $CH_3CH{=}CHCH_2Br$ | $CH_3CH{=}C(CH_3)C(CH_2CH{=}CHCH_3)(CN)CO_2C_2H_5$ | 30 | $NaOC_2H_5$ | Ethanol | 64 |
| | $CH_2{=}C(CH_3)CH_2Cl$ | $CH_3CH{=}C(CH_3)C[CH_2C(CH_3){=}CH_2](CN)CO_2C_2H_5$† | 20–35 | $NaOC_2H_5$ | Ethanol | 64 |
| | $C_6H_5CH{=}CHCH_2Br$ | $CH_3CH{=}C(CH_3)C(CH_2CH{=}CHC_6H_5)(CN)CO_2C_2H_5$* | Poor | $NaOC_2H_5$ | Ethanol | 64 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)\text{-}CO_2C_2H_5$ | $CH_3I$ | $C_2H_5CH{=}C(CH_3)C(CH_3)(CN)CO_2C_2H_5$ | 68 | $NaOC_2H_5$ | Ethanol | 37 |
| | $C_2H_5Br$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$ | 41 | $NaOC_2H_5$ | Ethanol | 37 |
| | $C_2H_5I$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$ | 63 | $NaOC_2H_5$ | Ethanol | 37 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)\text{-}CO_2CH_3$ | $C_2H_5I$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)CO_2CH_3$ | 17 | $NaOCH_3$ | $CH_3OH$ | 41 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)\text{-}CO_2C_2H_5$ | $(C_2H_5)_2SO_4$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$ | 45 | $NaOC_2H_5$ | Ethanol | 37 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)\text{-}CO_2C_3H_7\text{-}i$ | $(C_2H_5)_2SO_4$ | $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)\text{-}CO_2C_3H_7\text{-}i$ | 73 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 41 |
| $n\text{-}C_3H_7C(CH_3){=}C(CN)\text{-}CO_2C_2H_5$ | $n\text{-}C_3H_7I$ | $C_2H_5CH{=}C(CH_3)C(C_3H_7\text{-}n)(CN)\text{-}CO_2C_2H_5$ | 43 | $NaOC_2H_5$ | Ethanol | 37 |
| | $i\text{-}C_3H_7I$ | $C_2H_5CH{=}C(CH_3)C(C_3H_7\text{-}i)(CN)\text{-}CO_2C_2H_5$ | 42 | $NaOC_2H_5$ | Ethanol | 37 |
| | $CH_2{=}CHCH_2Br$ | $C_2H_5CH{=}C(CH_3)C(CH_2CH{=}CH_2)(CN)\text{-}CO_2C_2H_5$ | 40 | $NaOC_2H_5$ | Ethanol | 37 |
| $(C_2H_5)_2C{=}C(CN)\text{-}CO_2C_2H_5$ | $CH_3I$ | $CH_3CH{=}C(C_2H_5)C(CH_3)(CN)CO_2C_2H_5$ | 87 | $NaOC_2H_5$ | Ethanol | 37 |
| | $C_2H_5I$ | $CH_3CH{=}C(C_2H_5)C(C_2H_5)(CN)\text{-}CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 37 |
| | $n\text{-}C_3H_7Br$ | $CH_3CH{=}C(C_2H_5)C(C_3H_7\text{-}n)(CN)\text{-}CO_2C_2H_5$ | 57 | $NaOC_2H_5$ | Ethanol | 37 |
| | $i\text{-}C_3H_7I$ | $CH_3CH{=}C(C_2H_5)C(C_3H_7\text{-}i)(CN)\text{-}CO_2C_2H_5$ | 63 | $NaOC_2H_5$ | Ethanol | 37 |
| [cyclopropane] $>CHC{=}C(CN)\text{-}CO_2C_2H_5$ (with $CH_2$, $CH_3$) | $C_2H_5I$ | [cyclopropane] $>CHCC(C_2H_5)(CN)CO_2C_2H_5$ (with $CH_2$, ${=}CH_2$) | 12 | $NaOC_2H_5$ | Ethanol | 995 |

*Note:* References 577–1080 are on pp. 322–331.

\* The poor yield obtained precluded purification of product.

† The product isomerized partially on distillation.

TABLE IX—*Continued*

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### ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $CH_2$<br>$\triangleright CHC{=}C(CN){-}$<br>$CH_2 \mid CO_2C_3H_7\text{-}i$<br>$CH_3$ | $(C_2H_5)_2SO_4$ | $CH_2$<br>$\triangleright CHCC(C_2H_5)(CN)CO_2C_3H_7\text{-}i$<br>$CH_2 \parallel$<br>$CH_2$ | 60 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 995 |
| $n\text{-}C_4H_9C(CH_3){=}C(CN){-}$<br>$CO_2C_2H_5$ | $CH_3I$ | $n\text{-}C_3H_7CH{=}C(CH_3)C(CH_3)(CN){-}$<br>$CO_2C_2H_5$ | 78 | $NaOC_2H_5$ | Ethanol | 37 |
| | $C_2H_5I$ | $n\text{-}C_3H_7CH{=}C(CH_3)C(C_2H_5)(CN){-}$<br>$CO_2C_2H_5$ | 70 | $NaOC_2H_5$ | Ethanol | 37 |
| $i\text{-}C_4H_9C(CH_3){=}C(CN){-}$<br>$CO_2C_2H_5$ | $CH_3I$ | $i\text{-}C_3H_7CH{=}C(CH_3)C(CH_3)(CN){-}$<br>$CO_2C_2H_5$ | 79 | $NaOC_2H_5$ | Ethanol | 41 |
| $i\text{-}C_4H_9C(CH_3){=}C(CN){-}$<br>$CO_2CH_3$ | $CH_3I$ | $i\text{-}C_3H_7CH{=}C(CH_3)C(CH_3)(CN)CO_2CH_3$ | 46 | $NaOCH_3$ | $CH_3OH$ | 37 |
| | $C_2H_5I$ | $i\text{-}C_3H_7CH{=}C(CH_3)C(C_2H_5)(CN)CO_2CH_3$ | 32 | $NaOCH_3$ | $CH_3OH$ | 37 |
| $(CH_3)_2C{=}CHC(CH_3){=}$<br>$C(CN)CO_2C_3H_7\text{-}i$ | $CH_3I$ | $CH_2{=}C(CH_3)CH{=}C(CH_3){-}$<br>$C(CH_3)(CN)CO_2C_3H_7\text{-}i$ | 47 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 575 |
| Ethyl cyclohexyl-<br>idenecyanoacetate | $CH_3I$ | Ethyl methyl-(1-cyclohexenyl)-<br>cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 996, 997 |
| | $C_2H_5I$ | Ethyl ethyl-(1-cyclohexenyl)-<br>cyanoacetate | 45 | $NaOC_2H_5$ | Ethanol | 259 |
| | $CH_2{=}CHCH_2Br$ | Ethyl allyl-(1-cyclohexenyl)-<br>cyanoacetate | 79 | $NaOC_2H_5$ | Ethanol | 215 |
| | $n\text{-}C_4H_9I$ | Ethyl $n$-butyl-(1-cyclohexenyl)-<br>cyanoacetate | 60 | $NaOC_2H_5$ | Ethanol | 259 |
| | 2-Methyl-2-cyclo-<br>pentenyl bromide | Ethyl (2-methyl-2-cyclo-<br>pentenyl)-(1-cyclohexenyl)-<br>cyanoacetate | 52 | $NaOC_3H_7\text{-}i$ | $i\text{-}C_3H_7OH$ | 247 |
| $n\text{-}C_6H_{13}CH{=}C(CN){-}$<br>$CO_2C_2H_5$ | $n\text{-}C_4H_9I$ | $n\text{-}C_5H_{11}CH{=}CHC(C_4H_9\text{-}n)(CN){-}$<br>$CO_2C_2H_5$ | 10 | $NaOC_2H_5$ | Ethanol | 259 |
| $n\text{-}C_5H_{11}C(CH_3){=}C(CN){-}$<br>$CO_2CH_3$ | $CH_3I$ | $n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN){-}$<br>$CO_2CH_3$ | 23 | $NaOCH_3$ | $CH_3OH$ | 37 |
| $n\text{-}C_5H_{11}C(CH_3){=}C(CN){-}$<br>$CO_2C_2H_5$ | $CH_3I$ | $n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN){-}$<br>$CO_2C_2H_5$ | 62 | $NaOC_2H_5$ | Ethanol | 41 |
| $n\text{-}C_5H_{11}C(CH_3){=}C(CN){-}$<br>$CO_2CH_3$ | $C_2H_5I$ | $n\text{-}C_4H_9CH{=}C(CH_3)C(C_2H_5)(CN){-}$<br>$CO_2CH_3$ | 18 | $NaOCH_3$ | $CH_3OH$ | 37 |
| | $(C_2H_5)_2SO_4$ | $n\text{-}C_4H_9CH{=}C(CH_3)C(C_2H_5)(CN){-}$<br>$CO_2CH_3$ | 13 | $NaNH_2$ | Toluene | 37 |
| $n\text{-}C_5H_{11}C(CH_3){=}C(CN){-}$<br>$CO_2C_2H_5$ | $CH_2{=}C(CH_3)CH_2Cl$ | $n\text{-}C_4H_9CH{=}C(CH_3){-}$<br>$C[CH_2C(CH_3){=}CH_2](CN)CO_2C_2H_5$† | 20–35 | $NaOC_2H_5$ | Ethanol | 64 |
| $(n\text{-}C_3H_7)_2C{=}C(CN){-}$<br>$CO_2C_2H_5$ | $CH_3I$ | $C_2H_5CH{=}C(C_3H_7\text{-}n)C(CH_3)(CN){-}$<br>$CO_2C_2H_5$ | 81 | $NaOC_2H_5$ | Ethanol | 41 |
| $(n\text{-}C_3H_7)_2C{=}C(CN){-}$<br>$CO_2CH_3$ | $C_2H_5I$ | $C_2H_5CH{=}C(C_3H_7\text{-}n)C(C_2H_5)(CN){-}$<br>$CO_2CH_3$ | 78 | $NaOCH_3$ | $CH_3OH$ | 37 |
| | $(C_2H_5)_2SO_4$ | $C_2H_5CH{=}C(C_3H_7\text{-}n)C(C_2H_5)(CN){-}$<br>$CO_2CH_3$ | 58 | Na | Ether | 37 |
| Ethyl 2-methylcyclo-<br>hexylidenecyanoacetate | $CH_3I$ | Ethyl methyl-(2-methyl-1-cyclo-<br>hexenyl)cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 353 |
| Ethyl 3-methylcyclo-<br>hexylidenecyanoacetate | $CH_3I$ | Ethyl methyl-(3-methyl-1-cyclo-<br>hexenyl)cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 353 |
| Ethyl 4-methylcyclo-<br>hexylidenecyanoacetate | $CH_3I$ | Ethyl methyl-(4-methyl-1-cyclo-<br>hexenyl)cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 353 |
| | $C_6H_5COCH_2Br$ | Ethyl phenacyl-(4-methyl-1-<br>cyclohexenyl)cyanoacetate | — | $NaOC_2H_5$ | Ethanol | 997 |
| $C_6H_5CH_2C(CH_3){=}C(CN){-}$<br>$CO_2C_2H_5$ | $C_2H_5X$‡ | $C_6H_5CH{=}C(CH_3)C(C_2H_5)(CN){-}$<br>$CO_2C_2H_5$ | — | Na | $C_6H_6$ | 74 |
| $C_6H_5C(C_2H_5){=}C(CN){-}$<br>$CO_2C_2H_5$ | $C_2H_5X$‡ | $CH_3CH{=}C(C_6H_5)C(C_2H_5)(CN){-}$<br>$CO_2C_2H_5$ | — | Na | $C_6H_6$ | 74 |

*Note:* References 577–1080 are on pp. 322—331.

† The product isomerized partially on distillation.

‡ The halogen was not specified.

TABLE IX—*Continued*

ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Ethyl 1-indanylidene-cyanoacetate | CH$_3$I | Ethyl methyl-(3-indenyl)cyanoacetate | 70 | NaOC$_2$H$_5$ | Ethanol | 181 |
| | C$_2$H$_5$I | Ethyl ethyl-(3-indenyl)cyanoacetate | — | NaOC$_2$H$_5$ | Ethanol | 181 |
| | $n$-C$_3$H$_7$I | Ethyl $n$-propyl-(3-indenyl)cyanoacetate | — | NaOC$_2$H$_5$ | Ethanol | 181 |
| | $i$-C$_3$H$_7$I | Ethyl isopropyl-(3-indenyl)cyano-acetate | 60 | NaOC$_2$H$_5$ | Ethanol | 181 |
| | CH$_2$=CHCH$_2$Br | Ethyl allyl-(3-indenyl)cyanoacetate | 36 | NaOC$_2$H$_5$ | Ethanol | 217 |
| | CH$_2$=CHCH$_2$I | Ethyl allyl-(3-indenyl)cyanoacetate | 65 | NaOC$_2$H$_5$ | Ethanol | 181 |
| | $i$-C$_4$H$_9$I | Ethyl $i$-butyl-(3-indenyl)cyanoacetate | — | NaOC$_2$H$_5$ | Ethanol | 181 |
| | $i$-C$_5$H$_{11}$I | Ethyl $i$-amyl-(3-indenyl)cyanoacetate | — | NaOC$_2$H$_5$ | Ethanol | 181 |
| Ethyl 2-indanyl-idenecyanoacetate§ | CH$_3$I | Ethyl methyl-(2-indenyl)cyanoacetate | 70 | NaOC$_2$H$_5$ | Ethanol | 181 |
| <br><br>C(CN)CO$_2$C$_2$H$_5$<br><br> | ClCH$_2$CO$_2$C$_2$H$_5$ | CH$_2$CO$_2$C$_2$H$_5$<br>\|<br>NCCCO$_2$C$_2$H$_5$<br> | 55 | NaOCH$_3$ | C$_6$H$_6$ | 998 |

§ This ester may be ethyl 2-indenylcyanoacetate as designated in ref. 181.

## TABLE X

### ALKYLATION OF MALONONITRILE AND MONOALKYLMALONONITRILES, $RCH(CN)_2$

| R | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| | $C_1$ | | | | | |
| H | $CH_3I$ | $(CH_3)_2C(CN)_2$ | Poor | Dry silver salt | None | 104 |
| | $CH_3I$ | $\{(CH_3)_2C(CN)_2$ / $(CH_3)_2C(CN)C(\!=\!NH)OCH_3\}$ | ca. 14 / 55 | $NaOCH_3$ | $CH_3OH$ | 104 |
| | $CH_3I$ | $(CH_3)_2C(CN)_2$ | 36 | $NaOC_2H_5$ | None | 104, 999 |
| | $CHCl_3$ | $(NC)_2CHCH\!=\!C(CN)C(\!=\!NH)OC_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 231 |
| | $C_2$ | | | | | |
| | $C_2H_5I$ | $(C_2H_5)_2C(CN)_2$ | 32 | $NaOC_2H_5$ | None | 104, 999 |
| | $C_2H_5I$ | $\{(C_2H_5)_2C(CN)C(\!=\!NH)OC_2H_5$ / $(C_2H_5)_2C(CN)_2\}$ | Good / — | $NaOC_2H_5$ | Ethanol | 104 |
| | $C_3\text{-}C_9$ | | | | | |
| | $n\text{-}C_3H_7Cl$ | $(n\text{-}C_3H_7)_2C(CN)_2$ | — | $NaOC_2H_5$ | Ethanol | 999 |
| | $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CN)_2$ | — | Na | Ether | 95 |
| | $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CN)_2$ | 32 | $NaOC_2H_5$ | Ethanol | 95, 999 |
| | 2,3-Dibromoindone | Bromoindonylmalononitrile* | 100 | $NaOC_2H_5$ | Ethanol | 781 |
| $C_2H_5$ | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_2H_5)(CN)C(\!=\!NH)OC_2H_5$ | 71 | $NaOC_2H_5$ | Ethanol | 95 |
| $C_6H_5$ | $CH_3I$ | $C_6H_5C(CH_3)(CN)C(\!=\!NH)OC_2H_5$ | ca. 100 | $NaOC_2H_5$ | Ethanol | 333 |
| | $Cl(CH_2)_3Br$ | $Cl(CH_2)_3C(C_6H_5)(CN)_2$ | 40 | $NaOC_2H_5$ | Ethanol | 1000 |
| | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)(CN)_2$ | 100 | $NaOC_2H_5$ | Ethanol | 333 |
| $C_6H_5CH_2$ | $CH_3I$ | $C_6H_5CH_2C(CH_3)(CN)_2$ | — | Dry sodium salt | None | 95 |
| | $CH_3I$ | $C_6H_5CH_2C(CH_3)(CN)_2$ | 92 | Dry silver salt | Ether | 95 |
| | $CH_3I$ | $C_6H_5CH_2C(CH_3)(CN)C(\!=\!NH)OC_2H_5$ | 85 | $NaOC_2H_5$ | Ethanol | 95 |
| | $C_2H_5I$ | $C_6H_5CH_2C(C_2H_5)(CN)C(\!=\!NH)OC_2H_5$ | 75 | $NaOC_2H_5$ | Ethanol | 95 |

*Note :* References 577–1080 are on pp. 322–331.

* The structure of this product was not determined.

## TABLE XI

### ALKYLATION OF MONOCARBOXYLIC ESTERS, RCH(R')CO$_2$R''

(The ethyl ester was used unless otherwise indicated.)

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| H | H | C$_2$H$_5$Br | n-C$_3$H$_7$CO$_2$C$_2$H$_5$ | 5 | K | Ether | 196 |
| | | C$_6$H$_5$CH$_2$Cl | C$_3$H$_5$(CH$_2$)$_2$CO$_2$C$_2$H$_5$ | Poor | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| H | i-C$_3$H$_7$ | C$_2$H$_5$I | i-C$_3$H$_7$CH(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | 22 | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| | | C$_6$H$_5$SO$_3$C$_2$H$_5$ | i-C$_3$H$_7$CH(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | 33 | NaC(C$_6$H$_5$)$_3$ | Ether | 69 |
| H | C$_6$H$_5$ | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | 35 | K | Ether | 196 |
| | | (C$_2$H$_5$)$_2$SO$_4$ | C$_6$H$_5$CH(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | — | Na | Ether | 249 |
| | | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate | — | NaOC$_2$H$_5$ | Ethanol | 504 |
| | | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$CH(C$_6$H$_5$)CO$_2$C$_2$H$_5$ | 17 | KOH | CH$_3$CH(OC$_2$H$_5$)$_2$ | 81 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$CH(C$_6$H$_5$)CO$_2$C$_2$H$_5$ | 38 | KOH | 1-Butoxy-2-ethoxyethane | 81 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$CH(C$_6$H$_5$)CO$_2$C$_2$H$_5$ | 30 (50) | KOH | CH$_3$CH(OC$_3$H$_7$-n)$_2$ | 83, 81 |
| | | C$_6$H$_5$CH$_2$Cl | None | — | NaOC$_2$H$_5$ | Ethanol | 1001 |
| | | 4,7-Dichloro-quinoline | Ethyl α-phenyl-α-(7-chloro-4-quinolyl)acetate | 1 | NaNH$_2$ | C$_6$H$_6$ | 178 |
| | | | α-Phenyl-α-(7-chloro-4-quinolyl)acetamide | 20 | | | |
| CH$_3$ | CH$_3$ | I$_2$ | C$_2$H$_5$O$_2$CC(CH$_3$)$_2$C(CH$_3$)$_2$CO$_2$C$_2$H$_5$ | 26 | NaC(C$_6$H$_5$)$_3$ | Ether | 69 |
| | | CH$_3$I | (CH$_3$)$_3$CCO$_2$C$_2$H$_5$ | 55 | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| | | C$_2$H$_5$I | C$_2$H$_5$C(CH$_3$)$_2$CO$_2$C$_2$H$_5$ | 58 | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| | | CH$_2$—CH$_2$ (epoxide) | CH$_2$CH$_2$C(CH$_3$)$_2$ / O——CO | 55 | NaC(C$_6$H$_5$)$_3$ | Ether | 69 |
| | | (CH$_3$)$_2$CBrCO$_2$C$_2$H$_5$ | C$_2$H$_5$O$_2$CC(CH$_3$)$_2$C(CH$_3$)$_2$CO$_2$C$_2$H$_5$ | 30 | NaC(C$_6$H$_5$)$_3$ | Ether | 69 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(CH$_3$)$_2$CO$_2$C$_2$H$_6$ | 23 | KOH | CH$_3$CH(OC$_2$H$_5$)$_2$ | 81 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(CH$_3$)$_2$CO$_2$C$_2$H$_5$ | 24 | KOH | 1-Butoxy-2-ethoxyethane | 81 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(CH$_3$)$_2$CO$_2$C$_2$H$_6$ | 42 | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| CH$_3$ | C$_2$H$_6$ | n-C$_3$H$_7$I | n-C$_3$H$_7$C(CH$_3$)(C$_2$H$_5$)CO$_2$C$_2$H$_6$ | 61 | NaC(C$_6$H$_5$)$_3$ | Ether | 68 |
| (2-thienyl ring) C$_6$H$_5$ | (2-thienyl ring) C$_6$H$_5$ | β-(4-Morpholinyl)-ethyl chloride | Ethyl α,α-di-(2-thienyl)-γ-(4-morpholinyl)butyrate | 57 | NaNH$_2$ | Toluene | 1002 |
| | | I$_2$ | CH$_3$O$_2$CC(C$_6$H$_5$)$_2$C(C$_6$H$_5$)$_2$CO$_2$CH$_3$* | — | NaC(C$_6$H$_5$)$_3$ | Ether | 67 |
| | | CH$_3$I | (C$_6$H$_5$)$_2$C(CH$_3$)CO$_2$C$_2$H$_5$ | — | KNH$_2$ | Liquid NH$_3$ | 1003 |
| | | CH$_3$X† | (C$_6$H$_5$)$_2$C(CH$_3$)CO$_2$CH$_2$C$_6$H$_5$‡ | Good | NaNH$_2$ | Ether | 62 |
| | | C$_2$H$_5$I | (C$_6$H$_5$)$_2$C(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | 81 | NaOC$_2$H$_5$ | None | 180 |
| | | C$_2$H$_5$I | (C$_6$H$_5$)$_2$C(C$_2$H$_5$)CO$_2$C$_2$H$_5$ | 100 | KOC$_2$H$_5$ | C$_6$H$_6$-ether | 1003 |
| | | i-C$_3$H$_7$X† | (C$_6$H$_5$)$_2$C(C$_3$H$_7$-i)CO$_2$CH$_2$C$_6$H$_5$‡ | 30 | NaNH$_2$ | Ether | 62 |
| | | CH$_2$=CHCH$_2$X† | CH$_2$=CHCH$_2$C(C$_6$H$_5$)$_2$CO$_2$H§ | 77 | NaNH$_2$ | C$_6$H$_6$ | 1004 |
| | | CH$_2$=CHCH$_2$X† | CH$_2$=CHCH$_2$C(C$_6$H$_5$)$_2$CO$_2$CH$_2$C$_6$H$_5$‡ | 100 | NaNH$_2$ | Ether | 62 |
| | | β-(4-Morpholinyl)-ethyl chloride | Ethyl α,α-diphenyl-γ-(4-morpholinyl)butyrate | — | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$-C$_6$H$_5$Cl | 93 |
| | | C$_6$H$_5$CH$_2$Cl | None* | — | NaOC$_2$H$_5$ | Ethanol | 564 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_6$H$_5$)$_2$CO$_2$CH$_3$* | — | NaC(C$_6$H$_5$)$_3$ | C$_6$H$_6$ | 67 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_6$H$_5$)$_2$CO$_2$CH$_2$C$_6$H$_5$‡ | — | NaNH$_2$ | Ether | 61, 1005 |
| | | β-(2-Methyl-1-pyrrolidyl)ethyl chloride | Ethyl α,α-diphenyl-γ-(2-methyl-1-pyrrolidyl)butyrate | — | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$-C$_6$H$_5$Cl | 93 |
| | | β-(1-Piperidyl)ethyl chloride | Ethyl α,α-diphenyl-γ-(1-piperidyl)butyrate | 80 | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$ | 91, 93 |
| | | β-(4-Morpholinyl)-propyl chloride | Ethyl α,α-diphenyl-γ-(4-morpholinyl)valerate | — | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$ | 91 |
| | | γ-(1-Piperidyl)-propyl chloride | Ethyl α,α-diphenyl-δ-(1-piperidyl)valerate | — | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$ | 91 |
| | | β-(1-Piperidyl)-propyl chloride | Ethyl α,α-diphenyl-γ-(1-piperidyl)valerate | — | [(C$_6$H$_5$)$_2$CCN]Na | C$_6$H$_6$ | 91 |
| | | C$_6$H$_5$CHBrCO$_2$CH$_3$ | CH$_3$O$_2$CCH(C$_6$H$_5$)CH(C$_6$H$_5$)CO$_2$CH$_3$* | Poor | (C$_6$H$_5$)$_3$CNa | Ether | 67 |
| | | β-(2-Methyl-5-ethyl-1-piperidyl)propyl chloride | Ethyl α,α-diphenyl-γ-(2-methyl-5-ethyl-1-piperidyl)valerate | — | [(C$_2$H$_6$)$_2$CCN]Na | C$_6$H$_6$ | 91 |
| | | (C$_6$H$_5$)$_2$CHBr | (C$_6$H$_5$)$_2$CHC(C$_6$H$_5$)$_2$CO$_2$CH$_3$* | — | NaC(C$_6$H$_5$)$_3$ | Toluene | 67 |
| | | (C$_6$H$_5$)$_3$CCl | (C$_6$H$_5$)$_3$CC(C$_6$H$_5$)$_2$CO$_2$CH$_3$* | — | NaC(C$_6$H$_6$)$_3$ | Ether | 67 |
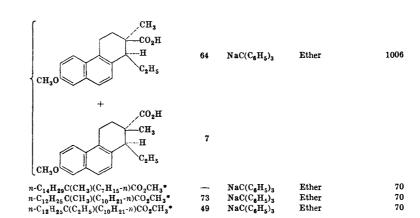
Note: References 577–1080 are on pp. 322–331.
* The methyl ester was used in this experiment.
† The halogen was not specified.
‡ The benzyl ester was used in this experiment.
§ The allyl ester was used in this experiment.

TABLE XI—*Continued*

ALKYLATION OF MONOCARBOXYLIC ESTERS, RCH(R')CO$_2$R''

(The ethyl ester was used unless otherwise indicated.)

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| *o,o'*-Diphenylene | | I$_2$ | Diethyl 2,3-bis-(*o,o'*-diphenylene)-succinate | — | NaOC$_2$H$_5$ | Ethanol-ether | 248 |
| | | I$_2$ | Diethyl 2,3-bis-(*o,o'*-diphenylene)-succinate | — | KOC$_2$H$_5$ | Ethanol-ether | 248 |
| | | CH$_3$I | Ethyl 9-methylfluorene-9-carboxylate | Good | KOC$_2$H$_5$ | Ether | 248 |
| | | C$_2$H$_5$I | Ethyl 9-ethylfluorene-9-carboxylate | Good | KOC$_2$H$_5$ | Ether | 248 |
| | | Br(CH$_2$)$_2$Br | Diethyl α,α'-bis-(*o,o'*-diphenylene)-adipate | — | KOC$_2$H$_5$ | Ethanol | 248 |
| | | CH$_2$=CHCH$_2$Br | Ethyl 9-allylfluorene-9-carboxylate | — | KOC$_2$H$_5$ | Ether | 248 |
| | | ClCH$_2$CO$_2$C$_2$H$_5$ | Diethyl α-(*o,o'*-diphenylene)succinate | — | KOC$_2$H$_5$ | Ether | 248 |
| | | I(CH$_2$)$_2$CO$_2$C$_2$H$_5$ | Diethyl α-(*o,o'*-diphenylene)glutarate | — | KOC$_2$H$_5$ | Ether | 248 |
| | | C$_6$H$_5$I | None | — | KOC$_2$H$_5$ | Ether | 248 |
| | | 2,4-Dinitro-bromobenzene | Ethyl 9-(2',4'-dinitrophenyl)fluorene-9-carboxylate | — | KOC$_2$H$_5$ | Ether | 248 |
| | | β-(4-Morpholinyl)-ethyl chloride | Ethyl 9-[β-(4-morpholinyl)ethyl]-fluorene-9-carboxylate | 40 | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$-C$_6$H$_5$Cl | 91, 93 |
| | | C$_6$H$_5$CH$_2$Cl | Ethyl 9-benzylfluorene-9-carboxylate | 85 | KOC$_2$H$_5$ | Ether | 248 |
| | | β-(1-Piperidyl)-ethyl chloride | Ethyl 9-[β-(1-piperidyl)ethyl]fluorene-9-carboxylate | — | KOC$_2$H$_5$ | Ethanol-ether | 93 |
| | | C$_6$H$_5$COCH$_2$Br | Ethyl 9-phenacylfluorene-9-carboxylate | — | KOC$_2$H$_5$ | Ether | 248 |
| C$_6$H$_5$ | *p*-Tolyl | CH$_3$I | *p*-CH$_3$C$_6$H$_4$C(CH$_3$)(C$_6$H$_5$)CO$_2$CH$_2$C$_6$H$_5$‡ | — | NaNH$_2$ | Ether | 60 |
| | | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(C$_6$H$_5$)(C$_6$H$_4$CH$_3$-*p*)-CO$_2$CH$_2$C$_6$H$_5$‡ | 65 | NaNH$_2$ | Ether | 60 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(C$_6$H$_5$)(C$_6$H$_4$CH$_3$-*p*)-CO$_2$CH$_2$C$_6$H$_5$‡ | — | NaNH$_2$ | Ether | 60 |
| *n*-C$_7$H$_{15}$ | *n*-C$_7$H$_{15}$I | CH$_3$I | (*n*-C$_7$H$_{15}$)$_2$C(CH$_3$)CO$_2$CH$_3$* | 77 | NaC(C$_6$H$_5$)$_3$ | Ether | 70 |
| C$_6$H$_5$ | Veratryl | β-(4-Morpholinyl)-ethyl chloride | Ethyl α-phenyl-α-veratryl-γ-(4-morpholinyl)butyrate | 48 | [(C$_2$H$_5$)$_2$CCN]Na | C$_6$H$_6$-C$_6$H$_5$Cl | 93 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  | | CH$_3$I |  | 64 | NaC(C$_6$H$_5$)$_3$ | Ether | 1006 |
| | | | | 7 | | | |
| *n*-C$_7$H$_{15}$ | *n*-C$_{14}$H$_{29}$ | CH$_3$I | *n*-C$_{14}$H$_{29}$C(CH$_3$)(C$_7$H$_{15}$-*n*)CO$_2$CH$_3$* | — | NaC(C$_6$H$_5$)$_3$ | Ether | 70 |
| *n*-C$_{10}$H$_{21}$ | *n*-C$_{12}$H$_{25}$ | CH$_3$I | *n*-C$_{12}$H$_{25}$C(CH$_3$)(C$_{10}$H$_{21}$-*n*)CO$_2$CH$_3$* | 73 | NaC(C$_6$H$_5$)$_3$ | Ether | 70 |
| | | C$_2$H$_5$I | *n*-C$_{12}$H$_{25}$C(C$_2$H$_5$)(C$_{10}$H$_{21}$-*n*)CO$_2$CH$_3$* | 49 | NaC(C$_6$H$_5$)$_3$ | Ether | 70 |

*Note:* References 577-1080 are on pp. 322-331.
* The methyl ester was used in this experiment.
‡ The benzyl ester was used in this experiment.

TABLE XII

ALKYLATION OF 3-ARYL-2-BENZOFURANONES TO

| Substituents | Alkylating Agent | R in Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| None | I$_2$ |  | — | NaOC$_2$H$_5$ | Ether | 262 |
| | CH$_3$I | —CH$_3$ | ca. 100 | KOC$_2$H$_5$ | Ethanol | 262 |
| | C$_2$H$_5$I | —C$_2$H$_5$ | 85 | — | — | 262 |
| | CH$_2$=CHCH$_2$Br | —CH$_2$CH=CH$_2$ | 80 | KOC$_2$H$_5$ | Ether | 262 |
| | Br(CH$_2$)$_3$Cl | —(CH$_2$)$_3$Cl | 42 | NaH | C$_6$H$_6$ | 574 |
| | Br(CH$_2$)$_3$CN | —(CH$_2$)$_3$CN | 68 | NaH | C$_6$H$_6$ | 574, 1007, 1008 |
| | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(CH$_3$)$_2$ | 24 | Na | Toluene | 574 |
| | n-C$_4$H$_9$NH(CH$_2$)$_2$Cl | —(CH$_2$)$_2$NHC$_4$H$_9$-n | — | Na | Toluene | 574 |
| | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(C$_2$H$_5$)$_2$ | 87 | Na | Toluene | 574, 1007, 1008 |
| | β-(4-Morpholinyl)ethyl chloride | β-(4-Morpholinyl)ethyl | 66 | NaH | C$_6$H$_6$ | 574, 1007, 1008 |
| | (C$_2$H$_5$)$_2$N(CH$_2$)$_3$Br | —(CH$_2$)$_3$N(C$_2$H$_5$)$_2$ | 16 | Na | Toluene | 574 |
| | (C$_2$H$_5$)$_2$NCH$_2$CH(CH$_3$)Cl | —CH(CH$_3$)CH$_2$N(C$_2$H$_5$)$_2$ | 80 | NaH | Toluene | 1007, 1008 |
| | (C$_2$H$_5$)$_2$NCH(CH$_3$)CH$_2$Cl | —CH$_2$CH(CH$_3$)N(C$_2$H$_5$)$_2$ | 81 | NaH | Toluene | 574, 1007, 1008 |
| | C$_6$H$_5$CH$_2$Br | —CH$_2$C$_6$H$_5$ | ca. 100 | — | — | 262 |
| | β-(1-Piperidyl)ethyl chloride | β-(1-Piperidyl)ethyl | 78 | Na | Toluene | 574 |
| | γ-(4-Morpholinyl)propyl chloride | γ-(4-Morpholinyl)propyl | 64 | NaH | C$_6$H$_6$ | 574, 1007, 1008 |
| | (C$_2$H$_5$)$_2$N(CH$_2$)$_4$Cl | —(CH$_2$)$_4$N(C$_2$H$_5$)$_2$ | 17 | Na | Toluene | 574 |
| |  | —CH$_2$C(CH$_3$)$_2$CH$_2$N | 73 | NaH | C$_6$H$_6$ | 574, 1007, 1008 |
| | (n-C$_4$H$_9$)$_2$N(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(C$_4$H$_9$-n)$_2$ | 74 | Na | Toluene | 574 |
| | (n-C$_4$H$_9$)$_2$N(CH$_2$)$_3$Cl | —(CH$_2$)$_3$N(C$_4$H$_9$-n)$_2$ | 33 | Na | Toluene | 574 |
| | C$_6$H$_5$CH$_2$N(C$_4$H$_9$-n)(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(C$_4$H$_9$-n)CH$_2$C$_6$H$_5$ | 63 | NaH | C$_6$H$_6$ | 1007, 574, 1008 |
| | (C$_2$H$_5$)$_2$N(CH$_2$)$_{11}$Cl | —(CH$_2$)$_{11}$N(C$_2$H$_5$)$_2$ | — | — | — | 1007, 1008 |
| |  |  | 42 | Na | Ether | 263 |
| 5-Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(C$_2$H$_5$)$_2$ | 70 | Na | Toluene | 574, 1007, 1008 |
| 5-Br | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | —(CH$_2$)$_2$N(C$_2$H$_5$)$_2$ | 71 | Na | Toluene | 574, 1007, 1008 |

*Note :* References 577–1080 are on pp. 322–331.

TABLE XII—*Continued*

ALKYLATION OF 3-ARYL-2-BENZOFURANONES TO



| Substituents | Alkylating Agent | R in Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| 5-CH₃ | I₂ |  | 78 | Na | Ether | 263, 262 |
|  | CH₃I | —CH₃ | 80 | KOC₂H₅ | Ethanol | 262 |
|  | C₂H₅I | —C₂H₅ | — | — | — | 262 |
|  | (C₂H₅)₂N(CH₂)₂Cl | —(CH₂)₂N(C₂H₅)₂ | 76 | NaH | C₆H₆ | 574, 1007, 1008 |
|  | C₆H₅CH₂Cl | —CH₂C₆H₅ | — | — | — | 262 |
|  | C₆H₅COCH₂Br | —CH₂COC₆H₅ | — | Na | Ether | 262 |
|  |  |  | 43 | Na | Ether | 263 |
| 6-CH₃ | I₂ |  | 60 | Na | Ether | 263 |
| 7-CH₃ | (C₂H₅)₂N(CH₂)₂Cl | —(CH₂)₂N(C₂H₅)₂ | 69 | Na | Toluene | 574, 1007, 1008 |
| 3′-CH₃ | (C₂H₅)₂N(CH₂)₂Cl | —(CH₂)₂N(C₂H₅)₂ | 33 | Na | Toluene | 574, 1007 |
| 5-CH₃, 4′-OCH₃ | I₂ |  | — | Na | Ether | 263 |
| 5-n-C₃H₇ | (C₂H₅)₂N(CH₂)₂Cl | —(CH₂)₂N(C₂H₅)₂ | 75 | Na | Toluene | 574, 1007, 1008 |
| 4,5-Benzo | CH₃I | —CH₃ | 90 | KOC₂H₅ | Ethanol | 262 |
|  | C₂H₅I | —C₂H₅ | — | KOC₂H₅ | Ethanol | 262 |
|  | CH₂=CHCH₂Br | —CH₂CH=CH₂ | — | KOC₂H₅ | Ethanol | 262 |
|  | (C₂H₅)₂N(CH₂)₂Cl | —(CH₂)₂N(C₂H₅)₂ | 59 | NaH | C₆H₆ | 574, 1007, 1008 |
|  | C₆H₅COCH₂Br | —CH₂COC₆H₅ | — | Na | Ether | 262 |

*Note :* References 577–1080 are on pp. 322–331.

## TABLE XIII

### ALKYLATION OF SUCCINIC, GLUTARIC, AND GLUTACONIC ESTERS

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| $C_2H_5O_2C(CH_3)_2CHBrCO_2C_2H_5$ | None | Cyclopropane-*trans*-1,2-dicarboxylic acid | 35 | KOH | $CH_3OH$ | 80 |
| | | Cyclopropane-*cis*-1,2-dicarboxylic acid | 4 | | | |
| | None | Cyclopropane-*trans*-1,2-dicarboxylic acid | — | KOH | Ethanol | 80 |
| $CH_2(CHBrCO_2CH_3)_2$ | None | 1-Bromocyclopropane-1,2-dicarboxylic acid | — | $Na_2CO_3$ | $H_2O$ | 80 |
| $CH_2(CHBrCO_2C_2H_5)_2$ | None | 1-Bromocyclopropane-1,2-dicarboxylic acid | — | $Na_2CO_3$ | $H_2O$ | 80 |
| $CH_2(CHBrCO_2C_3H_7\text{-}i)_2$ | None | 1-Bromocyclopropane-1,2-dicarboxylic acid and 1-Hydroxycyclopropane-1,2-dicarboxylic acid | — | $Na_2CO_3$ | $H_2O$ | 80 |
| $C_2H_5O_2CCH_2C(CH_3)_2CHBrCO_2C_2H_5$ | None | 3,3-Dimethylcyclopropane-*cis*-1,2-dicarboxylic acid and 3,3-dimethylcyclopropane-*trans*-1,2-dicarboxylic acid | — | KOH | Ethanol | 250 |
| Dimethyl *endo*-3,6-methanohexahydrophthalate | $CH_3I$ | Dimethyl *cis*-1,2-dimethyl-*endo*-3,6-methanohexahydrophthalate | 62 | $(C_6H_5)_3CNa$ | Ether | 202 |
| | | Dimethyl *trans*-1,2-dimethyl-3,6-methanohexahydrophthalate | 7 | | | |
| Dimethyl *exo*-3,6-epoxyhexahydrophthalate | $CH_3I$ | None | — | $(C_6H_5)_3CNa$ | Ether | 202 |
| $C_2H_5O_2CCH=CHCH_2CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH=CHCH(CH_3)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ether | 252 |
| | $CH_3I$ | $C_2H_5O_2CCH=CHC(CH_3)_2CO_2C_2H_5$ | — | $NaOC_2H_5$ (excess) | Ether | 252 |
| $C_2H_5O_2CCH=CHCH(CH_3)CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CC(CH_3)=CH\text{-}CH(CH_3)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 252 |
| $C_2H_5O_2CCH=C(CH_3)CH_2CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH=C(CH_3)\text{-}CH(CH_3)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ethanol | 252 |
| | $CH_3I$ | $C_2H_5O_2CCH=C(CH_3)\text{-}CH(CH_3)CO_2C_2H_5$ and $C_2H_5O_2CC(CH_3)=C(CH_3)\text{-}CH_2CO_2C_2H_5$ | — | $KOC_2H_5$ | Ether | 1009 |
| | $C_6H_5CH_2Cl$ | $C_2H_5O_2CCH=C(CH_3)\text{-}CH(CH_2C_6H_5)CO_2C_2H_5$ | — | K | $C_6H_6$ | 253 |
| $C_2H_5O_2CCH=C(CH_3)\text{-}CH(CH_3)CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH=C(CH_3)\text{-}C(CH_3)_2CO_2C_2H_5$ | — | Na | Ether | 1010 |
| (cyclopentene ring) $CO_2C_2H_5$ / $CH_2CO_2C_2H_5$ | $CH_3I$ | (cyclopentene ring) $CO_2C_2H_5$ / $CH(CH_3)CO_2C_2H_5$ | — | K | $C_6H_6$ | 1011 |
| (cyclohexene ring) $CO_2C_2H_5$ / $CH_2CO_2C_2H_5$ | $CH_3I$ | (cyclohexene ring) $CO_2C_2H_5$ / $CH(CH_3)CO_2C_2H_5$ | — | K | $C_6H_6$ | 1011 |
| $C_2H_5O_2CCH=C(C_6H_5)CH_2CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH=C(C_6H_5)\text{-}CH(CH_3)CO_2C_2H_5$ | — | $KOC_2H_5$ | Ether | 251 |
| $C_2H_5O_2CCH=CH\text{-}CH(CH_2C_6H_5)CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CC(CH_3)=CH\text{-}CH(CH_2C_6H_5)CO_2C_2H_5$ and $C_2H_5O_2CCHCH=CCO_2C_2H_5$ with $CH_3$ and $CH_2C_6H_5$ | — | $KOC_2H_5$ | Ether | 253 |
| $C_2H_5O_2CCH=C(C_6H_4OCH_3\text{-}p)\text{-}CH_2CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH=C(C_6H_4OCH_3\text{-}p)\text{-}CH(CH_3)CO_2C_2H_5$ | — | $NaOC_2H_5$ | Ether | 1012 |
| $C_2H_5O_2CCH_2C(CH_3)=C(CH_2C_6H_5)\text{-}CO_2C_2H_5$ | $CH_3I$ | $C_2H_5O_2CCH(CH_3)\text{-}C(CH_3)=C(CH_2C_6H_5)CO_2C_2H_5$ | — | $KOC_2H_5$ | Ether | 253 |

*Note:* References 577–1080 are on pp. 322–331.

# TABLE XIV

## Alkylation of Mononitriles, RCH(R')CN

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|----|------------------|---------|----------|------|---------|-----------|
| | | $C_2$ | | | | | |
| H | H | $C_2H_5Cl$ | $(C_2H_5)_3CCN$ | — | $NaNH_2$ | Paraffin oil | 122, 1013 |
| | | $C_2H_5Br$ | $\begin{cases} C_2H_5CH_2CN \\ (C_2H_5)_2CHCN \end{cases}$ | 58<br>20 | $NaNH_2$ | Liquid $NH_3$ | 323 |
| | | $C_2H_5Br$ | $(C_2H_5)_2CHCN$ | ca. 70 | $NaNH_2$ | Ether | 53 |
| | | $C_2H_5Br$ | $\begin{cases} n\text{-}C_3H_7CN \\ (C_2H_5)_2CHCN \\ (C_2H_5)_3CCN \end{cases}$ | 23<br>24<br>15 | $NaNH_2$ | Ether | 1014 |
| | | $C_3$–$C_5$ | | | | | |
| | | $CH_2{=}CHCH_2Cl$ | $(CH_2{=}CHCH_2)_3CCN$ | 87 | $NaNH_2$ | Ether | 122, 1013 |
| | | $CH_2{=}CHCH_2Cl$ | $(CH_2{=}CHCH_2)_3CCN$ | 80–90 | $NaNH_2$ | $C_6H_6$ | 53, 122 |
| | | $CH_2{=}CHCH_2Cl$ | $CH_2{=}CHCH_2CH_2CN$ | — | $NaNH_2$ | $CH_3CN$ | 1013 |
| | | $CH_2{=}CHCH_2Br$ | $CH_2{=}CHCH_2CH_2CN$ | — | $NaNH_2$ | $CH_3CN$ | 1013 |
| | | $n\text{-}C_4H_9Br$ | $\begin{cases} n\text{-}C_4H_9CH_2CN \\ (n\text{-}C_4H_9)_2CHCN \end{cases}$ | 56<br>27 | $NaNH_2$ | Liquid $NH_3$ | 323 |
| | | $n\text{-}C_4H_9Br$ | $\begin{cases} n\text{-}C_4H_9CH_2CN \\ (n\text{-}C_4H_9)_2CHCN \end{cases}$ | 60<br><br>9 | $NaNH_2$ | Ether | 53, 122, 1013 |
| | | $n\text{-}C_4H_9Br$ | $(n\text{-}C_4H_9)_3CCN$ | 80 | $NaNH_2$ | Toluene | 1015 |
| | | $n\text{-}C_4H_9OSO_2C_6H_4CH_3\text{-}p$ | $\begin{cases} n\text{-}C_4H_9CH_2CN \\ (n\text{-}C_4H_9)_2CHCN \end{cases}$ | 63<br>20 | $NaNH_2$ | Liquid $NH_3$ | 323 |
| | | $n\text{-}C_5H_{11}Br$ | $(n\text{-}C_5H_{11})_3CCN$ | 57 | $NaNH_2$ | Toluene | 1015 |
| | | 2-Bromopyridine | Di-(2-pyridyl)acetonitrile | 25 | $NaNH_2$ | Toluene | 1016 |
| | | $C_6$–$C_7$ | | | | | |
| | | $C_6H_5Cl$ | $\begin{cases} C_6H_5CH_2CN \\ (C_6H_5)_2CHCN \end{cases}$ | 31<br>28 | $KNH_2$ | Liquid $NH_3$ | 323 |
| | | $C_6H_5CH_2Cl$ | None | — | Na | $C_6H_6$ | 1017 |
| | | $C_6H_5CH_2Cl$ | None | — | $NaOC_2H_5$ | Ethanol | 1017 |
| | | $C_6H_5CH_2Cl$ | $\begin{cases} C_6H_5CH_2CH_2CN \\ (C_6H_5CH_2)_2CHCN \\ (C_6H_5CH_2)_3CCN \end{cases}$ | 15–38<br>16–49<br>2 | $NaNH_2$ | Liquid $NH_3$ | 323 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH_2CN$ | 49 | $NaNH_2$ | $C_6H_6$ | 53 |
| | | $C_2$–$C_{10}$ | | | | | |
| H | $CH_3$ | $C_2H_5I$ | $C_2H_5CH(CH_3)CN$ | — | Na | Ether | 71 |
| | | $C_2H_5I$ | None | — | Na | $C_6H_6$ | 71 |
| | | $C_6H_5Cl$ | $C_6H_5CH(CH_3)CN$ | 43 | $KNH_2$ | Liquid $NH_3$ | 323 |
| | | $n\text{-}C_7H_{15}Br$ | $(n\text{-}C_7H_{15})_2C(CH_3)CN$ | 43 | $NaNH_2$ | Toluene | 1015 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CH_3)CN$ | 90 | $NaNH_2$ | Dioxane | 122 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(CH_3)CN$ | 55 | $NaNH_2$ | $C_6H_6$ | 53 |
| | | $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(CH_3)CN$ | 100 | $NaNH_2$ | $C_6H_6$ | 53 |
| | | $C_6H_5CH_2X^*$ | $(C_6H_5CH_2)_2C(CH_3)CN$ | — | $NaNH_2$ | Ether | 1018 |
| | | $n\text{-}C_{10}H_{21}Br$ | $n\text{-}C_{10}H_{21}CH(CH_3)CN$ | — | $NaNH_2$ | Toluene | 289 |
| | | $C_2$–$C_8$ | | | | | |
| H | $C_2H_5$ | $C_2H_5Br$ | $\begin{cases} (C_2H_5)_2CHCN \\ (C_2H_5)_3CCN \end{cases}$ | 77<br><br>3 | $NaNH_2$ | Ether | 53, 122, 1013 |
| | | $n\text{-}C_3H_7Br$ | $\begin{cases} n\text{-}C_3H_7CH(C_2H_5)CN \\ (n\text{-}C_3H_7)_2C(C_2H_5)CN \end{cases}$ | 65<br>13 | $NaNH_2$ | Ether | 53 |
| | | $i\text{-}C_3H_7Br$ | $i\text{-}C_3H_7CH(C_2H_5)CN$ | 71 | $NaNH_2$ | Ether | 53 |
| | | $CH_2{=}CHCH_2Cl$ | $(CH_2{=}CHCH_2)_2C(C_2H_5)CN$ | 83 | $NaNH_2$ | $C_6H_6$ | 53, 122 |
| | | $n\text{-}C_4H_9Cl$ | $n\text{-}C_4H_9CH(C_2H_5)CN$ | 68 | $NaNH_2$ | $n\text{-}C_4H_9Cl$ | 53, 122 |
| | | $C_6H_5O(CH_2)_2Cl$ | $C_6H_5O(CH_2)_2CH(C_2H_5)CN$ | — | $NaNH_2$ | Ether | 53 |
| | | $C_6H_5O(CH_2)_2Br$ | $C_6H_5O(CH_2)_2CH(C_2H_5)CN$ | — | $NaNH_2$ | $C_6H_6$ | 122 |
| H | $ClCH_2CH_2$ | None | Cyclopropanecarbonitrile | 42 | NaOH | None | 75, 78 |
| | | None | Cyclopropanecarbonitrile | — | KOH | None | 476, 478 |
| | | None | Cyclopropanecarbonitrile | 80–90 | $NaNH_2$ | Liquid $NH_3$ | 1019, 1020, 1021 |
| H | $CH_2{=}CH$ | $CH_2{=}CHCH_2Br$ | $(CH_2{=}CHCH_2)_2C(CH{=}CH_2)CN$ | 31 | $NaNH_2$ | Liquid $NH_3$ | 171 |
| H | $n\text{-}C_3H_7$ | $(C_2H_5)_2SO_4$ | $n\text{-}C_3H_7CH(C_2H_5)CN$ | — | $NaNH_2$ | Inert solvent | 249 |
| | | $n\text{-}C_3H_7Br$ | $(n\text{-}C_3H_7)_3CCN$ | 76 | $NaNH_2$ | Toluene | 1015 |
| H | $ClCH_2CH(CH_3)$ | None | 2-Methylcyclopropane-carbonitrile | 57 | $NaNH_2$ | Liquid $NH_3$–ether | 1022 |
| H | $CH_2{=}CHCH_2$ | $C_2H_5Br$ | $CH_2{=}CHCH_2C(C_2H_5)_2CN$ | Excellent | $NaNH_2$ | $C_6H_6$ | 122 |
| H | $n\text{-}C_4H_9$ | $n\text{-}C_4H_9Br$ | $\begin{cases} (n\text{-}C_4H_9)_2CHCN \\ (n\text{-}C_4H_9)_3CCN \end{cases}$ | —<br>81 | $NaNH_2$ | Toluene | 1015 |
| | | $n\text{-}C_7H_{15}Br$ | $(n\text{-}C_7H_{15})_2C(C_4H_9\text{-}n)CN$ | 62 | $NaNH_2$ | Toluene | 1015 |

*Note:* References 577–1080 are on pp. 322–331.
* The halogen was not specified.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R′)CN

| R | R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| H | $n$-C$_4$H$_9$ (*Cont.*) | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$CH(C$_4$H$_9$-$n$)CN | — | NaNH$_2$ | Ether | 59 |
| | | $n$-C$_8$H$_{17}$Br | ($n$-C$_8$H$_{17}$)$_2$C(C$_4$H$_9$-$n$)CN | 70 | NaNH$_2$ | C$_6$H$_6$ | 53, 1013 |
| H |  (=C$_4$H$_3$S) | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_4$H$_3$S)CN | 42 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| | | 2-Cyclopentenyl chloride | 2-Thienyl-(2-cyclo-pentenyl)acetonitrile | 60 | NaNH$_2$ | Toluene | 187 |
| | | Cyclohexyl bromide | Cyclohexyl-(2-thienyl)-acetonitrile | 48 | NaNH$_2$ | Toluene | 1023 |
| | | 2-Cyclohexenyl bromide | 2-Thienyl-(2-cyclohexenyl)-acetonitrile | 54 | KOH | CH$_3$CH(OC$_4$H$_9$-$n$)$_2$ | 187 |
| | | 2-Cyclohexenyl bromide | 2-Thienyl-(2-cyclohexenyl)-acetonitrile | 42 | NaOCH$_3$ | Dioxane | 187 |
| | | 2-Cyclohexenyl bromide | None | — | LiNH$_2$ | Toluene | 187 |
| | | 2-Cyclohexenyl bromide | 2-Thienyl-(2-cyclohexenyl)-acetonitrile | 56 | NaNH$_2$ | Toluene | 187 |
| H | CH$_2$CH=C(C$_2$H$_5$) | CH$_2$=CHCH$_2$Br | CH$_2$CH=C(C$_2$H$_5$)-CH(CH$_2$CH=CH$_2$)CN | 38 | NaNH$_2$ | Ether | 171 |
| H | (C$_2$H$_5$)$_2$NCH$_2$ | $n$-C$_4$H$_9$Br | (C$_2$H$_5$)$_2$NCH$_2$CH(C$_4$H$_9$-$n$)CN | 16 | NaNH$_2$ | Toluene | 1015 |
| | | | (C$_2$H$_5$)$_2$NCH$_2$C(C$_4$H$_9$-$n$)$_2$CN | 72 | | | |
| H |  | (CH$_3$)$_2$NCH$_2$Cl | (CH$_3$)$_2$NCH$_2$CH(C$_6$H$_5$S)CN | 31 | NaNH$_2$ | Toluene | 254 |
| H |  | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_5$H$_4$N)CN | 48 | NaNH$_2$ | Toluene | 254 |
| H |  | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_5$H$_4$N)CN | 40 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| H | $n$-C$_6$H$_{13}$ | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$CH(C$_6$H$_{13}$-$n$)CN | — | NaNH$_2$ | Ether | 59 |
| H | *cyclo*-C$_6$H$_{11}$ | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_6$H$_{11}$)CN | 59 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| H | 1-Cyclohexenyl (=C$_6$H$_9$) | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$CH(C$_6$H$_9$)CN | 19 | NaNH$_2$ | Liquid NH$_3$-ether | 171 |
| | | | (CH$_2$=CHCH$_2$)$_2$C(C$_6$H$_9$)CN | 40 | | | |
| | | $C_1$ | | | | | |
| H | C$_6$H$_5$ | CH$_3$I | C$_6$H$_5$CH(CH$_3$)CN | — | NaOC$_2$H$_5$ | Ethanol | 256, 1024 |
| | | CH$_3$I | C$_6$H$_5$CH(CH$_3$)CN | — | Na | Liquid NH$_3$ | 1025 |
| | | CH$_3$I | C$_6$H$_5$CH(CH$_3$)CN | 68–72 | NaNH$_2$ | None | 1026, 806 |
| | | CH$_3$I | C$_6$H$_5$CH(CH$_3$)CN | 66 | NaNH$_2$ | Ether | 583 |
| | | CH$_3$I | C$_6$H$_5$C(CH$_3$)$_2$CN | 62 | NaNH$_2$ | Ether | 1027, 1028 |
| | | CH$_3$I | C$_6$H$_5$CH(CH$_3$)CN | 50 | NaNH$_2$ | Liquid NH$_3$-ether | 195 |
| | | | C$_6$H$_5$C(CH$_3$)$_2$CN | 19 | | | |
| | | (CH$_3$)$_2$SO$_4$ | C$_6$H$_5$CH(CH$_3$)CN | 67 | NaNH$_2$ | Ether | 359, 992 |
| | | CH$_2$I$_2$ | C$_6$H$_5$CH(CN)CH$_2$CH(C$_6$H$_5$)CN | 31 | NaOH | None | 76 |
| | | CHCl$_3$ | C$_6$H$_5$CH(CN)CH=C(C$_6$H$_5$)-C(=NH)OC$_2$H$_5$ | — | NaOC$_2$H$_5$ | Ethanol | 231 |
| | | $C_2$ | | | | | |
| | | C$_2$H$_5$Cl | C$_6$H$_5$CH(C$_2$H$_5$)CN | Good | [C$_6$H$_5$CH$_2$N(C$_2$H$_5$)$_3$]OH | H$_2$O | 84 |
| | | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CN | Poor | [C$_6$H$_5$CH$_2$N(C$_2$H$_5$)$_3$]OH | H$_2$O | 84 |
| | | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CN | — | Na | Liquid NH$_3$ | 1025 |
| | | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CN | — | NaNH$_2$ | Liquid NH$_3$ | 1029 |
| | | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CN | 87 | NaNH$_2$ | Ether | 1030, 1031 |
| | | C$_2$H$_5$Br | C$_6$H$_5$CH(C$_2$H$_5$)CN | 86 | NaNH$_2$ | C$_6$H$_6$ | 1032 |
| | | C$_2$H$_5$I | None | — | [C$_2$H$_5$CH$_2$N(C$_2$H$_5$)$_3$]OH | H$_2$O | 84 |
| | | C$_2$H$_5$I | C$_6$H$_5$CH(C$_2$H$_5$)CN | Poor | NaOC$_2$H$_5$ | Ethanol | 564 |
| | | C$_2$H$_5$I | C$_6$H$_5$CH(C$_2$H$_5$)CN | — | NaNH$_2$ | None | 1033 |
| | | C$_2$H$_5$I | C$_6$H$_5$CH(C$_2$H$_5$)CN | 70–80 | NaNH$_2$ | Ether | 1034 |
| | | C$_2$H$_5$I | C$_6$H$_5$C(C$_2$H$_5$)$_2$CN | — | NaNH$_2$ | Ether | 1035 |
| | | C$_2$H$_5$I | C$_6$H$_5$C(C$_2$H$_5$)$_2$CN | 65 | NaNH$_2$ | Toluene | 1036 |
| | | (C$_2$H$_5$)$_2$SO$_4$ | C$_6$H$_5$CH(C$_2$H$_5$)CN | 89 | NaNH$_2$ | Ether | 249, 359 |
| | | Cl(CH$_2$)$_2$Br | 1-Phenylcyclopropane-1-carbonitrile | 44 | NaNH$_2$ | Ether | 305 |
| | | Br(CH$_2$)$_2$Br | 1-Phenylcyclopropane-1-carbonitrile | 38 | NaNH$_2$ | Ether | 306, 305 |
| | | Br(CH$_2$)$_2$Br | 1-Phenylcyclopropane-1-carbonitrile | 51 | NaNH$_2$ | C$_6$H$_6$ | 307 |
| | | HO(CH$_2$)$_2$Cl | HO(CH$_2$)$_2$CH(C$_6$H$_5$)CN | 39 | NaNH$_2$ | Ether | 305 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| H | $C_6H_5$ (*Cont.*) | $HO(CH_2)_2Cl$ | None | — | $NaNH_2$ | Toluene | 1037 |
| | | $HO(CH_2)_2Br$ | None | — | $NaNH_2$ | Toluene | 1037 |
| | | $CH_2$——$CH_2$ $\diagdown O \diagup$ | $HO(CH_2)_2CH(C_6H_5)CN$ | 20 | $NaNH_2$ | Liquid $NH_3$ | 1037 |
| | | $C_3$ | | | | | |
| | | $n\text{-}C_3H_7Br$ | None | — | NaOH | None | 279 |
| | | $n\text{-}C_3H_7Br$ | $n\text{-}C_3H_7CH(C_6H_5)CN$ | 70–80 | $NaNH_2$ | Ether | 1031, 359, 1034, 1035 |
| | | $n\text{-}C_3H_7Br$ | $(n\text{-}C_3H_7)_2C(C_6H_5)CN$ | 60 | $NaNH_2$ | Toluene | 1036 |
| | | $n\text{-}C_3H_7X^*$ | $n\text{-}C_3H_7CH(C_6H_5)CN$ | — | Na | Liquid $NH_3$ | 1025 |
| | | $n\text{-}C_3H_7I$ | $n\text{-}C_3H_7CH(C_6H_5)CN$ | — | NaOH | None | 279, 79, |
| | | $i\text{-}C_3H_7Br$ | $i\text{-}C_3H_7CH(C_6H_5)CN$ | 70–80 | $NaNH_2$ | Ether | 1031, 566 1034 |
| | | $CH_2\!=\!CHCH_2Br$ | $CH_2\!=\!CHCH_2CH(C_6H_5)CN$ | 30 | $NaNH_2$ | Ether | 60 |
| | | $Cl(CH_2)_3I$ | 1-Phenylcyclobutane-1-carbonitrile | 18 | Na | Ether | 92 |
| | | $CH_3CHBrCH_2Br$ | 1-Phenyl-2-methylcyclopropane-1-carbonitrile | 18 | $NaNH_2$ | Ether | 305 |
| | | $Br(CH_2)_3Br$ | 1-Phenylcyclobutane-1-carbonitrile | 15 | $NaNH_2$ | Ether | 306 |
| | | $I(CH_2)_3I$ | 1-Phenylcyclobutane-1-carbonitrile | 39 | — | Ether | 92 |
| | | $C_4$ | | | | | |
| | | $CH_3OCH_2O(CH_2)_2Cl$ | $[CH_3OCH_2O(CH_2)_2]_2C(C_4H_5)CN$ | 61 | $NaNH_2$ | $C_6H_6$ | 1038, 1039 |
| | | $n\text{-}C_4H_9Br$ | $n\text{-}C_4H_9CH(C_6H_5)CN$ | — | $NaNH_2$ | None | 142 |
| | | $n\text{-}C_4H_9Br$ | $n\text{-}C_4H_9CH(C_6H_5)CN$ | — | $NaNH_2$ | Ether | 359 |
| | | $n\text{-}C_4H_9Br$ | $(n\text{-}C_4H_9)_2C(C_6H_5)CN$ | 26 | $NaNH_2$ | Ether | 566 |
| | | $n\text{-}C_4H_9Br$ | $(n\text{-}C_4H_9)_2C(C_6H_5)CN$ | 66 | $NaNH_2$ | Toluene | 1015 |
| | | $C_2H_5O(CH_2)_2Br$ | $C_2H_5O(CH_2)_2CH(C_6H_5)CN$ | 33 | $NaNH_2$ | $C_6H_6$ | 1022 |
| | | $C_2H_5O(CH_2)_2Br$ | $[C_2H_5O(CH_2)_2]_2C(C_6H_5)CN$ | 54 | $NaNH_2$ | Toluene | 500 |
| | | $i\text{-}C_4H_9Br$ | $i\text{-}C_4H_9CH(C_6H_5)CN$ | 70–80 | $NaNH_2$ | Ether | 1031, 1034, |
| | | $i\text{-}C_4H_9Br$ | $(i\text{-}C_4H_9)_2C(C_6H_5)CN$ | 65 | $NaNH_2$ | Toluene | 1036 |
| | | $CH_2\!=\!CHO(CH_2)_2Cl$ | $[CH_2\!=\!CHO(CH_2)_2]_2C(C_6H_5)CN$ | 76 | $NaNH_2$ | $C_6H_6$ | 1038, 1040 |
| | | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2CH(C_6H_5)CN$ | 80–90 | $NaNH_2$ | $C_6H_6$ | 178, 254, 1041, 1042 |
| | | $C_2H_5CHClCH_2Cl$ | 1-Phenyl-2-ethylcyclopropane-1-carbonitrile | 40 | $NaNH_2$ | Ether | 258 |
| | | $(CH_3)_2CClCH_2Cl$ | $\alpha$-Phenyl-$\beta$-isopropylacrylo-nitrile | 38 | $NaNH_2$ | Ether | 258 |
| | | $Br(CH_2)_4Br$ | 1-Phenylcyclopentane-1-carbonitrile | 46 | $NaNH_2$ | Ether | 306 |
| | | $Cl(CH_2)_2O(CH_2)_2Cl$ | 4-Phenyltetrahydropyran-4-carbonitrile | 49 | $NaNH_2$ | Toluene | 77, 499 |
| | | $Cl(CH_2)_2S(CH_2)_2Cl$ | 4-Phenyltetrahydrothiapyran-4-carbonitrile | 47 | $NaNH_2$ | Toluene | 77, 499 |
| | | $Cl(CH_2)_2NH(CH_2)_2Cl$ | 4-Phenylpiperidine-4-carbonitrile | Poor | $NaNH_2$ | Toluene | 505 |
| | | $C_5$ | | | | | |
| | | $n\text{-}C_5H_{11}I$ | $n\text{-}C_5H_{11}CH(C_6H_5)CN$ | — | NaOH | None | 279 |
| | | $n\text{-}C_5H_{11}X^*$ | $n\text{-}C_5H_{11}CH(C_6H_5)CN$ | — | Na | Liquid $NH_3$ | 1025 |
| | | $CH_2(OCH_2CH_2Cl)_2$ | $CH_2[OCH_2CH_2CH(C_6H_5)CN]_2$ | 65 | $NaNH_2$ | Toluene | 1037 |
| | | $Br(CH_2)_5Br$ | 1-Phenylcyclohexane-1-carbonitrile | 58 | $NaNH_2$ | Ether | 307, 306 |
| | | $CH_3N[(CH_2)_2Cl]_2$ | 1-Methyl-4-phenylpiperidine-4-carbonitrile | 66 | $NaNH_2$ | Toluene | 77, 503, 505 |

*Note:* References 577–1080 are on pp. 322–331.

* The halogen was not specified.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| H | $C_6H_5$ (*Cont.*) | Cyclopentyl bromide | ($\alpha$-Cyclopentyl)phenyl-acetonitrile | — | $NaNH_2$ | Ether | 1043 |
| | | 2-Chloropyridine | Phenyl-(2-pyridyl)acetonitrile | 70 | $NaNH_2$ | Toluene | 1044 |
| | | 4-Chloropyridine | Phenyl-(4-pyridyl)acetonitrile | — | $NaNH_2$ | Toluene | 1044 |
| | | $C_6$ | | | | | |
| | | $n$-$C_6H_{13}Br$ | $n$-$C_6H_{13}CH(C_6H_5)CN$ | — | KOH | None | 77 |
| | | $n$-$C_6H_{13}I$ | $n$-$C_6H_{13}CH(C_6H_5)CN$ | — | NaOH | None | 279 |
| | | $(C_2H_5O)_2CHCH_2Br$ | $(C_2H_5O)_2CHCH_2CH(C_6H_5)CN$ | 38 | $NaNH_2$ | Ether | 188 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$ | 74 | $NaNH_2$ | Ether | 1007 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$ | 80-90 | $NaNH_2$ | $C_6H_6$ | 178, 77 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$ | — | $NaNH_2$ | Toluene | 1041 |
| | | Cyclohexyl bromide | ($\alpha$-Cyclohexyl)phenyl-acetonitrile | — | $NaNH_2$ | Ether | 1045 |
| | | Cyclohexyl bromide | ($\alpha$-Cyclohexyl)phenyl-acetonitrile | 72 | $NaNH_2$ | $C_6H_6$ | 171, 1046 |
| | | Cyclohexyl bromide | ($\alpha$-Cyclohexyl)phenyl-acetonitrile | 65-77 | $NaNH_2$ | Toluene | 576 |
| | | 2-Cyclohexenyl bromide | Phenyl-(2-cyclohexenyl)-acetonitrile | 53 | $NaNH_2$ | Toluene | 192 |
| | | 2-Bromo-3-methyl-pyridine | Phenyl-(3-methyl-2-pyridyl)-acetonitrile | 68 | $NaNH_2$ | Toluene | 254 |
| | | $C_7$ | | | | | |
| | | $n$-$C_7H_{15}I$ | $n$-$C_7H_{15}CH(C_6H_5)CN$ | — | NaOH | None | 279 |
| | | $i$-$C_3H_7CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(C_3H_7$-$i)$-$CH(C_6H_5)CN$ | — | $NaNH_2$ | Ether | 1047 |
| | | $CH_3N(CH_2CHClCH_3)_2$ | 1,3,5-Trimethyl-4-phenylpiperidine-4-carbonitrile | 39 | $NaNH_2$ | Toluene | 505 |
| | | $CH_3N(CH_2CHClCH_3)_2$ | 1,3,5-Trimethyl-4-phenylpiperidine-4-carbonitrile | 41 | $KNH_2$ | Toluene | 503 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | 55 | NaOH | None | 34 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | 50 | NaOH | $(C_2H_5)_3N$-$H_2O$ | 84 |
| | | $C_6H_5CH_2Cl$ | None | — | NaOH | ($i$-$C_3H_7)_2NC_2H_5$-$H_2O$ | 84 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | 13 | $NaOCH_3$ | $CH_3OH$ | 34 |
| | | $C_6H_5CH_2Cl$ | $C_2H_5CH_2CH(C_6H_5)CN$ | 33 | $NaOC_2H_5$ | Ethanol | 34, 1001, 1048 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | 28 | $NaOC_3H_7$-$n$ | $n$-$C_3H_7OH$ | 34 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | Poor | $NaOC_5H_{11}$-$n$ | $n$-$C_5H_{11}OH$ | 34 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2CH(C_6H_5)CN$ | 34 | $NaNH_2$ | Ether | 566 |
| | | $C_6H_5CH_2Cl$ | $\{C_6H_5CH_2CH(C_6H_5)CN$ $\{(C_6H_5CH_2)_2C(C_6H_5)CN$ | 33 / 30 | $NaNH_2$ | Liquid-$NH_3$-ether | 195 |
| | | $C_2H_5CH_2Br$ | $C_6H_5CH_2CH(C_6H_5)CN$ | — | $NaOC_2H_5$ | Ethanol | 34 |
| | | $C_2H_5CH_2I$ | $C_6H_5CH_2CH(C_6H_5)CN$ | — | $NaOC_2H_5$ | Ethanol | 34 |
| | | $C_6H_5CHCl_2$ | $C_2H_5CH$=$C(C_6H_5)CN$ | — | NaOH | None | 564 |
| | | $C_8$ | | | | | |
| | | $n$-$C_8H_{17}I$ | $n$-$C_8H_{17}CH(C_6H_5)CN$ | — | NaOH | None | 279 |
| | | $C_6H_5CH(CH_3)Cl$ | $C_6H_5CH(CH_3)CH(C_6H_5)CN$ | 99 | $KNH_2$ | Liquid $NH_3$-ether | 195 |
| | | [benzene ring with CH₂Br, CH₂Br] | [ring with CH₂, C(C₆H₅)CN, CH₂] | 8 | $NaNH_2$ | Ether | 306 |
| | | $C_9$ | | | | | |
| | | $C_6H_5O(CH_2)_3Br$ | $C_6H_5O(CH_2)_3CH(C_6H_5)CN$ | 63 | $NaNH_2$ | Ether | 1049 |
| | | $CH_2[O(CH_2)_6Cl]_2$ | $CH_2[O(CH_2)_6CH(C_6H_5)CN]_2$ | 23 | $NaNH_2$ | Toluene | 1037 |
| | | 4-Chloroquinoline | Phenyl-(4-quinolyl)acetonitrile | 76 | $NaNH_2$ | $C_6H_6$ | 178 |
| | | 4,5-Dichloroquinoline | Phenyl-(5-chloro-4-quinolyl)-acetonitrile | 100 | $NaNH_2$ | $C_6H_6$ | 178 |
| | | 4,7-Dichloroquinoline | Phenyl-(7-chloro-4-quinolyl)-acetonitrile | 90 | $NaNH_2$ | $C_6H_6$ | 178 |
| | | $C_{10}$ | | | | | |
| | | $C_6H_5CH_2N(CH_3)(CH_2)_2Cl$ | $C_6H_5CH_2N(CH_3)(CH_2)_2$-$CH(C_6H_5)CN$ | 68 | $NaNH_2$ | Ether | 188 |
| | | *cyclo*-$C_6H_{11}N(CH_2CH_2Cl)_2$ | 1-Cyclohexyl-4-phenyl-piperidine-4-carbonitrile | 61 | $NaNH_2$ | Toluene | 503, 505 |
| | | $C_6H_5N(CH_2CH_2Cl)_2$ | 1,4-Diphenylpiperidine-4-carbonitrile | 66 | $NaNH_2$ | Toluene | 503, 505 |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE XIV—*Continued*
### ALKYLATION OF MONONITRILES, RCH(R′)CN

| R | R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| H | C$_6$H$_5$ (*Cont.*) | $C_{11}$–$C_{13}$ | | | | | |
| | | C$_6$H$_5$CH$_2$N(CH$_2$CH$_2$Cl)$_2$ | 1-Benzyl-4-phenylpiperidine-4-carbonitrile | 65 | NaNH$_2$ | Toluene | 505, 77, 503 |
| | | 3-Phthalimidopropyl bromide | None | — | — | — | 1037 |
| | | p-CH$_3$C$_6$H$_4$SO$_2$-N(CH$_2$CH$_2$Cl)$_2$ | p-CH$_3$C$_6$H$_4$SO$_2$N〈CH$_2$CH$_2$/CH$_2$CH$_2$〉C(CN)C$_6$H$_5$ | 37 | NaNH$_2$ | Toluene | 77 |
| | | (C$_6$H$_5$)$_2$CHCl | (C$_6$H$_5$)$_2$CHCH(C$_6$H$_5$)CN | 99 | KNH$_2$ | Liquid NH$_3$-ether | 195 |
| H | o-ClC$_6$H$_4$ | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_6$H$_4$Cl-o)CN | 58 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| | | 2-Bromopyridine | o-Chlorophenyl-(2-pyridyl)-acetonitrile | 42 | NaNH$_2$ | Toluene | 254 |
| H | p-ClC$_6$H$_4$ | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_6$H$_4$Cl-p)CN | 66 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| | | 2-Bromopyridine | p-Chlorophenyl-(2-pyridyl)-acetonitrile | 73 | NaNH$_2$ | Toluene | 254 |
| | | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$-CH(C$_6$H$_4$Cl-p)CN | 64 | NaNH$_2$ | Toluene | 1042, 1041 |
| | | (C$_2$H$_5$)$_2$N(CH$_2$)$_3$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_3$-CH(C$_6$H$_4$Cl-p)CN | 58 | NaNH$_2$ | C$_6$H$_6$ | 1042, 1041 |
| H | 3,4-Dichlorophenyl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$-CH(C$_6$H$_3$Cl$_2$-3,4)CN | 43 | NaNH$_2$ | C$_6$H$_6$ | 1042, 1041 |
| H | 〈 〉NCH$_2$ | n-C$_4$H$_9$Br | 〈 〉NCH$_2$C(C$_4$H$_9$-n)$_2$CN | 93 | NaNH$_2$ | Toluene | 1015 |
| H | C$_6$H$_5$CH$_2$ | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(CH$_2$C$_6$H$_5$)CN | 54 | NaNH$_2$ | Toluene | 254 |
| H | o-CH$_3$C$_6$H$_4$ | CH$_2$=CHO(CH$_2$)$_2$Cl | [CH$_2$=CHO(CH$_2$)$_2$]$_2$-C(C$_6$H$_4$CH$_3$-o)CN | — | NaNH$_2$ | Toluene | 1038 |
| H | o-CH$_3$OC$_6$H$_4$ | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(2'-methoxyphenyl)-piperidine-4-carbonitrile | — | NaNH$_2$ | Toluene | 190 |
| | | Cyclohexyl bromide | Cyclohexyl-(o-methoxyphenyl)-acetonitrile | 65 | NaNH$_2$ | C$_6$H$_6$ | 1007, 1008 |
| H | m-CH$_3$OC$_6$H$_4$ | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(3'-methoxyphenyl)-piperidine-4-carbonitrile | — | — | — | 501 |
| H | p-CH$_3$C$_6$H$_4$ | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$-CH(C$_6$H$_4$CH$_3$-p)CN | 79 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| H | p-CH$_3$OC$_6$H$_4$ | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(4'-methoxyphenyl)-piperidine-4-carbonitrile | 63 | NaNH$_2$ | Toluene | 503, 505 |
| | | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$-CH(C$_6$H$_4$OCH$_3$-p)CN | 70 | NaNH$_2$ | C$_6$H$_6$ | 1042, 1041 |
| H | 2-Methoxy-5-methylphenyl | n-C$_3$H$_7$Br | n-C$_3$H$_7$-CH[C$_6$H$_3$(OCH$_3$)(CH$_3$)-2,5]CN | 92 | NaNH$_2$ | C$_6$H$_6$ | 1007, 1008 |
| | | (C$_2$H$_6$)$_2$N(CH$_2$)$_2$Cl | (C$_2$H$_5$)$_2$N(CH$_2$)$_2$ CH[C$_6$H$_3$(OCH$_3$)(CH$_3$)-2,5]CN | 83 | NaNH$_2$ | C$_6$H$_6$ | 1007, 1008 |
| H | 3,4-Dimethoxyphenyl | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(3',4'-dimethoxyphenyl)piperidine-4-carbonitrile | — | NaNH$_2$ | Toluene | 190 |
| H | n-C$_9$H$_{19}$ | n-C$_6$H$_{17}$Br | n-C$_9$H$_{19}$CH(C$_6$H$_{17}$-n)CN | 25 | NaNH$_2$ | C$_6$H$_6$ | 289 |
| H | α-Naphthyl | (CH$_3$)$_2$N(CH$_2$)$_2$Cl | (CH$_3$)$_2$N(CH$_2$)$_2$CH(C$_{10}$H$_7$-α)CN | 75 | NaNH$_2$ | C$_6$H$_6$ | 254 |
| | | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(α-naphthyl)-piperidine-4-carbonitrile | 50 | NaNH$_2$ | Toluene | 503 |
| | | 2-Chloropyridine | 2-Pyridyl-(α-naphthyl)-acetonitrile | — | NaNH$_2$ | Toluene | 1044 |
| H | o-Benzyloxyphenyl | CH$_3$N(CH$_2$CH$_2$Cl)$_2$ | 1-Methyl-4-(o-benzyloxyphenyl)-piperidine-4-carbonitrile | — | NaNH$_2$ | Toluene | 190 |
| H | n-C$_{16}$H$_{33}$ | CH$_3$I | n-C$_{16}$H$_{33}$C(CH$_3$)$_2$CN | 39 | LiN(C$_2$H$_5$)$_2$ | Ether | 65 |
| CH$_3$ | CH$_3$ | CH$_3$O(CH$_2$)$_2$Br | CH$_3$O(CH$_2$)$_2$C(CH$_3$)$_2$CN | 54 | NaNH$_2$ | C$_6$H$_6$ | 53, 122 |
| | | CH$_2$=CHCH$_2$Cl | CH$_2$=CHCH$_2$C(CH$_3$)$_2$CN | 70 | LiNH$_2$ | Ether | 53 |
| | | CH$_2$=CHCH$_2$Cl | CH$_2$=CHCH$_2$C(CH$_3$)$_2$CN | Good | NaNH$_2$ | None | 122 |
| | | CH$_2$=CHCH$_2$Cl | CH$_2$=CHCH$_2$C(CH$_3$)$_2$CN | — | NaNH$_2$ | Inert solvent | 1013 |
| | | CH$_2$=CHCH$_2$Cl | CH$_2$=CHCH$_2$C(CH$_3$)$_2$CN | 83 | NaN(C$_2$H$_5$)$_2$ | Ether | 53 |
| | | CH$_2$=CHCH$_2$Br | CH$_2$=CHCH$_2$C(CH$_3$)$_2$CN | 61 | BrMgN(C$_2$H$_5$)$_2$ | Ether | 53 |
| | | Cl(CH$_2$)$_3$Br | Cl(CH$_2$)$_3$C(CH$_3$)$_2$CN | — | NaNH$_2$ | C$_6$H$_6$ | 122 |
| | | C$_6$H$_5$CH$_2$Cl | None | — | NaOC$_2$H$_5$ | Ethanol | 1017 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(CH$_3$)$_2$CN | Good | NaH | Toluene | 122, 66 |
| | | C$_6$H$_5$CH$_2$Cl | C$_6$H$_5$CH$_2$C(CH$_3$)$_2$CN | 97 | LiN(C$_2$H$_5$)$_2$ | Ether | 255 |
| C$_2$H$_5$ | C$_2$H$_5$ | C$_2$H$_5$Br | (C$_2$H$_5$)$_3$CCN | 31 | Na | Ether | 1050 |

*Note:* References 577–1080 are on pp. 322-331.

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| $C_2H_5$ | $C_2H_5$ (*Cont.*) | $(C_2H_5)_2SO_4$ | $(C_2H_5)_3CCN$ | — | LiN⬡ | Ether | 255 |
| | | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 81 | LiN⬡ | Ether | 255 |
| | | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 60 | $LiNHC_6H_{11}$ | Ether | 53 |
| | | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 91 | $NaC_6H_5$ | $C_6H_6$ | 90 |
| | | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | ca. 100 | $NaNH_2$ | $C_6H_6$ | 53, 122, 1013 |
| | | $CH_2=CHCH_2Cl$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 88 | $NaN(C_2H_5)_2$ | Ether | 53 |
| | | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | — | Na | Xylene | 1050 |
| | | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | — | K | Ether | 1050 |
| | | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | — | K | $C_6H_6$ | 1050 |
| | | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | — | Cu | Toluene | 1051 |
| | | $CH_2=CHCH_2Br$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 78 | $BrMgN(C_6H_{11})_2$ | Ether | 53 |
| | | $CH_2=CHCH_2I$ | $CH_2=CHCH_2C(C_2H_5)_2CN$ | 80 | $NaNH_2$ | $C_6H_6$ | 1013 |
| | | $n\text{-}C_4H_9Br$ | $n\text{-}C_4H_9C(C_2H_5)_2CN$ | 78 | $NaNH_2$ | $C_6H_6$ | 53, 122 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2C(C_2H_5)_2CN$ | — | $NaNH_2$ | $C_6H_6$ | 53, 122 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_2H_5)_2CN$ | — | K | Ether | 1050 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_2H_5)_2CN$ | — | $NaNH_2$ | Ether | 59 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_2H_5)_2CN$ | — | $NaNH_2$ | $C_6H_6$ | 122 |
| $C_2H_5$ | $i\text{-}C_3H_7$ | $i\text{-}C_3H_7Br$ | $(i\text{-}C_3H_7)_2C(C_2H_5)CN$ | 45 | $NaNH_2$ | $C_6H_6$ | 53, 122, 1013 |
| $C_2H_5$ | $CH_2=CHCH_2$ | $CH_2=CHCH_2Br$ | α-Allyl-α-isopropylbutyronitrile | 44 | K | $C_6H_6$ | 1050 |
| $C_2H_5$ | $n\text{-}C_4H_9$ | $CH_2=CHCH_2Cl$ | $(CH_2=CHCH_2)_2C(C_2H_5)CN$ | 73 | $NaC_6H_5$ | $C_6H_6$ | 90 |
| | | $CH_2=CHCH_2Cl$ | α-Allyl-α-ethylcapronitrile | 90 | $NaC_6H_5$ | $C_6H_6$ | 90 |
| $CH_2=CHCH_2$ | $CH_2=CHCH_2$ | $C_2H_5I$ | $(CH_2=CHCH_2)_2C(C_2H_5)CN$ | 80 | $BrMgN(C_6H_{11})_2$ | Inert solvent | 255 |
| | | $CH_2=CHCH_2Cl$ | $(CH_2=CHCH_2)_3CCN$ | 88 | $NaC_6H_5$ | $C_6H_6$-ligroin | 90 |
| | | $CH_2=CHCH_2Cl$ | $(CH_2=CHCH_2)_3CCN$ | — | $BrMgN(C_6H_{11})_2$ | Inert solvent | 255 |
| | | $CH_2=CHCH_2Br$ | $(CH_2=CHCH_2)_3CCN$ | — | K | Ether | 1050 |
| | | $CH_2=CHCH_2Br$ | $(CH_2=CHCH_2)_3CCN$ | — | $BrMgN(C_6H_{11})_2$ | Inert solvent | 255 |
| | | $i\text{-}C_5H_{11}Cl$ | $(CH_2=CHCH_2)_2C(C_6H_{11}\text{-}i)CN$ | 79 | $NaC_6H_5$ | $C_6H_6$ | 90 |
| † | | $C_6H_5CH_2Cl$ | ⬡(CN)$CH_2C_6H_5$ / $CH_3$ | Good | $NaNH_2$ | $C_6H_6$ | 122 |
| $CH_3$ | $C_6H_5$ | $Cl(CH_2)_2Cl$ | $Cl(CH_2)_2C(CH_3)(C_6H_5)CN$ | 20 | $NaNH_2$ | $C_6H_6$ | 359 |
| | | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2\text{-}C(CH_3)(C_6H_5)CN$ | 66 | $NaNH_2$ | Toluene | 1023, 501 |
| | | $CH_3CHBrCO_2C_2H_5$ | $C_2H_5O_2CCH(CH_3)\text{-}C(CH_3)(C_6H_5)CN$ | 15 | $NaNH_2$ | Ether | 583 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(CH_3)(C_6H_5)CN$ | — | $NaOC_2H_5$ | Ethanol | 34 |
| $C_2H_5$ | $C_6H_5$ | $C_2H_5I$ | $C_6H_5C(C_2H_5)_2CN$ | — | Na | Ether | 1052 |
| | | $C_2H_5I$ | $C_6H_5C(C_2H_5)_2CN$ | 75 | $NaNH_2$ | Ether | 1035 |
| | | $Cl(CH_2)_2Cl$ | $Cl(CH_2)_2C(C_2H_5)(C_6H_5)CN$ | 53 | $NaNH_2$ | $C_6H_6$ | 1032, 359 |
| | | Cyclopentyl bromide | α-Phenyl-α-cyclopentyl-butyronitrile | — | $NaNH_2$ | Ether | 1043 |
| | | 2-Chloropyridine | α-Ethyl-α-phenyl-α-(2-pyridyl)-acetonitrile | — | $NaNH_2$ | Toluene | 1044 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2\text{-}C(C_2H_5)(C_6H_5)CN$ | 67 | $NaNH_2$ | Toluene | 190 |
| $Cl(CH_2)_2$ | $C_6H_5$ | None | 1-Phenylcyclopropane-1-carbonitrile | 73 | $NaNH_2$ | Liquid $NH_3$ | 305 |
| $C_2H_5$ | $C_6H_5CH_2$ | $CH_3I$ | $C_6H_5CH_2C(CH_3)(C_2H_5)CN$ | — | $NaNH_2$ | Ether | 1018 |
| $(CH_3)_2N(CH_2)_2$ | ⬠S | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2\text{-}C(C_4H_3S)(C_5H_4N\text{-}2)CN$ | 36 | $NaNH_2$ | Toluene | 254 |
| $n\text{-}C_3H_7$ | $C_6H_5$ | $Cl(CH_2)_2Cl$ | $Cl(CH_2)_2C(C_6H_5)(C_3H_7\text{-}n)CN$ | 24 | $NaNH_2$ | $C_6H_6$ | 359 |
| | | $i\text{-}C_4H_9Br$ | $i\text{-}C_4H_9C(C_6H_5)(C_3H_7\text{-}n)CN$ | 75 | $NaNH_2$ | Ether | 1035 |
| | | $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2\text{-}C(C_3H_7\text{-}n)(C_6H_5)CN$ | 75 | $NaNH_2$ | $C_6H_6$ | 1053 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)(C_3H_7\text{-}n)CN$ | — | NaOH | None | 279 |
| $(CH_3)_2N(CH_2)_2$ | ⬡N | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2\text{-}C(C_5H_4N\text{-}2)(C_5H_4N\text{-}3)CN$ | 35 | $NaNH_2$ | Toluene | 254 |
| $n\text{-}C_4H_9$ | $C_6H_5$ | $Cl(CH_2)_2Cl$ | $Cl(CH_2)_2C(C_6H_5)(C_4H_9\text{-}n)CN$ | — | $NaNH_2$ | $C_6H_6$ | 359 |

*Note:* References 577–1080 are on pp. 322–331.

† The nitrile alkylated was ⬡ CN / $CH_3$

## TABLE XIV—*Continued*

### ALKYLATION OF MONONITRILES, RCH(R′)CN

| R | R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| $i$-$C_4H_9$ | $C_6H_5$ | $(CH_3)_2N(CH_2)_2Cl \cdot HCl$ | $(CH_3)_2N(CH_2)_2C(C_6H_5)$- $(C_4H_9$-$i)CN$ | 68 | $NaNH_2$ | $C_6H_6$ | 191 |
| | | $(C_2H_5)_2N(CH_2)_2Cl \cdot HCl$ | $(C_2H_5)_2N(CH_2)_2$- $C(C_6H_5)(C_4H_9$-$i)CN$ | 81 | $NaNH_2$ | $C_6H_6$ | 191 |
| | | $\beta$-(1-Piperidyl)ethyl chloride hydrochloride | $\alpha$-($i$-Butyl)-$\alpha$-phenyl-$\gamma$-(1-piperidyl)butyronitrile | 79 | $NaNH_2$ | $C_6H_6$ | 191 |
| $(CH_3)_2C$=$CH$ | $C_6H_5$ | $\beta$-(1-Piperidyl)ethyl chloride hydrochloride | $\alpha$-($i$-Butenyl)-$\alpha$-phenyl-$\gamma$-(1-piperidyl)butyronitrile | 75 | $NaNH_2$ | $C_6H_6$ | 191 |
| $CH_2$=$C(CH_3)CH_2$ | $C_6H_5$ | $\beta$-(1-Piperidyl)ethyl chloride hydrochloride | $\alpha$-(2-Methylallyl)-$\alpha$-phenyl-$\gamma$-(1-piperidyl)butyronitrile | 72 | $NaNH_2$ | $C_6H_6$ | 191 |
| $(CH_3)_2N(CH_2)_2$ | *Cyclo*-$C_6H_{11}$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_6H_{11}$-*cyclo*)$(C_5H_4N$-2)$CN$ | 50 | $NaNH_2$ | Toluene | 254 |
| $(CH_3)_2N(CH_2)_2$ | $C_6H_5$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_5H_4N$-2)$(C_6H_5)CN$ | 78 | $NaNH_2$ | Toluene | 254 |
| | | 4-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_5H_4N$-4)$(C_6H_5)CN$ | 76 | $NaNH_2$ | Toluene | 254 |
| | | *Cyclo*-$C_6H_{11}Br$ | $(CH_3)_2N(CH_2)_2$- $C(C_6H_5)(C_6H_{11}$-*cyclo*)$CN$ | 82 | $NaNH_2$ | Toluene | 254 |
| | | 2-Bromo-6-methyl-pyridine | $\alpha$-Phenyl-$\alpha$-(6-methyl-2-pyridyl)-$\gamma$-(dimethylamino)-butyronitrile | 74 | $NaNH_2$ | Toluene | 254 |
| | | 4-Chloroquinoline | $(CH_3)_2N(CH_2)_2$- $C(C_6H_5)(C_9H_6N$-4)$CN$ | 88 | $NaNH_2$ | $C_6H_6$ | 178 |
| | | 4,5-Dichloroquinoline | $\alpha$-Phenyl-$\alpha$-(5-chloro-4-quinolyl)-$\gamma$-(dimethylamino)-butyronitrile | 86 | $NaNH_2$ | $C_6H_6$ | 178 |
| | | 4,7-Dichloroquinoline | $\alpha$-Phenyl-$\alpha$-(7-chloro-4-quinolyl)-$\gamma$-(dimethylamino)-butyronitrile | 95 | $NaNH_2$ | $C_6H_6$ | 178 |
| $(CH_3)_2N(CH_2)_2$ | $p$-$ClC_6H_4$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_5H_4N$-2)$(C_6H_4Cl$-$p)CN$ | 67 | $NaNH_2$ | Toluene | 254 |
| [thiophene structure] | *Cyclo*-$C_6H_{11}$ | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2$- $C(C_4H_3S)(C_6H_{11}$-*cyclo*)$CN$ | 90 | $NaNH_2$ | Toluene | 1023 |
| [pyridyl-methyl structure] | [pyridyl structure] | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2C(C_5H_4N$-2)$_2CN$ | 78 | $NaNH_2$ | Toluene | 254 |
| $CH_3$ | $n$-$C_{10}H_{21}$ | $n$-$C_{10}H_{21}Br$ | $(n$-$C_{10}H_{21})_2C(CH_3)CN$ | — | $NaNH_2$ | Toluene | 289 |
| $n$-$C_3H_7$ | 2-Methoxy-5-methylphenyl | $(C_2H_5)_2N(CH_2)_2Cl$ | $\alpha$-(2-Diethylaminoethyl)-$\alpha$-(2-methoxy-5-methylphenyl)valeronitrile | 79 | $NaNH_2$ | $C_6H_6$ | 1007, 1008 |
| $(CH_3)_2N(CH_2)_2$ | $C_6H_5CH_2$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(CH_2C_6H_5)(C_5H_4N$-2)$CN$ | 41 | $NaNH_2$ | Toluene | 254 |
| $(CH_3)_2N(CH_2)_2$ | $p$-$CH_3C_6H_4$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_6H_4CH_3$-$p)(C_5H_4N$-2)$CN$ | 44 | $NaNH_2$ | Toluene | 254 |
| $(CH_3)_2N(CH_2)_2$ | $p$-$CH_3OC_6H_4$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2$- $C(C_6H_4OCH_3$-$p)(C_5H_4N$-2)$CN$ | 80 | $NaNH_2$ | Toluene | 254 |
| $n$-$C_5H_{11}$ | $C_6H_5$ | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)(C_5H_{11}$-$n)CN$ | — | $NaOH$ | None | 279 |
| *cyclo*-$C_5H_9$ | $C_6H_5$ | $(CH_3)_2N(CH_2)_2Cl \cdot HCl$ | $(CH_3)_2N(CH_2)_2$- $C(C_6H_5)(C_5H_9)CN$ | 73 | $NaNH_2$ | $C_6H_6$ | 191 |
| | | Cyclopentyl bromide | $C_6H_5C(C_5H_9)_2CN$ | — | $NaNH_2$ | Ether | 1043 |
| 2-Pyridyl | $C_6H_5$ | $C_2H_5Br$ | $C_6H_5C(C_2H_5)(C_5H_4N$-2)$CN$ | 85 | $NaNH_2$ | Toluene | 1044 |
| | | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2$- $C(C_6H_5)(C_5H_4N$-2)$CN$ | 74 | $NaNH_2$ | Toluene | 254 |
| | | $(CH_3)_2N(CH_2)_3Cl$ | $(CH_3)_2N(CH_2)_3$- $C(C_6H_5)(C_5H_4N$-2)$CN$ | 82 | $NaNH_2$ | Toluene | 254 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2$- $C(C_6H_5)(C_5H_4N$-2)$CN$ | 92 | $NaNH_2$ | Toluene | 254 |
| | | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha$-Phenyl-$\alpha$-(2-pyridyl)-$\gamma$-(1′-piperidyl)butyronitrile | 89 | $NaNH_2$ | Toluene | 254 |
| 2-Pyridyl | $o$-$ClC_6H_4$ | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2$- $C(C_6H_4Cl$-$o)(C_5H_4N$-2)$CN$ | 33 | $NaNH_2$ | Toluene | 254 |
| 2-Pyridyl | $C_6H_5CH_2$ | $(CH_3)_2NCH_2Cl$ | $(CH_3)_2NCH_2$- $C(CH_2C_6H_5)(C_5H_4N$-2)$CN$ | 46 | $NaNH_2$ | Toluene | 254 |
| $n$-$C_6H_{13}$ | $C_6H_5$ | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2$- $C(C_6H_5)(C_6H_{13}$-$n)CN$ | 75 | $NaNH_2$ | Toluene | 77, 191 |
| | | $C_6H_5CH_2Cl$ | None | — | $NaOH$ | None | 279 |
| $(C_2H_5)_2N(CH_2)_2$ | $C_6H_5$ | Cyclohexene oxide | $\gamma$-Diethylamino-$\alpha$-(-2-hydroxycyclohexyl)-$\alpha$-phenylbutyronitrile | — | $NaNH_2$ | Ether | 1007 |
| | | 4-Chloroquinoline | $(C_2H_5)_2N(CH_2)_2$- $C(C_6H_5)(C_9H_6N$-4)$CN$ | 97 | $NaNH_2$ | $C_6H_6$ | 178 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

| R | R' | Alkylating Agent | Product | Yield %. | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| (C₂H₅)₂N(CH₂)₂ | C₆H₅ (*Cont.*) | 4,5-Dichloroquinoline | α-Phenyl-α-(5-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile | 98 | NaNH₂ | C₆H₆ | 178 |
| | | 4,7-Dichloroquinoline | α-Phenyl-α-(7-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile | 91 | NaNH₂ | C₆H₆ | 178 |
| Cyclohexyl (=C₆H₁₁) | C₆H₅ | CH₃X† | C₆H₅C(CH₃)(C₆H₁₁)CN | — | NaNH₂ | Ether | 1054 |
| | | C₂H₅Br | C₆H₅C(C₂H₅)(C₆H₁₁)CN | 94 | NaNH₂ | C₆H₆ | 1004 |
| | | n-C₃H₇I | n-C₃H₇C(C₆H₅)(C₆H₁₁)CN | 70 | NaNH₂ | Liquid NH₃ | 171 |
| | | (CH₃)₂N(C₇H₇)₂Cl·HCl | (CH₃)₂N(CH₂)₂-C(C₆H₅)(C₆H₁₁)CN | 72 | NaNH₂ | C₆H₆ | 191, 1055 |
| | | (CH₃)₂NCH₂CH(CH₃)Br | (CH₃)₂NCH₂CH(CH₃)-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | (CH₃)₂NCH(CH₃)CH₂Br | (CH₃)₂NCH(CH₃)CH₂-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | Cyclopentyl bromide | Cyclopentyl(cyclohexyl)phenyl-acetonitrile | — | NaNH₂ | Ether | 1043 |
| | | (C₂H₅)₂N(CH₂)₂Cl·HCl | (C₂H₅)₂N(CH₂)₂-C(C₆H₅)(C₆H₁₁)CN | 82 | NaNH₂ | C₆H₆ | 191, 1055 |
| | | β-(1-Pyrrolidyl)ethyl chloride hydrochloride | α-Cyclohexyl-α-phenyl-γ-(1-pyrrolidyl)butyronitrile · | 90 | NaNH₂ | C₆H₆ | 191 |
| | | (C₂H₅)₂NCH(C₂H₅)Cl | (C₂H₅)₂NCH(C₂H₅)-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | β-(1-Piperidyl)ethyl chloride hydrochloride | α-Cyclohexyl-α-phenyl-γ-(1-piperidyl)butyronitrile | 82 | NaNH₂ | C₆H₆ | 191 |
| | | (C₂H₅)₂NCH(C₂H₅)CH₂Cl | (C₂H₅)₂NCH(C₂H₅)CH₂-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | [piperidyl ring]NCH₂CH(CH₃)Cl | [piperidyl ring]NCH₂CH(CH₃)-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | δ-(4-Morpholinyl)butyl chloride | Cyclohexyl-[δ-(4-morpholinyl)butyl]phenylacetonitrile | — | NaNH₂ | C₆H₂ | 1055 |
| | | (C₂H₅)₂NCH₂C(CH₃)₂-CH₂Cl | (C₂H₅)₂NCH₂C(CH₃)₂-CH₂C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| | | (n-C₄H₉)₂N(CH₂)₆Cl | (n-C₄H₉)₂N(CH₂)₆-C(C₆H₅)(C₆H₁₁)CN | — | NaNH₂ | C₆H₆ | 1055 |
| 1-Cyclohexenyl | C₆H₅ | (C₂H₅)₂N(CH₂)₂Cl | β-[Diethylaminoethyl]-(1-cyclohexenyl)phenyl-acetonitrile | 81 | NaNH₂ | Toluene | 1056 |
| C₆H₅ | C₆H₅ | I₂ | (C₆H₅)₂C(CN)C(C₆H₅)₂CN | 100 | NaOC₂H₅ | Ethanol | 264 |
| | | *C₂* | | | | | |
| | | C₂H₅I | (C₆H₅)₂C(C₂H₅)CN | 88 | NaNH₂ | C₆H₆ | 1004 |
| | | Cl(CH₂)₂Cl | { Cl(CH₂)₂C(C₆H₅)₂CN / NCC(C₆H₅)₂(CH₂)₂C(C₆H₅)₂CN | 70 / — | NaNH₂ | C₆H₆ | 1057 |
| | | Br(CH₂)₂Br | Br(CH₂)₂C(C₆H₅)₂CN | 74–80 | NaNH₂ | C₆H₆ | 1057, 91 |
| | | CH₂—CH₂ (ethylene oxide) | None | — | NaOC₂H₅ | Ethanol | 25 |
| | | CH₂—CH₂ (ethylene oxide) | (')H₂CH₂C(C₆H₅)₂, O——CO | 52 | NaOC₂H₅ | C₆H₆ | 25 |
| | | CH₂—CH₂ (ethylene oxide) | CH₂CH₂C(C₆H₅)₂, O——CO | 57 | NaNH₂ | C₆H₆ | 25 |
| | | *C₃* | | | | | |
| | | n-C₃H₇I | n-C₃H₇C(C₆H₅)₂CN | 88 | KOC₄H₉-t | Xylene-t-C₄H₉OH | 27 |
| | | i-C₃H₇I | i-C₃H₇C(C₆H₅)₂CN | 72 | KOC₄H₉-t | Xylene | 27 |
| | | CH₂=CHCH₂Cl | CH₂=CHCH₂C(C₆H₅)₂CN | 94 | NaNH₂ | C₆H₆ | 25, 329 |
| | | CH₂=CHCH₂Br | CH₂=CHCH₂C(C₆H₅)₂CN | 72 | KOC₄H₉-t | Xylene-t-C₄H₉OH | 27 |
| | | CH₃CHClCH₂Br | CH₃CHClCH₂C(C₆H₅)₂CN | 47 | NaNH₂ | C₆H₆ | 25 |
| | | Br(CH₂)₃Br | Br(CH₂)₃C(C₆H₅)₂CN | — | NaNH₂ | C₆H₆ | 1057 |
| | | H₃CCH——CH₂ (propylene oxide) | CH₂——C(C₆H₅)₂ / H₃CCH  C=NH \O | 57 | KOC₄H₉-t | t-C₄H₉OH | 27 |
| | | H₃CCH——CH₂ (propylene oxide) | CH₂——C(C₆H₅)₂ / H₃CCH  C=NH \O | 80 | NaNH₂ | C₆H₆ | 329 |

*Note:* References 577–1080 are on pp. 322–331.

† The methylating agent was not specified.

## TABLE XIV—Continued

### ALKYLATION OF MONONITRILES, RCH(R′)CN

| R | R′ | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| $C_6H_5$ | $C_6H_5$ (*Cont.*) | $H_3CCH\!\!-\!\!-\!\!CH_2$, O | $CH_2\!-\!C(C_6H_5)_2$, $H_3CCH$  CO, O | 69 | $NaNH_2$ | $C_6H_6$ | 25 |
| | | $CH_2=CBrCH_2Br$ | $CH_2=CBrCH_2C(C_6H_5)_2CN$ | 71 | $NaNH_2$ | $C_6H_6$ | 25 |
| | | **$C_4$** | | | | | |
| | | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2C(C_6H_5)_2CN$ | 70 | $NaNH_2$ | $C_6H_6$ | 1057, 26 |
| | | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2C(C_6H_5)_2CN$ | 92 | $NaNH_2$ | Toluene | 1023 |
| | | $BrCH_2CO_2C_2H_5$ | $C_2H_5O_2CCH_2C(C_6H_5)_2CN$ | 90 | $NaOC_2H_5$ | Ethanol | 1058 |
| | | $Br(CH_2)_4Br$ | $Br(CH_2)_4C(C_6H_5)_2CN$ | 30 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | **$C_5$** | | | | | |
| | | $(CH_3)_2NCH_2CH(CH_3)Cl$ | $(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ | ca. 46 | $KOC_4H_9\text{-}t$ | Xylene-$t$-$C_4H_9OH$ | 27 |
| | | | $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$ | ca. 46 | | | |
| | | $(CH_3)_2NCH_2CH(CH_3)Cl$ | $(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ | ca. 39 | $NaNH_2$ | $C_6H_4$ | 27, 26, 91 |
| | | | $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$ | ca. 39 | | | |
| | | $(CH_3)_2NCH(CH_3)CH_2Cl$ | $(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ | 36 | $NaNH_2$ | $C_6H_6$ | 25 |
| | | | $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$ | --- | | | |
| | | $CH_3CHCl(CH_2)_2CN$ | $NC(CH_2)_2CH(CH_3)\text{-}C(C_6H_5)_2CN$ | Low | $NaNH_2$ | $C_6H_5$ | 1059 |
| | | | (cyclic structure) NH, $(C_6H_5)_2$  CN, $H_3C$ | 9 | | | |
| | | $ClCH_2CH(CH_3)CH_2CN$ | $NCCH_2CH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ | — | $NaNH_2$ | $C_6H_6$ | 1059 |
| | | $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2C(C_6H_5)_2CN$ | ca. 75 | $NaNH_2$ | $C_6H_6$ | 1053 |
| | | **$C_6$** | | | | | |
| | | $(C_2H_5O)_2CHCH_2Cl$ | $(C_2H_5O)_2CHCH_2C(C_6H_5)_2CN$ | — | $NaNH_2$ | $C_6H_6$ | 1060 |
| | | $(C_2H_5)_2N(CH_2)_2Cl$ | $(C_2H_5)_2N(CH_2)_2C(C_6H_5)_2CN$ | 70–87 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | $\beta$-(1-Pyrrolidyl)ethyl chloride hydrochloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(1-pyrrolidyl)-butyronitrile | 84 | $NaNH_2$ | $C_6H_6$ | 1057, 191 |
| | | $\beta$-(4-Morpholinyl)ethyl chloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(4-morpholinyl)-butyronitrile | 56 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(1-piperidyl)-butyronitrile | 73 | $NaNH_2$ | $C_6H_6$ | 91, 93, 1057 |
| | | **$C_7$** | | | | | |
| | | $(C_2H_5)_2N(CH_2)_3Cl$ | $(C_2H_5)_2N(CH_2)_3C(C_6H_5)_2CN$ | 75 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | $(C_2H_5)_2NCH_2CH(CH_3)Cl$ | $(C_2H_5)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$ and $(C_2H_5)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ | — | $NaNH_2$ | $C_6H_6$ | 1061 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)_2CN$ | 83 | $NaOC_2H_5$ | Ethanol | 564 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)_2CN$ | — | $NaNH_2$ | Ether | 61 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2C(C_6H_5)_2CN$ | 99 | $KNH_2$ | Liquid $NH_3$-ether | 195 |
| | | $\beta$-(2-Methyl-1-pyrrolidyl)ethyl chloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(2-methyl-1-pyrrolidyl)butyronitrile | 78 | $NaNH_2$ | $C_6H_6$ | 191 |
| | | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(1-piperidyl)-butyronitrile | — | $NaNH_2$ | $C_6H_6$ | 26 |
| | | 1-(4-Morpholinyl)-2-chloropropane | $\alpha,\alpha$-Diphenyl-$\gamma$-(4-morpholinyl)-valeronitrile | 48 | $NaNH_2$ | $C_6H_6$ | 25, 91 |
| | | | $\alpha,\alpha$-Diphenyl-$\gamma$-(4-morpholinyl)-$i$-valeronitrile | 32 | | | |
| | | 2-(4-Morpholinyl)propyl chloride | $\alpha,\alpha$-Diphenyl-$\gamma$-(4-morpholinyl)-valeronitrile | 30 | $NaNH_2$ | $C_6H_6$ | 25 |
| | | | $\alpha,\alpha$-Diphenyl-$\gamma$-(4-morpholinyl)-$i$-valeronitrile | 20 | | | |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE XIV—*Continued*

### ALKYLATION OF MONONITRILES, RCH(R')CN

| R | R' | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|---|
| | | $C_8$ | | | | | |
| $C_6H_5$ | $C_6H_5$ (Cont.) | $C_6H_5CH(CH_3)Cl$ | $C_6H_5CH(CH_3)C(C_6H_5)_2CN$ | 89 | $KNH_2$ | Liquid $NH_3$-ether | 195 |
| | | $\gamma$-(1-Piperidyl)propyl chloride | $\alpha,\alpha$-Diphenyl-$\delta$-(1-piperidyl)-valeronitrile | 64 | $NaNH_2$ | $C_6H_6$ | 1061 |
| | | 1-(1'-Piperidyl)-2-chloropropane | $\alpha,\alpha$-Diphenyl-$\gamma$-(1-piperidyl)-valeronitrile and $\alpha,\alpha$-Diphenyl-$\gamma$-(1-piperidyl)-$i$-valeronitrile | — | $NaNH_2$ | $C_6H_6$ | 91. 1061, 1062 |
| | | $C_9$ | | | | | |
| | | $C_6H_5N(CH_3)(CH_2)_2Cl$ | $C_6H_5N(CH_2)(CH_2)_2C(C_6H_5)_2CN$ | 77 | $NaNH_2$ | $C_6H_6$ | 1063 |
| | | $C_{10}$ | | | | | |
| | | $(n\text{-}C_4H_9)_2N(CH_2)_2Cl$ | $(n\text{-}C_4H_9)_2N(CH_2)_2C(C_6H_5)_2CN$ | 66 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | $C_6H_5CH_2N(CH_2)_2Cl$ with $CH_3$ | $C_6H_5CH_2N(CH_3)(CH_2)_2\text{-}C(C_6H_5)_2CN$ | 81 | $NaNH_2$ | $C_6H_6$ | 1093 |
| | | $C_{11}$ | | | | | |
| | | $C_6H_5CH_2N(CH_3)\text{-}CH_2CH(CH_2)Cl$ | $\{C_6H_5CH_2N(CH_3)CH_2\text{-}CH(CH_3)C(C_6H_5)_2CN$ | 16 | $NaNH_2$ | $C_6H_6$ | 1063 |
| | | | $C_6H_5CH_2N(CH_3)CH(CH_3)\text{-}CH_2C(C_6H_5)_2CN$ | 23 | | | |
| | | $C_{13}$ | | | | | |
| | | $(C_6H_5)_2CHCl$ | $(C_6H_5)_2CHC(C_6H_5)_2CN$ | 96 | $KNH_2$ | Liquid $NH_3$-ether | 195 |
| | | $C_{16}$ | | | | | |
| | | $(C_6H_5)_2CHN(CH_3)\text{-}(CH_2)_2Cl$ | $(C_6H_5)_2CHN(CH_3)(CH_2)_2\text{-}C(C_6H_5)_2CN$ | — | $NaNH_2$ | Toluene | 1060 |
| | | $(C_6H_5CH_2)_2N(CH_2)_2Cl$ | $(C_6H_5CH_2)_2N(CH_2)_2\text{-}C(C_6H_5)_2CN$ | 53 | $NaNH_2$ | $C_6H_6$ | 1057 |
| Cyclohexyl | $o$-Methoxyphenyl | $(C_2H_5)_2N(CH_2)_2Cl$ | $\alpha$-Cyclohexyl-$\alpha$-($o$-methoxyphenyl)-$\gamma$-(diethylamino)-butyronitrile | 75 | $NaNH_2$ | $C_6H_6$ | 1007, 1008 |
| $C_2H_5$ | $n\text{-}C_7H_{15}$ | $C_6H_5CH_2Cl$ | None | — | NaOH | None | 279 |
| $C_2H_5$ | $C_6H_5CH_2$ | $Br(CH_2)_2CO_2C_2H_5$ | $C_2H_5O_2C(CH_2)_2\text{-}C(C_6H_5)(CH_2C_6H_5)CN$ | ca. 75 | $NaNH_2$ | $C_6H_6$ | 1053 |
| | | $C_6H_5CH_2Cl$ | $(C_6H_5CH_2)_2C(C_6H_5)CN$ | 39 | $NaNH_2$ | Ether | 566 |
| | | $C_6H_5CH_2I$ | None | — | $NaOC_2H_5$ | Ethanol | 34 |
| | | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha$-Phenyl-$\alpha$-benzyl-$\gamma$-(1-piperidyl)butyronitrile | 33 | $NaNH_2$ | Toluene | 77 |
| $C_6H_5$ | $p\text{-}CH_3C_6H_4$ | $Br(CH_2)_2Br$ | $\alpha$-Phenyl-$\alpha$-($p$-tolyl)-$\gamma$-bromobutyronitrile | 68 | $NaNH_2$ | $C_6H_6$ | 1057 |
| | | $C_6H_5CH_2Cl$ | $C_6H_5CH_2\text{-}C(C_6H_5)(C_6H_4CH_3\text{-}p)CN$ | — | $NaOC_2H_5$ | Ethanol | 564 |
| $(CH_3)_2N(CH_2)_2$ | $\alpha\text{-}C_{10}H_7$ | 2-Bromopyridine | $(CH_3)_2N(CH_2)_2\text{-}C(C_{10}H_7\text{-}\alpha)(C_5H_4N\text{-}2)CN$ | 76 | $NaNH_2$ | Toluene | 254 |
| $C_6H_5$ | $n\text{-}C_8H_{17}$ | $C_6H_5CH_2Cl$ | None | — | NaOH | None | 279 |
| $C_6H_5$ | $cyclo\text{-}C_6H_{11}(CH_2)_2$ | $(CH_3)_2N(CH_2)_2Cl$ | $(CH_3)_2N(CH_2)_2C(C_6H_5)\text{-}[cyclo\text{-}C_6H_{11}(CH_2)_2]CN$ | 81 | $NaNH_2$ | Toluene | 1023 |
| $o\text{-}CH_3C_6H_4$ | $o\text{-}CH_3C_6H_4$ | $\beta$-(4-Morpholinyl)ethyl chloride | $\alpha,\alpha$-Di-($o$-tolyl)-$\gamma$-(4-morpholinyl)-butyronitrile | 70 | $NaNH_2$ | $C_6H_6$ | 1057 |
| $p\text{-}CH_3OC_6H_4$ | $p\text{-}CH_3OC_6H_4$ | $I_2$ | None | — | NaOH | Ethanol | 1064 |
| $n\text{-}C_{12}H_{25}$ | $n\text{-}C_{12}H_{25}$ | $CH_2{=}CHCH_2Cl$ | $CH_2{=}CHCH_2C(C_{12}H_{25}\text{-}n)_2CN$ | — | $NaC_6H_5$ | $C_6H_6$ | 90 |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE XV

### Alkylation of Alkylideneacetonitriles

| Compound Alkylated | Alkylating Agent | Product | Yield, % | Base | Solvent | Reference |
|---|---|---|---|---|---|---|
| Cyclopentylidene-(2-thienyl)-acetonitrile | $(CH_3)_2N(CH_2)_2Cl$ | $\alpha$-(1-Cyclopentenyl)-$\alpha$-(2-thienyl)-$\gamma$-(dimethylamino)butyronitrile | — | $NaNH_2$ | $C_6H_6$ | 193 |
| | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha$-(1-Cyclopentenyl)-$\alpha$-(2-thienyl)-$\gamma$-(1-piperidyl)butyronitrile | — | $NaNH_2$ | $C_6H_6$ | 193 |
| Cyclopentylidene(phenyl)-acetonitrile | $(CH_3)_2N(CH_2)_2Cl$ | $\alpha$-(1-Cyclopentenyl)-$\alpha$-phenyl-$\gamma$-(dimethylamino)butyronitrile | 65 | $NaNH_2$ | $C_6H_6$ | 193 |
| | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha$-(1-Cyclopentenyl)-$\alpha$-phenyl-$\gamma$-(I-piperidyl)butyronitrile | — | $NaNH_2$ | $C_6H_6$ | 193 |
| Cyclopentylidene-($p$-methoxyphenyl)acetonitrile | $(CH_3)_2N(CH_2)_2Cl$ | $\alpha$-(1-Cyclopentenyl)-$\alpha$-($p$-methoxyphenyl)-$\gamma$-(dimethylamino)-butyronitrile | — | $NaNH_2$ | $C_6H_6$ | 193 |
| Cyclohexylidene(phenyl)-acetonitrile | $n$-$C_3H_7I$ | $n$-Propyl-(1-cyclohexenyl)phenylacetonitrile | 82 | $NaNH_2$ | $C_6H_6$ | 171 |
| | $CH_2\!=\!CHCH_2Br$ | Allyl-(1-cyclohexenyl)phenylacetonitrile | 77 | $NaNH_2$ | Ether | 171 |
| | $n$-$C_4H_9I$ | None | — | $NaOC_2H_5$ | Ethanol | 259 |
| | $\beta$-(1-Piperidyl)ethyl chloride | $\alpha$-(1-Cyclohexenyl)-$\alpha$-phenyl-$\gamma$-(1-piperidyl)butyronitrile | 92 | $NaNH_2$ | Toluene | 192 |

## TABLE XVI

### REDUCTIONS LEADING TO ALKYLMALONIC ESTERS OR ACIDS

| Compound Reduced | Reducing Agent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_2{=}C(CO_2C_2H_5)_2$ | $H_2$—Ni | $CH_3CH(CO_2C_2H_5)_2$ | 95 | 1065 |
| $CH_3CH{=}C(CO_2C_2H_5)_2$ | $AlHg_x$ | $C_2H_5CH(CO_2C_2H_5)_2$ | — | 1066 |
| | $H_2$—Pd/C | $C_2H_5CH(CO_2C_2H_5)_2$ | 90 | 340 |
| | $H_2$—PdCl$_2$ | $C_2H_5CH(CO_2C_2H_5)_3$ | — | 346 |
| | $H_2$—Ni | $C_3H_6CH(CO_2C_2H_5)_2$ | 93 | 1065 |
| $C_2H_5CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Pd/C | $n\text{-}C_3H_7CH(CO_2C_2H_5)_2$ | 90 | 340 |
| $(CH_3)_2C{=}C(CO_2C_2H_5)_2$ | $H_2$—Ni | $i\text{-}C_3H_7CH(CO_2C_2H_5)_2$ | 96 | 340, 1068 |
| $n\text{-}C_3H_7CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Pd/C | $n\text{-}C_4H_9CH(CO_2C_2H_5)_2$ | 93–96 | 340 |
| | $H_2$—Ni | $n\text{-}C_4H_9CH(CO_2C_2H_5)_2$ | 95 | 1065 |
| $C_2H_5C(CH_3){=}C(CO_2C_2H_5)_2$ | $H_2$* | $C_2H_5CH(CH_3)CH(CO_2C_2H_5)_2$ | 95–100 | 1067 |
| $CH_2{=}CH(CH_2)_2CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Pd/C | $n\text{-}C_5H_{11}CH(CO_2C_2H_5)_2$ | 79 | 277 |
| $i\text{-}C_4H_9CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Pd/C | $i\text{-}C_5H_{11}CH(CO_2C_2H_5)_2$ | 96–97 | 340 |
| Diethyl cyclopentylidenemalonate | $H_2$* | Diethyl cyclopentylmalonate | 95–100 | 1067 |
| Diethyl 2-cyclopentenylmalonate | $H_2$—PtO$_2$ | Diethyl cyclopentylmalonate | 99 | 927 |
| Furfurylidenemalonic acid | $NaHg_x$ | Furfurylmalonic acid | — | 355 |
| Diethyl furfurylidenemalonate | $H_2$—Ni | Diethyl furfurylmalonate | 96 | 1069, 1065 |
| 2-Thenylidenemalonic acid | $NaHg_x$ | 2-Thenylmalonic acid | 85 | 358 |
| Diethyl (2-pyrrylmethylene)malonate | $H_2$—PtO$_2$ | Diethyl (2-pyrrolidylmethyl)malonate | 95 | 1070 |
| $CH_2{=}CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | $H_2$—Ni | $n\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | 232 |
| $CH_3CH{=}CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ | $H_2$—Ni | $n\text{-}C_4H_9C(NHCOCH_3)(CO_2C_2H_5)_2$ | — | 442 |
| $n\text{-}C_6H_{13}CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Ni | $n\text{-}C_7H_{15}CH(CO_2C_2H_5)_2$ | 97 | 1065 |
| $C_6H_5CH{=}C(CO_2H)_2$ | $NaHg_x$ | $C_6H_5CH_2CH(CO_2H)_2$ | — | 354 |
| $C_6H_5CH{=}C(CO_2C_2H_5)_2$ | $AlHg_x$ | $C_6H_5CH_2CH(CO_2C_2H_5)_2$ | 60 | 350, 343 |
| | $H_2$—Ni | $C_6H_5CH_2CH(CO_2C_2H_5)_2$ | 97 | 1065 |
| $p\text{-}CH_3OC_6H_4CH{=}C(CO_2C_2H_5)_2$ | $H_2$—Ni | $p\text{-}CH_3OC_6H_4CH_2CH(CO_2C_2H_5)_2$ | 100 | 950, 360, 1071 |
| Diethyl (2,5-dimethoxybenzylidene)-malonate | $H_2$* | Diethyl (2,5-dimethoxybenzyl)malonate | — | 1072 |
| (2,3,4-Trimethylbenzylidene)malonic acid | $H_2$—Pd | (2,3,4-Trimethylbenzyl)malonic acid | — | 361 |
| Diethyl di-(2-cyclopentenyl)malonate | $H_2$—Ni | Diethyl di(cyclopentyl)malonate | — | 925 |
| Dimethyl phenyl-(2-cyclohexenyl)malonate | $H_2$—PtO$_2$ | Dimethyl phenyl(cyclohexyl)malonate | 90 | 534 |
| Diethyl allyl-($\beta$-naphthyl)malonate | $H_2$—Pd/C | Diethyl $n$-propyl-($\beta$-naphthyl)malonate | 82 | 952 |
| Diethyl allyl-(9-phenanthryl)malonate | $H_2$—Pd/C | Diethyl $n$-propyl-(9-phenanthryl)malonate | 98 | 955 |

*Note :* References 577–1080 are on pp. 322–331.

\* The catalyst employed was not stated.

## TABLE XVII

### REDUCTION OF THE ALKYLIDENE AND ARYLIDENE DERIVATIVES OF CYANOACETIC ACID, CYANOACETIC ESTERS, AND MALONONITRILE

| Compound Reduced | Reducing Agent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_3CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $C_2H_5CH(CN)CO_2C_2H_5$ | 80–85 | 363 |
| $C_2H_5CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $n\text{-}C_3H_7CH(CN)CO_2C_2H_5$ | 94 | 363 |
| $(CH_3)_2C=C(CN)CO_2C_2H_5$ | $AlHg_x$ | $i\text{-}C_3H_7CH(CN)CO_2C_2H_5$ | 63 | 351 |
| $(CH_3)_2CO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $i\text{-}C_3H_7CH(CN)CO_2C_2H_5$ | 90–93 | 363 |
| $n\text{-}C_3H_7CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $n\text{-}C_4H_9CH(CN)CO_2C_2H_5$ | 94–96 | 1073, 363 |
| $C_2H_5C(CH_3)=C(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$ | 90 | 340 |
| $i\text{-}C_3H_7CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $i\text{-}C_4H_9CH(CN)CO_2C_2H_5$ | 98 | 363 |
| $CH_3CH(OH)CH_2CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $n\text{-}C_4H_9CH(CN)CO_2C_2H_5$ | 66 | 364 |
| $n\text{-}C_3H_7C(CH_3)=C(CN)_2$ | $H_2$—Pd/C | $n\text{-}C_3H_7CH(CH_3)CH(CN)_2$ | 67 | 277 |
| $n\text{-}C_3H_7C(CH_3)=C(CN)CO_2C_2H_3$ | $H_2$—Pd/C | $n\text{-}C_3H_7CH(CH_3)CH(CN)CO_2C_2H_5$ | 90–97 | 340, 363 |
| $i\text{-}C_4H_9CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $i\text{-}C_5H_{11}CH(CN)CO_2C_2H_5$ | 95 | 363 |
| Ethyl cyclopentylidenecyaonacetate | $AlHg_x$ | Ethyl cyclopentylcyanoacetate | 79 | 351 |
| $i\text{-}C_4H_9COCH_3+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | Ethyl (1,3-dimethylbutyl)cyanoacetate | 41–63 | 363 |
| $(CH_3)_2C=CHC(CH_3)=C(CN)CO_2CH_3$ | $H_2$—Pd/C | $i\text{-}C_4H_9CH(CH_3)CH(CN)CO_2CH_3$ | 84 | 575 |
| Ethyl cyclohexylidenecyanoacetate | $H_2$—Pd/C | Ethyl cyclohexylcyanoacetate | 92 | 340 |
| Ethyl cyclohexylidenecyanoacetate | $AlHg_x$ | Ethyl cyclohexylcyanoacetate | 84 | 351 |
| Cyclohexanone+$CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | Ethyl cyclohexylcyanoacetate | 91–98 | 363 |
| $n\text{-}C_6H_{13}CHO+CH_2(CN)CO_2C_3H_5$ | $H_2$—Pd/C | Ethyl n-heptylcyanoacetate | 71 | 363 |
| $n\text{-}C_5H_{11}COCH_3+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | Ethyl (1-methylhexyl)cyanoacetate | 71 | 363 |
| $n\text{-}C_5H_{11}C(CH_3)=C(CN)CO_2C_2H_6$ | $H_2$—Pd/SrCO_3 | Ethyl (1-methylhexyl)cyanoacetate | — | 317 |
| $(n\text{-}C_3H_7)_2CO+CH_2(CN)CO_2C_2H_6$ | $H_2$—Pd/C | Ethyl [1-(n-propyl)butyl]cyanoacetate | 39 | 363 |
| $n\text{-}C_6H_{13}COCH_3+CH_2(CN)CO_2C_2H_6$ | $H_2$—Pd/C | Ethyl (1-methylheptyl)cyanoacetate | 73–81 | 363 |
| Ethyl 2-methylcyclohexylidenecyano-acetate | $AlHg_x$ | Ethyl (2-methylcyclohexyl)cyanoacetate | — | 353 |
| Ethyl 3-methylcyclohexylidenecyano-acetate | $AlHg_x$ | Ethyl (3-methylcyclohexyl)cyanoacetate | 83 | 352 |
| Ethyl 4-methylcyclohexylidenecyano-acetate | $AlHg_x$ | Ethyl (4-methylcyclohexyl)cyanoacetate | 87 | 352 |
| $C_6H_5CH=C(CN)CO_2H$ | $NaHg_x$ | $C_6H_5CH_2CH(CN)CO_2H$ | ca. 85 | 357 |
| $C_6H_5CH=C(CN)CO_2C_2H_5$ | $NaHg_x$ | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 86 | 993 |
| $C_6H_5CHO+CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $C_6H_5CH_2CH(CN)CO_2C_2H_5$ | 63 | 363, 364 |
| $o\text{-}HOC_6H_4CH=C(CN)CO_2H$ | $NaHg_x$ | $o\text{-}HOC_6H_4CH_2CH(CN)CO_2H$ | ca. 85 | 357 |
| $m\text{-}HOC_6H_4CH=C(CN)CO_2H$ | $NaHg_x$ | $m\text{-}HOC_6H_4CH_2CH(CN)CO_2H$ | ca. 85 | 357 |
| 2,4-Dihydroxybenzylidenecyanoacetic acid | $NaHg_x$ | (2,4-Dihydroxybenzyl)cyanoacetic acid | ca. 85 | 357 |
| Ethyl cycloheptylidenecyanoacetate | $AlHg_x$ | Ethyl cycloheptylcyanoacetate | 72 | 351 |
| $p\text{-}CH_3OC_6H_4CH=C(CN)CO_2H$ | $NaHg_x$ | p-Methoxybenzylcyanoacetic acid | ca. 85 | 357 |
| Piperonylidenecyanoacetic acid | $NaHg_x$ | (3,4-Methylenedioxybenzyl)cyanoacetic acid | ca. 85 | 357 |
| $C_6H_5CH_2C(CH_3)=C(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $C_6H_5CH_2CH(CH_3)CH(CN)CO_2C_2H_5$ | 94 | 340 |
| Ethyl 1-indanylidenecyanoacetate | $H_2$—Pd/C | Ethyl 1-indanylcyanoacetate | 51 | 217 |
| $(C_2H_5O_2C)_2CH(CH_2)_3CHO+$ $CH_2(CN)CO_2C_2H_6$ | $H_2$—Pd/C | $(C_2H_5O_2C)_2CH(CH_2)_3CH(CN)CO_2C_2H_5$ | 39 | 362 |
| $(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_3CHO+$ $CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_3CH(CN)CO_2C_2H_5$ | 85 | 362 |
| $(C_2H_5O_2C)_2C(OCOCH_3)(CH_2)_3CHO+$ $CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $(C_2H_5O_2C)_2C(OCOCH_3)(CH_2)_3\text{-}$ $CH(CN)CO_2C_2H_5$ | 35 | 362 |
| $(C_2H_5O_2C)_2C(NHCOCH_3)(CH_2)_3CHO+$ $CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $(C_2H_5O_2C)_2C(NHCOCH_3)(CH_2)_3\text{-}$ $CH(CN)CO_2C_2H_5$ | 27 | 362 |
| $o\text{-}C_6H_5C_6H_4CH=C(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $o\text{-}C_6H_5C_6H_4CH_2CH(CN)CO_2C_2H_5$ | 60 | 340 |
| $(C_2H_5O_2C)_2C(C_{10}H_{21}\text{-}n)(CH_2)_3CHO+$ $CH_2(CN)CO_2C_2H_5$ | $H_2$—Pd/C | $(C_2H_5O_2C)_2C(C_{10}H_{21}\text{-}n)(CH_2)_3\text{-}$ $CH(CN)CO_2C_2H_5$ | 32 | 362 |

*Note:* References 577–1080 are on pp. 322–331.

## TABLE XVIII

### Addition of Grignard Reagents to Alkylidenemalonic Esters

| Alkylidene Ester | Grignard Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $(CH_3)_2C=C(CO_2C_2H_5)_2$ | $CH_3MgI$ | $(CH_3)_3CCH(CO_2C_2H_5)_2$ | 37 | 157 |
| | $n\text{-}C_4H_9MgBr$ | $n\text{-}C_4H_9C(CH_3)_2CH(CO_2C_2H_5)_2$ | 31 | 157 |
| | $n\text{-}C_4H_9MgBr$ | $\begin{cases} n\text{-}C_4H_9C(CH_3)_2CH(CO_2C_2H_5)_2 \\ (CH_3)_2CHCH(CO_2C_2H_5)_2 \end{cases}$ | 40 / 20 | 367 |
| | $C_6H_5MgBr$ | $C_6H_5C(CH_3)_2CH(CO_2C_2H_5)_2$ | 40 | 367 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(CH_3)_2CH(CO_2C_2H_5)_2$ | 60 | 367 |
| $C_6H_5CH=C(CO_2C_2H_5)_2$ | $CH_3MgI$ | $C_6H_5CH(CH_3)CH(CO_2C_2H_5)_2$ | — | 954 |
| | $C_6H_5MgBr$ | $(C_6H_5)_2CHCH(CO_2C_2H_5)_2$ | 82 | 954, 156 |
| | $o\text{-}CH_3C_6H_4MgBr$ | $o\text{-}CH_3C_6H_4CH(C_6H_5)CH_2CO_2H$ | — | 1074 |
| | $p\text{-}CH_3C_6H_4MgBr$ | $p\text{-}CH_3C_6H_4CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 23 | 829 |
| | $p\text{-}CH_3OC_6H_4MgBr$ | $p\text{-}CH_3OC_6H_4CH(C_6H_5)CH(CO_2C_2H_5)_2$ | — | 829 |
| | $\alpha$-Naphthylmagnesium bromide | $\alpha\text{-}C_{10}H_7CH(C_6H_5)CH(CO_2C_2H_5)_2$ | 74 | 829 |
| $o\text{-}CH_3OC_6H_4CH=C(CO_2C_2H_5)_2$ | $C_6H_5MgBr$ | $o\text{-}CH_3OC_6H_4CH(C_6H_5)CH(CO_2C_2H_5)_2$ | — | 1074 |
| $p\text{-}CH_3C_6H_4CH=C(CO_2C_2H_5)_2$ | $p\text{-}CH_3C_6H_4MgBr$ | $(p\text{-}CH_3C_6H_4)_2CHCH(CO_2C_2H_5)_2$ | 90 | 156 |
| $p\text{-}CH_3OC_6H_4CH=C(CO_2C_2H_5)_2$ | $p\text{-}CH_3OC_6H_4MgBr$ | $(p\text{-}CH_3OC_6H_4)_2CHCH(CO_2C_2H_5)_2$ | 32 | 829 |

*Note :* References 577–1080 are on pp. 322–331.

## TABLE XIX

### ADDITION OF GRIGNARD REAGENTS TO ALKYLIDENECYANOACETIC ACIDS AND ESTERS AND TO ALKYLIDENEMALONONITRILES

| Alkylidene Derivative | Grignard Reagent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $(CH_3)_2C{=}C(CN)CO_2H$ | $n\text{-}C_4H_9MgBr$ | $n\text{-}C_4H_9C(CH_3)_2CH_2CN$ | 41 | 367 |
| | $C_6H_5MgBr$ | $C_6H_5C(CH_3)_2CH_2CN$ | 60 | 367 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(CH_3)_2CH_2CN$ | 68 | 367 |
| $(CH_3)_2C{=}C(CN)CO_2K$ | $n\text{-}C_4H_9MgBr$ | $n\text{-}C_4H_9C(CH_3)_2CH_2CN$ | 17 | 367 |
| | $C_6H_5MgBr$ | $C_6H_5C(CH_3)_2CH_2CN$ | 30 | 367 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(CH_3)_2CH_2CN$ | 33 | 367 |
| $(CH_3)_2C{=}C(CN)CO_2C_2H_5$ | $CH_3MgI$ | $(CH_3)_3CCH(CN)CO_2C_2H_5$ | 75 | 159 |
| | $n\text{-}C_4H_9MgBr$ | $n\text{-}C_4H_9C(CH_3)_2CH(CN)CO_2C_2H_5$ | 42 | 159 |
| | $n\text{-}C_4H_9MgBr$ | $\begin{cases} n\text{-}C_4H_9C(CH_3)_2CH(CN)CO_2C_2H_5 \\ (CH_3)_2CHCH(CN)CO_2C_2H_5 \end{cases}$ | 40<br>15 | 367 |
| | $C_6H_5MgBr$ | $C_6H_5C(CH_3)_2CH(CN)CO_2C_2H_5$ | 63 | 367, 159 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(CH_3)_2CH(CN)CO_2C_2H_5$ | 85 | 367 |
| | $C_6H_5CH_2MgBr$ | $C_6H_5CH_2C(CH_3)_2CH(CN)CO_2C_2H_5$ | 49 | 159 |
| $C_2H_5C(CH_3){=}C(CN)CO_2C_2H_5$ | $CH_3MgI$ | $C_2H_5C(CH_3)_2CH(CN)CO_2C_2H_5$ | 41 | 159 |
| | $n\text{-}C_3H_7MgBr$ | $\begin{cases} n\text{-}C_3H_7C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 27–44<br>31–44 | 368, 1075 |
| | $i\text{-}C_3H_7MgBr$ | $\begin{cases} i\text{-}C_3H_7C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 39<br>20 | 1075 |
| | $n\text{-}C_4H_9MgBr$ | $\begin{cases} n\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 42–73<br>10–32 | 368, 1075 |
| | $i\text{-}C_4H_9MgBr$ | $\begin{cases} i\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 34<br>54 | 368, 1075 |
| | $sec\text{-}C_4H_9MgBr$ | $\begin{cases} sec\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 8<br>40 | 1075 |
| | $t\text{-}C_4H_9MgCl$ | $\begin{cases} t\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 3<br>63 | 1075 |
| | $n\text{-}C_5H_{11}MgBr$ | $\begin{cases} n\text{-}C_5H_{11}C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 49<br>22 | 1075 |
| | $n\text{-}C_6H_{13}MgBr$ | $\begin{cases} n\text{-}C_6H_{13}C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5 \\ C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5 \end{cases}$ | 45<br>24 | 1075 |
| | $C_6H_5MgBr$ | $C_6H_5C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$ | 79 | 367 |
| | $p\text{-}ClC_6H_4MgBr$ | $p\text{-}ClC_6H_4C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$ | 73 | 367 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$ | 88 | 367 |
| $(CH_3)_2C{=}C(CN)_2$ | $n\text{-}C_4H_9MgBr$ | $\begin{cases} n\text{-}C_4H_9C(CH_3)_2CH(CN)_2 \\ (CH_3)_2CHCH(CN)_2 \end{cases}$ | 35<br>19 | 367 |
| | $C_6H_5MgBr$ | $C_6H_5C(CH_3)_2CH(CN)_2$ | 6 | 367 |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2C(CH_3)_2CH(CN)_2$ | 76 | 367 |

*Note:* References 577–1080 are on pp. 322–331.

TABLE XIX—*Continued*

ADDITION OF GRIGNARD REAGENTS TO ALKYLIDENECYANOACETIC ACIDS
AND ESTERS AND TO ALKYLIDENEMALONONITRILES

| | | | | |
|---|---|---|---|---|
| Ethyl cyclohexylidene-cyanoacetate | $CH_6MgI$ | (cyclohexyl)—$CH(CN)CO_2C_2H_5$, $CH_3$ | 45 | 1076 |
| | $C_6H_5MgBr$ | (cyclohexyl)—$CH(CN)CO_2C_2H_5$, $C_6H_5$ | 44 | 1077 |
| | $n\text{-}C_{10}H_{21}MgBr$ | (cyclohexyl)—$CH(CN)CO_2C_2H_5$, $C_{10}H_{21}\text{-}n$ | 14 | 1076 |
| $C_6H_5CH=C(CN)CO_2C_2H_5$ | $CH_3MgI$ | $C_6H_5CH(CH_3)CH(CN)CO_2C_2H_5$ | — | 994 |
| | $i\text{-}C_3H_7MgBr$ | $C_6H_5CH(C_3H_7\text{-}i)CH(CN)CO_2C_2H_5$ | — | 994 |
| | $C_6H_5MgBr$ | $(C_6H_5)_2CHCH(CN)CO_2C_2H_5$ | — | 994 |
| | $C_6H_5C\equiv CMgBr$ | $C_6H_5C\equiv CCH(C_6H_5)CH(CN)CO_2C_2H_5$ | — | 994 |
| | $\alpha$-Naphthylmagnesium bromide | $\alpha\text{-}C_{10}H_7CH(C_6H_5)CH(CN)CO_2C_2H_5$ | — | 994 |
| (cyclohexyl)$=C(CN)CO_2C_2H_5$, $CO_2C_2H_5$ | $C_6H_5MgBr$ | (cyclohexyl), $C_6H_5$, $CH(CN)CO_2C_2H_5$, $CO_2C_2H_5$ | 14 | 1077 |

*Note*   References 577–1080 are on pp. 322–331.

## TABLE XX

### ARYLATION OF DERIVATIVES OF MESOXALIC AND TARTRONIC ACIDS

| Compound Arylated | Arylating Agent | Product | Yield, % | Catalyst | Solvent | Reference |
|---|---|---|---|---|---|---|
| $OC(CO_2C_2H_5)_2$ | $C_6H_6$ | $(C_6H_5)_2C(CO_2C_2H_5)_2$ | 33 | $H_2SO_4$ | $C_6H_6$ | 278, 180, 1078 |
| | $C_6H_5OH$ | $(p-HOC_6H_4)_2C(CO_2C_2H_5)_2$ | — | HCl | None | 278 |
| | $CH_3C_6H_6$ | $(p-CH_3C_6H_4)_2C(CO_2C_2H_5)_2$ | — | $H_2SO_4$ | Toluene | 1079, 278, 1078 |
| | $CH_3OC_6H_6$ | $(p-CH_3OC_6H_4)_2C(CO_2C_2H_5)_2$ | — | $H_2SO_4$ | Anisole | 1080 |
| | $CH_3OC_6H_5$ | $(p-CH_3OC_6H_4)_2C(CO_2C_2H_5)_2$ | — | $SnCl_4$ | Anisole | 371 |
| $OC(CO_2CH_3)_2$ | $CH_3OC_6H_5$ | $(p-CH_3OC_6H_4)_2C(CO_2CH_3)_2$ | — | $H_2SO_4$ | Anisole | 1080 |
| $OC(CO_2C_2H_5)_2$ | $o-CH_3C_6H_4OH$ | Diethyl di-(4-hydroxy-3-methylphenyl)malonate | 66 | HCl | None | 278 |
| | $p-CH_3C_6H_4CH_3$ | Diethyl (2,5-dimethylphenyl)-tartronate | 51–57 | $SnCl_4$ | $p$-Xylene | 370 |
| | $o-CH_3C_6H_4CH_3$ | Diethyl di-(3,4-dimethylphenyl)-malonate | — | $H_2SO_4$ | $c$-Xylene | 1079 |
| $OC(CO_2CH_3)_2$ | $o-CH_3C_6H_4CH_3$ | Dimethyl di-(3,4-dimethylphenyl)-malonate | — | $H_2SO_4$ | $o$-Xylene | 1079 |
| | $C_2H_5OC_6H_5$ | Dimethyl di-($p$-ethoxyphenyl)-malonate | — | $H_2SO_4$ | Phenetole | 1080 |
| $OC(CO_2C_2H_5)_2$ | $C_2H_5OC_6H_5$ | Diethyl di-($p$-ethoxyphenyl)-malonate | — | $H_2SO_4$ | Phenetole | 1080 |
| | $\alpha$-Naphthylmagnesium bromide | $\alpha$-$C_{10}H_7C(OCOC_6H_5)(CO_2C_2H_5)_2$ | — | — | Ether-toluene | 372 |
| | 9-Phenanthryl-magnesium bromide | $9$-$C_{14}H_9C(OH)(CO_2C_2H_5)_2$ | 46 | — | Ether-toluene | 372 |
| $C_6H_5C(OH)(CO_2C_2H_5)_2$ | $CH_3C_6H_6$ | $p-CH_3C_6H_4C(C_6H_5)(CO_2C_2H_5)_2$ | — | $H_2SO_4$ | Toluene | 1079 |
| $p-CH_3C_6H_4\cdot C(OH)(CO_2C_2H_5)_2$ | $C_6H_6$ | $p-CH_3C_6H_4C(C_6H_5)(CO_2C_2H_5)_2$ | — | $H_2SO_4$ | $C_6H_6$ | 1079 |
| $p-(CH_3)_2NC_6H_4\cdot C(OH)(CO_2C_2H_5)_2$ | $C_6H_5N(CH_3)_2$ | $[p-(CH_3)_2NC_6H_4]_2C(CO_2C_2H_5)_2$ | 80 | $POCl_3$ | $C_6H_5N(CH_3)_2$ | 373 |
| | $C_6H_5N(C_2H_5)_2$ | $p-(C_2H_5)_2NC_6H_4\cdot C[C_6H_4N(CH_3)_2-p](CO_2C_2H_5)_2$ | — | $POCl_3$ | $C_6H_5N(C_2H_5)_2$ | 373 |
| $p-(CH_3)_2NC_6H_4\cdot C(OH)(CO_2CH_3)_2$ | $C_6H_5N(CH_3)_2$ | $[p-(CH_3)_2NC_6H_4]_2C(CO_2CH_3)_2$ | — | $POCl_3$ | $C_6H_5N(CH_3)_2$ | 373 |
| | $C_6H_5N(C_2H_5)_2$ | $p-(C_2H_5)_2NC_6H_4\cdot C[C_6H_4N(CH_3)_2-p](CO_2CH_3)_2$ | — | $POCl_3$ | $C_6H_5N(C_2H_6)_2$ | 373 |
| $p-(C_2H_5)_2NC_6H_4\cdot C(OH)(CO_2C_2H_6)_2$ | $C_6H_6N(C_2H_5)_2$ | $[p-(C_2H_6)_2NC_6H_4]_2C(CO_2C_2H_5)_2$ | — | $POCl_3$ | $C_6H_5N(C_2H_5)_2$ | 373 |

*Note:* References 577–1080 are on pp. 322–331.

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# CHAPTER 5

# THE REACTION OF HALOGENS WITH SILVER SALTS OF CARBOXYLIC ACIDS

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## CONTENTS

## INTRODUCTION

The action of halogens with *dry* metallic salts, particularly silver salts of carboxylic acids has merited earlier reviews.[1-2a]  It has been pointed out that the halogen used, the ratio of silver salt to halogen, and the presence or absence of other active materials, such as olefins, acetylenes, or readily substituted aromatic rings play a large part in determining the

[1] Kleinberg, *Chem. Revs.*, **40**, 381 (1947).
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course of the reactions. Thus, it is possible to produce (A) organic halides containing one less carbon atom than the original acid, $RCO_2H$; (B) esters, $RCO_2R$, derived from two molecules of the acid by loss of one molecule of carbon dioxide; (C) esters of 1,2-diols or of halohydrins; (D) halogenated aromatic compounds; and (E) halogenated acetylenes. These reactions may be represented by the following general equations.

(A)  $$RCO_2Ag + X_2 \rightarrow RX + CO_2 + AgX$$

(B)  $$2RCO_2Ag + X_2 \rightarrow RCO_2R + CO_2 + 2AgX$$

(AB)  $$3RCO_2Ag + 2X_2 \rightarrow RCO_2R + RX + 2CO_2 + 3AgX$$

(C)  $$RCO_2Ag + X_2 + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHXR'' + AgX$$

$$2RCO_2Ag + X_2 + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CH(OCOR)R''$$
$$+ 2AgX$$

(D)  $$RCO_2Ag + X_2 + ArH \rightarrow RCO_2H + ArX + AgX$$

$$ArCO_2Ag + X_2 \rightarrow X{-}Ar{-}CO_2H + AgX$$

(E)  $$RCO_2Ag + X_2 + R'C{\equiv}CH \rightarrow R'C{\equiv}CX + RCO_2H + AgX$$

The reaction represented by A in which the molar silver salt-halogen ratio is 1 : 1, is due chiefly to Hunsdiecker;[3-5] it makes available a variety of compounds that are prepared only with difficulty by other procedures. Reaction B is generally known as the Simonini reaction;[6,7] it is carried out with a 2 : 1 molar ratio of silver salt to halogen (iodine only). Reaction AB, discovered by Oldham and Ubbelohde,[8] makes use of a 3 : 2 molar ratio of reactants. Reactions C and E are usually attributed to Prévost.[9-14] Reaction D proceeds only in the presence of a phenyl group (Ar) which undergoes electrophilic substitution readily,[15-18] or when R is of such a nature that the $RCO_2^-$ ion is a very weak base, such as $CF_3CO_2^-$.[19]

[3] Hunsdiecker, Hunsdiecker, and Vogt, U.S. pat. 2,176,181 (1939) [C. A., **34**, 1685 (1940)].

[4] Hunsdiecker and Hunsdiecker, Ber., **75**, 291 (1942).

[5] Hunsdiecker, Hunsdiecker, and Vogt, Ger. pat. 730,410 (1942) [C. A., **38**, 374 (1944)].

[6] Simonini, Monatsh., **13**, 320 (1892).

[7] Simonini, Monatsh., **14**, 81 (1893).

[8] Oldham and Ubbelohde, J. Chem. Soc., **1941**, 368.

[9] Prévost, Compt. rend., **196**, 1129 (1933).

[10] Prévost, Compt. rend., **197**, 1661 (1933).

[11] Prévost and Lutz, Compt. rend., **198**, 2264 (1934).

[12] Prévost, Compt. rend., **200**, 942 (1935).

[13] Prévost and Wiemann, Compt. rend., **204**, 700 (1937).

[14] Prévost and Wiemann, Compt. rend., **204**, 989 (1937).

[15] Birnbaum and Reinherz, Ber., **15**, 456 (1882).

[16] Barnes and Prochaska, J. Am. Chem. Soc., **72**, 3188 (1950).

[17] Dauben and Tilles, J. Am. Chem. Soc., **72**, 3185 (1950).

[18] Papa, Schwenk, and Klingsberg, J. Am. Chem. Soc., **72**, 2623 (1950).

[19] Haszeldine and Sharp, J. Chem. Soc., **1952**, 993.

## NATURE OF THE REACTIONS

It is well established [20-22] that the primary product of the reaction between a dry silver salt of a carboxylic acid and halogen is an acyl hypohalite.

$$RCO_2Ag + X_2 \rightarrow RCO_2X + AgX$$

Thermal cleavage of this intermediate results in the formation of an alkyl halide with loss of carbon dioxide, and this is the basis of reaction A.

$$RCO_2X \rightarrow RX + CO_2$$

Extensive evidence favors a mechanism with the free radical R· as an intermediate in the conversion of $RCO_2Br$ to RBr. First the reaction of optically active silver salts with bromine or of the intermediate acyl hypobromites I and II under a variety of conditions leads to totally racemized bromides III and IV.[23]   Although the alkyl bromide, if it had

$$C_2H_5CH(CH_3)CO_2Br \qquad n\text{-}C_3H_7CH(C_2H_5)CO_2Br$$
$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$

$$C_2H_5CH(CH_3)Br \qquad n\text{-}C_3H_7CH(C_2H_5)Br$$
$$\text{III} \qquad\qquad\qquad\qquad \text{IV}$$

been obtained optically active in these reactions, would have been racemized slowly by the silver bromide present, it was shown by control experiments that such racemization is too slow to account for most of the loss of optical activity observed during the reaction of the silver salt with bromine.   The reactions of optically active silver salts with bromine had previously been reported to yield optically inactive bromides,[24-26] but the significance of the results remained in doubt since it was not shown at that time that the loss in activity was not entirely due to racemization of the bromide by silver bromide.

It should be mentioned that silver (+)-α-phenylpropionate was reported to react with bromine in carbon tetrachloride to yield phenethyl bromide with 43% of the optical activity retained.[27]   It has been shown, however, that (+)-phenethyl bromide, when boiled with silver bromide in carbon tetrachloride under conditions of the reaction of the silver salt with bromine, is essentially completely racemized.[28,29]   This would

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[20] Bockemüller and Hoffmann, *Ann.*, **519**, 165 (1935).

[21] Birckenbach, Goubeau, and Berninger, *Ber.*, **65**, 1339 (1932).

[22] Uschakov and Chistov, *Ber.*, **68**, 824 (1935).

[23] Winstein and Berr, Unpublished work; C. E. Berr, Ph.D. Thesis, University of California, Los Angeles, 1952; Winstein, *Bull soc. chim. France*, [5] **18**, 70c (1951).

[24] Arnold and Morgan, *J. Am. Chem. Soc.*, **70**, 4248 (1948).

[25] Heintzeler, *Ann.*, **569**, 102 (1950).

[26] Bell and Smyth, *J. Chem. Soc.*, **1949**, 2372.

[27] Arcus, Campbell and Kenyon, *Nature*, **163**, 287 (1949); *J. Chem. Soc.*, **1949**, 1510.

[28] Abbott and Arcus, *J. Chem. Soc.*, **1952**, 3195.

[29] Arcus and Boyd, *J. Chem. Soc.*, **1951**, 1580.

indicate that the substance responsible for the optical activity observed in the product of the silver salt reaction was not phenethyl bromide. This conclusion has been strengthened by the failure of several investigators[23,28,30] to isolate any phenethyl bromide from the reaction of silver α-phenylpropionate with bromine in carbon tetrachloride. A report[28] that silver (+)-2-ethylhexanoate with bromine gives (+)-3-bromoheptane requires further investigation.

That it is the intermediate R·, rather than R⁺ or R⁻,[31] which is responsible for the observed loss of activity during reaction has been supported by evidence from several sources. Thus, reactions that might have been expected to lead to the neopentyl carbonium ion invariably lead to products derived from its rearrangement product, the *t*-amyl carbonium ion.[32] Silver *t*-butylacetate, however, reacts with bromine to yield neopentyl bromide with no detectible amount of *t*-amyl bromide.[23,33] Similarly, reactions that might be expected to proceed by way of the cyclobutyl carbonium ion lead to mixtures of cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl products.[34] The reaction of silver cyclobutanecarboxylate with bromine, however, yields cyclobutyl bromide accompanied by only a very small amount of rearranged products.[35]

While the neopentyl radical, $(CH_3)_3CCH_2\cdot$, does not rearrange under conditions used to prepare it, the neophyl radical, $C_6H_5C(CH_3)_2CH_2\cdot$, has been shown to rearrange in part to the more stable tertiary radical, $(CH_3)_2CCH_2C_6H_5$.[36] Examination of the reaction of the acyl hypobromite V has indicated that some of the tertiary bromide VI was formed by

$$C_6H_5C(CH_3)_2CH_2CO_2Br \qquad\qquad BrC(CH_3)_2CH_2C_6H_5$$
$$\text{V} \qquad\qquad\qquad\qquad\qquad \text{VI}$$

rearrangement in addition to the unrearranged product.[23] A control experiment showed that the unrearranged product, neophyl bromide, was stable toward the reaction conditions.

Additional evidence for the radical intermediate is provided by a study of the reaction of the silver salt of apocamphane-1-carboxylic acid.[37] Reactions proceeding by way of the apocamphyl carbonium ion have been

[30] Cason, Kalm, and Mills, *J. Org. Chem.*, **18**, 1670 (1953).

[31] Compare Rottenberg, *Experientia*, **7**, 432, (1951) [*C. A.*, **46**, 4336 (1952)].

[32] Ingold, *Structure and Mechanism in Organic Chemistry*, pp. 485–486, Cornell University Press, Ithaca, New York, 1953.

[33] Smith and Hull, *J. Am. Chem. Soc.*, **72**, 3309 (1950).

[34] Roberts and Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

[35] Cason and Way, *J. Org. Chem.*, **14**, 32 (1949); Roberts and Chambers, *J. Am. Chem. Soc.*, **73**, 5039 (1951); Buchman and Conly, *ibid.*, **75**, 1990 (1953).

[36] Urry and Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944); Winstein and Seubold, *ibid.*, **69**, 2916 (1947); Urry and Nicolaides, *ibid.*, **74**, 5162 (1952).

[37] Wilder and Winston, *J. Am. Chem. Soc.*, **75**, 5370 (1953).

shown to be very much slower than their counterparts in acyclic systems.[38] On the other hand, there is no such retardation when the apocamphyl radical is involved.[39]   It was found, in fact, that silver apocamphane-1-carboxylate reacts readily with bromine in boiling petroleum ether to yield 1-bromoapocamphane in 50% yield, with no evidence of any retardation in rate by the bicyclic system.   The reaction in carbon tetrachloride was accompanied by the formation of a chlorine-containing by-product.[37]

Other observations which are suggestive of a free-radical chain mechanism are side-chain bromination of toluene,[19] the indication that there is an induction period when the reaction is carried out at low temperatures,[40] and an acceleration of the reaction by light.[20]

The most probable mechanism would appear to be the following.[41]

$$\text{Initiation } RCO_2Br \rightarrow RCO_2\cdot + Br\cdot$$

$$\text{Propagation } RCO_2\cdot \rightarrow R\cdot + CO_2$$

$$R\cdot + RCO_2Br \rightarrow RBr + RCO_2\cdot$$

$$\text{Termination } 2R\cdot \rightarrow R\text{---}R \text{ or } RH + \text{olefin}$$

and/or $\qquad\qquad RCO_2\cdot + R\cdot \rightarrow RCO_2R$

Another piece of evidence consistent with this picture is the following. The reaction of silver benzoate with bromine in carbon tetrachloride gives 53% of bromobenzene, 5% of chlorobenzene, and 6.7% of bromotrichloromethane.   These products are readily explained if, superimposed on the sequence of reactions above, there is reaction of the phenyl radical with carbon tetrachloride as shown below.[16,17,*]

$$C_6H_5\cdot + ClCCl_3 \rightarrow C_6H_5Cl + \cdot CCl_3$$

$$\cdot CCl_3 + BrO_2CC_6H_5 \rightarrow BrCCl_3 + \cdot O_2CC_6H_5$$

$$\text{(or BrBr)} \qquad\qquad\qquad \text{(or Br}\cdot\text{)}$$

[38] Bartlett and Knox, J. Am. Chem. Soc., 61, 3184 (1939).

[39] Kharasch, Engelmann, and Urry, J. Am. Chem. Soc., 65, 2428 (1943).

[40] Conly, J. Am. Chem. Soc., 75, 1148 (1953).

[41] Compare Price, Mechanisms of Reactions at Carbon-Carbon Double Bonds, p. 55, Interscience Publishers, New York, 1946.

* Wiberg and Shryne,[41a] on the basis of the report that silver (+)-2-ethylhexanoate with bromine gives (+)-3-bromoheptane,[28] suggested that the mechanism is a 1,3-intramolecular shift involving an electron-deficient group in the transition state—a mechanism first proposed by Rottenberg.[31]   Since the reported retention of optical activity in this reaction is in contradiction with the reports of racemization described on p. 335, caution must be exercised until confirmation is available.

[41a] Wiberg and Shryne, J. Am. Chem. Soc., 77, 2774 (1955).

When the silver salt of a carboxylic acid reacts with iodine in a 2 : 1 molar ratio, the primarily formed acyl hypoiodite coordinates with the excess silver salt to form a complex.[6,7,42-47a]  Many such complexes can be

$$2RCO_2Ag + I_2 \rightarrow RCO_2I + RCO_2Ag + AgI$$
$$RCO_2Ag + RCO_2I \rightarrow RCO_2Ag \cdot RCO_2I$$

isolated.  With others, however, the difference between the temperatures of formation and decomposition is too small to permit isolation.  The thermal cleavage of the complex to give an ester is the basis of reaction B (Simonini reaction).

$$RCO_2Ag \cdot RCO_2I \rightarrow RCO_2R + CO_2 + AgI$$

It is not clear what role, if any, the complex formation plays in the reaction, which appears to be composed of two parts.  Available evidence suggests that the first stage, a reaction of the silver salt with iodine to give carbon dioxide and alkyl iodide, is closely related to the Hunsdiecker reaction discussed above.  The second stage is an ionic reaction of the alkyl iodide thus formed with a second molecule of silver salt.[19]  This

$$RCO_2Ag + I_2 \rightarrow RCO_2I + AgI$$
$$RCO_2I \rightarrow RI + CO_2$$
$$RI + RCO_2Ag \rightarrow RCO_2R + AgI$$

view is consistent with the fact that in the reaction of such substances as silver cyclobutanecarboxylate [44,48] a typical carbonium ion rearrangement occurs in the alcohol portion of the ester formed.  The products are cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl cyclobutanecarboxylates in yields of 32, 65, and 3%, respectively.

$$C_4H_7CO_2Ag + I_2 \rightarrow C_4H_7I + CO_2 + AgI$$
$$C_4H_7I + AgO_2CC_4H_7 \rightarrow C_4H_7O_2CC_4H_7 + C_3H_5CH_2O_2CC_4H_7$$
$$+ CH_2{=}CHCH_2CH_2O_2CC_4H_7$$

Failure to observe the formation of triphenylmethyl peroxide when silver triphenylacetate is treated with iodine in the presence of air has been interpreted as evidence that the triphenylmethyl radical is not an intermediate.[49]  Such an argument is valid, however, only if it can be

[42] Heiduschka and Ripper, *Ber.*, **56**, 1736 (1923).

[43] Birnbaum and Gaier, *Ber.*, **13**, 1270 (1880).

[44] Demjanov and Dojarenko, *Ber.*, **40**, 2594 (1907).

[45] Gascard, *Compt. rend.*, **153**, 1484 (1911).

[46] Gascard, *Ann. chim.* (Paris), [9] **15**, 332 (1921).

[47] Panics, *Monatsh.*, **15**, 10 (1894).

[47a] Birnbaum, *Ann.*, **152**, 111 (1869).

[48] Roberts and Simons, *J. Am. Chem. Soc.*, **73**, 5487 (1951).

[49] Wieland and Fischer, *Ann.*, **446**, 49 (1925-26).

shown that the reaction of the triphenylmethyl radical with oxygen under the conditions employed is faster than its reaction with iodine.

While the Hunsdiecker and Simonini reactions produce halides and esters respectively, the reaction represented by AB gives rise to both of these products. The iodine triacyl postulated as an intermediate can be isolated when R is a long-chain alkyl group. Formed by the action of 2 moles of iodine on 3 moles of the silver salt as indicated below, such compounds decompose thermally to yield both alkyl halide and ester.[8]   In the

$$3RCO_2Ag + 2I_2 \rightarrow I(OCOR)_3 + 3AgI$$
$$I(OCOR)_3 \rightarrow RCO_2R + RI + 2CO_2$$

presence of excess iodine, the iodine triacyl decomposes to give a high yield of alkyl iodide.

$$I(OCOR)_3 + I_2 \rightarrow 3RI + 3CO_2$$

Water decomposes the triacyl to yield iodine and iodic acid.

$$I(OCOR)_3 + 3H_2O \rightarrow I(OH)_3 + 3RCO_2H$$
$$5I(OH)_3 \rightarrow 3HIO_3 + I_2 + 6H_2O$$

This, and the fact that triacyls such as iodine tris(trichloromethylacetate) conduct electricity with the iodine migrating toward the cathode, indicates the positive nature of the iodine in such materials.[50]

Nothing is known of the mechanism of these reactions. It seems likely, however, that they are radical chain reactions initiated by the dissociation of the iodine triacyl to acyl hypoiodite and acyloxy radicals.[8]   It is entirely reasonable that those acyloxy radicals that lose carbon dioxide

$$I(OCOR)_3 \rightarrow IOCOR + 2RCO_2\cdot$$

give alkyl radicals that react with iodine triacyl as shown below.   A fuller

$$RCO_2\cdot \rightarrow R\cdot \xrightarrow{I(OCOR)_3} RCO_2R + IOCOR + RCO_2\cdot$$

understanding of the mechanism must await further investigation.

In the presence of ethylenic compounds the primarily formed acyl hypohalite adds to the double bond to form a haloester.

$$RCO_2X + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHXR''$$

This is the basis of reaction C. The Simonini complex undergoes a similar reaction to yield first the ester of an iodohydrin and, finally, a diester. Presumably the complex dissociates, the acyl hypoiodite adds to the double bond, and the iodine is replaced by the molecule of silver salt formed by dissociation of the complex.[10]

$$RCO_2I{\cdot}RCO_2Ag \rightarrow RCO_2I + RCO_2Ag$$
$$RCO_2I + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHIR''$$
$$R'CH(OCOR)CHIR'' + RCO_2Ag \rightarrow R'CH(OCOR)CH(OCOR)R'' + AgI$$

[50] Fichter and Stern, *Helv. Chim. Acta*, **11**, 1256 (1928).

The products of the reaction suggest an ionic mechanism. Evidence that might be considered support for such a mechanism arises from the following fact: Silver $(+)$ or $(-)$-2-ethylhexanoate when treated with bromine in carbon tetrachloride yields acyl hypohalites which add to styrene to give $(+)$ or $(-)$-2-bromo-1-phenethyl-2-ethylhexanoate, which on hydrolysis with alkali yields $(+)$ or $(-)$-2-ethylhexanoic acid in which a substantial percentage of the optical activity of the original acid is retained.[51] However, this reaction does not involve the asymmetric carbon atom and is not, therefore diagnostic as to mechanism. The partial racemization presumably occurs during hydrolysis, for it has been shown that racemization of such esters can accompany hydrolysis.

Substitution of halogen in the benzene nucleus, as represented by reaction D, occurs most readily when R is the trifluoromethyl group.[19,52,53] However, if the aryl group is activated sufficiently to electrophilic attack, substitution may occur when R is methyl. The substituted products obtained are those expected through halogenation by an entity which carries a positive charge. Thus *ortho* and *para* substitution occur in compounds containing groups known to activate the aromatic nucleus to electrophilic attack, whereas substitution fails or occurs in the *meta* position when the substituent deactivates the nucleus. On this basis, the fission of the acyl hypohalite would be expected to proceed by an ionic mechanism. Thus, either the acyl hypohalite itself or $X^+$ formed by its dissociation can serve as the halogenating agent.

$$RCO_2X + C_6H_6 \rightarrow C_6H_5X + H^+ + RCO_2^-$$

or

$$RCO_2X \rightarrow RCO_2^- + X^+$$

$$X^+ + C_6H_6 \rightarrow C_6H_5X + H^+$$

Fission by a free-radical mechanism would necessitate halogenation by halogen atoms. When an alkyl side chain is present, substitution of the side chain is the preferred reaction. However, the products of such a process have not been found in any of the reactions studied.

When the acyl hypohalite is derived from an ordinary alkyl or aryl carboxylic acid, it is a sufficiently poor halogenating agent in the absence of readily substituted aromatic rings to allow the free-radical dissociation followed by decarboxylation (Hunsdiecker reaction) to predominate. However, nuclear halogenation can be increased at the expense of the Hunsdiecker reaction either by adding a readily substituted aromatic compound such as veratrole[53a] or by using a more active acyl hypohalite

[51] Abbott and Arcus, *J. Chem. Soc.*, **1952**, 1515.

[52] Henne and Zimmer, *J. Am. Chem. Soc.*, **73**, 1362 (1951).

[53] Schwartz, *Anales soc. españ. fis. quim.*, **27**, 683 (1929) [*C. A.*, **24**, 589 (1930)].

[53a] Janssen, VanAllan, and Wilson, *J. Org. Chem.*, **20**, 1326 (1955).

as the halogenating agent. Trifluoroacetyl hypobromite shows little tendency to undergo the Hunsdiecker decarboxylation at temperatures ordinarily employed with other acyl hypohalites. It is, therefore, particularly useful as a brominating agent.[19,52]

The other phase of reaction D involves the presence of readily substituted aromatic rings in the silver salt and thus in the acyl hypohalite. Again, either the hypohalite itself or $X^+$ formed by its dissociation acts as the halogenating agent.[17]

$$2 \underset{}{\overset{R}{\bigcirc}}CO_2X \rightarrow \underset{X}{\overset{R}{\bigcirc}}CO_2X + \overset{R}{\bigcirc}CO_2H \rightarrow 2 \underset{X}{\overset{R}{\bigcirc}}CO_2H$$

or $$\overset{R}{\bigcirc}CO_2X \rightarrow \overset{R}{\bigcirc}CO_2^- + X^+$$

$$\overset{R}{\bigcirc}CO_2^- + X^+ \rightarrow \underset{X}{\overset{R}{\bigcirc}}CO_2^- + H^+ \rightarrow \underset{X}{\overset{R}{\bigcirc}}CO_2H$$

Substitution of halogen in acetylenes, as indicated by reaction E, probably occurs by a similar mechanism.

$$RCO_2X + R'C{\equiv}CH \rightarrow R'C{\equiv}CX + H^+ + RCO_2^-$$

or $$RCO_2X \rightarrow RCO_2^- + X^+$$

$$X^+ + R'C{\equiv}CH \rightarrow R'C{\equiv}CX + H^+$$

### SCOPE AND LIMITATIONS OF THE REACTIONS

### Thermal Cleavage of Acyl Hypohalites
### (Hunsdiecker Reaction)

The thermal decomposition of acyl hypohalites formed as intermediates in the halogen silver-salt reaction to produce compounds containing one carbon atom less than the original acid is perhaps the most important of the various silver salt-halogen reactions. The reaction is of general application in the aliphatic series, leading, with simple fatty acids of 2 to 18 carbon atoms, to excellent yields of alkyl halides.[3,20,25,30,54-58]

$$RCO_2Ag + X_2 \rightarrow RX + CO_2 + AgX$$

A substituent in the aliphatic chain in any position other than the

[54] Lüttringhaus and Schade, Ber., **74,** 1565 (1941).

[55] Mehta, Mehta, and Thosar, J. Indian Chem. Soc., Ind. Ed., **3,** 137 (1940).

[56] Borodine, Ann., **119,** 121 (1861).

[57] Birnbaum, Ann., **152,** 111 (1869).

[58] Cason and Winans, J. Org. Chem., **15,** 142 (1950).

$\alpha$-position does not interfere with the reaction unless it is itself capable of reaction with the acyl hypohalite. Thus, silver salts of alkyl-substituted fatty acids yield primary halides as do acids carrying a cycloalkyl substituent such as cyclopentylacetic acid.[5] Simple halogen derivatives, such as silver $\beta$-bromopropionate, yield dibromides.[40] Polyhalogen compounds have been obtained from silver salts of polyhalogen acids; thus, silver 9,10-dichloroöctadecanoate yields 1-bromo-8,9-dichloroheptadecane;[3] and 1,8,9,11,12-pentabromoheptadecane is obtained from silver 9,10,12,13-tetrabromoöctadecanoate.[59] When applied to acid esters, the reaction leads to $\omega$-halo esters.[4,5,60-62] This is a useful reaction because $\omega$-halo

$$RO_2C(CH_2)_nCO_2Ag + X_2 \rightarrow RO_2C(CH_2)_nX + CO_2 + AgX$$

esters are not easily prepared by other procedures. Silver salts of acids in which there is an aryl substituent such as phenyl[25,63] or deactivated phenyl[16] also give primary halides. If, however, the substituent is a phenyl group readily substituted by electrophilic agents, there is halogenation of the ring and formation of a free acid without loss of carbon dioxide. For example, silver $\beta$-3-methoxyphenylpropionate when treated with bromine or iodine gives an excellent yield of $\beta$-2-bromo-(or iodo-)5-methoxyphenylpropionic acid.[18] Such complex substances as $3(\alpha),12(\beta)$-diacetoxynordesoxycholanic acid (VII) and $3(\alpha), 12(\beta)$-diacetoxycholanic



VII

VIII

[59] Howton, Davis and Nevenzel, J. Am. Chem. Soc., **74**, 1109 (1952).
[60] Allen and Wilson, Org. Syntheses, **26**, 52 (1946).
[61] Duschinsky and Rubin, J. Am. Chem. Soc., **70**, 2546 (1948).
[62] Stoll and Rouvé, Helv. Chim. Acta, **34**, 98 (1951).
[63] Oldham, J. Chem. Soc., **1950**, 100.

acid (VIII) have been converted to the corresponding bromides in yields of 25–30%.[64]  Similar bromides have been prepared from triacetylcholic acid, 3($\beta$)-acetoxyetioallocholanic acid,[65] and similar bile acids.[65a]

In the aromatic series, the reaction is not so general.  Bromobenzene is formed from silver benzoate, but the yields are variable and are apparently dependent upon the temperature.[16,17,20,54,63]  Derivatives of benzoic acid possessing electron-attracting groups give satisfactory yields of halobenzenes.  Thus, $p$-nitrobenzoic acid gives a high yield of $p$-

$$O_2N\langle\overline{\bigcirc}\rangle CO_2Ag + Br_2 \rightarrow O_2N\langle\overline{\bigcirc}\rangle Br + CO_2 + AgBr$$

nitrobromobenzene.  In contrast, $p$-methoxybenzoic acid gives 3-bromo-4-methoxybenzoic acid, also in good yield.[16]

$$CH_3O\langle\overline{\bigcirc}\rangle CO_2Ag + Br_2 \rightarrow CH_3O\langle\overset{Br}{\overline{\bigcirc}}\rangle CO_2H + CO_2 + AgBr$$

The products obtained from the silver salts of $\alpha$-substituted acids depend upon the nature of the substituent.  Acids carrying one $\alpha$-alkyl group give rise to secondary alkyl halides.[25,26,28,66]  A report[27] that a similar

$$RR'CHCO_2Ag + X_2 \rightarrow RR'CHX + CO_2 + AgX$$

product is formed from silver $\alpha$-phenylpropionate has not been confirmed.[23,28,30]  The silver salts of the closely related alicyclic carboxylic acids form cycloalkyl halides.[5,35,63,67]  In one instance the reaction

$$(CH_2)_n \overset{CH_2}{\underset{CHCO_2Ag}{\Big|}} + X_2 \rightarrow (CH_2)_n \overset{CH_2}{\underset{CHX}{\Big|}} + CO_2 + AgX$$

proceeds with rearrangement; silver bicyclo[2.2.2]octane-2-carboxylate yields 2-bromobicyclo[3.2.1]octane.[68]  The rearrangement is effected by

[64] Brink, Clark and Wallis, *J. Biol. Chem.*, **162**, 695 (1946).

[65] Rottenberg, *Helv. Chim. Acta*, **35**, 1286 (1952).  Cf. Koechlin and Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

[65a] Bergström, Rottenberg, and Volz, *Acta. Chem. Scand.*, **7**, 481 (1953).

[66] Cason and Mills, *J. Am. Chem. Soc.*, **73**, 1354 (1951).

[67] Roberts and Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).

[68] Doering and Farber, *J. Am. Chem. Soc.*, **71**, 1514 (1949).

silver bromide, for 2-bromobicyelo[2.2.2]octane and silver bromide give the same product. By operating at —10°, it has been possible to isolate the expected bromide as well as the rearranged product.[69]



Silver salts of simple carboxylic acids having a tertiary α-carbon atom, such as silver trimethyl- and triphenyl-acetate, yield a variety of products when treated with bromine.[25] However, the silver salts of the complex alicyclic acids, adamantanedicarboxylic acid (IX)[70] and bicyclo[3.3.1]-nonan-9-one-1-carboxylic acid (X)[71] give the corresponding bromides in yields of 28 and 74%, respectively. These acids cannot be decarboxylated directly; the silver salt-halogen reaction, therefore, serves as an intermediate step in the preparation of the parent hydrocarbons.



The reaction has been used successfully as a preliminary step in the synthesis of cantharadin from the silver salt (XI) of the 2,3-dimethyl ester of 2,3-dimethylcyclohexane-1,2,3,4-tetracarboxylic acid.[72] Treatment of this silver salt with bromine in carbon tetrachloride results in a lactone XII, formed by loss of methyl bromide from the primarily formed dibromide. Saponification and pyrolysis of the lactone gives a mixture of cantharic acid (XIII) and cantharadin (XIV). (Formulas on p. 345.)

When substituents other than alkyl or aryl are present in the α-position, the decarboxylation leads to a variety of products. The silver salts of α-halogen acids yield 1,1-dihalogenated hydrocarbons.[3,40] Many di-, tri-, and tetra-halogenated methanes, exemplified by such substances as

$$RCHXCO_2Ag + X'_2 \rightarrow RCHXX' + CO_2 + AgX'$$

$CH_2ClF$, $CHBrClF$, $CBr_2F_2$ have been prepared by this reaction.[73] Any combination of hydrogen and halogen may be present in the silver salt,

$$RR'R''CCO_2Ag + X_2 \rightarrow RR'R''CX + CO_2 + AgX$$

[69] Martin, *Bull. soc. chim. France*, [5] **18**, 70 (1951).

[70] Prelog and Seiwerth, *Ber.*, **74**, 1769 (1941).

[71] Cope and Synerholm, *J. Am. Chem. Soc.*, **72**, 5229 (1950).

[72] Ziegler, Schenck, and Krockow, *Ann.*, **551**, 1 (1942).

[73] Haszeldine, *Nature*, **166**, 192 (1950); **168**, 1028 (1952); *J. Chem. Soc.*, **1952**, 4259.

XI → [ ... ] → XII

1. Saponification
2. Pyrolysis

XIII                          XIV

and X may be chlorine, bromine, or iodine. The yields vary widely
(see Table V). Perfluoro acids give perfluoroalkyl halides.[73–80] A high

$$CF_3(CF_2)_nCO_2Ag + X_2 \rightarrow CF_3(CF_2)_nX + CO_2 + AgX$$

temperature is required because of the stability, mentioned earlier, of the
trifluoroacetoxy radical toward decarboxylation. This is probably true
to a smaller extent with the silver salts of various halogenated derivatives
of acetic acid.

Other $\alpha$-substituted acids that undergo the reaction include $\alpha$-keto,
$\alpha$-hydroxy, and $\alpha$-amino acids; $\alpha$-keto acids give acyl halides whereas the
hydroxy and amino acids lead to aldehydes. If the remaining hydrogen
atom on the $\alpha$-carbon atom of the hydroxy and amino acids is replaced by

$$RCOCO_2Ag + X_2 \rightarrow RCOX + CO_2 + AgX$$

$$RCHOHCO_2Ag + X_2 \rightarrow RCHO + CO_2 + AgX + HX$$

$$RCHNH_2CO_2Ag + X_2 \rightarrow RCHNH_2X + CO_2 + AgX$$

$$\xrightarrow{\text{H}_2\text{O}} RCHO + NH_4X$$

an alkyl group, ketones result. For the most part, these reactions are
considered only in the original patent,[3] and little work has been done on
their development. Heyns and Stange, however, have shown that the

[74] Hauptschein and Grosse, *J. Am. Chem. Soc.*, **73**, 2461 (1951).

[75] Hauptschein, Kinsman, and Grosse, *J. Am. Chem. Soc.*, **74**, 849 (1952).

[76] Brice and Simons, *J. Am. Chem. Soc.*, **73**, 4016 (1951).

[77] Henne and Finnegan, *J. Am. Chem. Soc.*, **72**, 3806 (1950).

[78] Haszeldine, *J. Chem. Soc.*, **1951**, 584.

[79] Hauptschein, Nodiff, and Grosse, *J. Am. Chem. Soc.*, **74**, 1347 (1952).

[80] Henne and Francis, *J. Am. Chem. Soc.*, **75**, 993 (1953).

silver salts of acylated α-amino acids give halogen derivatives that can be isolated.[81] On hydrolysis these products form the carbonyl derivative, amide, and hydrogen halide.

$$RCHNH(COR')CO_2Ag + X_2 \rightarrow RCHBr(NHCOR') + CO_2 + AgX$$

$$RCHBr(NHCOR') + H_2O \rightarrow RCHO + R'CONH_2 + HBr$$

The silver salt of ethylmalonic acid, which may be considered an α-carboxy acid, gives a small yield of 1,1-dibromopropane together with some 1,1,1-tribromopropane; the tribromo derivative is presumably the result of some bromination before decarboxylation.[40] The potassium salts of the closely related alkyl α-carbethoxyacetic acids yield α-bromo[82] and α-chloro[83] fatty acid esters. Again there is some halogenation before

$$R'O_2CCHRCO_2K + X_2 \rightarrow R'O_2CHXR + CO_2 + KX$$

decarboxylation. The best yields result from compounds of intermediate chain length (6–8 carbon atoms).

The silver salts of unsaturated acids have not been useful in this reaction. Silver methacrylate added to bromine in carbon tetrachloride at 0° gives a polymeric product. Silver allylacetate yields a bromolactone.[40] Because of the ease with which acyl hypohalites add to the olefinic bond (see p. 350), a clear-cut reaction would not be expected. However, silver phenylpropiolate and iodine produce phenyliodoacetylene in excellent yield.[49]

Treatment of silver salts of α,ω-dicarboxylic acids with halogen leads to α, ω-dihalides.[3,20,40,54,63,84] Although this reaction is general, the yields of dihalide are poor with the lower members of the series. The formation of a bromo compound from silver succinate and bromine was observed by Bunge as early as 1870.[85] However, the yield is small even when the silver salt is added to a solution of bromine in carbon tetrachloride.[40] Silver glutarate and various alkyl-substituted derivatives give mainly γ-lactones though a small amount of dihalide is formed.[63]

$$AgO_2CCR_2CR_2CR_2CO_2Ag + X_2 \rightarrow \underline{CR_2CR_2CR_2CO_2} + CO_2 + 2AgX$$

Silver perfluoroglutarate reacts in a similar manner with iodine,[74] but with chlorine and bromine excellent yields of dihalogenated hexafluoropropanes

[81] Heyns and Stange, *Z. Naturforsch.*, **7b**, 677 (1952).

[82] Dice and Bowden, *J. Am. Chem. Soc.*, **71**, 3107 (1949).

[83] Campbell and Shaw, *J. Chem. Soc.*, **1952**, 5042.

[84] Schmid, *Helv. Chim. Acta*, **27**, 127 (1944).

[85] Bunge, *Ann. Suppl.*, **7**, 123 (1870).

are obtained.[86]   With silver adipate there is some lactone formation, but a substantial yield of dibromide is obtained by the reverse addition procedure.[84]   The higher members of the series give moderately good yields of dihalides.   In the one instance in which a tricarboxy acid was used, the yield of trihalide was very small.[40]

**Effect of the Halogen Employed.** Bromine is most generally used in the Hunsdiecker reaction.   In the few instances in which chlorine has been employed the yields have been satisfactory.[3,52,73,75,83,87]   Iodine was normally used in a 1:2 molar ratio with the silver salts in the early work, and, consequently, the so-called Simonini ester was the main product. More recent work[87] has shown that an iodine-to-silver ratio of 1:1 affords substantial yields of the iodide, though some ester is produced.   In fact, the yield of iodide rises, and that of the ester falls as the ratio of iodine to silver is gradually increased from 1:2 to 1:1.   In the presence of excess iodine, the silver salts of the long-chain acids give good yields of the iodides.[8]   Excellent yields of iodides have also been obtained from the silver salts of fluoro and perfluoro acids,[73] but the use of iodine in the preparation of iodides by this reaction has not been investigated thoroughly. It may well serve as a method for producing alkyl iodides as well as bromides.

**Effect of Temperature.** The effect of temperature has not been studied systematically.   From available reports, it appears that the optimum temperature depends upon the silver salt used.   Bromobenzene, for example, is obtained in 80% yield when bromine is added to a suspension of silver benzoate in boiling carbon tetrachloride,[20] but the yield is insignificant when the reaction is carried out in the cold.[20,54]   Mehta and co-workers point out that carbon tetrachloride is a better solvent than chloroform for the reaction and indicate that its higher boiling point is responsible for the advantage.[87]   They show that better yields of long-chain alkyl halides are obtained in boiling than in cold carbon tetrachloride. On the other hand, cyclobutyl bromide is obtained only when the reaction is run in carbon tetrachloride below —20°.[35]   In some instances, operation at a low temperature is necessary because of the instability of the silver salts.   The silver salts of α-bromovaleric acid, β-bromopropionic acid, α-bromobutyric acid, and δ-bromovaleric acid, for example, are stable at 0° but not at room temperature.   Silver β-bromopropionate changes into β-propiolactone on drying in a desiccator at room temperature.[40] Nevertheless, these silver salts undergo the Hunsdiecker reaction at 0° to give fairly good yields of the corresponding bromides.

**Effect of Solvent.** Carbon tetrachloride is probably the best general

[86] Hauptschein, Stokes, and Grosse, *J. Am. Chem. Soc.*, **74**, 848 (1952).

[87] Mehta, Mehta, and Thosar, *J. Indian Chem. Soc., Ind. Ed.*, **3**, 166 (1940).

solvent for the reaction, although there are isolated instances in which other solvents produce better results. The production of n-propyl bromide from silver butyrate, for example, is carried out in nitrobenzene; if carbon tetrachloride is used, separation of the n-propyl bromide from the solvent is difficult because the two materials have approximately the same boiling point.[20] Experiments carried out by Oldham and Ubbelohde have shown that good yields of undecyl iodide can be obtained in benzene (72-80%), carbon tetrachloride (70-78%), or petroleum ether (51-65%).[8] In the few instances recorded in which the silver salt was used in carbon disulfide, the yields were low.[25] Though Cason and Way prepared cyclobutyl bromide by operating in carbon tetrachloride at a low temperature,[35] the same halide has also been made by treatment of the mercuric salt of the acid with bromine in carbon disulfide.[5] Dichlorodifluoromethane has been used successfully as a solvent in the preparation of cyclopropyl bromide[67] and ethyl 4-bromobicyclo[2.2.2]octane-1-carboxylate.[88] Tetrachloroethane was also used as a solvent in the former reaction, but the yield was poor. Chloroform,[3,8] ether,[3,89] ethyl bromide,[65,65a] and trichloroethylene[62] have also been used. In trichloroethylene a surprisingly good yield of methyl ω-bromopentadecanoate was obtained from the requisite acid ester. Treatment of the silver salts of perfluoro acids with halogens is usually carried out without a solvent,[52,73-75,77,78] but in one instance perfluorotributylamine has been used successfully.[76]

**Salts of Other Metals.** Though silver salts have been generally used in this reaction, other salts have also been employed with varying success. Of these, the mercurous and mercuric salts have given the best results.[3-5] Thallium salts have also been satisfactory.[3] With some substituted malonic acid half-esters, the potassium salts have been used with yields varying from 23 to 80%.[82,83] The yields are highest when the substituent is n-butyl, n-hexyl, benzyl, or cyclohexyl and drop off rapidly when the number of carbons in the substituent is increased or decreased. Trifluoroacetic acid gives poorer yields of trifluoromethyl iodide when the sodium, potassium, barium, mercury, or lead salt is employed in place of the silver salt. The reaction is carried out in a steel autoclave at a high temperature.[78]

## Thermal Cleavage of the Simonini Complex
## (Simonini Reaction)

Iodine is the only halogen that is useful for the preparation of esters by the Simonini reaction; the other halogens give insignificant yields.

[88] Roberts, Moreland, and Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).

[89] Herzog and Leiser, *Monatsh.*, **22**, 357 (1901).

Since esters are usually secured more easily by other procedures, the reaction has little value as a synthetic method.   It has been of primary interest in connection with the mechanism of formation and decomposition of the complex, and because of a useful synthesis in which the complex is used, viz., the Prévost reaction (see p. 350).

Those silver salts that undergo the Hunsdiecker reaction readily also, in general, undergo the Simonini reaction.   Only in the case of silver salts of saturated monocarboxylic acids is any difference discernible.   The difference appears to be due to an ability of the primarily formed hypoiodites to give complexes or coordination compounds with the silver salt, an ability that apparently is not shared to any great degree by the acyl

$$RCO_2Ag + RCO_2I \rightarrow RCO_2Ag \cdot RCO_2I$$

hypobromites though a small quantity of ester is formed occasionally. Acyl hypoiodites also form stable coordination complexes with tertiary bases such as pyridine and $\alpha$-picoline.[90]

In the dibasic acid series, the products obtained by the Simonini procedure are comparable to those obtained with bromine.   Silver oxalate yields only carbon dioxide and silver halide.[43,49]   Silver malonate produces carbon dioxide, but no other product has been identified.[49] Silver succinate regenerates succinic acid and forms a little maleic anhydride, while silver glutarate and various substituted derivatives give $\gamma$-lactones in fair yields (40%).   The method has been suggested as a preparative procedure for $\gamma$-lactones.[91-93]   Similar products are obtained with bromine.[63]   Silver adipate yields a small amount of polymerized $\delta$-valerolactone.[49]   The reaction with homologs higher than adipic acid has not been investigated.

Unsaturated acids do not give clear-cut results.   Although the intermediate complex is formed in many cases and carbon dioxide is lost in the decomposition, the only other products identified are the unchanged acid or its anhydride.[43,49]   Hydroxy acids yield aldehydes or ketones. This reaction, first reported by Herzog and Leiser,[89] proceeds as well with bromine as with iodine.[3]   Thus, formaldehyde is formed from glycolic acid, while mandelic acid yields benzaldehyde.

In the aromatic series, the reaction has no value.   Silver benzoate gives a variety of products including ester, halide, and halogenated benzoic acid.[49]   Silver phthalate leads to phthalic anhydride, whereas silver hexahydrophthalate gives no identifiable products.[49]

[90] Zingaro, Goodrich, Kleinberg, and VanderWerf, *J. Am. Chem. Soc.*, **71**, 575 (1949).
[91] Windaus and Klänhardt, *Ber.*, **54**, 581 (1921).
[92] Windaus, Klänhardt, and Reverey, *Ber.*, **55**, 3981 (1922).
[93] Goldschmidt and Gräfinger, *Ber.*, **68**, 279 (1935).

## Thermal Cleavage of Iodine Triacyls

A reaction somewhat similar to the Simonini reaction takes place when a silver salt and iodine react in a 3 : 2 molar ratio.[8]   The product contains positive, trivalent iodine but no silver.   It is presumably an iodine triacyl, which decomposes thermally to produce both ester and alkyl

$$I(OCOR)_3 \xrightarrow{\text{Heat}} RCO_2R + RI + 2CO_2$$

halide.   Heating in the presence of excess iodine gives the alkyl iodide only.

$$I(OCOR)_3 + I_2 \rightarrow 3RI + 3CO_2$$

## Addition Reactions of Acyl Hypohalites
## (Prévost Reaction)

The intermediates formed in the Simonini and Hunsdiecker reactions, $RCO_2Ag \cdot RCO_2I$ and $RCO_2X$, respectively, will react with olefins, acetylenes, and sufficiently reactive phenyl groups.   The addition to olefins was first reported by Birckenbach, Goubeau, and Berninger,[21] who treated silver acetate with iodine in ether solution, removed the silver iodide formed, and treated the filtrate with cyclohexene.   The acetate of 2-iodocyclohexanol resulted.   The same substance had been obtained by Brunel some years earlier in a similar reaction with mercuric acetate,

$$CH_3CO_2Ag + I_2 + \underset{}{\bigcirc} \xrightarrow[-80°]{(C_2H_5)_2O} \underset{OCOCH_3}{\overset{I}{\bigcirc}} + AgI$$

iodine and cyclohexene.[94]   However, the method has been developed mainly by Prévost,[9–11,13,14] and the reaction is generally known by his name.   Its chief use lies in the preparation of 1,2-glycols.

When the Simonini complex obtained from silver benzoate and iodine is treated in benzene solution with an olefin, silver iodide precipitates and the dibenzoate of a 1,2-glycol is formed.   Although the complex from

$$C_6H_5CO_2Ag \cdot C_6H_5CO_2I + RCH{=}CH_2 \rightarrow RCH(OCOC_6H_5)CH_2OCOC_6H_5$$
$$+ AgI$$

silver benzoate and iodine can be isolated, this is unnecessary.   A mixture consisting of 2 moles of silver benzoate, 1 mole of the olefin, and 1 mole of iodine in dry benzene gives satisfactory results.[9]   Simple ethylenic compounds give yields of about 90%; biallyl, 60%; allylic esters, 70%; and acrylic esters, 35%.   Silver benzoate can be replaced by other silver salts, but the glycol dibenzoates have the advantages that they form more easily, crystallize more readily, and are saponified without difficulty.[9,10]

[94] Brunel, *Bull. soc. chim. France*, [3] **33**, 382 (1905).

Although benzoates are recommended, silver salts of acetic,[10,22] propionic,[22] and butyric acids[20,22] have also been used, especially in the preparation of the halo esters. Indeed, the second phase of the reaction of an olefin with silver acetate and an equimolar amount of iodine in benzene solution is slow, and the diester is accompanied by iodo acetates which are difficult to remove.[10]

The reaction also proceeds with silver salts of dicarboxylic acids. Thus, silver succinate, iodine, and cyclohexene in ether solution give di-2-iodocyclohexyl succinate. A small quantity of polymeric diester

$$
\begin{array}{c} CH_2CO_2Ag \\ | \\ CH_2CO_2Ag \end{array} + I_2 + 2 \; \left\langle \!\!\! \bigcirc \!\!\! \right\rangle \; \rightarrow \; \begin{array}{c} CH_2CO_2C_6H_{10}I\text{-}o \\ | \\ CH_2CO_2C_6H_{10}I\text{-}o \end{array} + 2AgI
$$

$(C_{10}H_{14}O_4)_n$ is formed simultaneously. Silver salts of oxalic and phthalic acids and even silver carbonate undergo similar reactions.[95]

Silver 3,5-dinitrobenzoate has been suggested as a reagent for identification of olefins. Simple olefins like ethylene and propylene give the 3,5-dinitrobenzoate of the iodohydrin when treated with equimolar amounts of iodine and silver 3,5-dinitrobenzoate.[96] When unsymmetrical

$$
3,5\text{-}(NO_2)_2C_6H_3CO_2Ag + I_2 + RCH{=}CHR' \rightarrow
$$
$$
RCHICH[OCOC_6H_3(NO_2)_2]R' + AgI
$$

olefins are used, the halogen appears exclusively on the less highly substituted carbon atom. This mode of addition, however, is not general, for preformed hypohalites from acetic, butyric, and benzoic acids add to allyl halides to give good yields of 2,3-dihalogenated propyl esters.[20,97]

Bromine or chlorine can be used in place of iodine.[14,22,51] With these halogens, however, it is advantageous to carry out the reaction in carbon tetrachloride rather than benzene, to avoid the undesirable side reaction with the latter solvent which leads to the formation of phenyl benzoate.[14] In the absence of detail in Prévost's papers, one is inclined to favor carbon tetrachloride as a solvent for all of the halogens. However, benzene has been used successfully by other experimenters.[98,99]

Studies on the addition of the complex from silver benzoate and iodine to butadiene have shown that the primary addition is mainly 1:2. Fractionation of the glycols obtained from the action of a limited quantity of the complex with butadiene gave 80% 1,2-glycol and 4% 1,4-glycol.[11] The reaction has been applied to the mixture of monohydric phenols

[95] Birckenbach, Goubeau, and Kolb, *Ber.*, **67**, 1729 (1934).

[96] Halperin, Donahoe, Kleinberg, and VanderWerf, *J. Org. Chem.*, **17**, 623 (1952).

[97] Edwards and Hodges, *J. Chem. Soc.*, **1954**, 761.

[98] Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

[99] Niemann and Wagner, *J. Org. Chem.*, **7**, 227 (1942).

from cashew nut oil with the formation of an iodinated mono- and di-glyeol. This established the heterogeneous nature of the monophenolic fraction. Subsequent oxidation of the monoglycol combined with synthesis established the structure of part of the phenolic product of the oil, as XV.[100] The Prévost reaction with silver benzoate and iodine followed by hydrolysis gives XVI.

OH                                    OH

⬡(CH$_2$)$_7$CH=CH(CH$_2$)$_5$CH$_3$        ⬡(CH$_2$)$_7$CHOHCHOH(CH$_2$)$_5$CH$_3$
                                        I
         XV                                    XVI

These addition reactions with unsymmetrical olefins should give a mixture of stereoisomers. Though Prévost has indicated that isomers are sometimes obtained, little attention has been given to this aspect of the reaction. McCasland,[101] however, has pointed out that, whereas hydroxylations of cyclohexadienes with permanganate or osmium tetroxide give *cis* products, the Prévost glycol synthesis, like perbenzoic acid, yields *trans* compounds. Thus, 1,4-cyclohexadiene and two molecular equivalents of silver benzoate in benzene give 37% of the *trans* dibenzoate. With four molecular equivalents of silver benzoate, one of the stereoisomeric forms of 1,2,4,5-cyclohexanetetrol tetrabenzoate can be isolated. The other stereoisomer is also present. No identifiable products could be obtained from 1,3-cyclohexadiene. Small yields of the *trans* dibenzoates and 3,5-dinitrobenzoates were obtained from cyclohexene, halogen, and 2 moles of the requisite silver salt.

## Substitution Reactions of Acyl Hypohalites

It has been indicated earlier (p. 342) that silver salts of fatty acids containing as a substituent a phenyl group reactive to electrophilic substitution undergo halogenation of the ring rather than the Hunsdiecker or Simonini reaction. The silver salt of β-3-methoxyphenylpropionic acid, for example, gives β-2-bromo-5-methoxyphenylpropionic acid when treated with bromine.[18] The first report of this kind was made by

                                           Br
⬡CH$_2$CH$_2$CO$_2$Ag + Br$_2$ →        ⬡CH$_2$CH$_2$CO$_2$H + AgBr
CH$_3$O                                  CH$_3$O

Peligot who observed some *m*-bromobenzoic acid among the products of the action of bromine on silver benzoate.[102] Small amounts of *m*-iodobenzoic acid and diiodosalicylic acid result from the action of iodine

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[100] Sletzinger and Dawson, *J. Am. Chem. Soc.*, **68**, 345 (1946): *J. Org. Chem.*, **14**, 671 (1949).

[101] McCasland and Horswill, *J. Am. Chem. Soc.*, **76**, 1654 (1954).

[102] Peligot, *Compt. rend.*, **3**, 9 (1836).

on the silver salts of the unhalogenated acids.[15]  Silver $\beta$-($p$-nitrophenyl)-propionate, however, gives $p$-nitrophenethyl bromide in excellent yield.[16]

$$O_2N\text{—}C_6H_4\text{—}CH_2CH_2CO_2Ag + Br_2 \rightarrow O_2N\text{—}C_6H_4\text{—}CH_2CH_2Br + CO_2 + AgBr$$

Although the method has little practical value for reasons that will appear below, it has been used to prepare a series of halogenated alkoxyphenyl fatty acids of the general formula.[18]

$$RO\text{—}C_6H_3(X)\text{—}(CH_2)_nCO_2H$$

The preparation of the silver salt of the acid to be halogenated is unnecessary.  It is sufficient to use dry silver acetate in combination with the halogen;  the acyl hypohalite first formed is the active halogenating agent.[17,18]  The reaction is carried out in acetic acid or carbon tetrachloride.  It proceeds as indicated only when a phenyl group active

$$RO\text{—}C_6H_4\text{—}(CH_2)_nCO_2H + CH_3CO_2Ag + X_2 \rightarrow$$

$$RO\text{—}C_6H_3(X)\text{—}(CH_2)_nCO_2H + AgX + CH_3CO_2H$$

toward electrophilic substitution is present.  It is, therefore, quite limited in application.  The method is preferred to the mercuric acetate-iodine procedure because of the difficulty of removing mercuric iodide from organic solvents in which it is soluble;  silver iodide can be removed quantitatively by filtration.

The silver salts of a variety of carboxylic acids react with iodine in the presence of benzene to yield, among other products, iodobenzene and/or the phenyl ester of the carboxylic acid.[103]  The yield of iodobenzene is highest from silver $o$-nitrobenzoate.  In the absence of benzene, however, this silver salt on treatment with bromine gives a 95% yield of $o$-nitrobromobenzene—the Hunsdiecker product.  Benzene, therefore, is not a good solvent for reactions involving acyl hypohalites because it enters into competition for the halogen.  When the acyl hypohalite undergoes the Hunsdiecker reaction sufficiently rapidly, benzene can be used as a solvent.  This is the case when R is a long chain such as $n$-$C_{11}H_{23}$ or $n$-$C_{17}H_{35}$.

The reaction between silver trifluoroacetate and iodine to yield carbon dioxide, silver iodide, and trifluoromethyl iodide does not occur appreciably

[103] Birckenbach and Meisenheimer, *Ber.*, **69**, 723 (1936).

below 100°,[77] and silver trifluoroacetate-halogen is, therefore, a useful halogenating agent. Excellent yields of bromo- and iodo-benzenes containing methyl, halogen, methoxyl, amino, dimethylamino, and carboxyl groups as substituents are obtained by this procedure.[19,52] Benzene is so deactivated, however, by the introduction of a nitro group that the normal Hunsdiecker product, $CF_3I$, is produced in 75% yield when nitrobenzene is treated with silver trifluoroacetate and iodine.

Normally no solvent is used in these reactions though carbon tetrachloride has been used successfully.[52] Nitrobenzene is often a suitable solvent.

The halogen enters in the *para* position to the group already present in the benzene derivative if the latter normally directs to that position. Infrared analyses indicate that a small amount of the *ortho* isomer is usually present. Benzoic acid is halogenated in the *meta* position, and there is no indication of *ortho* or *para* halogenation.

Although silver trifluoroacetate-halogen is not so powerful a halogenating agent as silver perchlorate-halogen, it possesses certain specific advantages.[19] Trifluoroacetic acid, formed in the reaction, is volatile and is easily removed by distillation. The danger attending the use of silver perchlorate is avoided. Silver trifluoroacetate is more soluble in organic solvents than silver trichloroacetate, acetate, perchlorate, or sulfate.[19]

It has been demonstrated that the Simonini complex from silver benzoate reacts with acetylenes to give excellent yields of iodoacetylenes. With phenylacetylene, the formation of phenyliodoacetylene is quantitative and benzoic acid and silver benzoate have been isolated in quantities corresponding to the following equation.[12] Acetylene itself reacts with

$$C_6H_5CO_2Ag \cdot C_6H_5CO_2I + C_6H_5C \equiv CH \rightarrow C_6H_5C \equiv CI + C_6H_5CO_2H$$
$$+ C_6H_5CO_2Ag$$

either one or two molecules of the complex to give iodo- and diiodoacetylene, respectively.[12]

It is not necessary to isolate the complex; addition of the acetylene derivative to the complex formed in benzene is satisfactory. However, the use of benzene as a diluent is not practical with chlorine or bromine because it takes part in the reaction. Carbon tetrachloride is satisfactory. Thus, the treatment of silver benzoate in carbon tetrachloride with bromine, chlorine, or iodine followed by addition of 1-heptyne gives good yields of the respective haloacetylenes.[14]

Prévost assumes that the Simonini complex is formed with chlorine and bromine in the same manner as with iodine.[14] Such a complex has not been isolated with these halogens, nor is it necessary to assume that it

forms. The reaction could proceed equally well with the intermediate acyl hypohalite.

$$RCO_2X + R'C \equiv CH \rightarrow R'C \equiv CX + RCO_2H$$

## EXPERIMENTAL PROCEDURES

### Preparation of Silver Salts

Two general methods are available for preparing the silver salts. The simplest and most direct method is the reaction between the potassium or sodium salt of the acid and silver nitrate. For acids of low molecular weight and for most dibasic acids, this is the most satisfactory method. For the higher acids (above $C_8$) especially when fairly large quantities are employed, it has been suggested that freshly prepared silver oxide be used.[4] Reaction of the potassium or sodium salts of the higher acids with silver nitrate leads to voluminous precipitates which are difficult to filter. For acids that are sparingly soluble in water the use of ethanol-water mixtures is recommended. For perfluoro acids unstable in water (undecafluorocyclohexanecarboxylic acid, for example), the use of silver oxide is a necessity. With these acids the reaction is run in perfluorobutyl ether as a solvent. A representative preparation by each of these methods follows. It is essential to the success of the subsequent reactions with the halogens to have the silver salts perfectly dry.

**Silver Laurate.**[54] Hot solutions of 50 g. of silver nitrate in 100 ml. of water and 59 g. of lauric acid in 200 ml. of 1.45 $N$ potassium hydroxide are added simultaneously to 100 ml. of hot water with stirring. The addition is controlled so that approximately equivalent quantities of the reactants are present at all times. The precipitated silver salt is collected on a filter, washed with water and acetone, and air-dried. This material is powdered and then dried in a vacuum at 60° over phosphorus pentoxide. The yield is 85 g. (94%).

**Silver Methyl Octadecanedioate.**[4] The silver oxide precipitated by the admixture of water solutions of 270 g. of silver nitrate and 150 g. of potassium hydroxide is washed free from alkali. The moist oxide is added to 520 g. of molten methyl hydrogen octadecanedioate and stirred vigorously while boiling water is added. The silver salt formed is collected on a filter, washed with hot ethanol, dried, finely powdered, and redried. The yield is 637 g. (99%).

**Substituted Silver Benzoates.**[17,90] The organic acid is dissolved in hot ethanol, and a hot aqueous solution of sodium carbonate is added until the solution is basic to litmus. Nitric acid is then added dropwise until the solution is just acid to litmus. Any solid present is filtered, and a hot aqueous solution of an equivalent amount of silver nitrate is added

to the filtrate. The silver salt is removed by filtration, washed with distilled water and ethanol, and dried at 70°.

**Silver Bicyclo[3.3.1]nonan-9-one-1-carboxylate.**[71] A solution of 20 g. of bicyclo[3.3.1]nonan-9-one-1-carboxylic acid in 50 ml. of methyl alcohol is titrated to the end point of phenolphthalein with a solution of potassium hydroxide in methyl alcohol. A solution of 18.6 g. of silver nitrate in 20 ml. of water and 50 ml. of methyl alchol is added dropwise with stirring; the silver salt is collected on a filter, washed with methyl alcohol, and dried at 70° under vacuum for eighteen hours. The product contains potassium nitrate but gives results in subsequent reaction that are as satisfactory as those obtained with the silver salt prepared in aqueous solution.

**Silver Undecafluorocyclohexanecarboxylate.**[76] To a solution of 9.05 g. of undecafluorocyclohexanecarboxylic acid in 66 ml. of perfluorobutyl ether is added 3.22 g. of alkali-free silver oxide. The mixture is shaken intermittently in the dark over a three-day period. Only a trace of unreacted silver oxide remains. The silver salt, 11.35 g. (94.3%), is collected on a Pyrex filter cone, washed with perfluorobutyl ether, and dried at 50° for ten hours. The salt is a white, light-sensitive, crystalline, non-hygroscopic material, soluble in water. All operations in its preparation are carried out in the dark.

## Products Formed by the Hunsdiecker Reaction

**Methyl 5-Bromovalerate.** The preparation of this material in 52–54% yield from methyl hydrogen adipate is described in *Organic Syntheses.*[60]

**n-Propyl Bromide.**[20] A solution of 40 g. of bromine in 250 ml. of freshly distilled nitrobenzene is added with vigorous shaking and cooling to 53.5 g. of silver butyrate. In about one minute, the bromine has reacted and the solution is yellow in color. This is followed by sudden, turbulent evolution of carbon dioxide, and the solution becomes quite warm. When gas evolution ceases, the silver bromide is removed by filtration and the filtrate is distilled through a Widmer column. There is obtained 17.2 g. (61%) of n-propyl bromide, 2.7 g. of butyric acid, and a trace (0.5 g.) of n-propyl butyrate.

**n-Heptyl Bromide.**[4] To a suspension of 102.5 g. of mercuric octanoate in 100 ml. of carbon disulfide (dried over phosphorus pentoxide) is added dropwise 22 ml. of dry bromine. There is a smooth evolution of carbon dioxide. When the initial reaction has subsided, the mixture is warmed for a short time on the steam bath. The mercuric bromide is removed by filtration and washed well with carbon disulfide. The solvent is removed from the filtrate and washings, and the residue is fractionated

under reduced pressure to yield 55.7 g. (75%) of *n*-heptyl bromide, b.p. 74°/18 mm.    A higher boiling fraction (133-137°/18 mm.) is octanoic acid (6.1 g., 10%).

*n*-Undecyl Bromide.[54]    To a suspension of 46 g. of silver laurate in 200 ml. of carbon tetrachloride (dried over phosphorus pentoxide) is added slowly, with stirring and cooling, 7.5 g. of dry bromine in 20 ml. of dry carbon tetrachloride.    The mixture is heated gradually until the evolution of carbon dioxide ceases and is then held for a short time at its boiling point.    The silver bromide is removed by filtration, placed in an extraction thimble, and extracted for one to two hours, the filtrate being used as an extracting solvent.    After the carbon tetrachloride solution is washed with dilute aqueous sodium hydroxide and water, the solvent is removed and the residue distilled to give 24 g. (67%) of undecyl bromide, b.p. 131–134°/15 mm.; 5.5 g. (18%) of lauric acid can be recovered from the alkaline wash liquid.

**1,4-Dibromobutane.**[84]    To a well-stirred solution of 48 ml. of dry bromine in 250 ml. of dry carbon tetrachloride is added (with the exclusion of water) 163 g. of silver adipate.    The addition is made in small portions over a seven-hour period.    After the addition of each portion of silver salt, the reaction is started by warming to 50° and is allowed to continue until the evolution of carbon dioxide ceases.    Heating is continued for one-half hour to complete the reaction.    The silver bromide is removed by filtration and washed thoroughly with ether.    The carbon tetrachloride and ether solutions are combined and decolorized by shaking with a saturated solution of sodium bisulfite; the decolorized solution is shaken with 10% aqueous potassium hydroxide solution, any emulsion that forms being broken with sodium chloride.    The solution is finally washed with sodium chloride solution and dried.    The solvents are removed through a fractionating column at ordinary pressure, and the residue is distilled.    The 1,4-dibromobutane distils at 78-81°/11 mm.; the yield is 58 g. (58%).

**1,10-Dibromodecane.**[3]    A mixture of 40 g. of the silver salt of dodecanedicarboxylic acid and 100 ml. of carbon tetrachloride is treated gradually with 9 ml. of bromine.    The silver bromide that separates during the reaction is removed by filtration and washed with hot carbon tetrachloride.    The filtrate and washings are combined and shaken with sodium bicarbonate solution to remove any free acid.    The solvent is removed and the residue distilled to give 16.8 g. (about 60%) of 1,10-dibromodecane, b.p. 190–195°, m.p. 35–36°.

**Methyl 17-Bromoheptadecanoate.**[4]    To a suspension of 673 g. of the silver salt of methyl 17-carboxyheptadecanoate in 750 ml. of carbon tetrachloride is added, with cooling and stirring, 81 ml. of bromine.

The mixture is finally warmed on a water bath for a short time, and the silver bromide formed is removed by filtration. When the filtrate is cooled to 0°, 58 g. of the monoester acid separates. The remainder can be removed by shaking the solution with dry potassium carbonate; aqueous alkalies form emulsions that are difficult to deal with. Removal of solvent and distillation gives 432 g. (75%) of methyl 17-bromo-heptadecanoate, b.p. 212–214°/2.5 mm.

**Trifluoromethyl Iodide.**[77] A mixture of 66 g. (0.3 mole) of finely ground silver trifluoroacetate and 81 g. (0.32 mole) of powdered iodine was placed in a horizontally held tube, 25 mm. in diameter and 25 cm. long; this tube was sealed at one end while the other end was connected to a wide trap cooled in ice water and backed by two traps cooled in solid carbon dioxide (Dry Ice) and a small water bubbler which served to show the rate of evolution of the carbon dioxide. The ice trap collected a fine sublimate of iodine and prevented clogging of the solid carbon dioxide (Dry Ice) traps, the first of which collected practically all of the trifluoromethyl iodide.

The mixture of silver salt and iodine was heated cautiously with a gas burner, starting at the closed end. The decomposition is smooth at about 100°, but tends to propagate spontaneously and escape control when the heating is not done patiently. The bubbling of carbon dioxide is used as an indicator for the speed at which the burner can be moved along the tube. With the small equipment used, it took ninety minutes to complete the reaction. The crude trifluoromethyl iodide amounted to 47 g. (85%). A series of larger runs gave an average yield of 87%. Fractional distillation gave a product boiling at 21.8°.

Trifluoromethyl iodide is conveniently stored in glass ampules. Exposed to light, it slowly becomes pink, then purple.

A comparable procedure is described by Haszeldine.[78]

**Cyclobutyl Bromide.**[35] To a flask equipped with a mercury-seal stirrer is added 560 ml. of carbon tetrachloride (dried over phosphorus pentoxide), and 50 ml. of carbon tetrachloride is distilled in order to dry the flask thoroughly. The system is protected with a drying tube and, after addition of 85.2 g. (0.534 mole) of bromine (dried over phosphorus pentoxide), the mixture is cooled to −25° with stirring. To this is added 111 g. (0.534 mole) of the silver salt of cyclobutanecarboxylic acid. The salt is added over a period of about fifty minutes through a wide rubber connection from the flask in which it had been dried. After an induction period of five to twenty minutes, a vigorous evolution of carbon dioxide sets in and continues as the remainder of the silver salt is added. Evolution of carbon dioxide is accompanied by the evolution of heat, but the temperature is easily maintained at −25 to −20° with a solid carbon

dioxide-acetone bath.   After addition is complete, the mixture is stirred briefly until gas evolution becomes slow and then is allowed to warm to room temperature with stirring.   When gas evolution has ceased, the silver bromide is removed and washed with carbon tetrachloride.   The filtrate is washed with $2 N$ sodium hydroxide and water and then dried over calcium chloride.   The combined alkaline extracts from a total of 2.6 moles of silver salt yield only 2.2 g. of acidic material.

The carbon tetrachloride solution is flash-distilled through a 1-meter column packed with glass helices and equipped with heated jacket and partial reflux head.   During flash distillation, the volume of solution in the distilling flask is kept sufficiently large so that the mole fraction of cyclobutyl bromide is kept below 0.2.   This avoids loss of bromide, and the carbon tetrachloride is collected at 76.9°.   After all the carbon tetrachloride solution has been added, removal of solvent is continued and an intermediate fraction (7.9 g.), b.p. 76.9–108.2°, is collected. Cyclobutyl bromide (36 g., 50%) is collected at 108.2–108.3°; $n_D^{20}$ 1.4801, $d^{20}$ 1.434, $MR_D$ 26.75 (calculated 26.72).   There is 15 g. of distillation residue.   By redistilling the intermediate fractions from several runs and stripping the residues in a vacuum, the total yield is raised to 53%. The same yield is obtained in larger (1.9 mole) runs.

**$p$-Nitrobromobenzene.**[16]   To a suspension of 34 g. of silver $p$-nitrobenzoate in 500 ml. of carbon tetrachloride 20 g. of bromine is added dropwise at room temperature.   The deep-red solution obtained at the end of the addition is heated slowly to boiling; there is no evolution of carbon dioxide below the reflux temperature.   The solution is boiled for three hours, during which time the color gradually fades.   The hot solution is filtered, and the filtrate is washed with sodium bisulfite and sodium bicarbonate solutions.   Acidification of the sodium bicarbonate extract produces 2 g. (10%) of $p$-nitrobenzoic acid.   Evaporation of the carbon tetrachloride leaves 20 g. (74%) of crystalline $p$-nitrobromobenzene, m.p. 126–127°.

**Ethyl α-Bromo-β-phenylpropionate.**[82]   To a solution of 37.5 g. (0.15 mole) of diethyl benzylmalonate in 100 ml. of absolute ethanol is added, with stirring, a solution of 8.7 g. (0.15 mole) of potassium hydroxide in 100 ml. of absolute ethanol.   The solution is allowed to stand at room temperature for four to twelve hours; the $p$H of the final mixture has a value between 7 and 8.   Any solids that have formed (assumed to be the dipotassium salt) are removed by filtration.   The ethanol is distilled until a thick syrup remains.   The last traces of ethanol are removed in vacuum, and the resulting crystals of the potassium salt of the half ester of benzylmalonic acid are placed in a vacuum desiccator for twelve hours.

The dried, finely powdered potassium salt is mixed with 100 ml. of

carbon tetrachloride. The ice-cold mixture is stirred vigorously while a solution of 25 g. (0.15 mole) of bromine in 50 ml. of carbon tetrachloride is added dropwise over a period of two to four hours. The bromine is decolorized rapidly at the start of the reaction, but persists after all of the bromine solution has been added. The mixture is filtered, and the solvent is removed in a current of air. The residue is distilled under reduced pressure to give colorless, strongly lachrymatory ethyl α-bromo-β-phenyl-propionate 38 g. (80%), b.p. 155–159°/15 mm.

## Products Formed by the Simonini Reaction

Because the esters produced by the Simonini reaction are usually procured more easily by other procedures, the reaction has not been developed as a synthetic method. Consequently, no detailed procedure is available. The following example is typical of the experimental work on this reaction.

**Benzyl Phenylacetate.**[49] When 24.3 g. of silver phenylacetate and 12.7 g. of iodine are mixed in ether, an exothermic reaction sets in and the ether boils. The solvent is removed by distillation and the residue heated for one hour at 80°. The residue is extracted with ether from which 1.35 g. (10%) of phenylacetic acid and 9.35 g. (68%) of benzyl phenyl-acetate are obtained.

## Products Formed by the Prévost Reaction

**2-Iodocyclohexyl Acetate.**[21] To 8.2 g. (0.1 mole) of cyclohexene in ether is added 25.4 g. (0.1 mole) of iodine and 16.6 g. (0.1 mole) of silver acetate. An exothermic reaction ensues, and the ether begins to boil. The silver iodide formed in the reaction is removed by filtration, the solvent removed, and the residue fractionated. The product, 2-iodocyclohexyl acetate, obtained in 80% yield, boils at 120°/12 mm.

**3-Phenyl-1,2-propyleneglycol Dibenzoate.**[98] To 11.8 g. of allylbenzene in 300 ml. of dry benzene is added 45.8 g. of silver benzoate and 25.4 g. of iodine (or the corresponding amount of the silver benzoate-iodine complex). This mixture is heated under reflux for fifteen hours with the careful exclusion of moisture. The reaction mixture is cooled, the precipitated silver iodide removed by filtration, and the filtrate washed several times with aqueous sodium bicarbonate solution and finally with water. The solution is dried, the benzene removed, and the reddish-brown residue crystallized in an ice-salt bath. Trituration with petroleum ether is necessary to induce crystallization. The product is collected on a filter, washed with petroleum ether, and dried. The yield of crude product melting at 70–71° is 28.5 g. (85%). The pure product

melts at 74–75°.    Hydrolysis to the glycol in a yield of about 85% is effected with sodium hydroxide.

**1,2-Hexadecanediol.**[99]    Iodine (10.6 g.) in 100 ml. of dry benzene is added, with shaking, to a suspension of 26.5 g. of silver benzoate in 150 ml. of benzene.    To this solution is added, slowly and with shaking, 10.5 g. of 1-hexadecene in 50 ml. of benzene.    The mixture is heated under reflux for one hour, cooled, and filtered, and the filtrate freed of solvent.    The residual glycol dibenzoate is saponified by heating under reflux for three hours with 12 g. of potassium hydroxide in 75 ml. of ethanol and 25 ml. of water.    The glycol is recovered by pouring the hydrolysate into 500 ml. of hot water.    After cooling, the crude glycol is collected, recrystallized twice from methanol, then from ligroin (b.p. 60–70°), and finally from methanol to give 4 g. (33%) of 1,2-hexadecanediol, m.p. 73–73.6°.

By a similar procedure, 288 g. of 1-octadecene, 620 g. of silver benzoate, and 290 g. of iodine give 239 g. (73%) of 1,2-octadecanediol, m.p. 79–79.5°.

**2-Bromocyclohexyl Benzoate.**[22]    To a suspension of 11 g. of silver benzoate in 75 ml. of carbon tetrachloride cooled to –10° is added one-half of a solution of 7.3 g. of bromine in 18 ml. of carbon tetrachloride and one-half of a solution of 3.8. g of cyclohexene in 15 ml. of the same solvent. After ten or fifteen minutes, the remainder of the bromine and cyclohexene solutions is added.    The precipitate is removed by filtration and washed with carbon tetrachloride.    The combined filtrates are washed first with dilute aqueous sodium hydroxide to remove any benzoic acid and then with water.    The solution is dried over calcium chloride, the solvent is removed, and the residue is recrystallized from petroleum ether.    The product (42%) melts at 64–64.5°.

## Products Formed by Substitution Reactions of Acyl Hypohalites

**β-(2-Iodo-5-methoxyphenyl)propionic Acid.**    *Method* 1.[18]    To a stirred solution of 0.1 mole of β-(3-methoxyphenyl)propionic acid in 100 ml. of acetic acid there is added alternately, in small portions, 25.4 g. (0.1 mole) of powdered iodine and 16.6 g. (0.1 mole) of silver acetate. Iodination proceeds rapidly at room temperature.    The iodinated mixture is stirred for one hour at room temperature after the addition is complete, filtered, and the filtrate is diluted with water.    The oily product that separates is extracted with ether, the ether extracts are washed free of acetic acid, and the iodinated acid is purified by recrystallization from a mixture of chloroform and petroleum ether.    The product obtained in 80% yield melts at 109–110°.

*Method II.*[18]   To a suspension of 14.3 g. (0.05 mole) of silver β-(3-methoxyphenyl)propionate in 100 ml. of anhydrous carbon tetrachloride in a 500-ml. three-necked flask equipped with an efficient stirrer, there is added dropwise at room temperature 25.4 g. (0.1 mole) of iodine dissolved in carbon tetrachloride. The iodine reacts immediately and silver iodide precipitates. After the addition is complete, the mixture is stirred for one hour, the silver iodide is separated, and the solvent is removed under reduced pressure. The iodinated acid is purified by crystallization from chloroform-petroleum ether. The yield is 90%, m.p. 109–110°.

*p*-Diiodobenzene.[19]   A mixture of 12 ml. (0.11 mole) of iodobenzene and 4.4 g. (0.02 mole) of silver trifluoroacetate is heated to 100° in a small flask fitted with a condenser which is connected by rubber tubing to liquid air traps. The mixture is cooled to room temperature and 5.1 g. (0.02 mole) of powdered iodine is added. There is an immediate precipitation of silver iodide. The mixture is heated rapidly to 160°, cooled to room temperature, and filtered. The liquid air traps contain only a small amount of trifluoroacetic acid. Distillation of the solution gives 1.85 g. (80%) of trifluoroacetic acid, b.p. 71–72°, iodobenzene, b.p. 80°/12 mm., and 5.1 g. (77%) of *p*-diiodobenzene, which may be crystallized from ethanol as plates, m.p. 128°.

4-Iodoveratrole.[53a]   A mixture of 110 g. (0.5 mole) of silver trifluoroacetate and 69 g. (0.5 mole) of dry veratrole was placed in a dry, 1-l. flask equipped with stirrer and dropping funnel. A chloroform solution of iodine was prepared from 127 g. (0.5 mole) of iodine and about 750 ml. of chloroform. The chloroform solution was added during one-half hour, after which any undissolved iodine was added as the solid. (Alternatively, sufficient chloroform to dissolve the iodine, about 15 : 1, may be used.) After stirring for two hours, the mixture was filtered and the precipitate washed with 100 ml. of chloroform. The solvent was removed and the residue distilled. The yield of product boiling at 152–155°/15 mm. was 112 g. (85%). Redistillation gave a pale-yellow product, $n_D^{25}$ 1.6117, which after crystallization from ethanol melted at 34–35°.

## TABULAR SURVEY OF SILVER SALT-HALOGEN REACTIONS

In Tables I–XVII are listed all the examples of silver salt-halogen reactions that have been noted in a survey of the literature through 1954.* In general, the substances are arranged in increasing order of molecular weight. Most of the tables provide the following information: silver salt employed, solvent, main product of the reaction, yield, and reference. A separate column for the halogen used is not included since the formula of the product will make this clear.

* The bibliography in reference 2a covers the literature through June 1955.

## TABLE I

FORMATION OF ALKYL HALIDES FROM ALIPHATIC MONOCARBOXYLIC ACIDS

| Acid | Solvent | Main Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_3CO_2H$ | None | $CH_3Br$ | — | 56 |
| | None | $CH_3Br$ | 80 | 3 |
| | $CCl_4$ | $CH_3Br$ | 69 | 20 |
| $n\text{-}C_3H_7CO_2H$ | $C_6H_5NO_2$ | $n\text{-}C_3H_7Br$ | 61 | 20 |
| $n\text{-}C_4H_9CO_2H$ | $CS_2$ | $n\text{-}C_4H_9Br$ | 31 | 25 |
| $C_2H_5CH(CH_3)CO_2H$* | $C_6H_5NO_2$ | $C_2H_5CHClCH_3$ | 74 crude | 25 |
| | $CS_2$ | $C_2H_5CHBrCH_3$ | 14 | 25 |
| $(CH_3)_3CCO_2H$ | $CS_2$ | No definite products | | 25 |
| $(CH_3)_2CHCH_2CO_2H$ | $CS_2$ | $(CH_3)_2CHCH_2Br$ | 15 | 25 |
| $n\text{-}C_5H_{11}CO_2H$ | $CCl_4$ | $n\text{-}C_5H_{11}Br$ | 92† | 63 |
| $n\text{-}C_3H_7CH(CH_3)CO_2H$ | $CCl_4$ | $n\text{-}C_3H_7CHBrCH_3$ | 55–65 | 66 |
| $(C_2H_5)_2CHCO_2H$ | $CCl_4$ | $(C_2H_5)_2CHBr$ | 76 | 66 |
| $(CH_3)_2CHCH_2CH_2CO_2H$ | $CS_2$ | $(CH_3)_2CHCH_2CH_2Br$ | 42 | 25 |
| $(CH_3)_3CCH_2CO_2H$ | $C_6H_5NO_2$ | $(CH_3)_3CCH_2Br$ | 62 | 33 |
| | $CCl_4$ | $(CH_3)_3CCH_2Br$ | 83† | 63 |
| $n\text{-}C_7H_{15}CO_2H$ | $CCl_4$ | $n\text{-}C_7H_{15}Br$ | 79 | 30 |
| $n\text{-}C_4H_9CH(C_2H_5)CO_2H$‡ | $CCl_4$ | $n\text{-}C_4H_9CHBrC_2H_5$§ | 30–50 | 24, 26, 28 |

\* The (+) acid gives an optically inactive chloride.

† The yield is not based on pure isolated material, but on a quantitative determination of bromine present in the neutral fraction of the reaction product.

‡ The silver salt was added to bromine in carbon tetrachloride, the reverse of the normal addition.

§ Both optically active forms of the silver salt gave the optically inactive bromide. However, in reference 28 it is reported that the bromide from silver (+)-2-ethylhexanoate had some optical activity.

## TABLE I—*Continued*

FORMATION OF ALKYL HALIDES FROM ALIPHATIC MONOCARBOXYLIC ACIDS

| Acid | Solvent | Main Product | Yield, % | Reference |
|---|---|---|---|---|
| $n\text{-}C_{11}H_{23}CO_2H$ | $CCl_4$ | $n\text{-}C_{11}H_{23}Br$ | 59–80 | 3, 54, 55 |
| | $CHCl_3$ | $n\text{-}C_{11}H_{23}Br$ | 75–80 | 3 |
| | Pet. ether | $n\text{-}C_{11}H_{23}I$ | 51–65 | 8 |
| | $C_6H_6$ | $n\text{-}C_{11}H_{23}I$ | 72–87 | 8 |
| | $CCl_4$ | $n\text{-}C_{11}H_{23}I$ | 70–78 | 8 |
| $(i\text{-}C_5H_{11})_2CHCO_2H$ | $CCl_4$ | $(i\text{-}C_5H_{11})_2CHBr$ | 66† | 63 |
| $n\text{-}C_{13}H_{27}CO_2H$ | $CCl_4$ | $n\text{-}C_{13}H_{27}Br$ | 65–77; 70 | 55, 58 |
| | $CCl_4$ | $n\text{-}C_{13}H_{27}I$ | 51 | 87 |
| $n\text{-}C_{15}H_{31}CO_2H$ | $CCl_4$ | $n\text{-}C_{15}H_{31}Cl$ | 18 | 87 |
| | $C_2H_4Cl_2$ | $n\text{-}C_{15}H_{31}Cl$ | 30 | 87 |
| | $CCl_4$ | $n\text{-}C_{15}H_{31}Br$ | 70–80 | 3, 55, 87 |
| | $CCl_4$ | $n\text{-}C_{15}H_{31}I$ | 15–47 | 87 |
| $n\text{-}C_{17}H_{35}CO_2H$ | None | $n\text{-}C_{17}H_{35}Cl$ | Variable | 3 |
| | $CCl_4$ | $n\text{-}C_{17}H_{35}Br$ | 73–86; 89† | 55, 63 |
| | $CCl_4$ | $n\text{-}C_{17}H_{35}Br$ | 38 crude | 20 |
| | $CCl_4$ | $n\text{-}C_{17}H_{35}I$ | 60 | 87 |
| | $C_6H_6$ | $n\text{-}C_{17}H_{35}I$ | 65 | 8 |

† The yield is not based on pure isolated material, but on a quantitative determination of bromine present in the neutral fraction of the reaction mixture.

TABLE II

FORMATION OF ALKYL HALIDES FROM PHENYL-SUBSTITUTED CARBOXYLIC ACIDS
Unless otherwise indicated, the solvent was carbon tetrachloride.

| Acid | Main Product | Yield, % | Reference |
|---|---|---|---|
| $C_6H_5CH_2CO_2H$ | $C_6H_5CH_2Br$ | 54* | 63 |
| | $C_6H_5CH_2Br$ | 20–37† | 25 |
| $p\text{-}O_2NC_6H_4CH_2CO_2H$ | $p\text{-}O_2NC_6H_4CH_2Br$ | 85 | 16 |
| $(C_6H_5)_2CHCO_2H$ | $(C_6H_5)_2CHBr$ | 8 | 25 |
| $(C_6H_5)_3CCO_2H$ | $(C_6H_5)_3COH$ | 8 | 25 |
| $CH_3CH(C_6H_5)CO_2H$ | $CH_3CHBrC_6H_5$ | —‡ | 27 |
| $C_6H_5CH_2CH_2CO_2H$ | $C_6H_5CH_2CH_2Br$ | 5–15 | 16, 25 |
| $p\text{-}O_2NC_6H_4CH_2CH_2CO_2H$ | $p\text{-}O_2NC_6H_4CH_2CH_2Br$ | 80 | 16 |
| $C_6H_5CH_2CH(C_6H_5)CO_2H$ | $C_6H_5CHBrCHBrC_6H_5$ | 52 | 16 |
| $(+)\text{-}C_6H_5CH_2CH(C_2H_5)CO_2H$ | $(+,-)\text{-}C_6H_5CH_2CHBrC_2H_5$ | 17 | 26 |
| $(-)\text{-}C_6H_5CH_2CH(C_2H_5)CO_2H$ | $(+,-)\text{-}C_6H_5CH_2CHBrC_2H_5$ | — | 26 |
| $C_6H_5C{\equiv}CCO_2H$§ | $C_6H_5C{\equiv}CI$ | 94‖ | 49 |

* This yield is based on a quantitative determination of bromine present in the neutral fraction of the reaction mixture and not on pure isolated material.

† The silver salt was added to bromine in carbon tetrachloride, the reverse of the normal procedure.

‡ It was originally reported[27] that 1-bromo-1-phenylethane was obtained in 55% yield. Other chemists[83,85] could not obtain this product, and, in attempts to repeat their own work, the original workers have also reported failure;[28] no alkyl bromide was obtained.

§ Although no identifiable substances were isolated from the products resulting from the action of iodine on silver cinnamate or silver crotonate, silver phenyl-propiolate gave an excellent yield of the iodide. A small amount of triiodostyrene was formed simultaneously.

‖ The solvent used in this experiment was benzene.

## TABLE III

### FORMATION OF HALIDES AND/OR LACTONES FROM DICARBOXYLIC ACIDS

Unless otherwise indicated, the solvent was carbon tetrachloride.

| Acid | Main Product | Yield, % | Reference |
|---|---|---|---|
| $HO_2C(CH_2)_2CO_2H$* | $Br(CH_2)_2Br$ | 32–37† | 40, 85 |
| $HO_2C(CH_2)_3CO_2H$ | $\overline{OCCH_2CH_2CH_2O}$ | 69‡ | 63 |
| $HO_2CCH(C_2H_5)CO_2H$* | $C_2H_5CHBr_2$§ | 28 | 40 |
| $HO_2CCH_2CH(CH_3)CO_2H$ | $BrCH_2CHBrCH_3$ | 12 | 63 |
| $HO_2C(CH_2)_4CO_2H$ | $Br(CH_2)_4Br$ | Small | 20 |
| | $Br(CH_2)_4Br$ | 21 | 54 |
| | $Br(CH_2)_4Br$* | 58 | 84 |
| | $Br(CH_2)_4Br\|$ | 28 | 63 |
| $HO_2C(CH_2)_2CH(CH_3)CO_2H$ | $\overline{OCCH_2CH_2CH(CH_3)O}$¶ | 87‡ | 63 |
| $HO_2C(CH_2)_5CO_2H$ | $Br(CH_2)_6Br$ | 44 ‡ | 63 |
| $HO_2C(CH_2)_2C(CH_3)_2CO_2H$ | $\overline{OCCH_2CH_2C(CH_3)_2O}$¶ | 50‡ | 63 |
| $2\text{-}HO_2CC_6H_4CO_2H$ | $2\text{-}BrC_6H_4Br$ | 10 | 63 |
| $3\text{-}HO_2CC_6H_4CO_2H$ | $3\text{-}BrC_6H_4Br$** | 4 | 63 |
| $4\text{-}HO_2CC_6H_4CO_2H$ | | —** | 63 |
| $HO_2C(CH_2)_7CO_2H$ | $Br(CH_2)_7Br$ | 82‡ | 63 |
| $HO_2CCH_2CH(C_5H_{11}\text{-}i)CO_2H$ | $BrCH_2CHBrC_5H_{11}\text{-}i$ | 25‡ | 63 |
| $HO_2C(CH_2)_8CO_2H$ | $Br(CH_2)_8Br$ | 62–81 | 3, 54, 63 |
| $HO_2C(CH_2)_2CH(C_5H_{11}\text{-}i)CO_2H$ | $\overline{OCCH_2CH_2CH(C_5H_{11}\text{-}i)O}$¶ | 60‡ | 63 |
| $HO_2CC(CH_2)_3CH(C_5H_{11}\text{-}i)CO_2H$ | $Br(CH_2)_3CHBrC_5H_{11}\text{-}i\|$ | 33‡ | 63 |
| $HO_2C(CH_2)_{10}CO_2H$ | $Br(CH_2)_{10}Br$ | 60 | 3 |
| $HO_2C(CH_2)_{14}CO_2H$ | $Br(CH_2)_{14}Br$ | 44 | 54 |
| $C_6H_5CH(CO_2H)CH(CO_2H)C_6H_5$ | $C_6H_5CHBrCHBrC_6H_5$†† | High | 26 |
| $HO_2C(CH_2)_2CH(CO_2H)CH_2CO_2H$* | $Br(CH_2)_2CHBrCH_2Br$ | 4–6 | 40 |

* The silver salt was added to bromine in carbon tetrachloride, the reverse of the normal procedure.

† No yield was reported when *sym*-tetrachloroethane was used as the solvent.[40]

‡ The yield is not based on isolated material, but on a quantitative determination of the halogen present in the neutral fraction of the reaction mixture.

§ A 24% yield of 1,1,1-tribromopropane was also obtained.

‖ A lactone was also formed.

¶ The halogen used was bromine; small quantities (3–15%) of the dibromides were also formed.

** A large percentage of the silver salt was recovered.

†† Both stereoisomers were obtained, "chiefly the *meso*-dibromide" with "about 15% of *dl*-isomer."

## TABLE IV

### FORMATION OF HALO ESTERS FROM ACID ESTERS

Unless otherwise indicated, the solvent was carbon tetrachloride.

| Silver Salt of Acid | Main Product | Yield, % | Reference |
|---|---|---|---|
| $CH_3O_2C(CH_2)_4CO_2H$ | $CH_3O_2C(CH_2)_4Br$ | 65–68 | 4, 60, 61 |
| $CH_3O_2C(CH_2)_6CO_2H$ | $CH_3O_2C(CH_2)_6Br$ | 70 | 4 |
| $CH_3O_2C(CH_2)_7CO_2H$ | $CH_3O_2C(CH_2)_7Br$ | 70 | 4 |
| $CH_3O_2C(CH_2)_8CO_2H$ | $CH_3O_2C(CH_2)_8Br$ | 75 | 3, 4 |
| $CH_3O_2C(CH_2)_9CO_2H$ | $CH_3O_2C(CH_2)_9Br$ | 71 | 3, 4 |
| $CH_3O_2C(CH_2)_{11}CO_2H$ | $CH_3O_2C(CH_2)_{11}Br$ | 78 | 4 |
| $CH_3O_2C(CH_2)_{12}CO_2H$ | $CH_3O_2C(CH_2)_{12}Br$ | 71 | 4 |
| $CH_3O_2C(CH_2)_{13}CO_2H$ | $CH_3O_2C(CH_2)_{13}Br$ | 73 | 4 |
| $CH_3O_2C(CH_2)_{14}CO_2H$ | $CH_3O_2C(CH_2)_{14}Br$ | 70 (65–70) | 4, 62 |
|  | $CH_3O_2C(CH_2)_{14}Br$ | 78–85* | 62 |
| $CH_3O_2C(CH_2)_{15}CO_2H$ | $CH_3O_2C(CH_2)_{15}Br$ | 70 | 4 |
| $CH_3O_2C(CH_2)_{16}CO_2H$ | $CH_3O_2C(CH_2)_{16}Br$ | 75 | 4 |

$$
\begin{array}{c}
CH_2\!-\!CH_2 \\
\diagup \qquad \diagdown \\
CH_2 \qquad\quad CHCO_2C_2H_5 \\
\diagdown \qquad \diagup \\
CH_2\!-\!CHCO_2H
\end{array}
\qquad
\begin{array}{c}
CH_2\!-\!CH_2 \\
\diagup \qquad \diagdown \\
CH_2 \qquad\quad CHCO_2C_2H_5 \\
\diagdown \qquad \diagup \\
CH_2\!-\!CHBr
\end{array}
\qquad 68\text{–}72 \qquad 5
$$

* The solvent in this experiment was trichloroethylene.

## TABLE V

### FORMATION OF ALKYL HALIDES FROM POLYHALO AND PERFLUORO ACIDS*

| Acid | Product | Yield, % | Reference |
|---|---|---|---|
| $CH_2FCO_2H$ | $CH_2FCl$ | 52 | 73 |
| | $CH_2FBr$ | 62 | 73 |
| | $CH_2FI$ | 55 | 73 |
| $CHFClCO_2H$ | $CHFCl_2$ | 73 | 73 |
| | $CHFClBr$ | 67 | 73 |
| | $CHFClI$ | 35 | 73 |
| $CHFBrCO_2H$ | $CHFBrCl$ | 67 | 73 |
| | $CHFBr_2$ | 64 | 73 |
| | $CHFBrI$ | 19 | 73 |
| $CHFICO_2H$ | $CHFI_2$ | 18 | 73 |
| $CHF_2CO_2H$ | $CHF_2Cl$ | 91 | 73 |
| | $CHF_2Br$ | 88–93 | 73 |
| | $CHF_2I$ | 93 | 73 |
| $CFClBrCO_2H$ | $CFCl_2Br$ | 63 | 73 |
| | $CFClBr_2$ | 71 | 73 |
| $CFCl_2CO_2H$ $\}$ mixture $CHFClCO_2H$ | $CFCl_3$ | 63 | 73 |
| | $CHFCl_2$ | 78 | 73 |
| | $CFCl_2Br$ | 58 | 73 |
| | $CHFClBr$ | 61 | 73 |
| | $CFCl_2I$ | 10 | 73 |
| | $CHFClI$ | 29 | 73 |
| $CF_2BrCO_2H$ | $CF_2Br_2$ | 81 | 73 |
| $CF_2ClCO_2H$ | $CF_2Cl_2$ | 88 | 73 |
| | $CF_2ClBr$ | 91 | 73 |
| | $CF_2ClI$ | 78 | 73 |
| $CCl_3CO_2H$ | — | — | 49 |

* Unless otherwise specified, the reactions with chlorine and bromine were carried out in sealed tubes or in a steel autoclave without a solvent; with iodine an intimate mixture of the halogen and silver salt was heated in an open flask.

TABLE V—*Continued*

FORMATION OF ALKYL HALIDES FROM POLYHALO
AND PERFLUORO ACIDS
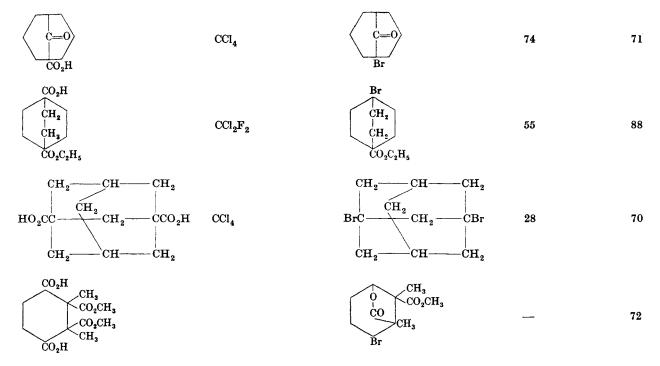
| Acid | Product | Yield, % | Reference |
|---|---|---|---|
| $CF_3CO_2H$ | $CF_3Cl$ | 90; 88 | 78, 79 |
| | $CF_3Br$ | 88; 98 | 78, 79 |
| | $CF_3I$ | 87–95 | 74, 77, 78 |
| $C_2F_5CO_2H$ | $C_2F_5Cl$ | 94; 83 | 73, 79 |
| | $C_2F_5Br$ | 98; 98 | 73, 79 |
| | $C_2F_5I$ | 94; 86 | 73, 74 |
| $n\text{-}C_3F_7CO_2H$ | $n\text{-}C_3F_7Cl$ | 91; 71 | 73, 79 |
| | $n\text{-}C_3F_7Br$ | 97; 95 | 73, 79 |
| | $n\text{-}C_3F_7I$ | 90; 86–93 | 73, 74, 80 |
| $n\text{-}C_4F_9CO_2H$ | $n\text{-}C_4F_9Cl$ | 89 | 73 |
| | $n\text{-}C_4F_9Br$ | 95 | 73 |
| | $n\text{-}C_4F_9I$ | 89 | 73 |
| $n\text{-}C_5F_{11}CO_2H$ | $n\text{-}C_5F_{11}Cl$ | 85; 71 | 73, 75 |
| | $n\text{-}C_5F_{11}Br$ | 91; 83 | 73, 75 |
| | $n\text{-}C_5F_{11}I$ | 89; 74 | 73, 75 |
| $n\text{-}C_6F_{13}CO_2H$ | $n\text{-}C_6F_{13}Cl$ | 83 | 73 |
| | $n\text{-}C_6F_{13}Br$ | 90 | 73 |
| | $n\text{-}C_6F_{13}I$ | 90 | 73 |
| $n\text{-}C_7F_{15}CO_2H$ | $n\text{-}C_7F_{15}Cl$ | 80 | 73 |
| | $n\text{-}C_7F_{15}Br$ | 86 | 73 |
| | $n\text{-}C_7F_{15}I$ | 85 | 73 |
| $HO_2C(CF_2)_3CO_2H$ | $Cl(CF_2)_3Cl$ | 64 | 86 |
| | $Br(CF_2)_3Br$ | 80 | 86 |
| | $I(CF_2)_3I$ | 18† | 74, 86 |

$$\begin{matrix} & CF_2\text{—}CF_2 & \\ \diagup & & \diagdown \\ CF_2 & & CFCO_2H \\ \diagdown & & \diagup \\ & CF_2\text{—}CF_2 & \end{matrix}$$

| | $C_6F_{11}Br‡$ | 54 | 76 |
|---|---|---|---|
| | $C_6F_{11}I‡$ | 63 | 76 |

† The main product of the reaction is perfluorobutyrolactone.
‡ Perfluorotributylamine was used as a solvent.

TABLE VI

FORMATION OF ALICYCLIC BROMIDES FROM ALICYCLIC CARBOXYLIC ACIDS

| Acid | Solvent | Main Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_2CH_2CHCO_2H$ | $C_2H_2Cl_2$ | $CH_2CH_2CHBr$* | 15–20 | 67 |
| | $CCl_2F_2$ | $CH_2CH_2CHBr$ | 53 | 67 |
| $CH_2(CH_2)_2CHCO_2H$ | $CCl_4$, $CF_2Cl_2$ | $CH_2(CH_2)_2CHBr$*† | 50, 57 | 35, 48 |
| $CH_2(CH_2)_3CHCO_2H$ | $CCl_4$ | $CH_2(CH_2)_3CHBr$ | 73–80 | 5 |
| $CH_2(CH_2)_4CHCO_2H$ | $CCl_4$ | $CH_2(CH_2)_4CHCl$ | 70 | 5 |
| | $CCl_4$ | $CH_2(CH_2)_4CHBr$ | 73–80; 57 | 5, 63 |
| $CH_2(CH_2)_5CHCO_2H$ | $CCl_4$ | $CH_2(CH_2)_5CHBr$ | 80 | 5 |
| cyclohexane-$CH_2$-$CO_2H$ | $CCl_4$ | cyclohexane-$CH_2$-$Br$ | 55 | 69 |
| cyclohexane ($CO_2H$, $H_3CCCH_3$) | Pet. ether | $Br$ | 50‡ | 37 |
| | $CCl_4$ (high temp.) | $H_3CCCH_3$ | 58‡ | 37 |
| | $CCl_4$ (low temp.) | | 60‡ | 37 |
| cyclohexane-$CH_2$-$CH_2$-$CO_2H$ | — | cyclohexane-$CH_2$-$CH_2$-$Br$ | — | 68, 69 |

| | | | | |
|---|---|---|---|---|
| cyclohexane ($C{=}O$, $CO_2H$) | $CCl_4$ | cyclohexane ($C{=}O$, $Br$) | 74 | 71 |
| cyclohexane ($CO_2H$, $CH_2$, $CH_2$, $CO_2C_2H_5$) | $CCl_2F_2$ | cyclohexane ($Br$, $CH_2$, $CH_2$, $CO_2C_2H_5$) | 55 | 88 |
| bicyclic ($HO_2CC$, $CH_2$, $CH$, $CH_2$, $CCO_2H$, $CH_2$, $CH$, $CH_2$) | $CCl_4$ | bicyclic ($BrC$, $CH_2$, $CH$, $CH_2$, $CBr$, $CH_2$, $CH$, $CH_2$) | 28 | 70 |
| cyclohexane ($CO_2H$, $CH_3$, $CO_2CH_3$, $CO_2CH_3$, $CH_3$, $CO_2H$) | | lactone ($CH_3$, $CO_2CH_3$, $CO$, $O$, $CH_3$, $Br$) | — | 72 |

* The silver salt was added to the bromine in the solvent at −25 to −35°, the reverse of the normal addition.
† This reaction has also been run with the mercuric salt. See Table IX.
‡ The products are mixtures of chloro- and bromo-apocamphane. Attempts at separation failed.

## TABLE VII

### FORMATION OF ARYL HALIDES FROM AROMATIC CARBOXYLIC ACIDS*

| Substituents in Aromatic Acid (Benzoic) | Substituents in Aryl Bromide (Bromobenzene) | Yield, % | Reference |
|---|---|---|---|
| None | None | 14–18 | 16, 20 |
| None | None | 46–80 | 17, 20, 63 |
| 2-Chloro | 2-Chloro | 38 | 16 |
| | | 46 | 17 |
| 3-Chloro | 3-Chloro | 44 | 16 |
| 4-Chloro | 4-Chloro | 55 | 16 |
| 2-Nitro | 2-Nitro | 95, 71 | 16, 63 |
| 3-Nitro | 3-Nitro | 89 | 16 |
| | | 68 | 17 |
| 4-Nitro | 4-Nitro | 79 | 16 |
| 3-Methyl | 3-Methyl† | 27 | 17 |
| 4-Methyl | 4-Methyl‡ | 17 | 16 |
| 3-Methoxy | 2-Carboxy-4-methoxy | 50 | 17 |
| 4-Methoxy | 3-Bromo-4-methoxy§ | 19–23 | 16 |
| 3-Bromo-4-methoxy | 3-Bromo-4-methoxy | 92 | 16 |

* In all the reactions recorded in this table carbon tetrachloride was used as the solvent.

† 3,4-Dibromotoluene was also obtained in 13% yield.

‡ The principal product was 3-bromo-*p*-toluic acid, obtained in 66% yield.

§ The principal product was 3-bromo-4-methoxybenzoic acid, obtained in 73% yield.

TABLE VIII

FORMATION OF SUBSTITUTED ALKYL HALIDES OR THEIR DECOMPOSITION PRODUCTS
FROM SUBSTITUTED MONOCARBOXYLIC ACIDS

| Acid | Solvent | Product | Yield, % | Reference |
|---|---|---|---|---|
| | | *A. Hydroxy Acids* | | |
| $C_6H_5CHOHCO_2H$ | $(C_2H_5)_2O$ | $C_6H_5CHO$ | Variable | 3 |
| $n\text{-}C_{14}H_{29}CHOHCO_2H$ | None | $n\text{-}C_{14}H_{29}CHO$ | — | 3 |
| | | *B. Halogen Acids* | | |
| $BrCH_2CH_2CO_2H$* | $CCl_4$ | $Br(CH_2)_2Br$ | 69 | 40 |
| $CH_3(CH_2)_2CHBrCO_2H$* | $CCl_4$ | $CH_3(CH_2)_2CHBr_2$ | 52 | 40 |
| $n\text{-}C_{16}H_{33}CHBrCO_2H$ | $CCl_4$ | $n\text{-}C_{16}H_{33}CHBr_2$ | 70–75 crude | 3 |
| $n\text{-}C_8H_{17}(CHCl)_2(CH_2)_7CO_2H$ | $CCl_4$ | $n\text{-}C_8H_{17}(CHCl)_2(CH_2)_7Br$ | 76 crude | 3 |
| $n\text{-}C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7CO_2H$* | $CCl_4$ | $n\text{-}C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7Br$ | — | 59 |
| | | *C. Keto Acids* | | |
| $CH_3COCO_2H$ | $CCl_4$ | $CH_3COBr$ | — | 3 |
| $CH_3CO(CH_2)_7CO_2H$ | $CCl_4$ | $CH_3CO(CH_2)_7Br$ | 39† | 63 |
| | | *D. Amino Acids‡* | | |
| $CH_3CH(NHCOC_6H_5)CO_2H$ | $CH_3CO_2H$ | $CH_3CH(NHCOC_6H_5)Br$ | Variable | 81 |
| $n\text{-}C_4H_9CH(NHCOCH_3)CO_2H$ | $(C_2H_5)_2O$ | $n\text{-}C_4H_9CH(NHCOCH_3)Br$ | Variable | 81 |
| $n\text{-}C_4H_9CH(NHCOC_6H_5)CO_2H$ | $CCl_4$ | $n\text{-}C_4H_9CH(NHCOC_6H_5)Br$ | Variable | 81 |
| $C_6H_5CH_2CH(NHCOC_6H_5)CO_2H$ | $CH_3CO_2H$ | $C_6H_5CH_2CH(NHCOC_6H_5)Br$ | Variable | 81 |

* The dry silver salt was added to the halogen in carbon tetrachloride at a low temperature.

† The yield is not based on isolated material, but on a quantitative determination of the halogen present in the neutral fraction of the reaction mixture.

‡ The substituted alkyl halides formed from acylated amino acids are highly hygroscopic materials which decompose in water with the formation of aldehyde, amide, and hydrogen bromide. The yields of aldehyde isolated through the dinitrophenylhydrazone are variable (20–45%).

TABLE VIII—*Continued*

FORMATION OF SUBSTITUTED ALKYL HALIDES OR THEIR DECOMPOSITION PRODUCTS
FROM SUBSTITUTED MONOCARBOXYLIC ACIDS

*E. Alicyclic Acetic Acid*

| | | | | |
|---|---|---|---|---|
| $CH_2CH_2CH_2CH_2CHCH_2CO_2H$ | $CCl_4$ | $CH_2CH_2CH_2CH_2CHCH_2Br$ | 67–73 | 5 |

*F. Bile Acids*

| Substituents in Acid | | | | Solvent | Substituents in Product | | | | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| R = | R′ = | R″ = | R‴ = | | R = | R′ = | R″ = | R‴ = | | |
| $CH_3CO_2$ | H | H | $CO_2H$ | $C_2H_5Br$ | $CH_3CO_2$ | H | H | Br | Very poor | 65 |
| $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)CO_2H$ | $CCl_4$ | $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)Br$ | 65 | 64 |
| $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)CH_2CO_2H$ | $CCl_4$ | $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)CH_2Br$ | 40 | 64 |
| H | H | H | $CH(CH_3)CH_2CH_2CO_2H$ | $C_2H_5Br$ | H | H | H | $CH(CH_3)CH_2CH_2Br$ | 89 | 65a |
| $CH_3CO_2$ | H | H | $CH(CH_3)CH_2CH_2CO_2H$ | $C_2H_5Br$ | $CH_3CO_2$ | H | H | $CH(CH_3)CH_2CH_2Br$ | 60 | 65a |
| $CH_3CO_2$ | H | O | $CH(CH_3)CH_2CH_2CO_2H$ | $CCl_4$ | $CH_3CO_2$ | H | O | $CH(CH_3)CH_2CH_2Br$ | 60 | 64 |
| $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)CH_2CH_2CO_2H$ | $CCl_4$ | $CH_3CO_2$ | H | $CH_3CO_2$ | $CH(CH_3)CH_2CH_2Br$ | 25 | 64 |
| | | | | $C_2H_5Br$ | | | | | — | 65a |
| $CH_3CO_2$ | $CH_3CO_2$ | H | $CH(CH_3)CH_2CH_2CO_2H$ | $C_2H_5Br$ | $CH_3CO_2$ | $CH_3CO_2$ | H | $CH(CH_3)CH_2CH_2Br$ | — | 65a |
| $CH_3CO_2$ | $CH_3CO_2$ | $CH_3CO_2$ | $CH(CH_3)CH_2CH_2CO_2H$ | $C_2H_5Br$ | {2OH, 1$CH_3CO_2$} | | | $CH(CH_3)CH_2CH_2Br$ | Poor | 65 |
| | | | | $C_2H_5Br$ | | | | | —§ | 65a |

§ The product was amorphous.

## TABLE IX

### FORMATION OF HALOGEN COMPOUNDS BY THE ACTION OF HALOGEN ON VARIOUS METALLIC SALTS OF CARBOXYLIC ACIDS

| Acid | Salt | Solvent | Product | Yield, % | Reference |
|------|------|---------|---------|----------|-----------|
| $HOCH_2CO_2H$ | $Hg^{++}$ | $CS_2$ | $CH_2O$ | 60–80 | 3 |
| $CF_3CO_2H$ | $Na^*$ | None | $CF_3I$ | 58–61 | 78 |
| | $K^*$ | None | $CF_3I$ | 40 | 73, 78 |
| | $Ba^*$ | None | $CF_3I$ | 32 | 78 |
| | $Hg^{++}*$ | None | $CF_3I$ | 35 | 78 |
| | $Pb^*$ | None | $CF_3I$ | 26 | 73, 78 |
| $\overline{CH_2(CH_2)_2}CHCO_2H$ | $Hg^{++}$ | $CS_2$ | $\overline{CH_2(CH_2)_2}CHBr$ | 45 | 5 |
| $C_2H_5O_2CCH_2CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCH_2Br$ | 23 | 82 |
| $n\text{-}C_6H_{13}CO_2H$ | $Tl^+$ | $CCl_4$ | $n\text{-}C_6H_{13}Cl$ | High | 3 |
| | $Tl^+$ | $CCl_4$ | $n\text{-}C_6H_{13}Br$ | 100 | 3 |
| $C_2H_5O_2CCH(C_2H_5)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHClC_2H_5$ | 41 | 83 |
| | $K$ | $CCl_4$ | $C_2H_5O_2CCHBrC_2H_5$ | 36 | 82 |
| $n\text{-}C_7H_{15}CO_2H$ | $K$ | $CCl_4$ | $n\text{-}C_7H_{15}Br$ | 45 | 4 |
| | $Hg^+$ | $CCl_4$ | $n\text{-}C_7H_{15}Br$ | 60 | 3 |
| | $Hg^+$ | $CS_2$ | $n\text{-}C_7H_{15}Br$ | 75 | 3, 4 |
| $C_2H_5O_2CCH(C_3H_7\text{-}i)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHBrC_3H_7\text{-}i$ | 30 | 82 |
| $C_2H_5O_2CCH(C_4H_9\text{-}n)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHClC_4H_9\text{-}n$ | 52 | 83 |
| | | | $C_2H_5O_2CCHBrC_4H_9\text{-}n$ | 67 | 82 |
| $C_2H_5O_2CCH(C_6H_{13}\text{-}n)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHClC_6H_{13}\text{-}n$ | 54 | 83 |
| $C_2H_5O_2CCH(C_6H_{11})CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHBrC_6H_{11}$ | 45 | 82 |
| $C_2H_5O_2CCH(CH_2C_6H_5)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHBrCH_2C_6H_5$ | 80 | 82 |
| $C_2H_5O_2CCH(C_8H_{17}\text{-}n)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHClC_8H_{17}\text{-}n$ | 20 | 83 |
| $C_2H_5O_2CCH(C_{10}H_{21}\text{-}n)CO_2H$ | $K$ | $CCl_4$ | $C_2H_5O_2CCHClC_{10}H_{21}\text{-}n$ | 16 | 83 |
| $n\text{-}C_{15}H_{31}CO_2H$ | $Hg^{++}$ | $CCl_4$ | $n\text{-}C_{15}H_{31}Br$ | 60–70 | 3 |

* The reaction was carried out in a steel autoclave at 270°.

TABLE X

FORMATION OF ESTERS BY THE ACTION OF IODINE ON THE SILVER SALTS OF MONOCARBOXYLIC ACIDS

| Acid | Diluent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_3CO_2H$ | None | $CH_3CO_2CH_3$ | — | 6, 7, 49 |
| $n\text{-}C_3H_7CO_2H$ | $C_6H_5NO_2$ | $n\text{-}C_3H_7CO_2C_3H_7\text{-}n$ | — | 7, 20 |
| $CH_2CH_2CH_2CHCO_2H$ | None | $CH_2CH_2CH_2CHCO_2CHCH_2CH_2CH_2$ | 10* | 44, 48 |
| $n\text{-}C_5H_{11}CO_2H$ | Quartz | $n\text{-}C_5H_{11}CO_2C_5H_{11}\text{-}n$ | 71 | 6, 7, 49 |
| $C_2H_5O_2C(CH_2)_2CO_2H$ | Quartz | $C_2H_5O_2C(CH_2)_2CO_2(CH_2)_2CO_2C_2H_5$ | — | 49 |
| $C_6H_5CO_2H$ | Quartz | $C_6H_5CO_2C_6H_5 + C_6H_5I$ | — | 49 |
| $C_2H_5CH_2CO_2H$ | $(C_2H_5)_2O$ | $C_6H_5CH_2CO_2CH_2C_6H_5$ | 68 | 49 |
| $n\text{-}C_{13}H_{27}CO_2H$ | $CCl_4$ | $n\text{-}C_{13}H_{27}CO_2C_{13}H_{27}\text{-}n$† | 27 | 87 |
| $n\text{-}C_{15}H_{31}CO_2H$ | None | $n\text{-}C_{15}H_{31}CO_2C_{15}H_{31}\text{-}n$ | — | 7, 45, 46 |
| | Porcelain | $n\text{-}C_{15}H_{31}CO_2C_{15}H_{31}\text{-}n$ | — | 47 |
| | $CCl_4$ | $n\text{-}C_{15}H_{31}CO_2C_{15}H_{31}\text{-}n$ | 20–40‡ | 87 |
| $n\text{-}C_{17}H_{35}CO_2H$ | None | $n\text{-}C_{17}H_{35}CO_2C_{17}H_{35}\text{-}n$ | 50–70 | 87 |
| | Porcelain | $n\text{-}C_{17}H_{35}CO_2C_{17}H_{35}\text{-}n$ | — | 42, 45, 46 |
| | $CCl_4$ | $n\text{-}C_{17}H_{35}CO_2C_{17}H_{35}\text{-}n$ | 23§ | 87 |
| $(C_6H_5)_3CCO_2H$ | $C_6H_6$ | $(C_6H_5)_3CCO_2C(C_6H_5)_3$ | 83 | 49 |
| $n\text{-}C_{31}H_{63}CO_2H$ | None | $n\text{-}C_{31}H_{63}CO_2C_{31}H_{63}\text{-}n$ | — | 46 |

* The yield of ester originally reported was 34%,[44] but this was shown to be a mixture containing 32% of cyclobutyl cyclobutanecarboxylate.[48]

† Two equivalents of iodine were used; 51% of the product was $n\text{-}C_{13}H_{27}I$.

‡ The percentage yield of ester increased as the amount of iodine was decreased from two to one equivalent.

§ Two equivalents of iodine were used; 60% of the product was $n\text{-}C_{17}H_{35}I$.

## TABLE XI

### FORMATION OF ALDEHYDES AND KETONES BY THE ACTION OF IODINE ON THE SILVER SALTS OF HYDROXY ACIDS

| Acid | Diluent | Product | Yield, % | Reference |
|------|---------|---------|----------|-----------|
| $HOCH_2CO_2H$ | $C_2H_5OH$ | $CH_2O$* | — | 49, 89 |
| $CH_2OHCHOHCO_2H$ | Quartz | $CH_2O$* | — | 89 |
| $CH_3CHOHCO_2H$ | $C_2H_5OH$ | $CH_3CHO$* | — | 49, 89 |
| $C_6H_5CHOHCO_2H$ | $(C_2H_5)_2O$ | $C_6H_5CHO$ | 60† | 49, 89 |
| $(CH_3)_2C(OH)CO_2H$ | $C_2H_5OH$ | $(CH_3)_2CO$* | — | 89 |
| $(C_6H_5)_2C(OH)CO_2H$ | $C_6H_6$ | $C_6H_5COC_6H_5$* | — | 49 |

* This material was identified as one product of the reaction mixture; no yields were recorded.

† The product was contaminated with benzene which was the solvent used in one case.[49]

## TABLE XII

FORMATION OF LACTONES OR ANHYDRIDES BY THE ACTION OF IODINE ON SILVER SALTS OF DICARBOXYLIC ACIDS

| Acid | Diluent | Products | Yield, % | Reference |
|---|---|---|---|---|
| Oxalic | Quartz | $CO_2$ | 98 | 43, 49 |
| Malonic | Quartz | — | — | 43, 49 |
| Succinic | Quartz | $CO_2$; maleic anhydride | — | 43, 49 |
| Fumaric | Quartz | $CO_2$; fumaric acid | — | 49 |
| Maleic | Quartz | Maleic anhydride | — | 49 |
| Glutaric | Quartz | $\overline{CH_2CH_2CH_2COO}$ | 30 | 49, 91 |
| Adipic | Quartz | $\overline{CH_2(CH_2)_3COO}$ | Small | 49 |
| $(CH_3)_2C(CH_2CO_2H)_2$ | Quartz | $\overline{(CH_3)_2CCH_2COOCH_2}$ | 40 | 91 |
| $HO_2CCH_2CH_2CH(C_2H_5)CO_2H$ | Quartz | $\overline{C_2H_5CHCH_2CH_2COO}$ | — | 91 |

For the cyclobutane/cyclopentane dicarboxylic acid entries (Sand/None diluent), the products are the corresponding bicyclic lactones:

| Acid | Diluent | Products | Yield, % | Reference |
|---|---|---|---|---|
| $\begin{array}{c} CH_2-CHCO_2H \\ CH_2 \quad CH_2 \ (cis) \\ CH_2-CHCO_2H \end{array}$ | Sand | $\begin{array}{c} CH_2-CH-CO \\ CH_2 \quad CH_2 \quad | \\ CH_2-CH-O \end{array}$ | 30 | 92 |
| Phthalic | None | Phthalic anhydride | 84 | 49 |
| $HO_2CCH(C_2H_5)CH_2CH(C_2H_5)CO_2H$ | Sand | $\overline{C_2H_5CHCH_2CH(C_2H_5)COO}$ | — | 91 |

| Acid | Diluent | Products | Yield, % | Reference |
|---|---|---|---|---|
| $\begin{array}{c} CH_2-CH_2 \\ CH_2 \quad CHCO_2H \ (cis)* \\ CH_2-CHCH_2CO_2H \end{array}$ | Sand | $\begin{array}{c} CH_2-CH_2 \\ CH_2 \quad CH-CO \\ \quad\quad\quad\quad O \\ CH_2-CH-CH_2 \end{array}$ | 26 | 49, 92 |
| $\begin{array}{c} CH_2-CH_2 \\ CH_2 \quad C(CH_2CO_2H)_2 \\ CH_2-CH_2 \end{array}$ | None | $\begin{array}{c} CH_2-CH_2 \quad CH_2CO \\ CH_2 \quad C \quad\quad | \\ CH_2-CH_2 \quad CH_2O \end{array}$ | — | 92 |
| $\begin{array}{c} CH_2-CHCO_2H \\ H_3CCCH_3 \\ CH_2-CCO_2H \\ \quad CH_3 \end{array}$ | Sand | $\begin{array}{c} CH_2-CH-CO \\ H_3CCCH_3 \\ CH_2-C-O \\ \quad CH_3 \end{array}$ | — | 92 |
| $\begin{array}{c} CH_2-CH_2 \\ H_3CCH \quad C(CH_2CO_2H)_2 \\ CH_2-CH_2 \end{array}$ | None | $\begin{array}{c} CH_2-CH_2 \quad CH_2CO \\ H_3CCH \quad C \quad | \\ CH_2-CH_2 \quad CH_2O \end{array}$ | 16 | 93 |

* The trans-isomer also gave the cis-lactone, but in a smaller yield.

## TABLE XIII

### Addition of Acyl Hypohalites to Olefins

The acyl hypohalite was prepared from the silver salt of the acid and halogen and was used without isolation.
Exceptions to this statement are indicated by footnotes.

| Olefin | Acyl Hypohalite | Solvent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| Ethylene | $C_6H_5CO_2I$ | $C_6H_6$ | Ethanediol dibenzoate | Good | 10 |
| | $3,5\text{-}(NO_2)_2C_6H_3CO_2I*$ | $(C_2H_5)_2O$ | 2-Iodoethyl 3,5-dinitrobenzoate | — | 96 |
| Propene | $C_6H_5CO_2I$ | $C_6H_6$ | 1,2-Propanediol dibenzoate | Good | 10 |
| | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | 1-Iodo-2-propyl 3,5-dinitro-benzoate | — | 96 |
| Allyl chloride | $CH_3CO_2Cl$ | $CCl_4$ | 2,3-Dichloropropyl acetate | 48 | 20 |
| Allyl bromide | $CH_3CO_2Br$ | $CCl_4$ | 2,3-Dibromopropyl acetate | — | 97 |
| | $C_4H_9CO_2Br$ | $CCl_4$ | 2,3-Dibromopropyl butyrate | 85 | 97 |
| | $C_6H_5CO_2Br$ | $CCl_4$ | 2,3-Dibromopropyl benzoate | — | 97 |
| 1-Butene | $3,5\text{-}(NO_2)_2C_6H_3CO_2Cl$ | $CHCl_3$ | 1-Chloro-2-butyl 3,5-dinitro-benzoate | — | 96 |
| | $3,5\text{-}(NO_2)_2C_6H_3CO_2Br$ | $CHCl_3$ | 1-Bromo-2-butyl 3,5-dinitro-benzoate | — | 96 |
| | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | 1-Iodo-2-butyl 3,5-dinitrobenzoate | — | 96 |
| cis-2-Butene | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | threo-3-Iodo-2-butyl 3,5-dinitro-benzoate | — | 96 |
| trans-2-Butene | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | erythro-3-Iodo-2-butyl 3,5-dinitro-benzoate | — | 96 |
| Isobutene | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | 1-Iodo-2-methyl-2-propyl 3,5-dinitrobenzoate | — | 96 |
| Butadiene | $C_6H_5CO_2I†$ | $C_6H_6$ | 1,2,3,4-Butanetetrol tetrabenzoate | 60 | 11 |
| | $C_6H_5CO_2I‡$ | $C_6H_6$ | 1-Butene-3,4-diol | 80 | 11 |
| | | | 2-Butene-1,4-diol | 4 | |
| 1-Pentene | $CH_3CO_2I$ | $C_6H_6$ | 1,2-Pentanediol diacetate | Good | 10 |
| | $C_6H_5CO_2I$ | $C_6H_6$ | 1,2-Pentanediol dibenzoate | Good | 10 |
| | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | I-Iodo-2-pentyl 3,5-dinitro-benzoate | — | 96 |
| Cyclopentene | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | 2-Iodocyclopentyl 3,5-dinitro-benzoate | — | 96 |
| 1-Hexene | $3,5\text{-}(NO_2)_2C_6H_3CO_2I$ | $(C_2H_5)_2O$ | 1-Iodo-2-hexyl 3,5-dinitro-benzoate | — | 96 |
| Cyclohexene | $CH_3CO_2Br$ | $CCl_4$ | 2-Bromocyclohexyl acetate | 32 | 22 |
| | $CH_3CO_2I§$ | $(C_2H_5)_2O$ | 2-Iodocyclohexyl acetate | 80 | 21, 94 |
| | $C_2H_5CO_2Br$ | $CHCl_3; \ C_5H_5N$ | 2-Bromocyclohexyl propionate | 48 | 22 |
| | $n\text{-}C_3H_7CO_2Br$ | $CHCl_3 + C_5H_5N$ | 2-Bromocyclohexyl n-butyrate | 47 | 22 |
| | | $CCl_4$ | 2-Bromocyclohexyl n-butyrate‖ | 50 | 20 |
| | $C_6H_5CO_2Cl$ | $CCl_4$ | 2-Chlorocyclohexyl benzoate | Good | 14, 22 |
| | $C_2H_5CO_2Br$ | $CCl_4$ | 2-Bromocyclohexyl benzoate | 40–42 | 20, 22 |
| | | $CCl_4$ | 2-Bromocyclohexyl benzoate | Good | 14 |
| | $C_6H_5CO_2I$ | $(C_2H_5)_2O; \ CCl_4$ | 2-Iodocyclohexyl benzoate | 60 | 14, 21 |
| | | $C_6H_6$ | (+, −)-trans-1,2-Cyclohexanediol dibenzoate | 44 | 101 |

* This reagent was used to identify olefins;[96] no yields were recorded though they are presumably high.
† A large excess of the complex and additional silver benzoate were employed.
‡ A limited quantity of the complex was employed.
§ Mercuric rather than silver acetate was used.
‖ Some dibromocyclohexane was formed simultaneously.

TABLE XIII—*Continued*

| Olefin | Acyl Hypohalite | Solvent | Product | Yield, % | Reference |
|---|---|---|---|---|---|
| Cyclohexene (*Contd.*) | | | | | |
| | $m$-NO$_2$C$_6$H$_4$CO$_2$Br | CCl$_4$ | 2-Bromocyclohexyl $m$-nitro-benzoate | 44 | 22 |
| | 3,5-(NO$_2$)$_2$C$_6$H$_3$CO$_2$Br | C$_6$H$_6$ | (+,−)-*trans*-2-Bromocyclohexyl 3,5-dinitrobenzoate | 27 | 101 |
| | | C$_6$H$_6$ | (+,−)-*trans*-1,2-Cyclohexanediol bis-3,5-dinitrobenzoate | 10 | 101 |
| | 3,5-(NO$_2$)$_2$C$_6$H$_3$CO$_2$I | (C$_2$H$_5$)$_2$O | 2-Iodocyclohexyl 3,5-dinitro-benzoate | — | 96 |
| | CO$_3$I$_2$ | (C$_2$H$_5$)$_2$O | Di-2-iodocyclohexyl carbonate | 80 | 95 |
| | IO$_2$CCO$_2$I | (C$_2$H$_5$)$_2$O | Di-2-iodocyclohexyl oxalate | — | 95 |
| | IO$_2$C(CH$_2$)$_2$CO$_2$I | (C$_2$H$_5$)$_2$O | Di-2-iodocyclohexyl succinate | 50 | 95 |
| | $o$-C$_6$H$_4$(CO$_2$I)$_2$ | (C$_2$H$_5$)$_2$O | Di-2-iodocyclohexyl phthalate | 60 | 95 |
| 1,5-Hexadiene | C$_3$H$_5$CO$_2$Br | C$_6$H$_6$ | 1,2,5,6-Hexanetetrol tetrabenzoate | — | 10 |
| 2,4-Hexadiene | CH$_3$CO$_2$I | C$_6$H$_6$ | Syrup; mixture of diacetates | — | 10, 11 |
| 1,4-Cyclohexadiene | C$_6$H$_5$CO$_2$Br | C$_6$H$_6$ | +,−)-*trans*-4,5-Cyclohexenediol dibenzoate | 37 | 101 |
| | | C$_6$H$_6$ | (1,4)R-1,2,4,5-Cyclohexanetetrol tetrabenzoate | 11 | 101 |
| 1-Heptene | 3,5-(NO$_2$)$_2$C$_6$H$_3$CO$_2$I | (C$_2$H$_5$)$_2$O | 1-Iodo-2-heptyl 3,5-dinitro-benzoate | — | 96 |
| Styrene | CH$_3$CO$_2$Br | CCl$_4$ | 2-Bromo-1-phenylethyl acetate | 60 | 51 |
| | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | Phenylethanediol dibenzoate | Good | 10 |
| | (+)-C$_4$H$_9$CH(C$_2$H$_5$)CO$_2$Br | CCl$_4$ | (+)-2-Bromo-1-phenylethyl 2-ethylhexanoate | 60 | 51 |
| | (−)-C$_4$H$_9$CH(C$_2$H$_5$)CO$_2$Br | CCl$_4$ | (−)-2-Bromo-1-phenylethyl 2-ethylhexanoate | 35 | 51 |
| Allylbenzene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 3-Phenyl-1,2-propanediol dibenzoate | 85 | 98 |
| 1-Phenylbutadiene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | Syrup; mixture of isomers | — | 11 |
| *trans*-Stilbene | C$_6$H$_5$CO$_2$Br | C$_6$H$_6$ | 1,2-Diphenylethanediol dibenzoate | Good | 10 |
| | | C$_6$H$_6$ | 2-Bromo-1,2-diphenylethyl benzoate | Good | 10 |
| 1,1-Diphenyl-ethylene | CH$_3$CO$_2$Br | C$_6$H$_6$ | 1,1-Diphenylethanediol diacetate | Good | 10 |
| | C$_6$H$_5$CO$_2$X | C$_6$H$_6$ | 1,1-Diphenylethanediol dibenzoate | Good | 10 |
| 1-Hexadecene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 1,2-Hexadecanediol dibenzoate¶ | 33 | 99 |
| $\beta$-Hydroxymethyl-styrene benzoate | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 1-Phenylglycerol tribenzoate | Good | 9 |
| 1-Octadecene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 1,2-Octadecanediol dibenzoate¶ | 73 | 99 |
| 1-Eicosene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 1,2-Eicosanediol dibenzoate¶ | 70 | 99 |
| 15-$m$-Hydroxy-phenyl-7-penta-decene | C$_6$H$_5$CO$_2$I | C$_6$H$_6$ | 15-(2-Iodo-5-hydroxyphenyl)-7,8-pentadecanediol dibenzoate | — | 100 |

¶ The yield recorded is based on the diol obtained.

TABLE XIV

NUCLEAR HALOGENATION WITHOUT DECARBOXYLATION BY THE ACTION OF HALOGEN ON SILVER SALTS OF ACIDS

| Acid | Solvent | Product | Yield, % | Reference |
|------|---------|---------|----------|-----------|
| $C_6H_5CO_2H$ | — | $3\text{-}BrC_6H_4CO_2H$ | — | 102 |
| | — | $3\text{-}IC_6H_4CO_2H$ | — | 15 |
| $2\text{-}HOC_6H_4CO_2H$ | — | $?\text{-}I_2\text{-}2\text{-}HOC_6H_2CO_2H$ | — | 15 |
| $3\text{-}CH_3OC_6H_4CO_2H$ | $CCl_4$ | $2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3CO_2H$ | 50 | 17 |
| $4\text{-}CH_3OC_6H_4CO_2H$ | $CCl_4$ | $3\text{-}Br\text{-}4\text{-}CH_3OC_6H_3CO_2H$ | 73–78 | 16 |
| $4\text{-}CH_3C_6H_4CO_2H$ | $CCl_4$ | $3\text{-}Br\text{-}4\text{-}CH_3C_6H_3CO_2H$ | 66 | 16 |
| $3\text{-}CH_3OC_6H_4(CH_2)_2CO_2H$ | $CCl_4$ | $2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$ | 88 | 18 |
| | $CCl_4$ | $2\text{-}I\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$ | 90 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_4CO_2H$ | $CCl_4$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_4CO_2H$ | 84 | 18 |

TABLE XV

NUCLEAR HALOGENATION OF AROMATIC SUBSTANCES BY THE ACTION OF SILVER ACETATE AND HALOGEN

| Aromatic Substance | Solvent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $CH_3OC_6H_5$ | $CCl_4$ | $4\text{-}BrC_6H_4OCH_3$ | 20 | 17 |
| $4\text{-}CH_3OC_6H_4CH_2CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3CH_2CO_2H$ | 82 | 18 |
| $3\text{-}CH_3OC_6H_4(CH_2)_2CO_2H$ | $CH_3CO_2H$ | $2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$ | 82 | 18 |
| | $CH_3CO_2H$ | $2\text{-}I\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$ | 84 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_3CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_3CO_2H$ | 86 | 18 |
| $4\text{-}C_2H_5OC_6H_4(CH_2)_3CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_3CO_2H$ | 80 | 18 |
| $3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_3CO_2H$ | $CH_3CO_2H$ | $?\text{-}I\text{-}3,4(CH_3O)_2C_6H_2(CH_2)_3CO_2H$ | 8I | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_4CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_4CO_2H$ | 80 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_5CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_5CO_2H$ | 84 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_9CO_2H$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_9CO_2H$ | 76 | 18 |
| $3\text{-}CH_3\text{-}4\text{-}CH_3OC_6H_3(CH_2)_3CO_2C_2H_5$ | $CH_3CO_2H$ | $3\text{-}I\text{-}5\ CH_3\text{-}4\text{-}CH_3OC_6H_2(CH_2)_3CO_2C_2H_5$ | 74 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_5CO_2C_2H_5$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_5CO_2C_2H_5$ | 88 | 18 |
| $2,5\text{-}(CH_3)_2C_6H_3(CH_2)_9CO_2C_2H_5$ | $CH_3CO_2H$ | $4\text{-}I\text{-}2,5\text{-}(CH_3)_2C_6H_2(CH_2)_9CO_2C_2H_5$ | 56 | 18 |
| $4\text{-}CH_3OC_6H_4(CH_2)_9CO_2C_2H_5$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_9CO_2C_2H_5$ | 76 | 18 |
| $4\text{-}C_2H_5OC_6H_4(CH_2)_9CO_2C_2H_5$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_9CO_2C_2H_5$ | 78 | 18 |
| $4\text{-}C_2H_5OC_6H_4(CH_2)_{10}CO_2C_2H_5$ | $CH_3CO_2H$ | $3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_{10}CO_2C_2H_5$ | 60 | 18 |

TABLE XVI

NUCLEAR HALOGENATION OF AROMATIC SUBSTANCES BY THE ACTION OF SILVER TRIFLUOROACETATE AND HALOGEN

| Aromatic Substance | Solvent | Product | Yield, % | Reference |
|---|---|---|---|---|
| $C_6H_6$ | None | $C_6H_5Br$ | 89 | 19 |
| | None | $C_6H_5I$* | 85 | 19 |
| $C_6H_5CH_3$ | $CCl_4$ | $4\text{-}BrC_6H_4CH_3$ | 73 | 52 |
| | None | $4\text{-}BrC_6H_4CH_3$ | 90 | 19 |
| | $CCl_4$ | $4\text{-}IC_6H_4CH_3$ | 84 | 52 |
| | None | $4\text{-}IC_6H_4CH_3$ | 88 | 19 |
| $C_6H_5Cl$ | None | $4\text{-}BrC_6H_4Cl$† | 58 | 19 |
| | None | $4\text{-}IC_6H_4Cl$† | 62 | 19 |
| $C_6H_5Br$ | None | $4\text{-}BrC_6H_4Br$† | 65 | 19 |
| | None | $4\text{-}IC_6H_4Br$ | 71 | 19 |
| $C_6H_5I$ | None | $4\text{-}BrC_6H_4I$ | 85 | 19 |
| | None | $4\text{-}IC_6H_4I$ | 77 | 19 |
| $C_6H_5OCH_3$ | None | $4\text{-}BrC_6H_4OCH_3$ | 76 | 19 |
| | None | $4\text{-}IC_6H_4OCH_3$ | 75 | 19 |
| $C_6H_4(OCH_3)_2\text{-}o$ | $CHCl_3$ | 4-Iodoveratrole | 85 | 53a |
| $C_6H_5NH_2$ | None | $4\text{-}BrC_6H_4NH_2$ | 62 | 19 |
| | None | $4\text{-}IC_6H_4NH_2$ | 51 | 19 |
| $C_6H_5N(CH_3)_2$ | None | $4\text{-}IC_6H_4N(CH_3)_2$ | 41 | 19 |
| $C_6H_5NO_2$ | None | $3\text{-}BrC_6H_4NO_2$‡ | 19 | 19 |
| | None | $CF_3I$§ | 75 | 19 |
| $C_6H_5CO_2H$ | $C_6H_5NO_2$ | $3\text{-}BrC_6H_4CO_2H$ | 61 | 19 |
| | $C_6H_5NO_2$ | $3\text{-}IC_6H_4CO_2H$‖ | 84 | 19 |
| 2-Methylnaphthalene | $(C_2H_5)_2O$ | 1-Bromo-2-methylnaphthalene | 60 | 52 |
| Thiophene | None | 2,5-Diiodothiophene | — | 19 |

* Six per cent of diiodobenzene was also formed.

† The infrared absorption indicates the presence of *ortho* derivative.

‡ Twenty-one per cent of $CF_3Br$ was also formed.

§ No 3-iodonitrobenzene was formed.

‖ The infrared absorption shows no *ortho* or *para* derivative.

## TABLE XVII

FORMATION OF HALOACETYLENES BY THE ACTION OF SILVER
BENZOATE AND HALOGEN ON ACETYLENES

| Acetylene | Acylhypohalite (or Simonini Complex) | Solvent | Product | Yield | Reference |
|---|---|---|---|---|---|
| $HC{\equiv}CH$ | $(C_6H_5CO_2)_2AgI$ | $C_6H_6$ | $HC{\equiv}CI$ | — | 12 |
| | $2(C_6H_5CO_2)_2AgI$ | $C_6H_6$ | $IC{\equiv}CI$ | — | 12 |
| $n\text{-}C_5H_{11}C{\equiv}CH$ | $C_6H_5CO_2Cl$ | $CCl_4$ | $C_5H_{11}C{\equiv}CCl$ | Good | 14 |
| | $C_6H_5CO_2Br$ | $CCl_4$ | $C_5H_{11}C{\equiv}CBr$ | Good | 14 |
| | $C_6H_5CO_2I$ | $CCl_4$ | $C_5H_{11}C{\equiv}CI$ | Good | 14 |
| $C_6H_5C{\equiv}CH$ | $(C_6H_5CO_2)_2AgI$ | $C_6H_6$ | $C_6H_5C{\equiv}CI$ | Quant. | 12 |

# CHAPTER 6

# THE SYNTHESIS OF β-LACTAMS

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## CONTENTS

## INTRODUCTION

The four-membered ring appears to be the smallest cyclic system that is capable of accommodating the amide function as a constituent. Such four-membered, cyclic amides (I), commonly referred to as β-lactams,[1] possess physical and chemical properties that diverge sharply, partially

$$\begin{array}{ccc} & \overset{\alpha}{\underset{|3}{C}}\!\!-\!\!-\!\!-\!\!\overset{}{\underset{2|}{C}}\!\!=\!\!O & \\ & | & | \\ & \underset{|4}{|} & \underset{1|}{|} \\ & \underset{\beta}{C}\!\!-\!\!-\!\!-\!\!N\!\!- & \end{array}$$

I

as a result of ring strain, from those of acyclic amides and lactams of greater ring size. Thus, in common with β-lactones and cyclobutanone derivatives, the simple β-lactams are unusually susceptible to reactions involving the carbonyl group and generally undergo facile ring cleavage. In addition, each of these small-ring systems presents considerable difficulty in synthesis. The reluctance with which β-lactams are formed, using the conventional methods of lactam synthesis, has necessitated the development of special and unique approaches to these compounds.

No authentic β-lactams were known until the beginning of the present century, probably because their synthesis by the method commonly used for γ-lactam formation, i.e. thermal dehydration of the appropriate amino acids, had not been realized. The first β-lactams were prepared by Staudinger and his co-workers,[2] using two highly novel methods which were discovered in connection with their studies on the chemistry of ketenes. During the twenty-odd years between the completion of Staudinger's work and 1943, two additional syntheses of β-lactams were discovered, and thereafter several more.

After 1943 interest in the synthesis and chemistry of β-lactams was stimulated by the importance of the natural penicillins and the problem of their structure and synthesis. When it became apparent that the natural penicillins might possess the β-lactam ring as a key feature, intensive studies were made of β-lactams, especially those possibly related

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[1] β-Lactams may also be named as keto derivatives of the parent saturated heterocycle azetidine, i.e. as 2-azetidinones. This system of nomenclature has been used widely, cf. C.A., **38**, 7061 (1944), and will be followed here in the naming of monocyclic β-lactams.

[2] Staudinger, *Die Ketene*, F. Enke, Stuttgart, 1912.

to the penicillins.   Early evidence in favor of the now accepted $\beta$-lactam-thiazolidine structure for the penicillins came from the investigation of the infrared absorption of the penicillins (II) and model $\beta$-lactams such as III.

$$
\begin{array}{ccc}
 & S & \\
 & \diagup\!\!\diagdown & \\
\text{RCONHCH---CH} & & \text{C(CH}_3)_2 \\
| \quad\quad | & & | \\
\text{CO---N} & \!\!\!\!\text{---CHCO}_2\text{H} & \\
\end{array}
\qquad\qquad
\begin{array}{ccc}
 & \text{C}_6\text{H}_5 & \\
 & | \;\; S & \\
 & \diagup\!\!\diagdown & \\
(\text{C}_6\text{H}_5)_2\text{C}\!\!-\!\!-\!\!-\!\!\text{C} & & \text{CH}_2 \\
| \quad\quad | & & | \\
\text{CO---N} & \!\!\!\!\text{---CH}_2 & \\
\end{array}
$$

<div align="center">II                       III</div>

After the $\beta$-lactam-thiazolidine formulation for the penicillins became generally accepted, it was realized that the known routes to $\beta$-lactams probably were inadequate for a practical synthesis of penicillin (II, R = $\text{C}_6\text{H}_5\text{CH}_2$). This fact, coupled with the curious differences in the chemical properties (rate of formation, and reactivity toward certain reagents) of various $\beta$-lactams, has provoked continued research and interest in the field of the $\beta$-lactams.

Although there are at present several useful approaches to the $\beta$-lactam ring system, the synthesis of $\beta$-lactams by a single general method is not possible.   Therefore, it is always necessary in problems of $\beta$-lactam synthesis to determine which of the available methods is best suited for the case at hand.   In general, the preparation of $\beta$-lactams is more readily accomplished if the lactam being formed is highly substituted. These highly substituted $\beta$-lactams are usually more stable to ring-cleavage reactions than are the simpler $\beta$-lactams.   The method of synthesis of these stable, easily formed $\beta$-lactams is commonly determined by the availability of the starting materials.

The problem of the synthesis of the less stable, highly reactive $\beta$-lactams, e.g. a penicillin, is much more difficult.   Usually a number of the standard synthetic approaches to $\beta$-lactams are excluded at the outset because the necessary starting materials are unstable or cannot be prepared readily.   Of the remaining methods, only those that involve mild reaction conditions, and hence highly reactive starting materials, present much likelihood of success.   Thus, the outstanding problem in $\beta$-lactam synthesis is the development of new and efficient routes to the less stable $\beta$-lactams.

In principle, the synthesis of the $\beta$-lactam ring system might be accomplished by the formation of one, two, three, or all four bonds of the ring during the cyclization step.   Of these four possibilities all but the last have been realized.   All presently known routes to $\beta$-lactams in which only one bond is formed during cyclization involve formation of the amide linkage or the $C_\alpha$ to $C_\beta$ bond.   The known syntheses of $\beta$-lactams that create two bonds all entail simultaneous formation of the same two bonds

i.e. carbonyl to nitrogen and $C_\alpha$ to $C_\beta$. The only reported synthesis in which three bonds are established simultaneously involves formation of all but the amide bond, and it is this route, as might be expected, that is the least general.

### CYCLIZATION OF $\beta$-AMINO ACID DERIVATIVES

As mentioned earlier, the thermal dehydration of $\beta$-amino acids to $\beta$-lactams has not as yet been achieved, partly because of the ease with which $\beta$-amino acids undergo $\beta$-elimination. However, a number of $\beta$-lactams have been formed from derivatives of $\beta$-amino acids. In particular, it is noteworthy that acyl derivatives of many $\beta$-amino acids are transformed into $\beta$-lactams in good yield by heating.[3] The reaction may be illustrated by the formation of 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (V) from the N-isobutyryl derivative IV in 50–60% yield.[3]

$$(CH_3)_2C-CO_2H$$
$$C_6H_5CH-NCOCH(CH_3)_2 \quad \rightarrow \quad$$
$$CH_2C_6H_5$$
$$IV$$

$$(CH_3)_2C-CO$$
$$H_5C_6CH-NCH_2C_6H_5 \quad + \quad (CH_3)_2CHCO_2H$$
$$V$$

This synthesis of $\beta$-lactams from $\beta$-acylamino acids was discovered by Staudinger[3] in connection with his studies of the reaction of ketenes with imines (which also leads to $\beta$-lactams). The ketene-imine reaction often affords piperidinediones, instead of, or in addition to, $\beta$-lactams, by the combination of one molecule of imine with two of the ketene, as shown below. In these cases the $\beta$-lactam can frequently be prepared indirectly.

$$R_2C=NR' + 2R''C=C=O \rightarrow O=C \begin{matrix} R_2''C-C=O \\ \diagdown \\ NR' \\ \diagup \\ R_2''C-CR_2 \end{matrix} \xrightarrow{H_2O} HO_2C \begin{matrix} R_2''CH-C=O \\ \diagdown \\ NR' \\ \diagup \\ R_2''C-CR_2 \end{matrix}$$

Hydrolysis of the piperidinediones proceeds readily and yields the $\beta$-acylamino acids, which can subsequently be cyclized to $\beta$-lactams. This three-step method is applicable not only to the preparation of monocyclic $\beta$-lactams but also to certain fused $\beta$-lactam-thiazolidines such as VI.[4]

$$(CH_3)_2C-C\begin{matrix} C_6H_5 \\ | \\ S \end{matrix}CH_2$$
$$CO-N-CH_2$$
$$VI$$

---

[3] Staudinger, Klever, and Kober, *Ann.*, **374**, 1 (1910).
[4] Clarke, Johnson, and Robinson, *The Chemistry of Penicillin*, Princeton University Press, 1949.

The relatively facile formation of $\beta$-lactams by this route may be due to the possibility of closing the $\beta$-lactam ring by O to N acyl rearrangement of an intermediate hydroxylactone, such as VII, in the formation of IV. Such a reaction path would explain the function of the acyl group in promoting cyclization.

$$
\begin{array}{c}
(CH_3)_2C\text{----}C{=}O \\
H_5C_6CH \quad \diagdown \quad O \\
N\text{----}CCH(CH_3)_2 \\
\mid \qquad \mid \\
C_6H_5CH_2 \quad OH \\
VII
\end{array}
$$

The cyclization of $\beta$-amino acids through the use of reagents such as acetyl chloride, phosphorus trichloride, and thionyl chloride has been accomplished in a limited number of cases. Thus $\beta$-benzylamino-$\beta$-phenyl-$\alpha,\alpha$-dimethylpropionic acid (VIII)[3] and $\beta$-phenyl-$\beta$-anilinopropionic acid (IX)[5] have been transformed into the corresponding $\beta$-lactams by treatment with acetyl chloride and phosphorus trichloride, respectively.

$$
\begin{array}{ll}
C_6H_5CHC(CH_3)_2CO_2H & \qquad C_6H_5CHCH_2CO_2H \\
\mid & \qquad\qquad \mid \\
NHCH_2C_6H_5 & \qquad\qquad NHC_6H_5 \\
\quad VIII & \qquad\qquad\quad IX
\end{array}
$$

An example of a cyclization of the above type is the synthesis of a phthaloylpenicillin (XI) from the corresponding phthaloylpenicilloic acid (X) in 12% yield by means of thionyl chloride.[6]  It is interesting also to note

$$
\begin{array}{ccc}
\overset{S}{\diagup\phantom{X}\diagdown} & & \overset{S}{\diagup\phantom{X}\diagdown} \\
XCH\text{---}CH \quad C(CH_3)_2 & & XCH\text{---}CH \quad C(CH_3)_2 \\
\mid \qquad \mid \qquad \mid & \rightarrow & \mid \qquad \mid \qquad \mid \\
HO_2C \quad HN\text{----}CHCO_2R & & CO\text{---}N\text{----}CHCO_2R
\end{array}
$$

X, X = phthalimido
    R = CH₃
XII, X = phenylacetamido
    R = H

XI, X = phthalimido
    R = CH₃
XIII, X = phenylacetamido
    R = H

that benzylpenicilloic acid (XII) has been converted in trace yield to benzylpenicillin (XIII)[7] using phosphorus trichloride.

Another variant of the route to $\beta$-lactams via $\beta$-amino acid derivatives is due to Breckpot.[8]  This synthesis, which involves the base-catalyzed cyclization of a $\beta$-amino acid ester using a Grignard reagent as the base, is illustrated by the synthesis of 1-ethyl-4-methyl-2-azetidinone (XIV).

[5] Ref. 4, p. 975.
[6] Sheehan, Henery-Logan, and Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953).
[7] Süs, *Ann.*, **571**, 201 (1951).
[8] Breckpot, *Bull soc. chim. Belg.*, **32**, 412 (1923).

The method is especially advantageous if there are only one or two substituents on the $\beta$-lactam ring being formed, or if the substituents are alkyl groups.

$$\begin{array}{ccc} \text{CH}_3\text{CH}-\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 & \xrightarrow[40\%]{\text{C}_2\text{H}_5\text{MgBr}} & \text{H}_3\text{CCH}-\text{CH}_2 \\ | & & | \qquad | \\ \text{C}_2\text{H}_5\text{NH} & & \text{H}_5\text{C}_2\text{N}\text{---}\text{CO} \\ & & \text{XIV} \end{array}$$

A large number of monocyclic $\beta$-lactams,[8-11] including 2-azetidinone itself,[11] have been synthesized by this method. The yields of $\beta$-lactam decrease markedly as the number of substituents on the $\beta$-lactam ring being formed decreases, but the method is frequently operable in instances where others fail. The yields obtained for a series of $\beta$-lactams possessing two, one, or no substituents are indicated below.

| Compound: | $\begin{array}{c} \text{H}_5\text{C}_6\text{CH}\text{---}\text{CO} \\ \quad\mid \qquad\quad\mid \\ \text{CH}_2\text{---}\text{NC}_6\text{H}_5 \end{array}$ | $\begin{array}{c} \text{CH}_2\text{---}\text{CO} \\ \mid \qquad\quad\mid \\ \text{H}_3\text{CCH}\text{---}\text{NC}_2\text{H}_5 \end{array}$ | $\begin{array}{c} \text{CH}_2\text{---}\text{CO} \\ \mid \qquad\quad\mid \\ \text{CH}_2\text{---}\text{NCH}_3 \end{array}$ | $\begin{array}{c} \text{CH}_2\text{---}\text{CO} \\ \mid \qquad\quad\mid \\ \text{CH}_2\text{---}\text{NH} \end{array}$ |
|---|---|---|---|---|
| Yield, %: | 94 | 40 | 11 | 0.76 |

### Experimental Procedures

**3,3-Dimethyl-1-ethyl-4-phenyl-2-azetidinone (Cyclization of a $\beta$-Acylamino Acid).**[4] (*a*) *1-Ethyl-6-phenyl-3,3,5,5-tetramethyl-2,4-piperidinedione.* To 5.6 g. of N-benzylideneëthylamine (prepared from benzaldehyde and ethylamine) in an atmosphere of nitrogen is added a solution of 5.9 g. of dimethylketene[12] in 60 ml. of ethyl acetate. The solution becomes colorless after about six hours and is stored at room temperature for an additional fourteen hours. The ethyl acetate is removed under reduced pressure, leaving a crystalline residue weighing 8.08 g. Recrystallization from benzene-petroleum ether gives a 43% yield of colorless crystals of the piperidinedione, m.p. 89–90°.

(*b*) *N-Isobutyryl-$\beta$-ethylamino-$\beta$-phenyl-$\alpha,\alpha$-dimethylpropionic Acid.* A suspension of 7 g. of the crude piperidinedione is heated to reflux for thirty minutes with 25 ml. of 10% aqueous sodium carbonate solution. The cooled solution is extracted with ether and acidified, and the precipitate of N-isobutyryl-$\beta$-ethylamino-$\beta$-phenyl-$\alpha,\alpha$-dimethylpropionic acid is collected by filtration; the yield is 7.0 g. (93%). Recrystallization from methanol affords material of m.p. 114–114.5°.

(*c*) *3.3-Dimethyl-1-ethyl-4-phenyl-2-azetidinone.* A 6.3-g. sample of the acid is heated in a small Claisen flask to 160–170° at 20 mm. for about an

[9] Ref. 4, p. 976.

[10] Holley and Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).

[11] Holley and Holley, *J. Am. Chem. Soc.*, **71**, 2129 (1949).

[12] Approximately 10% solutions of dimethylketene in ethyl acetate can be prepared in 50% yield by adding $\alpha$-bromoisobutyryl bromide dropwise to zinc wool in ethyl acetate under a positive pressure of nitrogen.

hour (until bubbling stops). During this time 1.9 g. of isobutyric acid is collected. The pressure is reduced, and the product is distilled at 92–100°/2 mm., yielding 3.8 g. (87%) of the azetidinone.

**1,4-Diphenyl-2-azetidinone (Cyclization of a β-Amino Acid).[4]** A mixture of 1.2 g. of β-anilino-β-phenylpropionic acid and 2.4 ml. of phosphorus trichloride is refluxed for one-half hour. The reagent is then removed as completely as possible under reduced pressure, and the gummy residue is triturated with two 15-ml. portions of water and crystallized from cold methanol. The yield of β-lactam, m.p. 154–155°, is 0.6 g. (53%).

**1-Benzyl-4-phenyl-2-azetidinone (Cyclization of a β-Amino Acid Ester).[10]** To a solution of 8.01 g. of ethyl β-benzylaminohydrocinnamate[10] in 70 ml. of dry ether is added 14 ml. of a 2N solution of ethylmagnesium bromide in ether as rapidly as the evolution of gases permits. The mixture that results is allowed to stand at room temperature for ninety minutes and is then decomposed by cautious addition of an éxcess of 10% aqueous ammonium chloride. The mixture is agitated until all the solid dissolves, and the ethereal solution is separated and washed with two small portions of water. The aqueous washes are extracted with ether, and the ethereal solutions are combined, dried, and evaporated to constant weight.

The neutralization equivalent of the residual oil is determined by titration with standard hydrochloric acid. From the neutralization equivalent, the amount of standard (ca. 4N) ethanolic hydrogen chloride required to neutralize the free amino groups is added to the oil. Most of the ethanol is removed by evaporation under reduced pressure. The residue is triturated with 25 ml. of ether, and the ethereal solution is separated from the hydrochloride by filtration. The filtrate is evaporated, and the residue is extracted with boiling ligroin. The ligroin is evaporated from the extracts, and the liquid remaining is distilled. The yield of slightly yellow 1-benzyl-4-phenyl-2-azetidinone, b.p. 145–150°/2 mm., is 3.0 g. (45%).

### REACTION OF IMINES WITH α-BROMOESTERS AND ZINC

In 1943 it was discovered that the reaction of benzylideneaniline with ethyl bromoacetate and zinc produces a β-lactam, 1,4-diphenyl-2-azetidinone (XV), in 56% yield.[13] Little work has been done to determine

$$C_6H_5CH{=}NC_6H_5 + BrZnCH_2CO_2C_2H_5 \rightarrow$$

$$\begin{array}{cc} H_2C\!\!-\!\!-\!\!CO \\ | \quad\quad | \\ H_5C_6CH\!\!-\!\!NC_6H_5 \\ \text{XV} \end{array}$$

[13] Gilman and Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

the scope of this synthesis although a number of β-lactams have been prepared by this method in yields as high as 85%.[4,13]   There is a strong resemblance between this reaction and that discovered by Breckpot in that both probably proceed by nucleophilic attack of an intermediate amide ion on the carbalkoxyl function with displacement of alkoxide ion and simultaneous closure of the β-lactam ring.

## Experimental Procedure

**1,4-Diphenyl-2-azetidinone.**[13]   A solution of 36.2 g. of benzylidene-aniline in 200 ml. of dry toluene is heated to boiling with 13.5 g. of sandpapered zinc foil and a crystal of iodine.   Three milliliters of ethyl bromoacetate is added, and on stirring an exothermic reaction sets in. An additional 20 ml. of the bromoester is added at a rate such as to maintain gentle refluxing.   When the addition is complete, the mixture is heated to reflux for one-half hour.   The reaction mixture is hydrolyzed with 200 ml. of concentrated ammonium hydroxide, and the toluene layer is separated, washed successively with water, dilute hydrochloric acid, sodium bisulfite solution, and water, and finally evaporated to dryness.   Two recrystallizations of the residue from methanol afford the β-lactam, m.p. 153–154°, in 56% yield.

### DIRECT COMBINATION OF KETENES WITH IMINES

The reaction of ketenes, in particular disubstituted or "ketoketenes," with imines provides a good route to some types of substituted mono- and bi-cyclic β-lactams.   Diphenylketene, for example, reacts readily with benzylideneaniline at room temperature to yield the crystalline β-lactam, 1,3,3,4-tetraphenyl-2-azetidinone (XVI) in 72% yield.[14] This was the first known β-lactam.[15]   Most of the β-lactams prepared by

$$(C_6H_5)_2C{=}C{=}O + C_6H_5CH{=}NC_6H_5 \rightarrow (C_6H_5)_2C\text{——}CO$$
$$H_5C_6CH\text{—}NC_6H_5$$
$$\text{XVI}$$

this method have been made from dimethyl-[2,16,17] or diphenyl-ketene,[2,14,18] which seem in general to react smoothly with Schiff bases derived from

[14] Staudinger, *Ann.*, **356**, 51 (1907).
[15] None of the substances that had been previously reported as β-lactams in the literature really appears to possess the β-lactam structure.   These cases are discussed in ref. 4, pp. 982–984.
[16] Staudinger and Klever, *Ber.*, **40**, 1149 (1907).
[17] Holley and Holley, *J. Am. Chem. Soc.*, **73**, 3172 (1951).
[18] Staudinger and Jelagin, *Ber.*, **44**, 365 (1911).

aromatic aldehydes or ketones and aromatic amines.  Other ketenes which have been used in this synthesis include diethylketene,[19] ethylcarbethoxy-ketene,[2,20]   phenylcarbomethoxyketene,[20]   methylphenylketene,[2]   2,2-biphenyleneketene,[2] and ketene itself.[20]  The order of reactivity for several of these ketenes toward benzophenoneanil has been determined by Staudinger to be as shown below.  This order of reactivity parallels

$$C{=}C{=}O > (C_6H_5)_2C{=}C{=}O > C_6H_5(CH_3)C{=}C{=}O \cong (CH_3)_2C{=}C{=}O$$

that observed by Staudinger in the reaction of ketenes with benzyl alcohol.[2]   Ketene itself is much less reactive than the substituted ketenes which have been studied, for the coupling of ketene with benzylidene-aniline takes place only at temperatures near 200°.[20]

The successful use of monosubstituted ketenes, "aldoketenes," in the synthesis of β-lactams has yet to be reported.  This is not surprising because monosubstituted ketenes react with imines extremely slowly and even under mild conditions show a great tendency to polymerize.[2]

The scope of the ketene-imine method for making β-lactams is limited drastically by the types and number of imines that can react to form the desired products.  All but one of the β-lactams which have been prepared by this method have been obtained from imines in which both the carbon and the nitrogen atom of the imino linkage are substituted by aromatic groups.  No systematic study has been made of the effect of varying the substituents on the aromatic groups, although Staudinger has found that the reactivity of benzylidene-$p$-nitroaniline with diphenylketene is slight compared to that of benzylideneaniline.  A $p$-dimethylamino substituent, on the other hand, appears to increase the reactivity of aromatic Schiff bases.  Perhaps it is also significant that acetophenoneanil is much less reactive to diphenylketene than is benzylideneaniline, although benzo-phenoneanil is much more reactive.[2]

Several other types of compounds containing the imino group, as for example the imido chloride XVII, the phenylhydrazone XVIII, and the oxime-ether XIX were found to be unreactive.[2,14]

$$\underset{\text{XVII}}{\overset{\displaystyle C_6H_5C{=}NC_6H_5}{\underset{\displaystyle Cl}{|}}} \qquad \underset{\text{XVIII}}{\overset{\displaystyle C_6H_5CH{=}NNC_6H_5}{\underset{\displaystyle CH_2C_6H_5}{|}}} \qquad \underset{\text{XIX}}{C_6H_5CH{=}NOCH_3}$$

---

[19] Staudinger and Maier, *Ann.*, **401**, 292 (1913).

[20] Staudinger, *Ber.*, **50**, 1035 (1917).

The presence of a sulfur substituent on the carbon of the imino grouping does not prevent β-lactam formation. The imido thioester XX reacts readily with dimethylketene to give the β-lactam XXI in 60% yield.[17]

$$(CH_3)_2C=C=O + C_6H_5C=NC_6H_5 \quad \rightarrow \quad (CH_3)_2C-CO$$



XX                          XXI

In a single instance a fused β-lactam-thiazolidine (XXII) has been prepared from 2-phenyl-2-thiazoline and diphenylketene.[21] This β-lactam served as a key model compound in the infrared studies on the structure of



XXII

penicillin.[22] Substitution of dimethylketene for diphenylketene in the reaction with 2-phenyl-2-thiazoline does not result in formation of a β-lactam but, as mentioned previously, a piperidinedione.

Although considerable study[4] has been made of the preparation of fused β-lactam-thiazolidines closely related to penicillin by the combination of ketenes with suitable thiazolines [e.g., 2-thiazoline (XXIII) and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate (XXIV)], no successful results have been reported.



XXIII                        XXIV

There are two cases in which the reaction of ketenes with imines is of special interest. The first is the combination of diphenylketene with cinnamylideneaniline which has been shown to lead to the β-lactam XXV instead of the δ-lactam XXVI to be expected from 1,4 addition.[14,23]

[21] Ref. 4, p. 996.
[22] Ref. 4, p. 405.
[23] Penicillin Program Report, Shell 14, 215.

The occurrence of 1,2 instead of 1,4-addition strikingly demonstrates the increased ease of formation of highly substituted $\beta$-lactams.

$$(C_6H_5)_2C\text{---}CO$$
$$C_6H_5CH\text{=}CHCH\text{---}NC_6H_5$$

XXV

$$(C_6H_5)_2C\text{---}CO$$
$$H_5C_6CH \qquad NC_6H_5$$
$$CH\text{=}CH$$

XXVI

The reaction of ethylcarbethoxyketene (XXVII) with benzylidene-aniline occurs readily at $-10°$ to give a crystalline 1 : 1 adduct which is not the $\beta$-lactam XXVIII and which was formulated by Staudinger as XXIX. The adduct is unstable and decomposes slowly at room temperature into the original imine and ketene. Upon heating this compound

$$C_2H_5C\text{=}C\text{=}O$$
$$CO_2C_2H_5$$

XXVII

$$C_2H_5$$
$$C_2H_5O_2CC\text{---}CO$$
$$H_5C_6CH\text{---}NC_6H_5$$

XXVIII

$$C_2H_5$$
$$C_2H_5O_2CC\text{---}CO$$
$$H_5C_6N\text{---}CHC_6H_5$$

XXIX

at 170° the isomeric $\beta$-lactam XXVIII is formed. The $\beta$-lactam can also be obtained directly from the ketene and the imine at 180°. At present there is no cogent evidence in favor of structure XXIX for the unstable adduct, and structure XXX must be regarded as being at least equally possible.

$$C_2H_5OC\text{=}CC_2H_5$$
$$O \qquad CO$$
$$H_5C_6CH\text{---}NC_6H_5$$

XXX

Phenylcarbomethoxyketene (XXXI) which might be expected to be more reactive to 1,2-addition than ethylcarbethoxyketene yields a $\beta$-lactam directly with benzylideneaniline. No intermediate product has been isolated. Dicarbethoxyketene (XXXII), on the other hand, does not appear to afford a $\beta$-lactam with benzylideneaniline under any conditions.

$$C_6H_5$$
$$CH_3O_2C\text{/}C\text{=}C\text{=}O$$

XXXI

$$(C_2H_5O_2C)_2C\text{=}C\text{=}O$$

XXXII

$$C_6H_5CH_2CONHCOCH_2N_2$$

XXXIII

Several unsuccessful attempts have been made to form $\beta$-lactams by the combination of imines with the rearrangement products, presumably

ketenes, of diazo ketones. The reaction of phenylacetylcarbamyldiazo-methane (XXXIII) with methyl 5,5-dimethyl-2-thiazoline-4-carboxylate in the presence of silver oxide, which might have afforded methyl benzyl-penicillinate, produced a complex mixture which had little or no bioactivity.[24]

## Experimental Procedure

**2,α,α-Triphenyl-2-thiazolidineacetic Acid β-Lactam.**[4] Three and nine-tenths grams of diphenylketene[25] is added to 3.3 g. of 2-phenyl-2-thiazoline.[26] After five minutes the spontaneous heating ceases, and the mixture is warmed to 60–70° for five minutes. The product is taken up in warm toluene, diluted with low-boiling petroleum ether and cooled to give 4.5 g. of the β-lactam (63% yield) as a colorless solid, m.p. 140–143°.

### REACTION OF KETENES WITH NITROSO COMPOUNDS

During the course of an investigation of the reaction of ketenes with nitroso compounds, Staudinger and Jelagin[18] found that equimolar amounts of diphenylketene and nitrosobenzene gave a 63–65% yield of a product assigned structure XXXIV, and that a 2:1 molar ratio of the ketene and nitroso compound gave a mixture of products consisting mainly of XXXIV together with a small amount of the β-lactam XXXV.[18] It was suggested that the β-lactam is formed by addition of diphenylketene to benzophenoneanil which is produced by the decarboxylation of the

$$(C_6H_5)_2C—CO \qquad (C_6H_5)_2C—CO \qquad (C_6H_5)_2C—CO$$
$$O—NC_6H_5 \qquad (C_6H_5)_2C—NC_6H_5 \qquad H_5C_6N—O$$

XXXIV          XXXV          XXXVI

intermediate XXXVI. p-Dimethylaminonitrosobenzene, which was found to be more reactive than nitrosobenzene, afforded a 65% yield of the β-lactam when treated with two moles of diphenylketene and yielded no product corresponding to XXXIV. Nitroso derivatives of secondary amines such as diphenylamine and diethylamine do not react with diphenylketene to give β-lactams.[18]

### REACTION OF AN IMINE, AN ACID CHLORIDE, AND A TERTIARY AMINE

One of the most recent syntheses of β-lactams, developed in connection with the problem of penicillin synthesis, involves the combination of an imine or thiazoline and an acid chloride, with loss of hydrogen chloride,

[24] Ref. 4, p. 990.
[25] *Org. Syntheses,* **20,** 47 (1940).
[26] Wenker, *J. Am. Chem. Soc.,* **57,** 1079 (1935).

in the presence of a tertiary amine.[27,28]   An example of this synthesis is the reaction of benzylideneaniline with phthaloylglycyl chloride in the presence of triethylamine to give 1,4-diphenyl-3-phthalimido-2-azetidinone (XXXVII) in 50% yield.[27]   The reaction proceeds rapidly at room temperature in inert solvents.   By hydrazinolysis of the phthaloyl group

$$XCH_2COCl + C_6H_5CH=NC_6H_5 \xrightarrow[\quad C_6H_6 \quad]{} \begin{array}{c} H_5C_6CH-NC_6H_5 \\ | \quad\quad | \\ XCH-CO \end{array} + (C_2H_5)_3\overset{+}{N}\overset{-}{H}Cl$$
$$+ (C_2H_5)_3N$$

<div align="center">XXXVII</div>
<div align="center">X = Phthalimido</div>

the phthalimido β-lactam XXXVII can be converted to an amino β-lactam and thence to other acylamino derivatives.[27]

Thiazolines bearing a 2-aryl or 2-carbalkoxy substituent also yield β-lactams in this reaction.   Thus, 2-phenyl-,[28] 2-p-nitrophenyl-,[29] and 2-furyl-thiazolines[30] react with phthaloylglycyl chloride and triethylamine to give good yields of the corresponding β-lactams.

$$XCH_2COCl + \begin{array}{c} R \\ | \quad S \\ C \quad\quad CH_2 \\ || \quad\quad | \\ N---CH_2 \end{array} \xrightarrow{(C_2H_5)_3N} \begin{array}{c} R \\ | \quad S \\ XCH-C \quad CH_2 \\ | \quad\quad | \\ CO-N---CH_2 \end{array}$$

The synthesis of a 5-phenylpenicillin (XXXIX) has been carried out by this approach, using methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate (XXXVIII) and succinylglycyl chloride as indicated below.[31,32]

$$XCH_2COCl + \begin{array}{c} C_6H_5 \\ | \quad S \\ C \quad\quad C(CH_3)_2 \\ || \quad\quad | \\ N---CHCO_2CH_3 \end{array} \xrightarrow{(C_2H_5)_3N} \begin{array}{c} C_6H_5 \\ | \quad S \\ XCH-C \quad C(CH_3)_2 \\ | \quad\quad | \\ CO-N---CHCO_2CH_3 \end{array}$$

<div align="center">XXXVIII</div>
<div align="center">X = succinimido</div>

<div align="right">1. OH⁻; H⁺<br>2. CH₂N₂</div>

$$\begin{array}{c} C_6H_5 \\ | \quad S \\ CH_3O_2C(CH_2)_2CONHCH-C \quad C(CH_3)_2 \\ | \quad\quad | \\ CO-N---CHCO_2CH_3 \end{array}$$

<div align="center">XXXIX</div>

[27] Sheehan and Ryan, J. Am. Chem. Soc., 73, 1204 (1951).

[28] Sheehan and Ryan, J. Am. Chem. Soc., 73, 4367 (1951).

[29] J. C. Sheehan and K. Henery-Logan, unpublished results.

[30] E. J. Corey, Ph.D. Thesis, Massachusetts Institute of Technology, 1951; J. A. Erickson, Ph.D. Thesis, Massachusetts Institute of Technology, 1953.

[31] Sheehan, Buhle, Corey, Laubach, and Ryan, J. Am. Chem. Soc., 72, 3828 (1950).

[32] Sheehan and Laubach, J. Am. Chem. Soc., 73, 4376 (1951).

The acid chloride-thiazoline reaction is apparently very sensitive to the nature of the ring substituents. No lactam was isolated with thiazolines possessing a hydrogen, sulfhydryl, or chlorine substituent in the 2-position.[33] In addition, the reaction proceeds better with 2-phenyl-2-thiazoline than with methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate, while ethyl 2-phenyl-2-thiazoline-4-carboxylate is intermediate in behavior. Thus, the yields of β-lactam obtained with these three thiazolines are 50%,[26] 20%,[34] and 34%[35] respectively.

To date the acid chloride-imine synthesis has been applied only to the synthesis of acylamino β-lactams. The acid chlorides that have been used successfully in the reaction include phthaloyl- and succinyl-glycyl chloride, 5-phenyl-2,4-diketo-3-oxazolidineacetyl chloride[36] (XL), and 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride[37] (XLI). The last two substances were employed because the heterocyclic systems which they contain can be degraded, once the β-lactam ring has been formed, to the phenylacetylamido substituent which is characteristic of benzylpenicillin (II, $R = C_6H_5CH_2$). These degradations are indicated by the accompanying formulas.[36,37]



It is important to note that acylamino acid chlorides of the type XLII are not generally available for use in the acid chloride-thiazoline synthesis

$$RCH_2CONHCH_2COCl \qquad RCH_2CONHCH_2CO_2H \rightarrow$$

XLII



XLIII

[33] J. C. Sheehan and co-workers, unpublished observations.

[34] Sheehan, Hill, Jr., and Buhle, *J. Am. Chem. Soc.*, **73**, 4373 (1951).

[35] D. A. Johnson, Ph.D. Thesis, Massachusetts Institute of Technology, 1952.

[36] Sheehan and Laubach, *J. Am. Chem. Soc.*, **73**, 4752 (1951).

[37] Sheehan and Corey, *J. Am. Chem. Soc.*, **73**, 4756 (1951).

since attempts to obtain them from the corresponding acids usually lead to formation of salts of azlactones (XLIII). Thus, it is necessary to employ systems in which the nitrogen atom is protected from azlactonization by the presence of a suitable blocking group.

Benzenesulfonylglycyl chloride (XLIV) and carbobenzoxyglycyl chloride (XLV), which cannot azlactonize but which possess an unprotected nitrogen atom, react with benzylideneaniline to form 4-imidazolones in yields of about 75%.[38]

$$RNHCH_2COCl + \underset{NC_6H_5}{\overset{CHC_6H_5}{\|}} \xrightarrow{(C_2H_5)_3N} \underset{CO-NC_6H_5}{\overset{CH_2 \quad CHC_6H_5}{\overset{\displaystyle N}{\overset{|}{\diagdown}}}}$$

XLIV   R = C_6H_5SO_2
XLV    R = C_6H_5CH_2OCO

Although it is clear at present that the acid chloride-imine (or thiazoline) reaction is by no means general for acid chlorides or imines, the exact scope of the reaction is still unknown. In addition, nothing is known about the mechanism of the reaction. Under some conditions there have been isolated crystalline by-products which have been tentatively formulated as acyl derivatives of enolized piperidinediones on the basis of elemental and infrared analysis.[28,34] The formation of such by-products can usually be minimized by working at very high dilution and operating with refluxing chloroform rather than methylene chloride as the solvent.[28,30,34]

## Experimental Procedures

**1,4-Diphenyl-3-phthalimido-2-azetidinone.**[27] To a solution of 7.24 g. of benzylideneaniline and 2.02 g. of triethylamine in 70 ml. of benzene a solution of 4.48 g. of phthaloylglycyl chloride in 40 ml. of benzene is added dropwise with mechanical stirring over a period of one-half hour. A colorless precipitate forms, the mixture becomes yellow, and the temperature rises. After stirring for an additional half-hour, the mixture is filtered, and the insoluble triethylammonium chloride (2.65 g., 96.5%) is washed with benzene. The combined benzene solutions are evaporated under reduced pressure and the semi-solid residue is triturated with ether-petroleum ether (1:1) to remove unreacted benzylideneaniline. The insoluble orange solid is digested with 200 ml. of boiling ethanol and filtered. The residue is almost pure β-lactam, 3.68 g. (50%), m.p. 227–230°, which crystallizes from dioxane-water as a dioxane solvate, m.p. 230–231°.

[38] Sheehan and Smith, in press.

## 2-Phenyl-$\alpha$-succinimido-2-thiazolidineacetic Acid $\beta$-Lactam.[32]

To a solution of 1.63 g. of 2-phenyl-2-thiazoline[26] in 10 ml. of methylene chloride (dried over Drierite) in a 200-ml. three-necked flask is added 1.85 g. of succinylglycyl chloride in 25 ml. of methylene chloride. To this rapidly stirred solution at reflux is added through a high-dilution cycle[39] a solution of 1.02 g. of triethylamine in 50 ml. of methylene chloride over a six-hour period. The resulting amber solution is concentrated under reduced pressure to a brown magma, which is shaken with 50 ml. of benzene. The colorless, crystalline residue of triethylammonium chloride (1.50 g., ca. 100%) is removed by filtration, and the filtrate is concentrated to a brown oil which partially crystallizes on standing for several days. The mixture is triturated with 20 ml. of 50% aqueous ethanol, allowed to stand overnight, and filtered. The crude lactam, crisp yellow needles, m.p. 148–160°, weighing 1.70 g., is purified by recrystallization from dioxane-water (Norit). The yield of essentially pure lactam, m.p. 166–168°, is 0.9 g. (30%).

### DEHYDROHALOGENATION OF N-$\alpha$-HALOACYLAMINOMALONIC ESTERS

Another reaction sequence by which a $\beta$-lactam can be formed is the establishment of an amide linkage by chloroacetylation of a substituted aminomalonic ester and subsequent base-catalyzed ring closure by the formation of a carbon-carbon bond. A specific example is furnished by the preparation of 1-phenyl-4,4-dicarbethoxy-2-azetidinone (XLVI) from anilinomalonic ester.[40]

$$C_6H_5NHCH(CO_2C_2H_5)_2 + (ClCH_2CO)_2O \rightarrow \begin{array}{c} C_6H_5NCH(CO_2C_2H_5)_2 \\ | \\ COCH_2Cl \end{array} \text{(92%)}$$

$$\downarrow (C_2H_5)_3N$$

$$\begin{array}{c} H_5C_6N\text{——}CHCO_2C_2H_5 \\ | \quad\quad | \\ CO\text{—}CH_2 \end{array} \xleftarrow{\text{Two steps}} \begin{array}{c} H_5C_6N\text{——}C(CO_2C_2H_5)_2 \\ | \quad\quad | \\ CO\text{—}CH_2 \text{ (95%)} \end{array}$$

$$\text{XLVII} \quad\quad\quad\quad\quad \text{XLVI}$$

The reaction appears to be general for N-substituted aminomalonic esters N-acylated with $\alpha$-haloacids, and the yields obtained are invariably high.[40,41] No dimeric or linear condensation products have been observed. The exact nature of the basic reagent is not important since triethylamine, diethylamine, benzylamine, alcoholic ammonia, and alcoholic potassium

[39] Cope and Herrick, *J. Am. Chem. Soc.*, **72**, 983 (1950).

[40] Sheehan and Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).

[41] Sheehan and Bose, *J. Am. Chem. Soc.*, **73**, 1761 (1951).

hydroxide all have been used successfully in the ring-closure.[41] The
β-lactams obtained by this process can be converted to β-lactams bearing
a single carbethoxyl substituent, e.g. XLVII, by selective hydrolysis of
one ester function and decarboxylation of the resulting acid.

This method of synthesis, although efficient, is obviously restricted to
the preparation of β-lactams which possess one or two carboxyl (or similar)
functions at the 4-position. A further limitation results from the fact
that N-unsubstituted N-haloacylaminomalonic esters containing a
hydrogen atom attached to the nitrogen atom, such as XLVIII, apparently
do not undergo cyclization upon treatment with tertiary amines or other
bases.[41]

$$ClCH_2CONHCH(CO_2C_2H_5)_2$$
XLVIII

## Experimental Procedure

**1-Phenyl-3-ethyl-4,4-dicarbethoxy-2-azetidinone.[41]** A solution
of 2 g. of α-bromo-$n$-butyric acid, 1 ml. of phosphorus trichloride, and 2 g. of
diethyl anilinomalonate[42] in 50 ml. of benzene is heated under reflux for
two hours. After removal of the solvent, the residue is taken up in
ether and washed with 5% aqueous sodium carbonate. Evaporation
of the ether affords 2.84 g. of crude diethyl N-(α-bromo-$n$-butyryl)-
anilinomalonate as a viscous oil. A benzene solution of this crude material
containing 2 g. of triethylamine is heated to 50–60° overnight. After
removal of the insoluble triethylammonium chloride and solvent and
evaporative distillation of the residue at 130–145°/0.4 mm., 2.29 g.
(78% yield based on the malonic ester) of β-lactam is obtained as a color-
less, viscous liquid, $n_D^{25}$ 1.5108.

### MISCELLANEOUS SYNTHESES

An unusual approach to the β-lactam ring system is provided by the
reaction of diazomethane with isocyanates. Diazomethane and phenyl
isocyanate combine, in a manner reminiscent of the formation of cyclo-
butanone from ketene and diazomethane, to form 1-phenyl-2-azetidinone.[43]
$p$-Bromophenylisocyanate is also converted to a β-lactam under these
conditions. The reaction does not appear to be general, however, since
no β-lactam could be isolated from the reaction of diazomethane with
either α-naphthyl-, $p$-nitrophenyl-, benzyl-, or benzoyl-isocyanate.

Several β-lactams have been prepared by modification of the substituents
present in preformed β-lactam systems. Examples were mentioned in

[42] Blank, *Ber.*, **31**, 1812 (1898).
[43] Sheehan and Izzo, *J. Am. Chem. Soc.*, **70**, 1985 (1948); **71**, 4059 (1949).

the preceding sections. Perhaps the best-known example of such a conversion, however, is the synthesis of methyl desthiobenzylpenicillinate (XLIX) by desulfurization of methyl benzylpenicillinate with Raney nickel.[4]

$$C_6H_5CH_2CONHCH\overset{\displaystyle S}{\overset{|}{\underset{CO——N——CHCO_2CH_3}{\underset{|}{——CH}}}}\overset{|}{\underset{}{C(CH_3)_2}}\xrightarrow[H_2]{Ni}$$

$$C_6H_5CH_2CONHCH—CH_2\quad CH(CH_3)_2$$
$$\underset{CO—N——CHCO_2CH_3}{\underset{|}{}\qquad\underset{|}{}}$$

XLIX

Oxidation of fused $\beta$-lactam-thiazolidines produces, in general, the corresponding $\beta$-lactam-thiazolidine-1,1-dioxides in good yield.[4]

Finally, a number of $\beta$-lactams substituted by cyclohexyl groups have been prepared by catalytic reduction of the corresponding phenyl-substituted $\beta$-lactams.[4]

### TABULAR SURVEY OF SYNTHESES OF $\beta$-LACTAMS

An attempt has been made to collect in the following tables all examples of $\beta$-lactam syntheses that have been published before 1953. A few syntheses published subsequently are also included. Table I includes monocyclic $\beta$-lactams, and Table II the fused $\beta$-lactam thiazolidines. The sections of each table are arranged in a sequence determined by the number of substituents on the $\beta$-lactam ring. The following abbreviations are used for preparative methods: $A$, cyclization of $\beta$-amino acid esters with organometallic compounds; $B$, cyclization of $\beta$-acylamino acids; $C$, from $\beta$-amino acids; $D$, from imines, $\alpha$-bromoesters, and zinc; $E$, from ketenes and imines; $F$, from ketenes and nitroso compounds; $G$, from acid chlorides, imines, and tertiary amines; $H$, dehydrohalogenation of N-$\alpha$-haloacylaminomalonic esters; $I$, from isocyanates and diazomethane; $J$, from a preformed $\beta$-lactam.
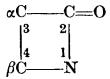
## TABLE I

MONOCYCLIC $\beta$-LACTAMS—AZETIDINONES

$$\alpha C \underset{\underset{\beta C}{|4\quad\ 1|}}{\overset{|3\quad\ 2|}{\underset{\rule{0pt}{1em}}{\underline{\quad\quad}}}}\overset{C=O}{\underset{N}{}}$$

| $\beta$-Lactam (Substituents on Azetidinone Ring) | Yield % | Method of Preparation | Refer- ence |
|---|---|---|---|
| *Monosubstituted* | | | |
| None | 0.76 | A | 11 |
| 1-Methyl | 11 | A | 10 |
| 1-Benzyl | 5 | A | 10 |
| 1-Phenyl | 20 | I | 43 |
| | — | A | 4 |
| 1-p-Bromophenyl | 12 | I | 43 |
| *Disubstituted* | | | |
| 1,4-Diphenyl | 54 | C | 4 |
| | 39 | E | 20 |
| | 56 | D | 13 |
| | 94 | A | 4 |
| 1-Benzyl-4-phenyl | 45 | A | 10 |
| 1-Benzhydryl-4-phenyl | 3.3 | A | 10 |
| 1-Phenyl-3-benzamido | ca. 25 | A | 4 |
| 1-Phenyl-3-phenylacetamido | 35 | A | 4 |
| 1-Phenyl-3-cyclohexylacetamido | 69 | J | 4 |
| 1-Ethyl-4-methyl | 35 | A | 8 |
| 1,4-Dimethyl | <35 | A | 8 |
| 1-Phenyl-4-carbethoxy | 89 | J | 40 |
| 1-Phenyl-4-carboxy | 96 | J | 40 |
| 1,4-Diphenyl | — | A | 4 |
| 1-(1-Carboxyisobutyl)-3-phenylacetamido (desthiobenzylpenicillin) | ca. 40 | J | 4 |
| 1-(1-Carbomethoxyisobutyl)-3-phenylacetamido (methyl desthiobenzylpenicillinate) | — | J | 4 |
| 1-(1-Carboxyisobutyl)-3-cyclohexylacetamido (hexahydrodesthiobenzylpenicillin) | — | J | 4 |
| *Trisubstituted* | | | |
| 1,4-Diphenyl-3-methyl | 85 | D | 13 |
| 1-Benzyl-3-methyl-4-phenyl | — | A | 4 |
| 1-Cyclohexylmethyl-3-methyl-4-cyclohexyl | — | D | 4 |
| 1-Phenyl-4,4-dicarbethoxy | — | J | 40 |
| 1-Phenyl-4,4-dicarbobenzoxy | 88 | H | 40 |
| 1-Phenyl-4,4-dicarboxy | 88 | H | 40 |
| 1-$\beta$-Naphthyl-4,4-dicarbethoxy | 95 | H | 40 |
| 1-Cyclohexyl-4,4-dicarbethoxy | 91 | H | 41 |
| 1-p-Tolyl-4,4-dicarbethoxy | 90 | H | 41 |
| 1-(4'-Methylcyclohexyl)-4,4-dicarbethoxy | 92 | H | 41 |
| 1,4-Diphenyl-3-phthalimido | 50 | G | 27 |

TABLE I—*Continued*

MONOCYCLIC $\beta$-LACTAMS—AZETIDINONES

```
αC——C=O
 |3   2|
 |4   1|
βC——N
```
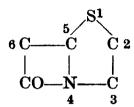
| $\beta$-Lactam (Substituents on Azetidinone Ring) | Yield, % | Method of Preparation | Reference |
|---|---|---|---|
| *Trisubstituted—Continued* | | | |
| 1,4-Diphenyl-3-amino (hydrochloride) | 54 | J | 27 |
| 1,4-Diphenyl-3-phenylacetamido | 56 | J | 27 |
| 1,4-Diphenyl-3-(2'-benzylidene-4',5'-diketo- | 17 | J | 37 |
| 3'-oxazolidyl) | 16 | G | 37 |
| 1,4-Diphenyl-3-(3'-nitrophthalimido) | 54 | G | 27 |
| 1,4-Diphenyl-3-dimethanesulfonamido | 39 | G | 38 |
| 1,4-Diphenyl-3-methanesulfonamido | — | J | 38 |
| *Tetrasubstituted* | | | |
| 1,3,3-Trimethyl-4-phenyl | 65 | B | 3, 4 |
| 1-Benzyl-3,3-dimethyl-4-phenyl | 10 | E | 3 |
|  | 70 | C | 4 |
|  | 50–60 | B | 3 |
| 1,4-Diphenyl-3,3-dimethyl | — | E | 16 |
| 1,4-Diphenyl-3,3-diethyl | 82 | E | 19 |
| 1,4-Diphenyl-3-ethyl-3-carbethoxy | 1 | E | 20 |
| 1,3,4-Triphenyl-3-carbomethoxy | — | E | 20 |
| 1,3,3,4-Tetraphenyl | 72 | E | 16 |
| 1,3,3-Triphenyl-4-styryl | 70 | E | 14 |
| 1-Phenyl-3,3-dimethyl-4-$p$-dimethylaminophenyl | — | E | 2 |
| 1-Benzhydryl-3,3-dimethyl-4-phenyl | — | E | 2 |
| 1-Phenyl-3,3-dimethyl-4-styryl | — | E | 2 |
| 1-$p$-Nitrophenyl-3,3-dimethyl-4-phenyl | — | E | 2 |
| 1-Ethyl-3,3-dimethyl-4-phenyl | 87 | B | 4 |
| 1,3,4-Triphenyl-3-methyl | — | B | 44 |
| 1-Phenyl-3-methyl-4,4-dicarbobenzoxy | ca. 90 | H | 41 |
| 1-Phenyl-3-ethyl-4,4-dicarbethoxy | ca. 90 | H | 41 |
| *Pentasubstituted* | | | |
| Pentaphenyl | 84 | E | 18 |
|  | — | F | 18 |
| 1-$p$-Dimethylaminophenyl-3,3,4,4-tetraphenyl | 100 | E | 18 |
|  | 65 | F | 18 |
| 1,4,4-Triphenyl-3,3-dimethyl | — | E | 2 |
| 1,4-Diphenyl-3,3,4-trimethyl | — | E | 2 |
| 1,3,4,4-Tetraphenyl-3-methyl | — | E | 2 |
| 1,4,4-Triphenyl-3,3-$o$-biphenylene | — | E | 2 |
| 1,4-Diphenyl-3,3-dimethyl-4-methylmercapto | 60 | E | 17 |

[44] Staudinger and Ruzicka, *Ann.*, **380**, 301 (1911).

## TABLE II

### FUSED $\beta$-LACTAM-THIAZOLIDINES



| $\beta$-Lactam (Substituents) | Yield, % | Method of Preparation | Reference |
|---|---|---|---|
| 5,6,6-Triphenyl | 63 | E | 4 |
| 5-Phenyl-6,6-dimethyl | 50 (3 steps) | B | 4 |
| 5,6,6-Trimethyl | 29 (3 steps) | B | 4 |
| 5-Phenyl-6-phthalimido* | 50 | G | 28 |
| 5-p-Nitrophenyl-6-phthalimido* | 65 | G | 29 |
| 5-Phenyl-6-(3-nitrophthalimido) | 17 | G | 28 |
| 5-Phenyl-6-succinimido* | 56 | G | 32 |
| 5-Phenyl-6-phenylacetamido* | 32 | J | 36, 37 |
| 5-Phenyl-6-(2'-benzylidene-4',5'-diketo-3'-oxazolidyl) | 45 | G | 37 |
| 5-Phenyl-6-(2',3'-diketo-3'-oxazolidyl)* | 28 | G | 36 |
| 5-Carbobenzoxy-6-phthalimido | 87 | G | 30 |
| 5-(2-Furyl)-3-phthalimido | 24 | G | 30 |
| 3-Carbethoxy-5-phenyl-6-phthalimido* | 34 | G | 35 |
| 2,2-Dimethyl-3-carbomethoxy-5-phenyl-6-phthalimido* | 20 | G | 34 |
| 2,2-Dimethyl-3-carbomethoxy-5-phenyl-6-succinimido* | 13 | G | 32 |
| 2,2-Dimethyl-3-carbomethoxy-5-phenyl-6-(3'-carbomethoxypropionamido) | — | J | 32 |
| 2,2-Dimethyl-3-carbomethoxy-5-furyl-6-phthalimido* | 17 | G | 30 |
| 2,2-Dimethyl-3-carbomethoxy-5-(m-nitrophenyl)-6-phthalimido* | 25 | G | 29 |
| 2,2-Dimethyl-3-carbomethoxy-6-phthalimido* | 12 | C | 6 |
| 2,2-Dimethyl-3-carbomethoxy-5-carbobenzoxy-6-phthalimido | — | G | 30 |

\* The corresponding sulfone was also prepared.

# CHAPTER 7

# THE PSCHORR SYNTHESIS AND RELATED DIAZONIUM RING CLOSURE REACTIONS

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## CONTENTS

## INTRODUCTION

In the middle eighteen nineties three groups of chemists independently discovered a new cyclization reaction of certain appropriately constituted diazonium salts. Fischer and Schmidt[1] reported that an aqueous

I   III   V

II   IV   VI

solution of 2-benzylbenzenediazonium chloride (I) furnished fluorene (II) on heating. Graebe and Ullmann[2] reported that 2-benzoylbenzene-

[1] Fischer and Schmidt, *Ber.*, **27**, 2786 (1894).
[2] Graebe and Ullman, *Ber.*, **27**, 3483 (1894).

diazonium chloride (III) yielded fluorenone (IV), and Staedel[3] reported a somewhat similar result from the action of nitrous acid on 2,2'-diamino-benzophenone, a reaction that produced a little 1-hydroxyfluorenone. Two years later Robert Pschorr[4] applied the ring closure reaction to the diazonium salt derived from *trans*-2-amino-α-phenylcinnamic acid (V) (aryl groups *cis*) to obtain phenanthrene-9-carboxylic acid (VI). The principal utility of these cyclization reactions has been the synthesis of substituted ring structures in which the positions of the substituents are known. In a series of papers Pschorr[5-21] reported the application of the reaction to the synthesis of a large number of phenanthrene derivatives with special emphasis on morphine degradation products. Although Pschorr was not the first to use the reaction, he was the first to exploit it extensively for the determination of structure. The phenanthrene synthesis, appropriately known as the Pschorr reaction, is still the best known of the various diazonium cyclization reactions. Various aspects of the cyclization reactions of diazonium salts have been reviewed previously.[22-25]

## MECHANISMS OF THE REACTIONS

### Comparison with the Gomberg-Bachmann Synthesis

Intermolecular analogs of the cyclization reactions have been recognized for many years. Pschorr[4] pointed out their similarity to the biphenyl

[3] Staedel, *Ber.*, **27**, 3362 (1894).

[4] Pschorr, *Ber.*, **29**, 496 (1896).

[5] Pschorr, Wolfes, and Buckow, *Ber.*, **33**, 162 (1900).

[6] Pschorr, *Ber.*, **33**, 176 (1900).

[7] Pschorr and Sumuleanu, *Ber.*, **33**, 1810 (1900).

[8] Pschorr and Jaeckel, *Ber.*, **33**, 1826 (1900).

[9] Pschorr and Buckow, *Ber.*, **33**, 1829 (1900).

[10] Pschorr, Seydel, and Klein, *Ber.*, **34**, 3998 (1901).

[11] Pschorr and Schröter, *Ber*, **35**, 2726 (1902).

[12] Pschorr, Seydel, and Stöhrer, *Ber.*, **35**, 4400 (1902).

[13] Pschorr and Vogtherr, *Ber.*, **35**, 4412 (1902).

[14] Pschorr, Stählin, and Silberbach, *Ber.*, **37**, 1926 (1904).

[15] Pschorr, Tappen, Hofmann, Quade, Schütz, and Popovici, *Ber.*, **39**, 3106 (1906).

[16] Pschorr and Busch, *Ber.*, **40**, 2001 (1907).

[17] Pschorr and Zeidler, *Ann.*, **373**, 75 (1910).

[18] Pschorr and Knöffler, *Ann.*, **382**, 50 (1911).

[19] Pschorr, Selle, Koch, Stoof, and Treidel, *Ann.*, **391**, 23 (1912).

[20] Pschorr, Zeidler, Dickhäuser, Treidel, and Koch, *Ann.*, **391**, 40 (1912).

[21] Avenarius and Pschorr, *Ber.*, **62**, 321 (1929).

[22] Saunders, *The Aromatic Diazo-compounds and Their Technical Applications*, 2d ed., p. 254, Longmans, Green & Co., New York, 1949.

[23a] Holzach, *Die Aromatischen Diazoverbindungen*, p. 231, Ferdinand Enke, Stuttgart, 1947.

[23b] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., pp. 8, 29, Reinhold Publishing Co., New York, 1949.

[24] Leake, *Chem. Revs.*, **56**, 27 (1956).

[25] Hey and Osbond, *J. Chem. Soc.*, **1949**, 3164.

syntheses of Möhlau and Berger[26] which employed a diazonium salt, an aromatic solvent, and anhydrous aluminum chloride, and to those of

$$
\text{Ph–}N_2^+ + \text{Ph} \xrightarrow{\text{AlCl}_3} \text{Ph–Ph} + N_2 + H^+
$$

Kühling and of Bamberger[27] which were forerunners of the Gomberg-Bachmann reaction.    More recently the analogy has generally been drawn with the Gomberg-Bachmann reaction itself[28,29] a typical example of which is the preparation of m-nitrobiphenyl by the reaction of m-nitrobenzenediazonium chloride, benzene, and alkali in a two-phase system.

$$
\text{(NO}_2)\text{Ph–}N_2^+Cl^- + \text{Ph} \xrightarrow[\text{or CH}_3\text{CO}_2\text{Na}]{\text{NaOH}} \text{(NO}_2)\text{Ph–Ph} + N_2 + \text{NaCl}
$$

There are, however, a number of points of difference between the two-phase, alkaline, Gomberg-Bachmann reactions and the cyclization reactions.    Many of the cyclization reactions, e.g. the fluorenone syntheses, are carried out in acidic solutions.    Such systems are initially single phase and only incidentally become multiphase owing to precipitation of reaction products.    The Pschorr reaction is usually carried out in strongly acidic solution in the presence of copper powder.    In a few cases it has been carried out in a homogeneous alkaline solution.    Thus, in considering the mechanisms of the cyclization reactions, evidence concerning these intermolecular reactions is helpful but must be interpreted with due caution.

### Evidence for a Heterolytic Cyclization

Preliminary work on the mechanisms of the cyclization reactions[30-34] has shown that the fluorenone synthesis as usually carried out takes place by a heterolytic[35] (ionic) mechanism as shown in the equation.    On the other hand, the copper-catalyzed Pschorr reactions may occur by a homolytic (free-radical) chain mechanism, though adequate evidence is

[26] Möhlau and Berger, Ber., 26, 1994 (1893).

[27] Kühling, Ber., 28, 523 (1895); Bamberger, Ber., 28, 403 (1895).

[28] Waters, The Chemistry of Free Radicals, p. 165, Oxford University Press, Oxford, 1946.

[29] Bachmann and Hoffman in Adams, Organic Reactions, Vol. II, p. 224, John Wiley & Sons, New York, 1944.

[30] DeTar and Sagmanli, J. Am. Chem. Soc., 72, 965 (1950).

[31] DeTar and Relyea, J. Am. Chem. Soc., 76, 1680 (1954).

[32] DeTar and Chu, J. Am. Chem. Soc., 76, 1686 (1954).

[33] Relyea and DeTar, J. Am. Chem. Soc., 76, 1202 (1954).

[34] DeTar and Relyea, J. Am. Chem. Soc., 78, 4302 (1956).

[35] For explanation of terms see e.g. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, New York, 1953.

not yet available.    The diazonium cyclization reactions therefore appear to belong to a lengthening list of reactions that occur by more than one mechanism.

Evidence for a heterolytic fluorenone formation is derived from (1) general studies of the mechanisms of diazonium salt reactions and (2) specific studies of the fluorenone cyclization reaction.

There is good evidence based both on rate studies and on product studies with several diazonium salts that in water and in alcohols the thermal decomposition of the diazonium group is a heterolytic process under acidic conditions in the absence of light or of reducing agents, and that under alkaline conditions the decomposition takes place at least in part by homolytic processes.

The evidence for a heterolytic mechanism for the thermal decomposition of several diazonium salts in acidic aqueous solutions is based on the observation that the reaction is accurately first order over the full course $(10-99\%)$[36-38] and is independent of the presence of or absence of a large variety of anions, or of acidity, over a considerable $p$H range.    This independence rules out various homolytic mechanisms involving hypothetical intermediate covalent diazo compounds such as the diazo chloride, $C_6H_5N=NCl$, or diazo hydroxide, $C_6H_5N=NOH$.    The diazonium cation itself can give rise to radicals only by reactions yielding ionized nitrogen or water molecules and hence requiring prohibitively high energies.    Thus homolytic mechanisms are excluded by the kinetic evidence.

$$C_6H_5N_2^+ \rightarrow C_6H_5\cdot + (\cdot N\vdots\vdots N\vdots)^+$$

$$C_6H_5N_2^+ + H_2O \rightarrow C_6H_5\cdot + (H\vdots\ddot{O}\vdots H)^+ + N_2$$

Product studies show that benzenediazonium chloride reacts with methanol under acidic conditions to give high yields $(90-95\%)$ of anisole.[39] In the presence of sodium acetate the principal product is benzene $(85-90\%)$, and the reaction is very sensitive to oxygen.    Such results

[36] DeTar and Ballentine, *J. Am. Chem. Soc.*, **78**, 3916 (1956).

[37] DeTar and Kwong, *J. Am. Chem. Soc.*, **78**, 3921 (1956).

[38] Moelwyn-Hughes and Johnson, *Trans. Faraday Soc.*, **36**, 948 (1940).

[39] DeTar and Turetzky, *J. Am. Chem. Soc.*, **77**, 1745 (1955); **78**, 3925, 3928 (1956).

require a homolytic mechanism in the presence of the acetate buffer and a heterolytic mechanism under acidic conditions.

In water the reaction of diazonium salts in the presence of alkali is highly complex, and the problem of unraveling mechanisms is difficult. However, the two-phase Gomberg-Bachmann reaction clearly requires some sort of homolytic mechanism as shown by the excellent orientation studies of Hey and his co-workers.[40] The activating effect and the ortho-para directing effect of the nitro group of nitrobenzene afford perhaps the clearest single item of evidence in favor of a homolytic mechanism for the Gomberg-Bachmann reaction.

The fluorenone ring closure occurs readily under acidic conditions. Accordingly, a heterolytic mechanism seems most probable. This hypothesis is easily subject to further experimental investigation by use of appropriately substituted benzophenones in the ring closure reaction. The thermal decomposition of the diazonium salts derived from 2-amino-benzophenone in aqueous solution gave 65% of fluorenone and 35% of 2-hydroxybenzophenone, these two products together accounting quantitatively for the starting material.[31] The product ratio and yield were insensitive to temperature in the range 25-75°. These products are ascribed to two competing heterolytic displacement reactions of the diazonium nitrogen; the one, intermolecular, involving a water molecule as the nucleophilic reagent and the other, intramolecular, involving an aryl group as the nucleophilic reagent.

Since a methyl group enhances and a nitro group diminishes the nucleophilic capabilities of the aryl ring, a methyl group should increase and a nitro group decrease the yield of fluorenone if the reaction is heterolytic. But, since the nitro group is an activating group for homolytic substitution reactions,[40] the ring closure should be more favored



VIII → IX (61%) + X (34%)

XI → XII (33%) + XIII (67%)

[40] Augood, Cadogan, Hey and Williams, *J. Chem. Soc.*, **1953**, 3412, and earlier papers. See also DeTar and Scheifele, *J. Am. Chem. Soc.*, **73**, 1442 (1953); Dannley and Gippin, *ibid.*, **74**, 332 (1952); Rondestvedt and Blanchard, *ibid.*, **77**, 1769 (1955).

with the nitro derivative if the reaction is homolytic. The yields given in the equations show that the methyl group of VIII is without effect, though the nitro group of XI does diminish the fluorenone yield. The results are, therefore, in satisfactory agreement with predictions based on a heterolytic mechanism for the ring closure. The small effect of the substituents on the product ratio and yield, kinetic evidence, and certain other product evidence have been cited[31] as favoring an $S_N1$ loss of nitrogen rather than an aromatic $S_N2$ type of replacement.

## Products of the Homolytic Reaction

Under alkaline conditions the diazonium salts derived from 2-amino-benzophenone can be expected to react to some extent by a mechanism involving homolytic C—N bond cleavage. With alkali present ($p$H 12), only about 25% of fluorenone is produced. A similar reduction in yield under alkaline conditions has been observed for many of the diazonium cyclization reactions. In view of the demonstrated simultaneous occurrence of heterolytic and homolytic mechanisms,[39] it is not at all certain that even these low yields of fluorenone have resulted from free-radical intermediates.

The usual hypothesis about the mechanistic details of the homolytic Gomberg-Bachmann reaction is shown in the equation. The substituting radical is pictured as adding to the aromatic ring to give the new radical



XIV which loses a hydrogen atom to some other radical present in the solution. The intramolecular version of this step (XV → XVI) might



be expected to occur even more readily by virtue of the proximity of the radical to the potential reaction site. Reactions in which there is closure of a five-membered ring usually occur much more readily than their intermolecular counterparts. For some unknown reason the o-benzoyl-phenyl radical (XV) does not undergo this cyclization reaction at all readily in comparison with competing reactions. Treatment of diazotized

2-amino-4'-methylbenzophenone (VIII) with alkali and with carbon tetrachloride leads to 3-methylfluorenone (IX), 2-chloro-4'-methylbenzophenone (XVII), and 2-chloro-4-methylbenzophenone (XVIII).[33,34] The 2-(4'-methylbenzoyl)phenyl radical (XIX) evidently reacts with carbon



tetrachloride to abstract a chlorine atom to give 2-chloro-4'-methylbenzophenone (XVII) and with itself by an intramolecular chain transfer step to give the isomeric radical XX, which leads to 2-chloro-4-methylbenzophenone (XVIII). Even if all of the 3-methylfluorenone is ascribed to free-radical cyclization of XIX or XX, the free-radical cyclization is a relatively inefficient process. The chlorobenzophenones XVII and XVIII are not expected from a carbonium ion intermediate. Although the general possibility of chlorine abstraction from carbon tetrachloride by a carbonium ion intermediate has perhaps not yet received a really rigorous investigation, the formation of the chlorobenzophenone XVIII from the carbonium ion VII is unlikely in view of the ease with which this ion cyclizes. Further evidence pointing to inefficiency of the free-radical cyclization step is the fact that the Gomberg-Bachmann reaction of diazotized 2-aminobenzophenone with benzene in the presence of alkali gives a 20% yield of 2-phenylbenzophenone (XXI) and little fluorenone. If these reactions are formulated as radical substitution processes, it is strange

that an intermolecular reaction should take precedence over an intramolecular one, especially since the carbonyl group is expected to aid the cyclization process, for the carbonyl group is probably an activating group for free-radical substitution reactions.[40]

Preliminary studies of the Pschorr reaction with the diazonium salt derived from cis-2-aminostilbene (XXII) have provided results quite different from the above.[32] The thermal decomposition in aqueous solutions gives low yields of nitrogen and of phenanthrene (15–40%), the yields being higher at 100° than at 25°. A search was made for a nitrogen-containing by-product which was thought likely to be 3-phenylcinnoline. The product turned out to be indazole (XXIII). Several workers had previously reported benzaldehyde in reactions of this type, but no one had isolated the other cleavage fragment.[41-43] These results then seem to typify the heterolytic process in the phenanthrene series.



XXII                                                                    XXIII

If copper powder is present, the reaction is faster and the phenanthrene yield is higher (60–85%). It may be that the copper is promoting a homolytic reaction as has been suggested by Waters,[28] or perhaps some quite different intermediate steps are involved. The assumption of a homolytic process finds some support in work on the mechanism of the reduction of diazonium salts with hypophosphorous acid, a free-radical chain reaction that is initiated by copper.[44] Treatment of diazotized cis-2-aminostilbene with hypophosphorous acid leads to phenanthrene, not to cis-stilbene.[42] Furthermore, sodium hypophosphite and copper powder have been used in a number of Pschorr reactions. Examples are to be found in Table I.

## SCOPE AND LIMITATIONS
### Examples of Different Types of Bridge

The diazonium cyclization reaction has been carried out with compounds having a number of different types of bridge. To the examples already mentioned (I, III, and V) may be added compounds XXIV–XXXIII.

[41] Sachs and Hilpert, Ber., 39, 899 (1906); Ullmann and Gschwind, Ber., 41, 2291 (1908).
[42] Ruggli and Staub, Helv. Chim. Acta, 19, 1288 (1936); 20, 37 (1937).
[43] Simpson, J. Chem. Soc., 1943, 447.
[44] Kornblum, Cooper, and Taylor, J. Am. Chem. Soc., 72, 3013 (1950).

(The percentages following the Roman numerals indicate the yield of normal Pschorr cyclization products.)

XXIV >20%[42]

XXV 48%[45]

XXVI 45%[30]

XXVII 40%[46]

XXVIII <30%[30]

XXIX 67%[47]

XXX 50%[48]

XXXI 52%[49]

XXXII 24%[50,51]

XXXIII trace[46]

For the success of the cyclization reaction the carbon atoms that are to be linked together must be near each other. Perhaps the most favorable bridging group is the rigid ethylenic bridge of a cis-2-aminostilbene derivative (V and XXII). The corresponding trans ethylenic derivative undergoes other reactions typical of the diazonium group,[32,42] but is quite

Aq. H₂SO₄ →

+

[45] Forrest and Tucker, J. Chem. Soc., 1948, 1137.
[46] Cullinane, Rees, and Plummer, J. Chem. Soc., 1939, 151.
[47] Hey and Mulley, J. Chem. Soc., 1952, 2276.
[48] Heacock and Hey, J. Chem. Soc., 1952, 1508.
[49] Schetty, Helv. Chim. Acta, 32, 24 (1949).
[50] Barger and Weitnauer, Helv. Chim. Acta, 22, 1036 (1939).
[51] Marion and Grassie, J. Am. Chem. Soc., 66, 1290 (1944).

incapable of giving phenanthrene. Hey and Mulley have calculated the distance of closest approach between the two relevant carbon atoms for several compounds (1.5 Å for V and XXII, 2.0 Å for XXIX, 2.2 Å for I, and 2.4 Å for III).[47] The calculated values are rather sensitive to the angle of the C—X—C bond of the bridge; unfortunately this angle is not accurately known for most of the systems of interest, and hence present calculations cannot be expected to have quantitative significance. However, the estimates do clearly show that the stilbene derivatives have the most favorable spacing. There is a definite decline in yield of cyclic product with increasing bridge size as in the sulfide XXVII and the sulfone XXVIII, while the still larger selenide XXXIII gave only traces of cyclic product. Electrical factors seem to play a somewhat secondary role. The decrease in yield from 65% for fluorenone (IV) or for 3-methylfluorenone (IX) to 35% for the nitrofluorenones (XII)[31] is important practically, but relatively small as such effects go. (Compare the factor of about a million in the difference in the rates of nitration of benzene and of nitrobenzene.) For the most part the data available are insufficient to permit an appraisal of the importance of the electrical effect of the groups present. Generally such effects may be neglected in planning a synthesis.

However, there is one electrical effect that seems to be of some importance. When a hydroxyl group is *ortho* to a diazonium group, a diazo oxide is formed (XXXIV). An *ortho*-quinoid structure is a possible resonance form even if the oxygen atom is part of an ether (XXXV). Similar structures are possible with *ortho* amino groups. Such structures may be responsible for resin-forming side reactions that often occur with compounds such as XXVI and XXXVI containing an oxygen atom or a nitrogen atom *ortho* to the diazonium function.[52]



XXXIV                XXXV                XXXVI

## Side Reactions

Because the diazonium group is highly reactive, a number of reactions with external reagents can compete successfully at the expense of the cyclization. Examples of four such reactions follow.

[52] Ullmann and Gross, *Ber.*, **43**, 2694 (1910).

**Replacement of the Diazonium Group by Hydroxyl.** This reaction is always a potential competitor. Examples are the formation of 2-hydroxy-4′-methylbenzophenone (X) and 2-hydroxy-3′-nitrobenzophenone (XIII), both of which were mentioned earlier (p. 414).

**Replacement of the Diazonium Group by Hydrogen.** This occurs in the presence of reagents known to promote such a replacement. For example, sodium hypophosphite and copper convert diazotized cis-2-aminostilbene (XXII) into phenanthrene in an 80% yield.[42] However, this combination is of little use outside the phenanthrene series since diazonium salts less susceptible to ring closure give the normal replacement by hydrogen.[44] Diazotized sym-2-aminodiphenylethane (XXIV) is thus converted into sym-diphenylethane rather than into 9,10-dihydrophenanthrene.[42] The use of alcohols as solvents also can lead to reduction.[53] A copper suspension in aqueous or in organic media sometimes gives reduction products even though such obvious hydrogen sources as the alcohols are absent.[54,55]



20%



> 50%

[54]*



92%

[47]

[53] Dunlop and Tucker, J. Chem. Soc., **1939**, 1945.
[54] Schaarschmidt and Herzenberg, Ber., **53**, 1388 (1920).
[55] Gadamer, Arch. Pharm., **249**, 680 (1911) [J. Chem. Soc. Abstr., **102**, i, 48 (1912)].
* Numbers in brackets at the right of equations are the reference numbers.

**Replacement of the Diazonium Group by Halogen.** The Gattermann reaction usually does not occur, but can compete if excess hydrochloric acid is present. A recently suggested procedure involving formation and decomposition of a triazene sometimes gives chlorine-containing by-products.[25]



**Coupling of the Aryl Groups.** The Vorländer-Meyer[56] coupling of diazonium salts leads either to biphenyl derivatives or to azobenzene derivatives. Ammoniacal cuprous hydroxide is one of the best reducing agents for the coupling reaction when this reaction is desired. The coupling side reaction has not usually been reported, but may well be the cause of some of the low yields obtained.





In addition to side reactions due to external agents, there are a number of side reactions that can occur intramolecularly.

**Formation of Xanthones.** An alkoxyl group in the 2'-position interferes with many of the cyclization reactions. In the fluorenone series the product is a xanthone derivative, e.g. XXXVII,[57-59] rather

[56] Vorländer and Meyer, *Ann.*, **320**, 122, (1902); Atkinson, Morgan, Warren, and Manning, *J. Am. Chem. Soc.*, **67**, 1513 (1945).

[57] Ullmann and Denzler, *Ber.*, **39**, 4332 (1906). Several xanthones are reported.

[58] Gilman and Van Ess, *J. Am. Chem. Soc.*, **61**, 1365 (1939).

[59] Cf. Tarbell, Frank, and Fanta, *J. Am. Chem. Soc.*, **68**, 502 (1946).

than a fluorenone derivative.   The failure of diazotized *trans*-2-amino-α-(2'-furyl)cinnamic acid (**XXXVIII**) to give identifiable products may have



[57]

XXXVII

XXXVIII

been a result of the occurrence of reaction at the oxygen atom rather than at the 3-position of the furan ring.[60]

**Elimination of Carboxyl and Nitro Groups.**   Examples of the elimination of 2'-nitro groups and of 2'-carboxyl groups have been reported. The 2'-nitro group of diazotized 2-amino-2'-nitrobenzophenone (**XXXIX**) is eliminated to an appreciable extent.[47]   The 2'-nitro group of 2-amino-2'-nitro-N-methyldiphenylamine (**XL**) is largely eliminated if copper



XXXIX



7%                  14%                                4%

+ o-HOC₆H₄COC₆H₄NO₂-o
21%



XL                   XLI                   XLII

[60] Amstutz and Spitzmuller, *J. Am. Chem. Soc.*, **65**, 367 (1943).

powder is used in the decomposition of the diazonium salt, and largely retained if the copper is omitted.[47]    Thermal decomposition in aqueous sulfuric acid solution of the diazonium salt derived from 2-amino-2'-carboxybenzophenone (XLI) in the absence of copper led to approximately 10% yields each of fluorenone and of fluorenone-1-carboxylic acid (XLII).[61]    Side reactions of these types seem to be less important in the phenanthrene series, though detailed product studies have yet to be made. Thus several 1-methoxy- and 1-carboxy-phenanthrene derivatives (XLIII–XLV) have been prepared by the Pschorr reaction.[5,15,62]



XLIII

XLIV

XLV

XLVI

**Deamination in Phenanthridone Syntheses.**    An intramolecular hydrogen abstraction and resultant demethylation reaction has been reported[63,64] in an attempted preparation of 4-substituted phenanthridones from 2-substituted N-(2'-aminobenzoyl)-N-methylanilines.[65]    Incidentally the phenanthridone ring closure has usually been unsuccessful if



[63, 65]

the amino group is not in the benzoyl ring;   the amide XLVI gave no phenanthridone.[66]

[61] Sieglitz, Ber., **57**, 316 (1924).

[62] Hill and Short, J. Chem. Soc., **1937**, 260.

[63] Hey and Turpin, Chemistry & Industry, **216**, 216, 221 (1954).

[64] Forrest, Haworth, Pinder, and Stevens, J. Chem. Soc., **1949**, 1311.

[65] Heacock and Hey, J. Chem. Soc., **1953**, 3.

[66] Chardonnens and Würmli, Helv. Chim. Acta, **33**, 1338 (1950).

**Formation of Indazoles, Cinnolines, and Triazoles.** There are also intramolecular side reactions in which nitrogen is retained: e.g., coupling at a carbon atom to give an indazole or a cinnoline, and coupling at a nitrogen atom to give a triazole or a triazene. Indazole formation is illustrated by the conversion of 2-methyl-5-nitrobenzenediazonium ion (XLVII) to 6-nitroindazole. Indazole formation rather than carbon



$$O_2N \overset{CH_3}{\underset{N_2^+HSO_4^-}{\bigcirc\!\bigcirc}} \quad \xrightarrow{\text{Heat}} \quad O_2N\overset{CH}{\underset{NH}{\bigcirc\!\bigcirc}}N \; + \; N_2 \; + \; H_2SO_4 \quad [67]$$

XLVII                        80%

ring closure occurred when aminopapavarine (XLVIII) was diazotized and heated,[14] but carbon ring closure occurred with the tetrahydro derivative, aminolaudanosine (XLIX) to give 2,3,5,6-tetramethoxy-



XLVIII                        80%

aporphine (L).[14] This result is reasonable since indazole formation



XLIX                        L

seems to require a very acidic hydrogen, and probably involves initial removal of this hydrogen by a base (perhaps as weak a base as a water



molecule). Electron-attracting groups (Z, Z') favor this ionization by aiding the *ortho* diazonium group, which itself is an especially powerful electron-attracting group.

[67] Nölting, *Ber.*, **37**, 2556 (1904).

Simpson[43] has discussed in admirable fashion the factors that lead to cinnoline formation rather than to carbon cyclization.   The diazonium salt derived from *cis*-2-(1'-naphthyl)-1-(2"-aminophenyl)-1-phenylethene



LI

Aq. CH₃CO₂H
H₂SO₄-NaNO₂ ⟶ ArN₂⁺

Heat or Cu

Room temp.

LII

LIII

LIV

(LI) reacted on warming to give 2-phenylchrysene (LII).   The presence or absence of 9-(1'-naphthylmethylene)fluorene (LIII) was not ascertained. At room temperature 3-(1'-naphthyl)-4-phenylcinnoline (LIV) was the major product.   Cinnoline formation, like the indazole (XXIII) production observed with diazotized *cis*-2-aminostilbene (XXII), evidently has a lower activation energy than does loss of nitrogen, for nitrogen elimination is favored by high reaction temperatures.   In general, the presence on the ethylenic bridge of electron-releasing groups aids and the presence of electron-attracting groups hinders cinnoline formation.   With a carboxyl group present on the bridge, cinnoline formation does not occur.

Cinnoline ring closure occurs if an active methylenic bridge is present; the ketone LV gives the cinnoline LVI rather than the phenanthrol LVII.



LV

LVI

but not

LVII

If a secondary amino group is in a position to form a five- or six-membered ring by coupling with the diazonium group, the coupling will usually take place in preference to loss of nitrogen. Examples are the formation of the triazine derivative LVIII from diazotized 2-amino-



LVIII



LIX                                    LX



LXI                                    H

benzanilide,[68] the formation of the thiatriazine derivative LIX from diazotized 2-aminobenzenesulfonanilide,[52] and the formation of 1-phenylbenzotriazole (LXI) from diazotized 2-aminodiphenylamine.[69] Carbon cyclization has been achieved in two of the examples. If the diazotized 2-aminobenzenesulfonanilide is heated, the sultam (LX) of 2'-amino-biphenyl-2-sulfonic acid is obtained. Furthermore, many 1-arylbenzo-triazoles such as LXI are converted to carbazole derivatives with loss of nitrogen when they are heated to 250–400°

## Factors Affecting the Direction of Ring Closure

In the cyclization reaction there are sometimes two or more possible products of the ring closure. Such possibilities always arise when substituents in the 3'- and 5'-positions of the aryl ring to which closure is made are not identical, providing that both the 2'- and the 6'-positions are free. Examples are given in the equations. Such reactions are usually to be avoided.

[68] König and Reissert, *Ber.*, **32**, 782 (1899). See, also, Pictet and Gonset, *Arch. sci. phys. nat. Genève.* [4] **3**, 37 (1897) (*Chem. Zentr.*, **1897**, I, 413).
[69] Graebe and Ullmann, *Ann.*, **291**, 16 (1896).

[70]



LXII (15%)

[71]

38%



[31]

In the phenanthrene series considerable use has been made of bromine[72,73] in the 6'-position as a blocking group, the bromine being removed eventually by reduction.   Although the phenanthrene ring can be formed with



$\xrightarrow[\text{C}_5\text{H}_{11}\text{ONO, then Cu}]{\text{CH}_3\text{OH, H}_2\text{SO}_4}$



LXIII

$\xrightarrow[\text{aq. C}_2\text{H}_5\text{OH}]{\text{Zn-Cu, NaOH}}$

[72]

[70] Mayer and Balle, *Ann.*, **403,** 167 (1914).

[71] Späth and Tharrer, *Ber.*, **66,** 904 (1933).

[72] Girardet, *Helv. Chim. Acta*, **14,** 513 (1931).

[73] Lewis and Elderfield, *J. Org. Chem.*, **5,** 290 (1940).

two alkoxyl groups in the 4- and 5-positions as shown by **LXII** and **LXIII**, two alkyl groups in the 4- and 5-positions are too bulky to permit closure. No identifiable product was obtained from the reaction of diazotized



LXIV



LXV



LXVI

Diazotize,
then heat



LXVII

*trans*-2-amino-3-methyl-α-(2'-bromo-5'-methylphenyl)cinnamic acid (**LXIV**).[73] (The acid **LXV** was *not* formed.) It is possible to use this effect to advantage in preparing dialkylphenanthrene derivatives. Diazotized *trans*-2-amino-3-methyl-α-(3'-ethylphenyl)cinnamic acid (**LXVI**) gave a good yield of 7-ethyl-4-methylphenanthrene-9-carboxylic acid (**LXVII**), uncontaminated with the 4,5-isomer.

With a 1-naphthyl group in the α-position of the cinnamic acid, closure takes place in the 2-position rather than in the 8-position. *trans*-2-Amino-α-(1'-naphthyl)cinnamic acid (**LXVIII**) when diazotized and treated with copper powder and sodium hypophosphite gave chrysene-5-carboxylic



LXVIII

Aq. $C_2H_5OH$
$H_2SO_4$, $NaNO_2$
then Cu, $NaH_2PO_2$



LXIX (28%)

[74]



LXX



LXXI

[75]

[74] Fieser and Joshel, *J. Am. Chem. Soc.*, **62**, 1211 (1940).
[75] Lothrop and Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943).

## Aliphatic Analogs

Simple aliphatic amines appear not to undergo ring closure. Geissman and Tess[79] report that the treatment of 2-aminomethylbiphenyl (LXXIX) with sodium nitrite in aqueous acetic acid yields 2-biphenylmethanol. The details reported do not seem to exclude entirely the possibility of some fluorene production. The action of nitrous acid on 3-phenylpropylamine



$$\text{LXXIX} \xrightarrow[\text{NaNO}_2]{\text{Aq.CH}_3\text{CO}_2\text{H}} \text{CH}_2\text{OH} \qquad \text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \quad \text{LXXX}$$

(LXXX) does not seem to give any indane.[80] However, a very interesting ring closure involving 2-(2'-naphthyl)diazoacetophenone (LXXXI) to give 6-chrysenol (LXXXII) has been reported by Cook and Schoental.[81]



$$\text{LXXXI} \xrightarrow[\text{in CH}_3\text{CO}_2\text{H}]{10\%\ \text{H}_2\text{SO}_4} \text{LXXXII}$$

This reaction almost surely involves an intermediate aliphatic diazonium salt.

### EXPERIMENTAL CONDITIONS

## Preparation of the Amines

The most troublesome aspect of most of the diazonium cyclization reactions is the preparation of the amine having the desired structure. Each of the different types of bridge systems requires a separate approach.

**Pschorr Reaction Intermediates.** The cinnamic acids required for the Pschorr reaction are generally obtained by a Perkin condensation



$$\text{CHO, NO}_2 + \text{CH}_2\text{CO}_2\text{H} \xrightarrow[\substack{\text{K}_2\text{CO}_3\ \text{or}\ (\text{C}_2\text{H}_5)_3\text{N} \\ 110°,\ 8\ \text{hr.}}]{(\text{CH}_3\text{CO})_2\text{O}} \text{LXXXIII}$$

[79] Geissman and Tess, J. Am. Chem. Soc., **62**, 514 (1940).
[80] Fort and Roberts, J. Am. Chem. Soc., **78**, 584 (1956).
[81] Cook and Schoental, J. Chem. Soc., **1945**, 288.

using o-nitrobenzaldehyde or a substituted o-nitrobenzaldehyde. The reaction is illustrated by the preparation of trans-2-nitro-α-phenylcinnamic acid (LXXXIII).[32,82]

Pschorr originally specified the use of fused zinc chloride in this reaction, but its presence appears to be detrimental[83] although many succeeding workers have followed the original procedure. For the condensation of o-nitrobenzaldehyde with phenylacetic acid, potassium carbonate proved a more convenient catalyst than potassium phenylacetate, and it gave the same yield. Small amounts of acetic acid or moisture had no effect on the yield.

Fortunately, the presence of the carboxyl group leads to the formation of more of the trans-cinnamic acid with the aryl groups in the proper cis relationship than of its undesired stereoisomer. A discussion of the preparation of the o-nitrobenzaldehydes and of the phenylacetic acid derivatives is beyond the scope of this chapter. Examples of such preparations are available in many of the references cited in Table I.

A few nitrocinnamic acids such as LXXXIV have been prepared from



LXXXIV

o-nitrophenylacetic acid,[70] which is readily available from o-nitrotoluene. Condensation of o-nitrotoluene with diethyl oxalate in the presence of sodium methoxide followed by hydrolysis gives o-nitrophenylpyruvic acid, which is readily oxidized to o-nitrophenylacetic acid with hydrogen peroxide.[84]

The most satisfactory reducing agent for the nitro group is an ammoniacal suspension of ferrous hydroxide. The hydrated iron oxides are readily removed. Catalytic hydrogenation is difficult to control and often leads to partial reduction of the ethylenic bond.

Some of the amino acids exhibit an interesting polymorphism.[4,84a] Crystallization of trans-2-amino-α-phenylcinnamic acid from ethyl acetate leads to a bright yellow modification, m. p. 186–187°, whereas crystallization from ethanol gives colorless prisms sintering at 170° to give the yellow form which then melts at 185–187°.

Several cis-stilbene derivatives have been obtained by decarboxylating the cinnamic acid derivatives using the copper chromite hydrogenation

[82] DeTar, Org. Syntheses, 35, 89 (1955).
[83] Bogert and Stamatoff, Rec. trav. chim., 52, 584 (1933).
[84] May and Mossetig, J. Org. Chem., 11, 435 (1946).
[84a] Gulland and Virden, J. Chem. Soc., 1928, 1478.

catalyst in refluxing quinoline.[32,42,85] Rearrangement to the *trans* isomer occurs to only a relatively minor extent during the decarboxylation.

**Intermediates for Dihydrophenanthrenes.** Catalytic reduction of the 2-nitro-α-phenylcinnamic acids leads to the formation of *sym*-2-aminodiphenylethane derivatives. Another method utilizes the condensation of *p*-methoxybenzaldehyde with oxindole, followed by catalytic



reduction to give 3-(4'-methoxybenzyl)oxindole (LXXXV). The oxindole LXXXV can be hydrolyzed by aqueous barium hydroxide at 170–180°, to give α-(2-aminophenyl)-β-(4'-methoxyphenyl)propionic acid.[86] A third synthesis utilizes the condensation of a benzyl chloride with a phenylacetonitrile as in the preparation of LXXXVI.[87] The nitro



compound was reduced catalytically with 2% palladium on strontium carbonate in dioxane solution.

**Intermediates for Fluoranthenes.** The required 1-(2'-nitrophenyl)-naphthalene is usually obtained by a mixed Ullmann biaryl synthesis, as



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[85] DeTar and Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

[86] Windaus and Eickel, *Ber.*, **57**, 1871 (1924). Compare, Kirchner, *Nachr. Akad. Wiss. Göttingen*, **1921**, 154 (*Chem. Zentr.*, **1923**, I, 944).

[87] Cook, Dickson, Ellis and Loudon, *J. Chem. Soc.*, **1949**, 1074.

illustrated for the preparation of 1-(2'-nitro-4'-methylphenyl)naphthalene (LXXXVII); this product was isolated by a combination of distillation and chromatography and was hydrogenated catalytically using Raney nickel.[88]

**Intermediates for the Preparation of N-Substituted Carbazoles and Dibenzofurans.** The required 2-aminodiphenylamine or 2-amino-diphenyl ether is obtained by either catalytic or chemical reduction of the corresponding nitro compound,[30,89] the latter being obtained from an appropriate o-chloro- or o-bromo-nitrobenzene by reaction with an



aniline derivative[47] or with a phenolate salt.[90] The purpose of the copper powder in the 2-nitrodiphenyl ether preparation is less that of a catalyst than of an inhibitor.   In the absence of the copper, an exothermic reaction takes place leading to a black resin, due perhaps to oxidation of the phenol by the nitro compound.

**Intermediates for Fluorenones.** The preparation of 2-amino-benzophenones has been reviewed.[91]   One useful method starts with anthranilic acid.[92]   The amino group is protected with a p-toluenesulfonyl group, and then a Friedel-Crafts synthesis is carried out on the carboxyl function as illustrated in the preparation of LXXXVIII.   The protective p-toluenesulfonyl group is removed by acid hydrolysis.   By this procedure



LXXXVIII

[88] Tucker and Whalley, *J. Chem. Soc.*, **1949**, 3213.
[89] Gilman and Broadbent, *J. Am. Chem. Soc.*, **69**, 2053 (1947).
[90] Brewster and Groening, *Org. Syntheses Coll. Vol.* **2**, p. 445 (1943).
[91] Simpson, Atkinson, Schofield, and Stephenson, *J. Chem. Soc.*, **1945**, 646.
[92] Ullmann and Bleier, *Ber.*, **35**, 4273 (1902).

2-aminobenzophenone and 2-amino-4'-methylbenzophenone are obtained in a 50% over-all yield from anthranilic acid.[93] Unfortunately o-nitrobenzoyl chloride gives very poor yields in Friedel-Crafts reactions.[54] o-Chlorobenzoyl chloride reacts normally, but ammonolysis of the halogen is difficult.[94] On the other hand the o-carboxyl group of o-benzoylbenzoic acids can usually be converted to an amino group via the Hofmann or the Curtius reaction.[95,96] An interesting oxidation of indole derivatives obtained from phenyl-



hydrazones by the Fischer indole synthesis makes available a number of hitherto inaccessible 2-aminobenzophenones.[94]

## The Cyclization Reaction

The amine is usually diazotized in aqueous sulfuric acid. Insoluble or unreactive amines have been diazotized in acetic acid, methanol, or ethanol with butyl nitrite and sulfuric acid or hydrochloric acid. Amino acids are often dissolved in alkaline solutions along with sodium nitrite, the mixture being run into sulfuric acid.

The numerous methods for bringing about cyclization by decomposition of the diazonium salt fall into a relatively few classes. Although some comparative quantitative data are available on the efficiency of these cyclization procedures, it is necessary in most cases to rely on the evaluation of semiquantitative preparative runs.

**Method 1.** The diazonium salt solution is merely heated. This procedure nearly always gives some of the cyclization product if cyclization

[93] DeTar and Scheifele, Org. Syntheses, **32,** 8 (1952).

[94] Schofield and Theobald, J. Chem. Soc., **1950,** 1505.

[95] Graebe and Ullmann, Ann., **291,** 8 (1896).

[96] Wallis and Lane, in Adams, Organic Reactions, Vol. III, 267, John Wiley & Sons, New York, 1946; Smith, ibid., 337.

is structurally possible. In the fluorenone series the use of 50% sulfuric acid gives somewhat better yields of the fluorenone and less of the hydroxy-benzophenone than does 1 $N$ sulfuric acid.[97] Concentrations of sulfuric acid greater than 75% tend to give lower yields of 3-methylfluorenone, probably because of sulfonation (however, cf. the preparation of 2-nitro-fluorenone below, p. 438). For the production of phenanthrene this method is definitely inferior to Method 2 using copper powder.[32]

**Method 2.** The diazonium salt solution is heated in the presence of copper powder. Gattermann copper[98] prepared by reducing cupric sulfate with zinc dust has been used frequently, though other types of copper may be as good or better. The use of copper powder in the presence of alcoholic solvents is inadvisable except for the phenanthrene cyclization. In other systems the procedure leads to extensive replacement of the diazonium group by hydrogen.

For 2-(4'-methylbenzoyl)benzenediazonium salts, thermal decomposition in 1 $N$ sulfuric acid gave 65% of 3-methylfluorenone, while copper powder in 1 $N$ sulfuric acid gave a 50% yield and led to the formation of some 4-methylbenzophenone. In 50% sulfuric acid an 80% yield of cyclic product was produced whether or not copper or solid cuprous chloride was present. On the other hand 2-(3'-nitrobenzoyl)benzenediazonium salts gave a 35% yield of cyclic product in 1 $N$ sulfuric acid and a 55% yield in 50% sulfuric acid, but with copper powder present a 95% yield of cyclic product was formed in 1 $N$ sulfuric acid and an 85% yield in 50%. sulfuric acid. From 2 to 5% of 3-nitrobenzophenone was also produced when copper powder was present. The above results were obtained with crystalline diazonium salts and are based on quantitative chromatographic isolation of the fluorenone-benzophenone mixtures, these being analyzed by their infrared absorption spectra.[97]

**Method 3.** The diazonium salt solution is made alkaline and heated. In most cases this method gives poor results. It has been used successfully with some Pschorr cyclizations and may have particular merit if there is a hydroxyl group ortho to the diazonium group (resulting in the formation of a relatively stable diazo oxide rather than a diazonium salt).

**Method 4.** The diazonium salt solution is treated with sodium hypophosphite and copper. This procedure is usable only with the Pschorr cyclization. In all other cases it leads to replacement of the diazonium group by hydrogen. This procedure was first described by Ruggli and Staub[42] and appears to have become fashionable, although there does not appear to be any information about its merit in comparison with Method 2.

[97] DeTar and Whiteley, *J. Am. Chem. Soc.*, **79**, in press (1957).
[98] Gattermann, *Ber.*, **23**, 1219 (1890).

**Other Methods.** In a few examples the crystalline fluoborate has been suspended in acetone and stirred with copper powder.[25] The method may prove to be of advantage in some cases, but the reported high yields are mostly based on the fluoborate. Yields calculated on the basis of the amine are less attractive.

Another method consists of reaction of the diazonium salt with dimethylamine to give a triazine. The triazine is suspended in an organic solvent and treated with hydrogen chloride. The reported examples seem to give relatively poor yields.[25]

The N-nitrosoamide decomposes on heating to give some cyclization product.[25,98a] This method also seems to be of no particular preparative use.

### EXPERIMENTAL PROCEDURES

**1 - Bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic Acid.** (Pschorr synthesis using Gattermann copper paste[98] in an aqueous acidic medium.)[99]

(a) *Preparation of the amine,* trans-2-amino-6-bromo-3,4-dimethoxy-α-phenylcinnamic acid. A mixture of 15 g. of 6-bromo-3,4-dimethoxy-2-nitrobenzaldehyde (6-bromo-2-nitroveratraldehyde), 8.3 g. of dry sodium phenylacetate, and 90 ml. of acetic anhydride is heated at 100° for thirty hours. Water (750 ml.) is added and, after hydrolysis of the excess anhydride, an excess of ammonia is added and the mixture extracted with two 400-ml. portions of ether. Acidification of the aqueous layer gives 13 g. of the crude nitrocinnamic acid which gives 10.7 g. of material, m. p. 193–200° after one crystallization from methanol. Recrystallization of the combined products of several runs gives the pure nitrocinnamic acid, m. p. 206–208° (30% yield). Reduction with ammoniacal ferrous sulfate gives the aminocinnamic acid in 98% yield.

(b) *Cyclization.* To a mixture of 2 g. of trans-2-amino-6-bromo-3,4-dimethoxy-α-phenylcinnamic acid, 20 ml. of ethanol, and 5.2 ml. of 3 N hydrochloric acid is added at 0° a 50% solution of butyl nitrite in ethanol. After one-half hour, the orange solution is diluted with 200 ml. of water, and copper paste is added in small portions with mechanical stirring.* The mixture consisting of light green solution, copper powder, and a white solid, is extracted with ether. Sodium carbonate extraction of the ether followed by acidification of the extract gives 1.57 g. of 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid. The yield of partly purified product from several runs was 72–82%. After washing

[98a] DeTar and Savat, *J. Am. Chem. Soc.,* **75,** 7117 (1953).

[99] Small and Turnbull, *J. Am. Chem. Soc.,* **59,** 1541 (1937).

* The quantity of copper paste is not specified in the original article, but the writer has found that quantities of the order of one gram are satisfactory.

with acetone followed by several reerystallizations from ethanol and from acetic acid, the product melts at 260–270° (evac. tube).

**4,6-Dimethylphenanthrene-9-carboxylic Acid.**    (Pschorr synthesis using 75% ethanol as the solvent with copper and sodium hypophosphite as promoters.)[73]

(a) *Preparation of the amine,* trans-2-*amino*-3-*methyl-α-*(4′-*methylphenyl*) *cinnamic acid.*    A mixture of 37.6 g. (0.2 mole) of potassium *p*-methyl-phenylacetate, 33 g. (0.2 mole) of 2-nitro-3-methylbenzaldehyde, and 204 g. (2 moles) of acetic anhydride is heated with stirring for eight hours at 105–110°.    The anhydride is decomposed at 100° by careful addition of water, and the reaction mixture is poured into 1 l. of cold 5% hydrochloric acid.    The solid is recrystallized from acetic acid and then from ethanol to give 38 g. (65%) of the nitrocinnamic acid, m. p. 250.5–251.5°.    A suspension of 36 g. of the nitro acid in 500 ml. of warm dilute aqueous ammonia is stirred into a boiling mixture of 240 g. of hydrated ferrous sulfate, 500 ml. of water, and 500 ml. of 12 *M* aqueous ammonia.    Boiling is continued for an hour, and the mixture is allowed to stand overnight.    The filtrate from the hydrated iron oxides is acidified to Congo Red with hydrochloric acid.    The resulting crude amino acid is recrystallized from 70% methanol to give 27.2 g. (84%) of product, m. p. 176.5–177.5°.

(b) *Cyclization.*    A suspension of 15 g. of *trans*-2-amino-3-methyl-α-(4′-methylphenyl)cinnamic acid in 150 ml. of 15% ethanolic hydrogen chloride is stirred for an hour at 0°, then 20 ml. of freshly distilled amyl nitrite is added and stirring continued for another hour.    The solution is then added to a suspension of 1 g. of copper powder in a solution of 50 g. of sodium hypophosphite in 50 ml. of water containing 2 drops of concentrated sulfuric acid.    A violent evolution of nitrogen occurs, and the phenanthroic acid separates.    After stirring for thirty minutes with gentle heating, the solution is cooled and the acid collected and dissolved in sodium hydroxide solution.    The filtered alkaline solution is acidified and the 4,6-dimethyl-9-phenanthroic acid is recrystallized from 80% methanol, using decolorizing carbon (Norit), to give 10 g. (71%) of fine colorless needles, m. p. 216–217°.

**3-Chlorophenanthrene-9-carboxylic Acid.**    (Pschorr reaction via *o*-nitrophenylacetic acid; cyclization with copper powder in aqueous ethanol.)[84]

(a) *Preparation of the amine,* trans-4-*chloro-α*-(2′-*aminophenyl*)*cinnamic acid.*    A mixture of 28 g. of sodium *o*-nitrophenylacetate, 19 g. of *p*-chloro-benzaldehyde, 2.5 g. of fused zinc chloride, and 100 ml. of acetic anhydride is heated on the steam bath for twenty hours.    Excess anhydride is hydrolyzed, and the crude product is precipitated with water and

recrystallized from acetic acid to give the nitrocinnamic acid; 14.9 g., m. p. 196–199°. For reduction, 5.1 g. of the nitrocinnamic acid is dissolved in 50 ml. of 4 $M$ aqueous ammonia and added to a hot (80–90°) slurry prepared by addition of 85 ml. of 12 $M$ aqueous ammonia to a solution of 34 g. of ferrous sulfate in 102 ml. of water. After ten minutes the mixture is filtered through diatomaceous silica (Filter-Cel). Acidification gives 3.4 g. of the aminocinnamic acid. Attempted crystallization from ethanol gives the lactam, 4-chlorobenzaloxindole.

(b) *Cyclization.* To 80 ml. of 5 $N$ sulfuric acid cooled to −3 to +2° is added during twenty minutes a suspension of 5 g. of *trans*-4-chloro-α-(2′-aminophenyl)cinnamic acid, 3 g. of sodium nitrite, 75 ml. of water, and 2 ml. of $M$ aqueous ammonia. After an additional hour of stirring at 0 to 5°, 20–30 ml. of ethanol and 5 g. of copper-bronze are added, and the mixture is heated to 70–80° for one-half hour. The precipitate is collected on a filter and the alkali-soluble material leached from the copper with hot dilute sodium hydroxide. The alkaline filtrate on acidification gives crude 3-chlorophenanthrene-9-carboxylic acid, which on recrystallization from glacial acetic acid has a m. p. of 249–251°; yield 1.4 g.

**2-Nitrofluorenone.** (Fluorenone cyclization in concentrated sulfuric acid.)[100] To a solution of 3 g. of 2-amino-5-nitrobenzophenone in 30 ml. of concentrated sulfuric acid, 1 g. of powdered sodium nitrite is added over a period of fifteen minutes at −5 to 0°. The solution is heated at 95° for two hours, then diluted with 60 ml. of water. The product on recrystallization from ethanol gives 1.7 g. (60%) of 2-nitrofluorenone, m. p. 220–221°, and 0.4 g. (13%) of 2-hydroxy-5-nitrobenzophenone, m. p. 119–121°.

With 85% sulfuric acid the yields are 56 and 16%, respectively; with 50% sulfuric acid and copper powder the yields are 15 and 6%.

**11-Chrysofluorenone (LXXXIX).** (Fluorenone synthesis, use of copper powder; diazotization with isoamyl nitrite.)[101]



LXXXIX

[100] Nunn, Schofield, and Theobald, *J. Chem. Soc.*, **1952**, 2797.
[101] Orchin and Reggel, *J. Am. Chem. Soc.*, **73**, 436 (1951). The authors give extensive details.

(a)  *Preparation of the amine, 1-benzoyl-2-aminonaphthalene.*  1-Benzoyl-2-benzoylaminonaphthalene is prepared from 99 g. of 2-benzoylamino-naphthalene and 160 ml. of benzoyl chloride at a temperature of 100–110°, adding 234 g. of stannic chloride as condensing agent during thirty minutes.  The total reaction time is forty-five minutes.  After hydrolysis, the product is isolated by crystallization from ethanol.  A total of 104 g. (74%) of tan material, m. p. 155–157°, is obtained.  1-Benzoyl-2-amino-naphthalene is obtained in 93% yield by hydrolysis with potassium hydroxide in refluxing 80% ethanol for twelve to sixteen hours.

(b)  *Cyclization.*  To a stirred solution of 50 g. of 1-benzoyl-2-amino-naphthalene in 1.5 l. of acetic acid containing 21 ml. of sulfuric acid is added in two minutes a solution of 53 ml. of isoamyl nitrite in 250 ml. of acetic acid.  After thirty minutes, the solution is cooled in an ice bath and 25.5 g. of copper powder is added; reaction proceeds at ice temperature for thirty minutes, at room temperature for two and one-half hours, and at steam-bath temperature for three hours.  The mixture is then allowed to stand overnight.  Part of the acetic acid (1.2 l.) is removed by distillation, and the remaining solution is filtered and diluted with water.  From the tarry residue, by extraction, distillation, and crystallization, there is obtained 15 g. (33%) of 11-chrysofluorenone, m. p. 133.2–134.8°.  No alkali-soluble product is found.

The above procedure has been carried out a number of times with consistent results.  Variations in the procedure gave the following results: (a) on addition of copper at room temperature the mixture became hot and the yield dropped to 11%; (b) use of ethanol gave a very low yield; (c) addition of sodium hypophosphite with ethanol or acetic acid as solvent gave very low yields; and (d) use of half as much acetic acid gave a 26% yield.

**2-Bromo-4-methyldibenzofuran.**  (Cyclization by heating acidic solution of diazonium salt.)[102]  (a)  *Preparation of the amine, 2-amino-4-bromo-6-methyldiphenyl ether.*  A mixture of 14.2 g. (0.048 mole) of 2,5-dibromo-3-nitrotoluene and 6.86 g. (0.052 mole) of potassium phenoxide is heated at 170° for three hours.  The cooled mixture is treated with water, and the product is extracted with ether and recrystallized from petroleum ether (b. p. 60–68°) to give 12 g. (81%) of phenyl 2-nitro-4-bromo-6-methylphenyl ether, m. p. 92–94°.  The nitro group is reduced by dissolving 12 g. (0.039 mole) of the nitro compound in 150 ml. of dry ether to which 20.85 g. (0.093 mole) of stannous chloride has been added, and then saturating the resulting solution with hydrogen chloride at 0°. The hydrochloride separates as a light brown solid (10.9 g.) which is diazotized without further purification.

[102] Gilman, Van Ess, and Hayes, *J. Am. Chem. Soc.*, **61**, 643 (1939).

(b) *Cyclization.* The diazonium solution is added slowly to 150 ml. of boiling 50% sulfuric acid, and the furan steam-distilled to give 4 g. (40% based on the nitro compound) of material, m. p. 106–106.5° after recrystallization from ethanol.

**3-Cyanocarbazole.** (Example of preparation of a triazine and of a carbazole by thermal decomposition of the triazine.)[103] 2-Nitro-4-cyanodiphenylamine is prepared in 78% yield by heating to the boiling point equimolecular quantities of aniline and of 4-chloro-3-nitrobenzonitrile. Reduction in 78% yield is carried out with stannous chloride in glacial acetic acid and hydrochloric acid. Diazotization yields the triazole in 65% yield. The triazole (1 g.) is heated in a metal bath until nitrogen evolution ceases. Extraction with ethanol and recrystallization from toluene gives 0.3 g. (35%) of 3-cyanocarbazole, m. p. 184–185°.

### TABULAR SURVEY OF DIAZONIUM RING CLOSURE REACTIONS

The various examples of the cyclization reaction have been grouped in the following tables according to the type of bridge group involved. The examples are intended to be complete through May, 1956, although by the very nature of the subject some references will certainly have been overlooked. Table IV, which lists a number of examples of carbazole derivatives that have been prepared by heating triazoles, does not aim at completeness.

[103] Preston, Tucker, and Cameron, *J. Chem. Soc.*, **1942**, 500.

## TABLE I

### PHENANTHRENE DERIVATIVES

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{14}H_{10}$ | cis-2-Aminostilbene | Phenanthrene | Aq. $H_2SO_4$ | 16–42 | 32 |
| | | | Aq. $H_2SO_4$, Cu | 60–80 | 32, 42 |
| | | | $C_2H_5OH$, $H_2SO_4$, Cu | 65 | 42 |
| | | | $Na_2CO_3$ | — | 104 |
| | | | Aq. $H_2SO_4$, $NaH_2PO_2$, Cu | 80 | 42 |
| | cis-2,4'-Diaminostilbene | Phenanthrene | $C_2H_5OH$, $H_2SO_4$, Cu | 18 | 105 |
| $C_{15}H_8Br_2O_2$ | trans-2-Amino-4-bromo-α-(4'-bromophenyl)-cinnamic acid | 3,6-Dibromophenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, $Na_2CO_3$, Cu, $NaH_2PO_2$ | 70–90 crude | 106 |
| $C_{15}H_8Cl_2O_2$ | trans-2-Amino-α-(3',4'-dichlorophenyl)cinnamic acid | 5,6- and 6,7-Dichlorophenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu, $NaH_2PO_2$ | 75 crude | 107 |
| $C_{15}H_9BrO_2$ | trans-2-Amino-α-(2'-bromophenyl)cinnamic acid | 8-Bromophenanthrene-9-carboxylic acid | $C_2H_5OH$, HCl, Cu | 50–60 | 20 |
| | trans-2-Amino-α-(4'-bromophenyl)cinnamic acid | 6-Bromophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | — | 15, 108 |
| $C_{15}H_9ClO_2$ | trans-2-Amino-5-chloro-α-phenylcinnamic acid | 2-Chlorophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 65 | 108 |
| | trans-4-Chloro-α-(2'-aminophenyl)cinnamic acid | 3-Chlorophenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, $H_2SO_4$, Cu | 30 | 84 |
| | trans-2-Amino-α-(4'-chlorophenyl)cinnamic acid | 6-Chlorophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 28 | 109, 110 |
| | | | Aq. $H_2SO_4$, Cu | 58 | |
| $C_{15}H_9NO$ | 3-(2'-Aminobenzylidene)oxindole | Lactam of 8-aminophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 75 | 15 |
| $C_{15}H_9NO_4$ | trans-2-Amino-α-(2'-nitrophenyl)cinnamic acid | 8-Nitrophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 24 | 111 |
| | | | Acetone, Cu | 57 | |
| $C_{15}H_{10}O_2$ | trans-2-Amino-α-phenylcinnamic acid | Phenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 93 crude | 4, 25 |
| | | | Aq. $H_2SO_4$, Cu | 86 | 47 |
| | | | Aq. HCl, Cu bronze | 40 | 25 |
| | | | Aq. $H_2SO_4$ | 60 | 47 |
| | | | Aq. $p$H 5 | 57 | 25 |
| | | | Aq. $p$H 7 | 75 | 47 |
| | | | Dry, acetone, Cu* | 81 | 25 |
| | | | Dry, acetone, Cu* | 94 | 47 |
| | | | Nitrosoamide, $C_6H_6$ | 43 | 25 |
| | | | Nitrosoamide, $(C_2H_5)_2O$ | 37 | 25 |
| | | | Triazene† | 58 | 25 |
| | trans-2-Amino-α-(4'-aminophenyl)cinnamic acid | Phenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, $H_2SO_4$, Cu | 18 | 105 |

*Note:* References 104–225 are listed on pp. 460–462.

* The crystalline diazonium chloride was used, and the yield is based on the diazonium salt.

† The triazene was obtained by coupling the diazonium salt with dimethylamine.

## TABLE I—*Continued*

### PHENANTHRENE DERIVATIVES

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{15}H_{10}O_3$ | trans-2-Amino-5-hydroxy-α-phenylcinnamic acid | 2-Hydroxyphenanthrene-9-carboxylic acid | Aq. NaOH | 55 | 15 |
| $C_{16}H_8O_3$ | trans-2-Amino-α-(2'-carboxyphenyl)cinnamic acid | Anhydride of phenanthrene-8,9-dicarboxylic acid | Aq. acid | 40–45 | 15 |
| $C_{16}H_9NO_2$ | trans-2-Amino-α-(4'-cyanophenyl)cinnamic acid | 6-Cyanophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 58 | 111 |
| $C_{16}H_{10}O_4$ | trans-2-Amino-α-(4'-carboxyphenyl)cinnamic acid | Phenanthrene-6,9-dicarboxylic acid | Aq. $H_2SO_4$, Cu | 48 | 111 |
| | trans-2-Amino-4,5-methylenedioxy-α-phenylcinnamic acid | 2,3-Methylenedioxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, $H_2SO_4$, Cu | 85 | 112, 113 |
| $C_{16}H_{12}O_2$ | trans-2-Amino-5-methyl-α-phenylcinnamic acid | 2-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 75 crude | 70 |
| | trans-2-Amino-3-methyl-α-phenylcinnamic acid | 4-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 75 crude | 70 |
| | trans-2-Amino-α-(4'-methylphenyl)cinnamic acid | 6-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 20 | 15 |
| | | | $Na_2CO_3$ | 20 | |
| | | | HCl, $C_2H_5OH$, Cu | 70 | |
| | trans-α-(2'-Amino-5'-methylphenyl)cinnamic acid | 7-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 3 | 70 |
| | trans-2-Amino-α-(2'-methylphenyl)cinnamic acid | 8-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 60–70 | 15 |
| | trans-3-Methyl-α-(2'-aminophenyl)cinnamic acid | 2- and 4-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | — | 70 |
| | trans-2-Amino-α-(3'-methylphenyl)cinnamic acid | 7- and 5-Methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | — | 70 |
| $C_{16}H_{12}O_3$ | trans-2-Amino-5-methoxy-α-phenylcinnamic acid | 2-Methoxyphenanthrene-9-carboxylic acid | $Na_2CO_3$ | 80 | 10 |
| | trans-2-Amino-3-methoxy-α-phenylcinnamic acid | 4-Methoxyphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | Quant. | 8 |
| | trans-2-Amino-α-(4'-methoxyphenyl)cinnamic acid | 6-Methoxyphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | 50 | 5 |
| | trans-2-Amino-α-(2'-methoxyphenyl)cinnamic acid | 8-Methoxyphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | 55 | 5 |
| $C_{16}H_{12}O_4$ | trans-2-Amino-3-methoxy-4-hydroxy-α-phenylcinnamic acid | 3-Hydroxy-4-methoxyphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | ca. 3 | 7 |
| | trans-2-Amino-3-hydroxy-4-methoxy-α-phenylcinnamic acid | 4-Hydroxy-3-methoxyphenanthrene-9-carboxylic acid | NaOH | 60 crude | 13 |
| $C_{17}H_{11}BrO_5$ | trans-2-Amino-3-methoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid | 8-Bromo-4-methoxy-5,6-methylenedioxy-phenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | 57 | 72 |
| $C_{17}H_{12}O_5$ | trans-2-Amino-3-methoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid | 4-Methoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | — | 72 |

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{17}H_{13}BrO_4$ | trans-2-Amino-3,4-dimethoxy-6-bromo-α-phenylcinnamic acid | 1-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 70–80 | 99 |
| | trans-2-Amino-3,4-dimethoxy-5-bromo-α-phenylcinnamic acid | 2-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid | $C_2H_5OH$, HCl, Cu | 95 crude | 99 |
| | trans-2-Amino-3,4-dimethoxy-α-(2'-bromophenyl)cinnamic acid | 8-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 60 | 15 |
| | trans-2-Amino-α-(2'-bromo-4',5'-dimethoxyphenyl)cinnamic acid | 8-Bromo-5,6-dimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 60–65 | 19, 99 |
| $C_{17}H_{13}ClO_4$ | trans-2-Amino-4,5-dimethoxy-α-(4'-chlorophenyl)cinnamic acid | 6-Chloro-2,3-dimethoxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, $H_2SO_4$, Cu | 35 | 115 |
| $C_{17}H_{14}O_2$ | trans-2-Amino-3-methyl-α-(4'-methylphenyl)cinnamic acid | 4,6-Dimethylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu, $NaH_2PO_2$ | 71 | 73 |
| | trans-2-Amino-α-(2',5'-dimethylphenyl)cinnamic acid | 5,8-Dimethylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 85 crude | 116 |
| | trans-2-Amino-α-(2',4'-dimethylphenyl)cinnamic acid | 6,8-Dimethylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 87 crude | 83 |
| | trans-2-Amino-α-(3'-ethylphenyl)cinnamic acid | 5- and 7-Ethylphenanthrene-9-carboxylic acid | $H_2SO_4$, Cu | 95 | 117 |
| | trans-2-Amino-α-(4'-ethylphenyl)cinnamic acid | 6-Ethylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu / Aq. $C_2H_5OH$, HCl, Cu | 40 / 80 crude | 83 |
| $C_{17}H_{14}O_3$ | trans-2-Amino-3-methoxy-α-(2'-methylphenyl)cinnamic acid | 4-Methoxy-8-methylphenanthrene-9-carboxylic acid | NaOH | 43 | 118 |
| | trans-2-Amino-α-(5'-methoxy-2'-methylphenyl)cinnamic acid | 5-Methoxy-8-methylphenanthrene-9-carboxylic acid | $CH_3OH$, $H_2SO_4$ | — | 119 |
| | trans-2-Amino-α-(4'-methoxy-2'-methylphenyl)cinnamic acid | 6-Methoxy-8-methylphenanthrene-9-carboxylic acid | NaOH | — | 120 |
| | trans-2-Amino-α-(2'-methoxy-3-methylphenyl)cinnamic acid | 8-Methoxy-7-methylphenanthrene-9-carboxylic acid | $Na_2CO_3$, Cu | — | 62 |
| | trans-2-Amino-α-(4'-ethoxyphenyl)cinnamic acid | 6-Ethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | — | 114 |
| $C_{17}H_{14}O_4$ | trans-2-Amino-4,5-dimethoxy-α-phenylcinnamic acid | 2,3-Dimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 50–60 | 9 |
| | trans-2-Amino-3,4-dimethoxy-α-phenylcinnamic acid | 3,4-Dimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 70–80 / 80 | 7 / 121, 122 |
| | trans-2-Amino-α-(3,4-dimethoxyphenyl)cinnamic acid | 6,7-Dimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 60 | 19 |
| | trans-2-Amino-5-methoxy-α-(3'-methoxyphenyl)cinnamic acid | 2,5-Dimethoxyphenanthrene-9-carboxylic acid | Aq. $Na_2CO_3$ | 35 | 123 |
| | | 2,7-Dimethoxyphenanthrene-9-carboxylic acid | | 28 | |

*Note:* References 104–225 are listed on pp. 460–462.

## TABLE I—*Continued*

### PHENANTHRENE DERIVATIVES

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{17}H_{14}O_5$ | trans-2-Amino-3-hydroxy-4-methoxy-α-(4'-methoxyphenyl)cinnamic acid | 3,6-Dimethoxy-4-hydroxyphenanthrene-9-carboxylic acid | Aq. KOH | 70 | 12 |
| | trans-2-Amino-3-methoxy-4-hydroxy-α-(2'-methoxyphenyl)cinnamic acid | 4,8-Dimethoxy-3-hydroxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 20–25 | 6 |
| $C_{18}H_{12}O_5$ | trans-2-Amino-3,4-dimethoxy-α-(2'-carboxyphenyl)cinnamic acid | Anhydride of 3,4-dimethoxyphenanthrene-8,9-dicarboxylic acid | Aq. $H_2SO_4$ | 75 | 15 |
| $C_{18}H_{14}O_4$ | trans-2-Amino-4,5-methylenedioxy-α-(2',5'-dimethylphenyl)cinnamic acid | 5,8-Dimethyl-2,3-methylenedioxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 80 crude | 124 |
| $C_{18}H_{13}BrO_6$ | trans-2-Amino-5,6-dimethoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid | 8-Bromo-1,2-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid | — | — | 125 |
| | trans-2-Amino-5,6-dimethoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid | 8-Bromo-2,3-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid | — | — | 125 |
| $C_{18}H_{14}O_6$ | trans-2-Amino-5,6-dimethoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid | 1,2-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid and 1,2-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid | — | — | 125 |
| | trans-2-Amino-4,5-dimethoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid | 2,3-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid and 2,3-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid | — | — | 125 |
| | trans-2-Amino-3,4-dimethoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid | 3,4-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid | — | — | 125 |
| $C_{18}H_{15}BrO_5$ | trans-2-Amino-3,4-dimethoxy-α-(5'-bromo-2'-methoxyphenyl)cinnamic acid | 5-Bromo-3,4,8-trimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | — | 126 |
| | trans-2-Amino-3,4-dimethoxy-α-(2'-bromo-5'-methoxyphenyl)cinnamic acid | 8-Bromo-3,4,5-trimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 35–50 | 20, 127 |
| $C_{18}H_{18}$ | trans-2-Amino-3-methyl-α-(4'-ethylphenyl)cinnamic acid | 6-Ethyl-4-methylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu, $NaH_2PO_2$ | 58 | 73 |
| | trans-2-Amino-3-methyl-α-(3'-ethylphenyl)cinnamic acid | 7-Ethyl-4-methylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu, $NaH_2PO_2$ | 30 | 73 |

| | | | | | |
|---|---|---|---|---|---|
| $C_{18}H_{16}O_4$ | trans-2-Amion-3,4-dimethoxy-α-(4'-methyl-phenyl)cinnamic acid | 3,4-Dimethoxy-6-methylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 80 | 15 |
| | trans-2-Amino-3,4-dimethoxy-α-(2'-methyl-phenyl)cinnamic acid | 3,4-Dimethoxy-8-methylphenanthrene-9-carboxylic acid | Aq. $Na_2CO_3$ | 90 crude | 15 |
| | trans-2-Amino-4-hydroxy-3-methoxy-α-(2',5'-dimethylphenyl)cinnamic acid | 5,8-Dimethyl-3-hydroxy-4-methoxy-phenanthrene-9-carboxylic acid | Dioxane, $H_2SO_4$, Cu, $NaH_2PO_2$ | 47 crude | 128 |
| $C_{18}H_{16}O_5$ | trans-2-Amino-3,4-dimethoxy-α-(4'-methoxy-phenyl)cinnamic acid | 3,4,6-Trimethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 70 | 12 |
| | trans-2-Amino-3,4-dimethoxy-α-(2'-methoxy-phenyl)cinnamic acid | 3,4,8-Trimethoxyphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | — | 16 |
| | trans-2-Amino-3,4-dimethoxy-α-(3'-methoxy-phenyl)cinnamic acid | 3,4,5- and 3,4,7-Trimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$ | — | 20 |
| $C_{19}H_{12}O_2$ | trans-2-Amino-α-(2'-naphthyl)cinnamic acid | Benzo[c]phenanthrene-6-carboxylic acid<br>Benz[a]anthracene-6-carboxylic acid | Aq. $H_2SO_4$, Cu | 6<br>0.6 | 76, 129, 130 |
| | trans-2-Amino-α-(1'-naphthyl)cinnamic acid | Chrysene-5-carboxylic acid | Aq. $C_2H_5OH$, $H_2SO_4$, Cu, $NaH_2PO_2$ | 28 | 74, 130 |
| $C_{19}H_{17}BrO_6$ | trans-2-Amino-3,4-dimethoxy-α-(2'-bromo-4',5'-dimethoxyphenyl)cinnamic acid | 8-Bromo-3,4,5,6-tetramethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 27 | 131, 132 |
| $C_{19}H_{18}O_2$ | trans-2-Amino-α-(2',3',4',5'-tetramethylphenyl)-cinnamic acid | 5,6,7,8-Tetramethylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 30 | 133a |
| | trans-2-Amino-α-(2'-methyl-5'-isopropylphenyl)-cinnamic acid | 8-Methyl-5-isopropylphenanthrene-9-carboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 65 crude | 83 |
| | trans-2-Amino-α-(2'-methyl-4'-isopropylphenyl)cinnamic acid | 6-Isopropyl-8-methylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 61 | 133b |
| $C_{19}H_{18}O_4$ | trans-2-Amino-3,4-dimethoxy-α-(2',5'-dimethylphenyl)cinnamic acid | 3,4-Dimethoxy-5,8-dimethylphenanthrene-9-carboxylic acid | Dioxane, $H_2SO_4$, $NaH_2PO_2$, Cu | 50 | 128 |
| | trans-2-Amino-4,5-dimethoxy-α-(2',5'-dimethylphenyl)cinnamic acid | 2,3-Dimethoxy-5,8-dimethylphenanthrene-9-carboxylic acid | Dioxane, $H_2SO_4$, $NaH_2PO_2$, Cu | 83 crude | 134 |
| $C_{19}H_{18}O_5$ | trans-2-Amino-3,4-dimethoxy-α-(2'-ethoxy-phenyl)cinnamic acid | 8-Ethoxy-3,4-dimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$,$H_2SO_4$ | 80 | 17 |
| $C_{19}H_{18}O_6$ | trans-2-Amino-3,4,5-trimethoxy-α-(4'-methoxy-phenyl)cinnamic acid | 2,3,4,6-Tetramethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 50 | 135, 136 |
| | trans-2-Amino-5-methoxy-α-(3',4',5'-trimethoxy-phenyl)cinnamic acid | 2,5,6,7-Tetramethoxyphenanthrene-9-carboxylic acid | Aq. dioxane, $NaH_2PO_2$, Cu, $H_2SO_4$ | 63 | 137 |
| | | | Aq. $Na_2CO_3$ | — | 138 |

*Note:* References 104–225 are listed on pp. 460–462.

## TABLE I—*Continued*

### PHENANTHRENE DERIVATIVES

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{19}H_{18}O_6$ (Cont.) | trans-2-Amino-3,4-dimethoxy-α-(2',5'-dimethoxyphenyl)cinnamic acid | 3,4,5,8-Tetramethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$ | 50 crude | 139 |
| | trans-2-Amino-3,4-dimethoxy-α-(2',4'-dimethoxyphenyl)cinnamic acid | 3,4,6,8-Tetramethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$ | 30 | 18 |
| | trans-3,4,5-Trimethoxy-α-(2'-amino-5'-methoxyphenyl)cinnamic acid | 2,3,4,7-Tetramethoxyphenanthrene-9-carboxylic acid | Dimethylformamide, $H_2SO_4$, Cu | 65 | 140 |
| | trans-2-Amino-3,4,5-trimethoxy-α-(3'-methoxy-phenyl)cinnamic acid | 2,3,4,5- and 2,3,4,7-Tetramethoxy-phenanthrene-9-carboxylic acid | Aq. $Na_2CO_3$ | — | 136 |
| | trans-2-Amino-3,4-dimethoxy-α-(3',4'-dimethoxyphenyl)cinnamic acid | 3,4,5,6-Tetramethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 6 | 131, 132 |
| | | 3,4,6,7-Tetramethoxyphenanthrene-9-carboxylic acid | | 13 | |
| $C_{20}H_{12}O_4$ | trans-2-Amino-4,5-methylenedioxy-α-(1'-naphthyl)cinnamic acid | 8,9-Methylenedioxychrysene-5-carboxylic acid | Aq. dioxane, $C_2H_5OH$, $H_2SO_4$, Cu, $NaH_2PO_2$ | 95 crude | 141 |
| $C_{20}H_{14}O_3$ | trans-2-Amino-5-methoxy-α-(1'-naphthyl)-cinnamic acid | 8-Methoxychrysene-5-carboxylic acid | Aq. $C_2H_5OH$, $Na_2CO_3$ | 25 | 81 |
| $C_{20}H_{20}O_5$ | trans-2-Amino-3,4-dimethoxy-α-(5'-ethyl-2'-methoxyphenyl)cinnamic acid | 5-Ethyl-3,4,8-trimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$<br>Aq. $CH_3OH$, $H_2SO_4$, Cu | 35<br>35 | 142 |
| $C_{20}H_{20}O_6$ | trans-2-Amino-3,4-dimethoxy-α-(4'-ethoxy-3'-methoxy)cinnamic acid | 6-Ethoxy-3,4,7-trimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | 35 | 143 |
| | | 6-Ethoxy-3,4,5-trimethoxyphenanthrene-9-carboxylic acid | | 13 | |
| | trans-2-Amino-3,4-dimethoxy-α-(3'-ethoxy-4'-methoxyphenyl)cinnamic acid | 7-Ethoxy-3,4,6-trimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | 35 | 143 |
| | | 5-Ethoxy-3,4,6-trimethoxyphenanthrene-9-carboxylic acid | | 9 | |
| $C_{21}H_{14}O_2$ | trans-2-Amino-α-(3'-acenaphthenyl)cinnamic acid | Cholanthrene-12-carboxylic acid | Dioxane, $C_2H_5OH$, Cu, $NaH_2PO_2$ | 5 | 144 |
| $C_{21}H_{16}O_2$ | trans-2-Amino-α-(3',4'-dimethyl-1'-naphthyl)-cinnamic acid | 11,12-Dimethylchrysene-5-carboxylic acid | Aq. $H_2SO_4$, Cu | 30 | 145 |
| $C_{21}H_{16}O_4$ | trans-2-Amino-3,4-dimethoxy-α-(1'-naphthyl)-cinnamic acid | 1,2-Dimethoxychrysene-6-carboxylic acid | Aq. (iso $C_5H_{11})_2O$, $H_2SO_4$, Cu, $NaH_2PO_2$ | 65 crude | 146 |

| | | | | | |
|---|---|---|---|---|---|
| $C_{21}H_{22}O_6$ | *trans*-2-Amino-3-ethoxy-4-methoxy-α-(3'-ethoxy-4'-methoxyphenyl)cinnamic acid | 4,5-Diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid and 4,7-diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | — | 71 |
| | *trans*-2-Amino-3-ethoxy-4-methoxy-α-(4'-ethoxy-3'-methoxyphenyl)cinnamic acid | 4,6-Diethoxy-3,5-dimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | 15 | 71 |
| | | 4,6-Diethoxy-3,7-dimethoxyphenanthrene-9-carboxylic acid | | 38 | |
| | *trans*-2-Amino-4-ethoxy-3-methoxy-α-(3'-ethoxy-4'-methoxyphenyl)cinnamic acid | 3,5-Diethoxy-4,6-dimethoxyphenanthrene-9-carboxylic acid | Aq. $CH_3OH$, $H_2SO_4$, Cu | 19 | 71 |
| | | 3,7-Diethoxy-4,6-dimethoxyphenanthrene-9-carboxylic acid | | 50 | |
| | *trans*-2-Amino-4,5-dimethoxy-α-(2'-ethyl-4',5'-dimethoxyphenyl)cinnamic acid | 8-Ethyl-2,3,5,6-tetraethoxyphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$ | 60 crude | 147 |
| $C_{22}H_{14}O_2$ | *trans*-2-Amino-α-(2'-fluorenyl)cinnamic acid | 13-Naphtho[1,2-a]fluorene-6-carboxylic acid | $C_2H_5OH$, HCl, Cu | 60 | 148 |
| $C_{23}H_{16}O_3$ | *trans*-2-Amino-α-(2'-phenoxymethylphenyl)cinnamic acid | 8-Phenoxymethylphenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 50 | 149 |
| $C_{24}H_{14}$ | 2,2'-Diamino-6,6'-diphenylbiphenyl | Dibenzo[el]pyrene | Aq. $H_2SO_4$ | 36–40‡ | 78 |
| $C_{24}H_{14}O_4$ | α,α'-Bis-(o-aminobenzylidene)-p-benzenediacetic acid | Dibenzo[cg]phenanthrene-2,5-dicarboxylic acid and dibenz[ah]anthracene-6,13-dicarboxylic acid | Aq. $H_2SO_4$, Cu | 95 crude | 150, 151 |
| | α,α'-Bis-(o-aminobenzylidene)-m-benzenediacetic acid | Dibenz[aj]anthracene-6,8-dicarboxylic acid | Aq. $H_2SO_4$, Cu | 12 | 77, 152 |
| | | 2-Hydroxy-α-(10-carboxy-2-phenanthryl)cinnamic acid | | 28 | |
| | α,α'-Bis-(o-aminobenzylidene)-o-benzenediacetic acid | Picene-6,7-dicarboxylic acid | Aq. $H_2SO_4$, Cu | 11 | 153 |
| $C_{24}H_{16}$ | *cis*-2-(1'-Naphthyl)-1-(2'-aminophenyl)-1-phenylethene | 6-Phenylchrysene | Aq. $CH_3CO_2H$, HCl | 65 crude | 43 |
| $C_{26}H_{18}O_4$ | α,α'-Bis-(o-aminobenzylidene)-2,5-dimethyl-p-benzenediacetic acid | 7,14-Dimethyldibenz[ah]anthracene-6,13-dicarboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 20 crude | 124 |
| $C_{26}H_{18}O_6$ | α,α'-Bis-(2-amino-5-methoxybenzylidene)-p-benzenediacetic acid | 8,13-Dimethoxydibenzo[cg]phenanthrene-2,5-dicarboxylic acid | Aq. $Na_2CO_3$ | 11 | 154 |
| | | 3,10-Dimethoxydibenz[ah]anthracene-6,13-dicarboxylic acid | | 8 | |
| $C_{28}H_{18}O_8$ | α,α'-Bis-(6-aminopiperonylidene)-2,5-dimethyl-p-benzenediacetic acid | 7,14-Dimethyl-2,3,9,10-bis(methylenedioxy)dibenz[ah]anthracene-6,13-dicarboxylic acid | Aq. $C_2H_5OH$, HCl, Cu | 25 crude | 124 |
| $C_{30}H_{26}O$ | α,α'-Bis-(6-aminoveratrylidene)-2,5-dimethyl-p-benzenediacetic acid | 2,3,9,10-Tetramethoxy-7,14-dimethyl-dibenz[ah]anthracene-6,13-dicarboxylic acid | Dioxane, $H_2SO_4$, Cu, $NaH_2PO_2$ | 60 crude | 155 |
| | | | Aq. $H_2SO_4$, Cu | — | 155 |

*Note:* References 104–225 are listed on pp. 460–462.

‡ The yield was independent of temperature and of the presence of or absence of copper powder.

## TABLE II

### DIHYDROPHENANTHRENE DERIVATIVES

| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{13}H_{11}N$ | 1-(2'-Aminophenyl)-2-(2''-pyridyl)ethane | 5,6-Dihydrobenzo[f]quinoline | Aq. dioxane, $H_2SO_4$, Cu | 4 | 25 |
| | | | Nitrosoamide | 40 | 25 |
| | | | Triazene* | 0 | 25 |
| $C_{14}H_{12}$ | 1-(2'-Aminophenyl)-2-phenylethane | 9,10-Dihydrophenanthrene | $C_2H_5OH$, $H_2SO_4$, Cu | 20 | 42 |
| $C_{15}H_{12}O_2$ | α-Phenyl-β-(2-aminophenyl)propionic acid | 9,10-Dihydrophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | — | 4, 86 |
| | α-(2-Aminophenyl)-β-phenyl)propionic acid | 9,10-Dihydrophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | — | 86 |
| $C_{16}H_{12}O_4$ | α-(2-Aminophenyl)-β-(3',4'-methylenedioxy-phenyl)propionic acid | 2,3(or 3,4-)-Methylenedioxy-9,10-dihydrop-henanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 20 | 86 |
| $C_{16}H_{14}O_3$ | α-(2-Aminophenyl)-β-(4'-methoxyphenyl)propionic acid | 3-Methoxy-9,10-dihydrophenanthrene-9-carboxylic acid | Aq. $H_2SO_4$, Cu | 15 | 86 |
| | α-(2-Aminophenyl)-β-phenylbutyric acid | 10-Methyl-9,10-dihydrophenanthrene-9-carboxylic acid | Aq. $H_2SO$, Cu | Small | 156 |
| $C_{19}H_{19}NO_4$ | α-(2-Amino-5-methoxyphenyl)-β-(3',4',5'-trimethoxyphenyl)propionitrile | 2,3,4,7-Tetramethoxy-9-cyano-9,10-dihydro-phenanthrene | Aq. dioxane, HCl, Cu | 45 | 87 |
| | | | $Na_2CO_3$ or $CH_3CO_2Na$ | None | |

*Note:* References 104–225 are listed on pp. 460–462.

* The triazene was prepared by coupling the diazonium salt with dimethylamine and was then heated in benzene solution while hydrogen chloride was bubbled in.

## TABLE III

### FLUORANTHENE DERIVATIVES

Numbering System for Fluoranthene



| Product Formula | Starting Amine | Product | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{16}H_{10}$ | 1-(2'-Aminophenyl)naphthalene | Fluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$, Cu | 48 | 45 |
| $C_{17}H_{12}$ | 1-(2'-Amino-6'-methylphenyl)naphthalene | 7-Methylfluoranthene | Aq. $H_2SO_4$, Cu | — | 88, 157 |
| | 1-(2'-Amino-3'-methylphenyl)naphthalene | 7-Methylfluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$ | 45* | 157 |
| | 1-(2'-Amino-4'-methylphenyl)naphthalene | 8-Methylfluoranthene | Aq. $H_2SO_4$, Cu | — | 88 |
| $C_{17}H_{12}O$ | 1-(2'-Aminophenyl)-2-methoxynaphthalene | 1-Methoxyfluoranthene | Aq. $H_2SO_4$, Cu | — | 158 |
| | 1-(2'-Aminophenyl)-4-methoxynaphthalene | 3-Methoxyfluoranthene | Aq. $H_2SO_4$, Cu | 48 | 158 |
| | 1-(2'-Methoxyphenyl)-8-aminonaphthalene | 7-Methoxyfluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$, Cu | — | 158 |
| | 1-(2'-Amino-4'-methoxyphenyl)naphthalene | 8-Methoxyfluoranthene | Aq. HCl, Cu | 52 | 159 |
| $C_{18}H_{14}$ | 1-(2'-Aminophenyl)-2,4-dimethylnaphthalene | 1,3-Dimethylfluoranthene | Aq. $H_2SO_4$, Cu | Poor | 45 |
| $C_{19}H_{14}O_2$ | 1-(2'-Amino-4'-carbethoxyphenyl)naphthalene | Ethyl fluoranthene-8-carboxylate | Aq. $H_2SO_4$, Cu | 15 | 88 |
| $C_{19}H_{16}$ | 1-(2'-Aminophenyl)-2,3,4-trimethylnaphthalene | 1,2,3-Trimethylfluoranthene | Aq. $H_2SO_4$, Cu | — | 160 |
| $C_{22}H_{12}$ | 3-(2'-Aminophenyl)fluoranthene | Indeno[1,2,3-cd]fluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$, Cu | 38 | 161 |
| $C_{23}H_{14}$ | 4-(2'-Aminophenyl)-1-methylfluoranthene | 5-Methylindeno[1,2,3-cd]fluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$, Cu | — | 162 |
| | 4-(2'-Aminophenyl)-2-methylfluoranthene | 5-Methylindeno[1,2,3-cd]fluoranthene | Aq. $CH_3CO_2H$, $H_2SO_4$, Cu | — | 162 |

*Note:* References 104–225 are listed on pp. 460–462.
* The use of copper did not increase the yield.

## TABLE IV

### CARBAZOLE DERIVATIVES PREPARED VIA TRIAZOLES

Numbering System for Carbazole



| Product | | | Product | | |
|---|---|---|---|---|---|
| Formula | Name | References | Formula | Name | References |
| $C_{11}H_8N_2$ | 5-Pyrid[4,3-b]indole | 163 | $C_{14}H_{13}N$ | 1,3-Dimethylcarbazole | 165 |
| $C_{12}H_7N_3O_4$ | 1,3-Dinitrocarbazole | 164 | $C_{16}H_9N_3O_4$ | 8,10-Dinitro-7-benz[kl]acridine | 164 |
| $C_{12}H_8ClN$ | 2-Chlorocarbazole | 165 | $C_{16}H_{11}N$ | Benzo[a]carbazole | 164 |
| | 3-Chlorocarbazole | 165, 166 | | 7-Benz[kl]acridine | 164 |
| $C_{12}H_8N_2$ | 2-Aminocarbazole | 163 | $C_{17}H_{13}N$ | 10-Methylbenzo[c]carbazole | 165 |
| | 3-Aminocarbazole | 165 | $C_{19}H_{13}NO$ | 3-Benzoylcarbazole | 169 |
| $C_{12}H_8N_2O_2$ | 1-Nitrocarbazole | 103 | $C_{20}H_{10}BrNO_2$ | 7-Bromo-12-naphtho[2,3-a]carbazole-5,13-dione | 168 |
| | 3-Nitrocarbazole | 103 | | | |
| $C_{12}H_9N$ | Carbazole | 69, 167 | $C_{20}H_{11}NO_2$ | 12-Naphtho[2,3-a]carbazole-5,13-dione | 168 |
| $C_{13}H_8N_2$ | 3-Cyanocarbazole | 103 | | | |
| $C_{13}H_{11}N$ | 1-Methylcarbazole | 165 | $C_{24}H_{16}N_2$ | 1,1'-Bicarbazole | 170 |
| | 3-Methylcarbazole | 165 | | 3,9'-Bicarbazole | 171 |
| $C_{13}H_{12}N_2$ | 3-Amino-6-methylcarbazole | 163 | | 3,3'-Bicarbazole | 172 |
| $C_{14}H_{11}NO$ | 3-Acetylcarbazole | 103 | $C_{26}H_{17}NO_2$ | 3,6-Dibenzoylcarbazole | 173 |

*Note:* References 104–225 are listed on pp. 460–462.

TABLE V

## TABLE V

### CARBAZOLE DERIVATIVES

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{13}H_{10}N_2O_2$ | N-Methyl-2-amino-2'-nitrodiphenylamine | 9-Methyl-1-nitrocarbazole | Aq. $H_2SO_4$,Cu | 9 | 47 |
| | | | Aq. $H_2SO_4$ | 38 | 47 |
| | | | Acetone, $HBF_4$, Cu* | 24 | 47 |
| $C_{13}H_{11}N$ | N-Methyl-2-aminodiphenylamine | 9-Methylcarbazole | Aq. $H_2SO_4$ | 60 | 47 |
| | | | Aq. $H_2SO_4$, Cu | 67 | 47 |
| | | | Acetone, $HBF_4$, Cu* | 43 | 47 |
| | | | Aq. NaOH | 60 | 166 |
| | N-Methyl-2-amino-2'-carboxydiphenylamine | 9-Methylcarbazole | Aq. NaOH | 30 crude | 174 |
| $C_{14}H_{13}N$ | N-Ethyl-2-aminodiphenylamine | 9-Ethylcarbazole | NaOH | — | 166 |
| | N-Ethyl-2-amino-2'-carboxydiphenylamine | 9-Ethylcarbazole | NaOH | 40 | 174 |
| $C_{18}H_{11}N$ | 9-(2'-Aminophenyl)carbazole | Indolo[3,2,1-jk]carbazole | Aq. $CH_3CO_2H$, $H_2SO_4$ | 55 | 53 |
| | | | Aq. $CH_3OH$, $H_2SO_4$ | Poor | 53 |
| | | | NaOH | Poor | 53 |
| | 9-Phenyl-1-aminocarbazole | Indolo[3,2,1-jk]carbazole | Aq. $CH_3CO_2H$, $H_2SO_4$ | 35 | 175 |
| $C_{19}H_{11}NO_2$ | 9-(2'-Aminophenyl)-3-carbethoxycarbazole | Indolo[3,2,1-jk]carbazole-6-carboxylic acid | Aq. $CH_3CO_2H$, $H_2SO_4$ | — | 53 |
| | 9-(2'-Amino-4'-carboxyphenyl)carbazole | Indolo[3,2,1-jk]carbazole-3-carboxylic acid | Aq. $CH_3CO_2H$, $H_2SO_4$ | 20 | 53 |
| $C_{19}H_{13}N$ | 9-(2'-Amino-4'-methylphenyl)carbazole | 3-Methylindolo[3,2,1-jk]carbazole | Aq. $CH_3CO_2H$, $H_2SO_4$ | — | 53 |
| $C_{24}H_{19}NO_4$ | 9-(2'-Aminophenyl)carbazole-3,6-dicarboxylic acid, diethyl ester | Indolo[3,2,1-jk]carbazole-3,6-dicarboxylic acid, diethyl ester | Aq. $CH_3CO_2H$, $H_2SO_4$ | 45 | 53 |

*Note:* References 104–225 are listed on pp. 460–462.

* The crystalline diazonium fluoborate was used.

## TABLE VI

### DIBENZOFURAN DERIVATIVES AND SULFUR ANALOGS

Numbering System for Dibenzofuran



| Product Formula | Starting Material | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{12}H_6Br_2O$ | 2-Amino-4',5-dibromodiphenyl ether | 2,7-Dibromodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| | 2-Amino-4,4'-dibromodiphenyl ether | 2,8-Dibromodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| $C_{12}H_6ClNO_3$ | 2-Amino-4'-chloro-5-nitrodiphenyl ether | 2-Chloro-7-nitrodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| $C_{12}H_6Cl_2O$ | 2-Amino-4,4'-dichlorodiphenyl ether | 2,8-Dichlorodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| $C_{12}H_7BrO$ | 2-Amino-4-bromodiphenyl ether | 2-Bromodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| | 2-Amino-4'-bromodiphenyl ether | 2-Bromodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| | 2-Amino-5-bromodiphenyl ether | 3-Bromodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| $C_{12}H_7ClO$ | 2-Amino-4-chlorodiphenyl ether | 2-Chlorodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| | 2-Amino-4'-chlorodiphenyl ether | 2-Chlorodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| | 2-Amino-5-chlorodiphenyl ether | 3-Chlorodibenzofuran | Aq. $H_2SO_4$ | 3 | 177 |
| $C_{12}H_7NO_3$ | 2-Amino-5-nitrodiphenyl ether | 3-Nitrodibenzofuran | Aq. $H_2SO_4$ | — | 176 |
| $C_{12}H_8O$ | 2-Aminodiphenyl ether | Dibenzofuran | Aq. $H_2SO_4$ | 30 | 178 |
| | | | Aq. $H_2SO_4$ | 45 | 30 |
| | | | Aq. NaOH + CuOH | 0 | 30 |
| | | | Aq. NaOH | 0 | 30 |
| $C_{13}H_7BrO_3$ | 2-Amino-4'-bromo-6-carboxydiphenyl ether | 2-Bromodibenzofuran-6-carboxylic acid | Aq. $H_2SO_4$ | 15 | 102 |
| $C_{13}H_9BrO$ | 2-Amino-4-bromo-6-methyldiphenyl ether | 2-Bromo-4-methyldibenzofuran | Aq. $H_2SO_4$ | 40 | 102 |
| $C_{13}H_9BrO_2$ | 2-Amino-4-bromo-4'-methoxydiphenyl ether | 2-Bromo-8-methoxydibenzofuran | Aq. $H_2SO_4$ | 8 | 58 |
| $C_{12}H_7NO_2S$ | 2-Amino-4-nitrodiphenyl sulfide | 2-Nitrodibenzothiophene | Aq. $H_2SO_4$ | 20 | 179 |
| $C_{12}H_8S$ | 2-Aminodiphenyl sulfide | Dibenzothiophene | Aq. $H_2SO_4$ | 40 | 46 |
| | | | Aq. $H_2SO_4$ | 15 | 30 |
| | | | Aq. $H_2SO_4$, Cu | 25–35 | 30 |
| | | | Aq. $H_2SO_4$, $CuSO_4$ | 25 | 30 |
| | | | $pH$ 8–9 | 10 | 30 |
| $C_{12}H_8O_2S$ | 2-Aminodiphenyl sulfone | Dibenzothiophene dioxide | $H_2SO_4$, $CuSO_4$ | 5 | 30 |
| | | | $H_2SO_4$, Cu | <30 | 30 |
| | | | NaOH | None | 30 |
| | | | HCl, Cu | 22 | 180 |
| $C_{12}H_8Se$ | 2-Aminodiphenyl selenide | Dibenzoselenophene | 85% $H_2SO_4$ | Trace | 46 |
| $C_{13}H_{10}S$ | 2-Amino-4'-methyldiphenyl sulfide | 2-Methyldibenzothiophene | Aq. $H_2SO_4$ | 22 | 30 |
| | | | Aq. $H_2SO_4$, Cu | 23–40 | 30 |
| | | | Aq. NaOH | None | 30 |
| $C_{13}H_{10}O_2S$ | 2-Amino-4'-methyldiphenyl sulfone | 2-Methyldibenzothiophene dioxide | Aq. $H_2SO_4$, Cu | 3 | 30 |
| $C_{14}H_{11}NO_3S$ | 2-Amino-4-nitro-4'-ethoxydiphenyl sulfide | 2-Ethoxy-8-nitrodibenzothiophene | Aq. $CH_3CO_2H$, HCl, Cu | 70 | 181 |
| $C_{16}H_{10}O_2S$ | 2-Aminophenyl-1'-naphthyl sulfone | Naphtho[1,2-b]thianaphthene-11-dioxide | Aq. $CH_3CO_2H$, HCl, Cu | 32 | 180 |
| | | | $H_2SO_4$ | Trace | 180 |
| | 2-Aminophenyl-2'-naphthyl sulfone | Naphtho[2,1-b]thianaphthene-7-dioxide | Aq. $CH_3CO_2H$, HCl, Cu | — | 180 |
| $C_{16}H_{10}S$ | 2-Aminophenyl-1'-naphthyl sulfide | Naphtho[1,2-b]thianaphthene | Aq. $CH_3COOH$, HCl, Cu | 0 | 180 |
| | 1-Amino-2-naphthyl phenyl sulfide | Naphtho[2,1-b]thianaphthene | 50% $H_2SO_4$ | 2 | 182 |

*Note:* References 104–225 are listed on pp. 460–462.

## TABLE VII

### FLUORENE DERIVATIVES

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{13}H_{10}$ | 2-Aminodiphenylmethane | Fluorene | Aq. HCl | 13 | 47 |
| | | | Aq. HCl, Cu | 0 | 47 |
| | | | $(C_2H_5)_2O$, Cu | 0 | 47 |
| | | | Acetone, Cu | 0 | 47 |
| | | | Aq. $H_2SO_4$ | — | 1 |
| | | | Nitrosamide, $C_6H_6$ | 0 | 47 |
| $C_{23}H_{23}N_3O_2$ | Bis-(4'-dimethylaminophenyl)-2-amino-5-nitrophenylmethane | 3,4'-Bis(dimethylamino)-7-nitro-9-phenyl-fluorene | Aq. $H_2SO_4$ | — | 183 |
| $C_{23}H_{24}N_2$ | Bis-(4'-dimethylaminophenyl)-2-aminophenyl-methane | 3,4'-Bis(dimethylamino)-9-phenylfluorene | Aq. $H_2SO_4$ | 16 | 183 |
| $C_{24}H_{24}N_2$ | Bis-(4'-dimethylaminophenyl)-2-amino-5-methylphenylmethane | 3,4'-Bis(dimethylamino)-7-methyl-9-phenylfluorene | Aq. $H_2SO_4$ | 22 | 183 |
| $C_{25}H_{29}N_3$ | Bis-(4'-dimethylaminophenyl)-2-amino-4-dimethylaminophenylmethane | 3,7,4'-Tris(dimethylamino)-9-phenylfluorene | 70% $H_2SO_4$ | 30 | 184 |
| $C_{27}H_{26}N_2$ | Bis-(4'-dimethylaminophenyl)-2-amino-1-naphthylmethane | 8,4'-Bis(dimethylamino)-11-phenylbenzo[a]-fluorene | Aq. $H_2SO_4$ | — | 183 |

*Note:* References 104–225 are listed on pp. 460–462.

## TABLE VIII

### FLUORENONE DERIVATIVES

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{13}H_6N_2O_5$ | 2-Amino-3,5-dinitrobenzophenone | 2,4-Dinitrofluorenone | Aq. $H_2SO_4$ | 78 crude | 185 |
| $C_{13}H_7BrO$ | 2-Amino-6-bromobenzophenone | 1-Bromofluorenone | Aq. $H_2SO_4$ | 25 | 186 |
| $C_{13}H_7NO_3$ | 2-Amino-6-nitrobenzophenone | 1-Nitrofluorenone | Aq. $H_2SO_4$ | 7 | 100 |
| | 2-Amino-2'-nitrobenzophenone | 1-Nitrofluorenone | Aq. $H_2SO_4$ | 9 | 47 |
| | | | Aq. $H_2SO_4$, Cu | 7 | 47 |
| | | | Acetone, Cu | 0 | 47 |
| | 2-Amino-5-nitrobenzophenone | 2-Nitrofluorenone | Aq. $H_2SO_4$ | 55–60 | 100, 187 |
| | | | Aq. $H_2SO_4$, Cu | 45 | |
| | 2-Amino-4-nitrobenzophenone | 3-Nitrofluorenone | Aq. $CH_3CO_2Na$, Cu | 95 crude | 100 |
| | 2-Amino-3-nitrobenzophenone | 4-Nitrofluorenone | Aq. $H_2SO_4$ | 48 | 100 |
| | 2-Amino-3'-nitrobenzophenone | 2-Nitrofluorenone | Aq. $H_2SO_4$ | 20* | 31 |
| | | 4-Nitrofluorenone | | 15* | |
| $C_{13}H_8O$ | 2-Aminobenzophenone | Fluorenone | Aq. $H_2SO_4$ | 65* | 31 |
| | | | Aq. $H_4SO_4$, $CuSO_4$ | 60* | 31 |
| | | | Aq. $H_2SO_4$, Cu | 71* | 31 |
| | | | $pH$ 9, 12 | 25* | 31 |
| | | | Acetone, Cu | 0 | 47 |
| | | | Aq. HCl, $H_3PO_2$, Cu | 0 | 47 |
| | | | $NH_4OH$ + Cu | 10 | 30 |
| | | | NaOH | 20 | 31, 47 |
| | | | Aq. $H_2SO_4$ | 80 | 95 |
| $C_{14}H_8N_2O_5$ | 2-Amino-6-methyl-3,5-dinitrobenzophenone | 1-Methyl-2,4-dinitrofluorenone | Aq. $H_2SO_4$ | 65 | 188 |
| | 2-Amino-4-methyl-3,5-dinitrobenzophenone | 3-Methyl-2,4-dinitrofluorenone | Aq. $H_2SO_4$ | 50 | 188 |
| $C_{14}H_8O_3$ | 2-Amino-2'-carboxybenzophenone | Fluorene-1-carboxylic acid | Aq. $H_2SO_4$ | 10 | 61 |
| | | Fluorene | | 10 | |

*Note:* References 104–225 are listed on pp. 460–462.

* These yields are based on the isolated diazonium fluoborate; the other yields in the table are based on the amine.

## TABLE VIII—*Continued*

### FLUORENONE DERIVATIVES

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{14}H_9NO_3$ | 2-Amino-6-methyl-3-nitrobenzophenone | 1-Methyl-4-nitrofluorenone | Aq. $H_2SO_4$ | 55 | 188 |
| | 2-Amino-4-methyl-5-nitrobenzophenone | 3-Methyl-2-nitrofluorenone | Aq. $H_2SO_4$ | 60 | 189 |
| | 2-Amino-4'-methyl-5-nitrobenzophenone | 3-Methyl-7-nitrofluorenone | Aq. $H_2SO_4$ | 75 crude | 189 |
| $C_{14}H_{10}O$ | 2-Amino-2'-methylbenzophenone | 1-Methylfluorenone | Aq. HCl | 50 | 75, 192 |
| | 2-Amino-3'-methylbenzophenone | 2-Methylfluorenone | Aq. HCl | low | 75 |
| | 2-Amino-4'-methylbenzophenone | 3-Methylfluorenone | Aq. $H_2SO_4$ | 60* | 31, 187, 189 |
| $C_{14}H_{10}O_2$ | 2-Amino-4'-methoxybenzophenone | 3-Methoxyfluorenone | Aq. $H_2SO_4$ | 80 crude | 92, 190 |
| $C_{15}H_{11}NO_3$ | 2-Amino-4',6-dimethyl-3-nitrobenzophenone | 1,6-Dimethyl-4-nitrofluorenone | Aq. $H_2SO_4$ | 55 | 188 |
| | 2-Amino-4,4'-dimethyl-5-nitrobenzophenone | 3,6-Dimethyl-2-nitrofluorenone | Aq. $H_2SO_4$ | 60 | 191 |
| $C_{15}H_{12}O$ | 2-Amino-2',4'-dimethylbenzophenone | 1,3-Dimethylfluorenone | Aq. $H_2SO_4$ | 70 | 66 |
| | 2-Amino-2',5'-dimethylbenzophenone | 1,4-Dimethylfluorenone | Aq. $H_2SO_4$, Cu | <50 | 54 |
| | 2-Amino-5,2'-dimethylbenzophenone | 1,7-Dimethylfluorenone | Aq. $H_2SO_4$ | 58 | 192 |
| | 2-Amino-4,4'-dimethylbenzophenone | 3,6-Dimethylfluorenone | Aq. $H_2SO_4$ | 70 | 191 |
| $C_{15}H_{12}O_3$ | 2-Amino-4,5-dimethoxybenzophenone | 2,3-Dimethoxyfluorenone | Aq. HCl | — | 193 |
| | 2-Amino-3',4'-dimethoxybenzophenone | 2,3-Dimethoxyfluorenone | Aq. $H_2SO_4$ | 60 crude | 57 |
| $C_{17}H_{10}O$ | 1-Benzoyl-2-naphthylamine | 11-Chrysofluorenone | $CH_3CO_2H$, $H_2SO_4$, Cu | 33 | 101 |
| | 1-(2'-Aminobenzoyl)naphthalene | 11-Chrysofluorenone | Aq. HCl | 25 | 75, 194 |
| | 3-Benzoyl-2-naphthylamine | 11-Benzo[b]fluoren-11-one | Aq. HCl | 13 | 75 |
| | 2-(2'-Aminobenzoyl)naphthalene | 7-Benzo[c]fluoren-7-one | Aq. HCl | Traces | 75 |
| $C_{18}H_{12}O$ | 1-(2'-Aminobenzoyl)-2-methylnaphthalene | 6-Methyl-7-benz[de]anthracene-7-one | Aq. HCl | 10 | 75 |
| $C_{18}H_{12}O_2$ | 1-(2'-Aminobenzoyl)-4-methoxynaphthalene | 5-Methoxy-11-chrysofluorenone | Aq. $CH_3CO_2H$, HCl | 55 | 57 |
| $C_{21}H_{12}O$ | 3-(2'-Naphthoyl)-2-naphthylamine | 12-Dibenzo[bh]fluoren-12-one | Aq. HCl | 20 | 75 |
| $C_{23}H_{14}O_3$ | 1-Amino-2-(2',5'-dimethylbenzoyl)anthraquinone | 9,12-Dimethyl-8-naphtho[2,3-c]fluoren-5,8,13-trione | Aq. $H_2SO_4$, Cu | 25 | 195 |

*Note:* References 104–225 are listed on pp. 460–462.

* These yields are based on the isolated diazonium fluoborate; the other yields in the table are based on the amine.

## TABLE IX

### PHENANTHRIDONES

Numbering System for Phenanthridone

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{14}H_8N_3O_5$ | N-(2'-Aminobenzoyl)-3,5-dinitro-N-methylaniline | 5-Methyl-1,3-dinitro-6(5)-phenanthridone | Acetone, Cu* | 35 | 65 |
| $C_{14}H_{10}BrNO$ | N-(2'-Aminobenzoyi)-4-bromo-N-methylaniline | 5-Methyl-2-bromo-6(5)-phenanthridone | Acetone, Cu* | 33 | 196 |
| $C_{14}H_{10}ClNO$ | N-(2'-Aminobenzoyl)-4-chloro-N-methylaniline | 5-Methyl-2-chloro-6(5)-phenanthridone | Acetone, Cu* | 44 | 196 |
| $C_{14}H_{10}N_2O_3$ | N-(2'-Aminobenzoyl)-4-nitro-N-methylaniline | 5-Methyl-2-nitro-6(5)-phenanthridone | Acetone, Cu* | 28 | 65 |
| $C_{14}H_{11}NO$ | N-(2'-Aminobenzoyl)-N-methylaniline | 5-Methyl-6(5)-phenanthridone | Aq. $H_2SO_4$ | 50 | 48 |
| | | | Aq. $H_2SO_4$, Cu | 50 | 48 |
| | | | Aq. HCl | 29 | 48, 197 |
| | | | Aq. NaOH | 11 | 48 |
| | | | Dioxane, $H_2SO_4$, $H_3PO_2$, Cu | 40 | 48 |
| | | | Acetone, $H_2SO_4$, Cu | 53 | 48 |
| | | | Acetone, $HBF_4$, Cu* | 50 | 48 |
| | | | $ArN_2BF_4$, pet. ether | 17 | 48 |
| $C_{15}H_{11}NO_3$ | N-(2'-Amino-4',5'-methylenedioxybenzoyl)-N-methylaniline | 5-Methyl-8,9-methylenedioxy-6(5)-phenanthridone | Aq. $H_2SO_4$ | 50 | 64 |
| $C_{15}H_{12}BrNO$ | N-(2'-Aminobenzoyl)-4-bromo-N-ethylaniline | 3-Bromo-5-ethyl-6(5)-phenanthridone | — | — | 225 |
| $C_{15}H_{13}NO$ | N-(2'-Aminobenzoyl)-N-methyl-4-toluidine | 2,5-Dimethyl-6(5)-phenanthridone | Acetone, Cu* | 50 | 196 |
| $C_{16}H_{13}NO_3$ | N-(2'Amino-4'carbomethoxybenzoyl)-N-methylaniline | 5-Methyl-9-carbomethoxy-6(5)-phenanthridone | Aq. $H_2SO_4$ or acetone, Cu* | 35 | 196 |
| $C_{16}H_{15}NO$ | N-(2'-Aminobenzoyl)-2,4,N-trimethylaniline | 2,4,5-Trimethyl-6(5)-phenanthridone | Aq. HCl, Cu | 10 | 66 |
| | N-(2'-Aminobenzoyl)-4-methyl-N-ethylaniline | 5-Ethyl-3-methyl-6(5)-phenanthridone | — | — | 225 |
| $C_{19}H_{11}NO$ | N-(2'-Aminobenzoyl)carbazole | 13-Indolo[3,2,1-de]phenanthridin-13-one | Aq. $H_2SO_4$ | — | 173 |
| $C_{20}H_{15}NO$ | N-(2'-Aminobenzoyl)-N-benzylaniline | 5-Benzyl-6(5)-phenanthridone | Aq. acid | 54† | 198 |
| $C_{22}H_{19}NO$ | N-(2'-Aminobenzoyl)-4-ethoxy-N-benzylaniline | 5-Benzyl-2-ethoxy-6(5)-phenanthridone | — | — | 198 |

*Note:* References 104–225 are listed on pp. 460–462.

\* The crystalline diazonium salt was used.

† The yield was the same in the presence or absence of copper.

## TABLE X

### APORPHINE DERIVATIVES

Numbering System for Aporphine



The *Chemical Abstracts* name is 6-methyl-5,6,6a,7-tetrahydro-4-dibenzo[de,g]quinoline, and the numbering starts at aporphine C5.

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{17}H_{15}NO_2$ | 1-(2'-Aminobenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline | 5,6-Methylenedioxynoraporphine | Aq. $CH_3OH$, $H_2SO_4$ | 22 | 50 |
| $C_{17}H_{17}N$ | 1-(2'-Aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline | Aporphine | Aq. HCl, Cu | 20 | 199 |
| $C_{18}H_{17}NO_2$ | 1-(2'-Aminobenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline | 5,6-Methylenedioxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 24 | 50, 51 |
| $C_{19}H_{15}NO_5$ | 1-(2'-Amino-4',5'-methylenedioxybenzoyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,3,5,6-Bis-methylenedioxy-12-ketoaporphine | Aq. $CH_3OH$, $H_2SO_4$, Cu | 30 | 200 |
| $C_{19}H_{19}NO_3$ | 1-(2'-Amino-5'-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline | 2-Methoxy-5,6-methylenedioxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 20 | 201, 202 |
| | 1-(2'-Amino-4'-methoxybenzyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3-Methoxy-5,6-methylenedioxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 24 | 201, 203 |
| | 1-(2'-Amino-3'-methoxybenzyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 4-Methoxy-5,6-methylenedioxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 15 | 204 |
| $C_{19}H_{21}NO_2$ | 1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3,4-Dimethoxyaporphine | Aq. $H_2SO_4$, Cu | 40 | 205, 21 |
| | 1-(2'-Aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline | 5,6-Dimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ / Aq. $H_2SO_4$, Cu | 15 / 10 | 206 / 206 |
| $C_{20}H_{21}NO_4$ | 1-(2'-Amino-4',5'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline | 2,3-Dimethoxy-5,6-methylenedioxyaporphine | Aq. $H_2SO_4$, Cu | 15 | 207 |
| | 1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline | 3,4-Dimethoxy-5,6-methylenedioxyaporphine | Aq. $CH_3CH$, $H_2SO_4$ | 25 | 208, 209 |
| | 1-(2'-Amino-4',5'-methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 5,6-Dimethoxy-2,3-methylenedioxyaporphine | Aq. $H_2SO_4$, Cu | 25 | 210 |

| Product Formula | Starting Amine | Product | Procedure | Yield, % | Reference |
|---|---|---|---|---|---|
| $C_{20}H_{23}NO_3$ | 1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline | 3,4,6-Trimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | — | 211 |
| | 1-(2'-Amino-4'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3,5,6-Trimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 24 | 212 |
| $C_{21}H_{23}NO_4$ | 1-(2'-Amino-4',5'-methylenedioxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 5-Ethoxy-6-methoxy-2,3-methylenedioxyaporphine | Aq. $H_2SO_4$, Cu | 15 | 213 |
| | 1-(2'-Amino-4',5'-methylenedioxybenzyl)-6-ethoxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 6-Ethoxy-5-methoxy-2,3-methylenedioxyaporphine | Aq. $H_2SO_4$, Cu | 20 | 214 |
| $C_{21}H_{23}NO_5$ | 1-(2'-Amino-4',5'-dimethoxybenzoyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,3,5,6-Tetramethoxy-12-ketoaporphine | Aq. $CH_3OH$, $H_2SO_4$, Cu | 30 | 200 |
| $C_{21}H_{25}NO_4$ | 1-(2'-Amino-4',5'-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,3,5,6-Tetramethoxyaporphine (glaucine) | Aq. $H_2SO_4$, Cu | — | 14, 55 |
| | 1-(2'-Amino-4',5'-dimethoxybenzyl)-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,3,6,7-Tetramethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 25 | 215 |
| | 1-(2'-Amino-3',4'-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3,4,5,6-Tetramethoxyaporphine | Aq. $H_2SO_4$, Cu / Aq. $CH_3OH$, $H_2SO_4$ | 35 / 15 | 216 / 217 |
| | 1-(2'-Amino-3',4'-dimethoxybenzyl)-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3,4,6,7-Tetramethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 25 | 215 |
| $C_{22}H_{26}N_2O_4$ | 1-(2'-Amino-4'-acetamino-3'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3-Acetamino-4,5,6-trimethoxyaporphine | Aq. $H_2SO_4$, Cu | 3 | 218 |
| $C_{22}H_{27}NO_3$ | 1-(2'-Amino-4'-ethoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline | 3-Ethoxy-5,6-dimethoxy-10-ethylnoraporphine | Cu | 11 | 219 |
| $C_{22}H_{27}NO_4$ | 1-(2'-Amino-4'-ethoxy-5'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3-Ethoxy-2,5,6-trimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 27 crude | 220 |
| | 1-(2'-Amino-4',5'-dimethoxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 5-Ethoxy-2,3,6-trimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 20 | 220 |
| $C_{23}H_{29}NO_4$ | 1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,5-Diethoxy-3,6-dimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 5–10 | 221 |
| | 1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-6-ethoxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 2,6-Diethoxy-3,5-dimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 10 | 221 |
| | 1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline | 2-Ethoxy-3,5,6-trimethoxy-10-ethylnoraporphine | Aq. $CH_3OH$, $H_2SO_4$ | 23 | 222 |
| | 1-(2'-Amino-4'-ethoxy-5'-methoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline | 3-Ethoxy-2,5,6-trimethoxy-10-ethylnoraporphine | Aq. $CH_3OH$, $H_2SO_4$ | 22–24 | 222 |
| $C_{25}H_{23}NO_3$ | 1-(2'-Amino-3',4'-dimethoxybenzyl)-6-benzyloxy-3,4-dihydroisoquinoline | 6-Benzyloxy-3,4-dimethoxy-10,11-dehydronoraporphine | Aq. $H_2SO_4$, Cu | — | 223 |
| $C_{27}H_{29}NO_4$ | 1-(2'-Amino-4'-benzyloxy-5'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 3-Benzyloxy-2,5,6-trimethoxyaporphine | Aq. $CH_3OH$, $H_2SO_4$ | 64 crude | 224 |

*Note:* References 104–225 are listed on pp. 460–462.

## TABLE XI

### Sultones and Sultams

| Molecular Formula of Sultone | Corresponding Sulfonic Acid | Yield, % | Reference |
|---|---|---|---|
| $C_{12}H_6Cl_2O_3S$ | 4,5′-Dichloro-2′-hydroxybiphenyl-2-sulfonic acid | 16* | 49 |
| $C_{12}H_7ClO_3S$ | 5′-Chloro-2′-hydroxybiphenyl-2-sulfonic acid | 15 | 49 |
| $C_{12}H_7ClO_3S$ | 5-Chloro-2′-hydroxybiphenyl-2-sulfonic acid | 80 | 49 |
| $C_{12}H_8O_3S$ | 2′-Hydroxybiphenyl-2-sulfonic acid | 52 | 49 |
| $C_{13}H_9ClO_3S$ | 5-Chloro-2′-hydroxy-5′-methylbiphenyl-2-sulfonic acid | 46 | 49 |
| $C_{16}H_{10}O_3S$ | 1-(2′-Sulfophenyl)-2-naphthol | 50 | 49 |
| $C_{16}H_{10}O_3S$ | 2-(2′-Sulfophenyl)-1-naphthol | 32 | 49 |
| $C_{17}H_{18}O_3S$ | 5′-tert-Amyl-2′-hydroxybiphenyl-2-sulfonic acid | 23 | 49 |

| Molecular Formula of Sultam | Sultams | | |
|---|---|---|---|
| $C_{12}H_9NO_3S$ | Sultam of 2′-amino-2-biphenylsulfonic acid | 76† | 52 |
| $C_{13}H_{11}NO_2S$ | Sultam of 2′-methylamino-2-biphenylsulfonic acid | 80† | 52 |
| $C_{16}H_{11}NO_2S$ | Sultam of 2-(2′-amino-1-naphthyl)-benzenesulfonic acid | 90‡ | 52 |

* The sultones were all prepared by heating the diazonium salt in the presence of copper powder

† The sultam was prepared by heating the aqueous solution of the diazonium salt.

‡ The sultam was prepared by pyrolysis of the triazene in the presence of sodium hydroxide and copper powder.

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