

CHAPTER 1

PREPARATION OF KETONES FROM THE REACTION OF ORGANOLITHIUM REAGENTS WITH CARBOXYLIC ACIDS

MARGARET J. JORGENSEN*

University of California, Berkeley, California

CONTENTS

	PAGE
INTRODUCTION	2
MECHANISM	4
SCOPE AND LIMITATIONS	5
The Organolithium Reagent	5
General Effects on Reactivity	5
Reaction with Solvents	7
Structural Variation and Complexities	8
Stereochemical Stability	13
The Carboxylic Acid	14
Failures Due to Steric Effects	14
Other Structural Effects on Reactivity	15
Reactions at Multiple Bonds	17
Competitive Metalation Reactions	21
Failures Due to Breakdown of Dilithio Intermediates	26
Interference by Other Functional Groups	28
Stereochemical Fate of the α -Carbon Atom	31
Design of Synthesis	32
FORMATION OF TERTIARY ALCOHOLS AS A SIDE REACTION	35
RELATED KETONE-FORMING REACTIONS	39
COMPARISON WITH OTHER KETONE SYNTHESSES	43
EXPERIMENTAL FACTORS	52
Preparation and Handling of Organolithium Reagents	52
Solvents	54
Selection of Experimental Conditions	55
Preparation of Lithium Carboxylates	57

* Deceased, March 12, 1970

EXPERIMENTAL PROCEDURES	57
4- <i>t</i> -Butylcyclohexyl Methyl Ketone	58
Cyclohexyl Methyl Ketone	58
<i>t</i> -Butyl Phenyl Ketone	59
Isobutenyl Phenyl Ketone	60
α, α, α -Trifluoroacetophenone	60
4- <i>t</i> -Butylcyclohexylideneacetone	61
6-Methyl-5-hepten-2-one-1- ¹⁴ C	61
4,4-Diphenyl-3-buten-2-one	62
1-Methyl-1-benzoyl-2,2-diphenylcyclopropane	63
(-)-4-Benzoyl[3.2]paracyclophane	63
3-Acetyl-5-methylpyrazole	64
TABULAR SURVEY	64
Table I. Reaction of Saturated Carboxylic Acids and Organolithium Reagents	65
A. Aliphatic Acyclic Carboxylic Acids	65
B. Aliphatic Alicyclic Carboxylic Acids	69
C. Aromatic Carboxylic Acids	78
Table II. Reactions of Unsaturated Carboxylic Acids and Organolithium Reagents	83
A. α, β -Unsaturated Carboxylic Acids	83
B. Other Unsaturated Carboxylic Acids	85
Table III. Reactions of Aromatic Carboxylic Acids and Organolithium Reagents	90
A. Benzoic and Naphthoic Acids	90
B. Heterocyclic Carboxylic Acids	93
REFERENCES TO TABLES	97

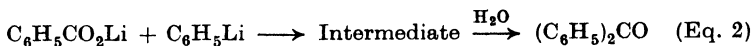
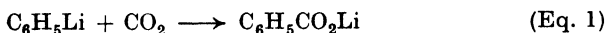
INTRODUCTION

The reaction of organolithium reagents and carboxylic acids constitutes a simple general method for the synthesis of ketones. Utilization of this reaction, known since 1933,¹ has received impetus in recent years from the commercial availability of numerous organolithium reagents. This preparative route is currently the method of choice for the direct conversion of carboxylic acids to ketones. Although a cursory evaluation of the reaction of methylolithium with carboxylic acids has been published,² no comprehensive review of the reactions of organolithium reagents with carboxylic acids has appeared. It is the purpose of this chapter to evaluate critically the scope and limitations of this reaction and to recommend optimal experimental conditions for its application.

¹ H. Gilman and P. R. van Ess, *J. Amer. Chem. Soc.*, **55**, 1258 (1933).

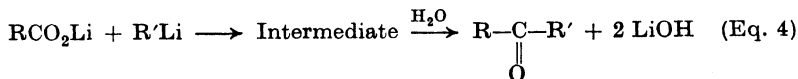
² C. Tegner, *Acta Chem. Scand.* **6**, 782 (1952).

The synthetic potential of the reaction of carboxylic acids with organolithium reagents was first recognized by Gilman and Van Ess who discovered this transformation as a side reaction during studies of the carbonation of organolithium reagents.¹ From the reaction of phenyllithium with carbon dioxide, benzophenone was formed in 70% yield. It was postulated that the process involved a two-step reaction sequence *via* lithium benzoate (Eqs. 1 and 2). The high yields of ketones obtained by



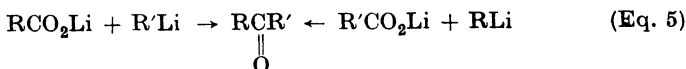
these authors from the reaction of lithium benzoate or lithium butyrate and phenyllithium furnished compelling support for this proposed scheme. It is evident that the reaction of organolithium reagents with carbon dioxide can serve as a useful synthesis of symmetrical ketones.

For a general case, the reaction of 2 moles of organolithium reagent with 1 mole of carboxylic acid can be viewed as taking place in two discrete steps: the first (Eq. 3) leads to the lithium salt of the carboxylic acid, the second, the reaction of the lithium carboxylate with another mole of organolithium reagent (Eq. 4), furnishes ketone after hydrolysis.



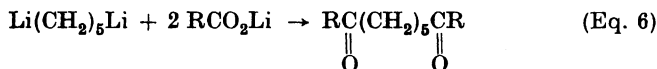
Hence, either the free acid or the lithium carboxylate can serve as the starting material in this preparation. The relative merits of the two methods are considered in the experimental section.

The reaction of organolithium reagents with carboxylic acids is limited to the preparation of acyclic ketones. Although the objective of this reaction is, generally, the formation of an unsymmetrical ketone, the method is clearly applicable to the synthesis of symmetrical ketones. Two different routes (Eq. 5)* to the same unsymmetrical ketone are possible; the group R may be derived either from the carboxylic acid or from the organolithium reagent. In practice, one of these routes will be preferred because of the availability of the reagents or structural limitations inherent in one of the reagents. This topic is treated under "Design of Synthesis."



* In this and subsequent reactions of organolithium reagents and carboxylic acids or their lithium salts the hydrolysis is not shown as a separate step.

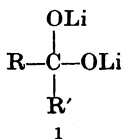
To date, the reaction has been applied only to the preparation of mono-ketones. However, the conversion of dilithium reagents to diketones, as exemplified in Eq. 6 for 1,5-dilithiopentane, should be viable. Such a transformation would constitute a valuable extension of this synthetic reaction, but its potential has not been explored.



MECHANISM

The singular feature believed to make the formation of ketones from carboxylic acids and organolithium reagents possible is the stability of the intermediate dilithium compounds. In this respect the reaction differs markedly from the reaction of organolithium reagents with carboxylic esters, acid chlorides, or anhydrides. With the latter three classes of compounds, the facile decomposition of the organometallic intermediate to a ketone in the reaction mixture makes tertiary alcohols rather than ketones the usual products.

The mechanistic course of the reaction of organolithium reagents and carboxylic acids, partially depicted in Eqs. 3 and 4, needs to be supplemented by a clear specification of the structure of the intermediate. This intermediate can be formulated as 1, on the basis of chemical and analytical studies conducted on the solid intermediate formed upon reaction of phenyllithium with lithium benzoate³ and from the isolation of an intermediate of this structure when $\text{R} = \text{R}' = \text{CF}_3$.⁴



A mechanistic study of this reaction has not been undertaken. By analogy with the reaction of ketones with organolithium reagents, which has been investigated,⁵ the reaction depicted in Eq. 4 can be considered to be a relatively slow nucleophilic attack by the organolithium reagent on the carbonyl carbon atom of the lithium carboxylate. The reaction between the free carboxylic acid and the organolithium reagent (Eq. 3) and the hydrolysis of 1 (Eq. 4) are very fast.

³ H. F. Bluhn, H. V. Donn, and H. D. Zook, *J. Amer. Chem. Soc.* **77**, 4406 (1955).

⁴ P. H. Ogden and G. C. Nicholson, *Tetrahedron Lett.*, **1968**, 3553.

⁵ (a) C. G. Swain and L. Kent, *J. Amer. Chem. Soc.*, **72**, 518 (1950). (b) S. G. Smith, *Tetrahedron Lett.*, **1968**, 6075.

Whether the stability of the dilithio intermediate is the sole factor responsible for the high yields of ketones is not known. Some success in ketone formation has been reported, for example, from the reaction of Grignard reagents with carboxylic acids or their salts.⁶ Yields from these reactions are inferior, probably owing to the better leaving-group tendency of OMg compared to OLi, so that intermediates in this reaction are less stable and give rise to alcohols. (For these reasons the reaction possesses no generality as a synthetic method.) It is reasonable to conclude that at least four factors are responsible for the higher yields of ketones from the reaction of carboxylic acids with organolithium reagents compared to those from the reaction with other organometallic reagents: the greater nucleophilicity of the organolithium reagent compared to that of organomagnesium reagents;¹ the appreciable solubility of the less ionic lithium carboxylate compared to other metal carboxylates (the critical role played by the solubility of the carboxylate salt in some reactions is discussed later); the greater susceptibility to nucleophilic attack at the carbonyl carbon atom of lithium carboxylates, compared to other metal carboxylates which have a more highly developed ionic character; and the greater stability of the dilithium intermediate **1** compared to other metal dialkoxides.

SCOPE AND LIMITATIONS

The Organolithium Reagent

General Effects on Reactivity. A comparative study of the reactivities of various alkyl- and aryl-lithium reagents with lithium carboxylates has not been undertaken. In general, reactions appear to take place readily with all organolithium reagents, since high yields of ketones are obtained after reaction at room temperature for periods as short as 10 minutes. The reactivity of various organolithium compounds with ketones^{5a} and nitriles⁷ conforms to the following order: phenyllithium > ethyllithium > isopropyllithium. This order differs from that recorded for the relative reactivities in the halogen-metal interchange reaction: *n*-propyl > ethyl > *n*-butyl > phenyl > methyl.⁸ In the aliphatic series, methyllithium has the lowest reactivity.

In addition to electronic factors inherent in the structure of the organolithium reagent, external factors also determine the reactivity of these

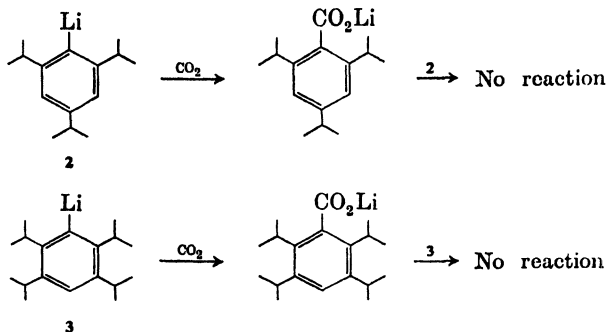
⁶ M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, pp. 948-960 and references therein, Prentice-Hall, Englewood Cliffs, N.J., 1954.

⁷ H. Gilman, E. St. John, N. St. John, and M. Lichtenwalter, *Rec. Trav. Chim. Pays-Bas*, **55**, 577 (1936).

⁸ R. R. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

reagents. The solvent for the reaction determines the nucleophilic reactivity of the organolithium reagent by affecting the degree of association⁹ and the degree of polarity of the carbon-lithium bond.¹⁰ Metalations occur more readily in tetrahydrofuran than in diethyl ether,¹¹ probably because of a more highly developed ionic character of the organolithium reagent in the former, better cation-solvating medium. Additives also affect the nucleophilic capacity of the organolithium reagent; thus in the presence of alkoxides, *n*-butyllithium has been shown to become more reactive.¹² An extensive literature exists on the structure and behavior of organolithium reagents which should be consulted for the properties of individual organolithium reagents.

Steric effects in the organolithium reagent have not been specifically studied. Such effects are probably relatively unimportant, since *t*-butyllithium reacts readily with lithium carboxylates. It is likely that steric effects in the organolithium reagent will exert themselves only when the reagent is employed in conjunction with a highly hindered lithium carboxylate. It has been reported that the substituted phenyllithium reagents **2** and **3** carbonate normally, but do not react further to yield ketones.¹³ Reaction of the intermediate lithium carboxylates with the aryllithium reagents **2** and **3** appears to be sterically precluded. It is not clear whether these reagents, **2** and **3**, would react even with unhindered carboxylic acid salts. Except for the indirect evidence for a steric effect in compounds **2** and **3**, no examples have been found of complete inhibition of ketone formation due to the large size of the organolithium reagent.



⁹ T. L. Brown, R. L. Gerteis, D. A. Bafus, and J. A. Ladd, *J. Amer. Chem. Soc.*, **86**, 2135 (1964); L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *ibid.*, **90**, 3244 (1968); P. West and R. Waack, *ibid.*, **89**, 4395 (1967); T. L. Brown, *Acc. Chem. Res.*, **1**, 23 (1968).

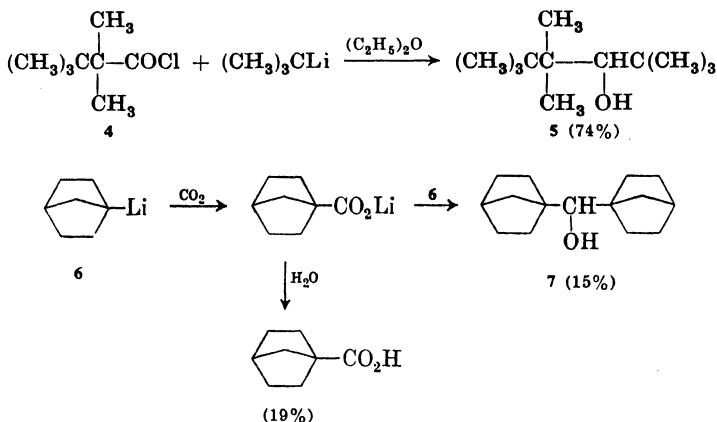
¹⁰ R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Commun.*, 117 (1969); L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *J. Amer. Chem. Soc.*, **91**, 1057 (1969).

¹¹ H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).

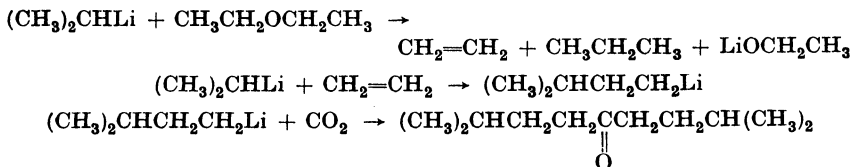
¹² M. Schlosser, *J. Organometal. Chem.*, **8**, 81 (1967).

¹³ G. Vavon and J. Thiec, *Compt. Rend.*, **233**, 1290 (1951).

Reduction of, rather than addition to, the carbonyl group of ketones is common with bulky organolithium reagents. A related example has been noted for the acid halide **4**; the product of this reaction, **5**, is derived from both addition and reduction by *t*-butyllithium.¹⁴ Although no examples of the comparable reaction of *t*-butyllithium with a carboxylate salt exist in the literature, it is likely that such reactions will occur when bulky organolithium reagents react with crowded carboxylic acids. Indirect evidence for such a reaction is afforded by carbonation of the norbornyl-lithium reagent **6** to furnish dinorbornylcarbinol (**7**)* in addition to the expected carboxylic acid.¹⁵



Reaction with Solvents. Reactive organolithium reagents such as *t*-butyllithium and isopropyllithium cannot be prepared or stored in common ethereal solvents at room temperature because they react with these solvents. The organolithium reagent will be destroyed and extraneous products may be obtained when reactions with carboxylic acids are conducted in these solvents. For example, carbonation of isopropyllithium in diethyl ether at ambient temperatures resulted in the formation of diisoamyl ketone as shown in the accompanying equations.¹⁶



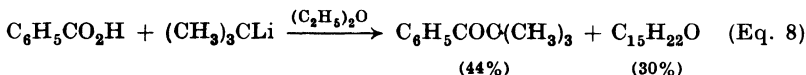
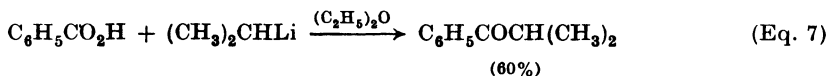
* Reduction of the ketone may have occurred by the unchanged lithium metal, present in large excess.

¹⁴ P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955).

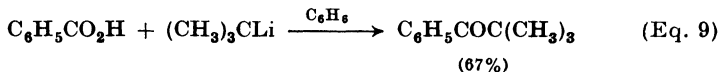
¹⁵ T. Traylor and A. Sieber, unpublished observations.

¹⁶ P. D. Bartlett, S. Friedman, and M. Stiles, *J. Amer. Chem. Soc.*, **75**, 1771 (1953).

At temperatures below -40° , solvent decomposition is sufficiently slow that *t*-butyllithium and isopropyllithium can be prepared and carbonated without complications.¹⁶ Whether these organolithium reagents react with lithium carboxylates at these low temperatures has not been determined. At ambient temperatures, isopropyllithium¹⁷ and *t*-butyllithium¹⁸ have reacted in diethyl ether to give ketones, but yields were not reported. In experiments designed to define the applicability of isopropyllithium and *t*-butyllithium as organolithium reagents at room temperature, each reagent was treated with benzoic acid in diethyl ether (Eqs. 7 and 8). Isobutyrophenone was obtained in 60% yield, accompanied by 15% of tertiary alcohol, and *t*-butyl phenyl ketone was produced in 44% yield, together with 30% of a $C_{15}H_{20}O$ ketone.¹⁹ (The latter is probably derived from the reaction of *t*-butyllithium with 2 molecules of ethylene, the decomposition product of ether, to give a new organolithium reagent whose reaction with benzoic acid furnishes the C_{15} ketone.)



It is evident from these examples that the reaction of isopropyllithium and *t*-butyllithium with carboxylic acids is faster than their reaction with diethyl ether. Thus reactions with these organolithium reagents can be conducted in that solvent, if extraneous ketonic products can be tolerated. For best results, however, reactions should be conducted in solvents that are more stable to the reagent. When benzene was substituted for diethyl ether in the reaction of *t*-butyllithium with benzoic acid (Eq. 9), the yield of *t*-butyl phenyl ketone was raised to 67% and complicating side reactions were averted.²⁰



Structural Variation and Complexities. Methyllithium is by far the most frequently employed aliphatic organolithium reagent in the

¹⁷ M. M. Green and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5190 (1967).

¹⁸ J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526 (1967).

¹⁹ M. J. Jorgenson and D. Dahlhauser, unpublished observations.

²⁰ C. H. Heathcock and R. Radcliffe, unpublished observations. This procedure is reproduced under "Experimental Procedures."

reaction with carboxylic acids. Ethyl-,²¹⁻²⁵ *n*-propyl-,²³ isopropyl-,¹⁷⁻¹⁹ *n*-butyl-,^{3, 23, 24} *t*-butyl-,¹⁸⁻²⁰ and *n*-pentyl-lithium²⁶ have been employed only occasionally. In the aromatic series, widest application has been made of phenyllithium, although *p*- and *m*-tolyllithium²⁷ and 2,6-difluorophenyllithium²⁸ have been used. Aromatic lithium reagents other than those related to phenyllithium have not been employed. Attempted reaction of 2-naphthyllithium with lithium crotonate in a variety of solvent failed to give the expected ketone.²⁹

Low yields have been reported from the reaction of alkenyllithium reagents with carboxylic acids or their salts. The best yield (42%) was reported for the preparation of benzoylcyclohexene from 1-cyclohexenyllithium and lithium benzoate.³⁰ The yield from the reaction of isobutenyllithium with various lithium carboxylates was in the range 0-40%.³¹ The yield of 40% for the reaction of lithium benzoate with isobutenyllithium³¹ should be compared with the high yields of 82% for the reaction of benzoic acid with methyllithium² and 70% for the reaction of lithium benzoate with phenyllithium.¹ The reduced yields are due to a large degree to the formation of Wurtz coupling products during the preparation of the alkenyllithium reagent or during the course of reaction. For example, large amounts of 2,5-dimethyl-2,4-hexadiene accompanied the ketone formed from isobutenyllithium.³¹ Higher yields of ketone were obtained when the alkenyllithium was generated in the presence of the carboxylate.³² The cyclopropenyl lithium derivative **8** has been reported to react with lithium acetate to furnish the methyl ketone **9** in unstated yields.³³ (Equation on p. 10.)

Reactions of acetylenic organolithium reagents with carboxylic acids have not been investigated, although such lithium reagents react with

²¹ H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968). This procedure is reproduced under "Experimental Procedures."

²² P. Doyle, J. R. Maclean, R. D. H. Murray, W. Parker, and R. A. Raphael, *J. Chem. Soc.* **1965**, 1344.

²³ K. Mislow and C. L. Hamermesh, *J. Amer. Chem. Soc.*, **77**, 1590 (1955).

²⁴ R. Ya. Levina, I. G. Bolesov, I. H. Wu, and N. P. Samoilova, *Zh. Org. Khim.*, **2**, 1897 (1966) [*C.A.*, **66**, 55179 (1967)].

²⁵ J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu, *J. Org. Chem.*, **30**, 1038 (1965).

²⁶ H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

²⁷ C. K. Bradsher and S. T. Webster, *J. Amer. Chem. Soc.*, **79**, 393 (1957).

²⁸ T. V. Talalaeva, G. V. Kazennikova, and K. A. Kocheshkov, *Zh. Obshch. Khim.*, **29**, 1593 (1959) [*J. Gen. Chem. (USSR)*, **29**, 1566 (1959)].

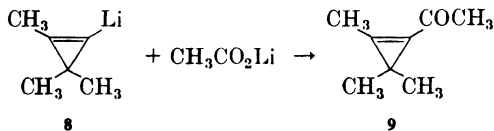
²⁹ M. J. Jorgenson and A. F. Thacher, unpublished observations.

³⁰ H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

³¹ E. A. Braude and J. A. Coles, *J. Chem. Soc.*, **1950**, 2012. This procedure is reproduced, under "Experimental Procedures."

³² E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, **1950**, 2000.

³³ G. L. Closs, in *Advances in Alicyclic Chemistry*, H. Hart and G. J. Karabatsos, Ed., Vol. 1, p. 102, Academic Press, New York, 1966.



ketones and carboxylic acid derivatives.³⁴⁻³⁶ Lithium phenylacetylide reacts with carbon dioxide to give phenylpropionic acid in good yield,³⁷ but no ketone was isolated from this reaction.³⁴

Aromatic heterocycles are readily metalated with simple organolithium reagents and the reactions of these lithium reagents with carbon dioxide to give acids has received considerable attention.³⁸ Reactions of heterocyclic lithium reagents with carboxylic acids are much less numerous, perhaps because these organolithium reagents frequently react with esters or acid halides to give high yields of ketones.³⁹⁻⁴³ There is no reason to believe, however, that the reaction with carboxylic acids will not produce ketones in high yield.

The quinoline acid salt **10** and pyridyllithium produced ketone **11** in 60% yield.⁴⁴ Lithiated phenothiazines are reported to give acylated products on reaction with lithium acetate, lithium propionate, or lithium benzoate.⁴⁵ A complication, characteristic for aromatic and heterocyclic compounds, arises in this case from the presence of more than one metalation site in the molecule. (The electronic factors controlling the site of metalation in such molecules have been discussed.³⁸) When the organolithium reagent obtained from phenothiazine and one equivalent of *n*-butyllithium was heated with lithium acetate, no ketonic products were formed. When phenothiazine was treated first with two equivalents of *n*-butyllithium and then with lithium acetate, a 40% yield of the 1-acetyl derivative **14** was formed. With 10-methylphenothiazine only 1 mole of *n*-butyllithium was required, and subsequent reaction with lithium acetate furnished a 20% yield of the 4-acetyl derivative **15**. Similar results were obtained for other 10-alkylphenothiazine derivatives.

³⁴ D. Nightingale and F. T. Wadsworth, *J. Amer. Chem. Soc.*, **69**, 1181 (1947).

³⁵ L. D. Bergelson and A. N. Grigoryan, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, [2] 286 (1966) [*C.A.*, **64**, 19400 (1966)].

³⁶ K. Suga, S. Watanabe, and T. Suzuki, *Can. J. Chem.*, **46**, 3041 (1968).

³⁷ H. Gilman and R. V. Young, *J. Org. Chem.*, **1**, 315 (1936).

³⁸ H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 258 (1954).

³⁹ N. T. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951).

⁴⁰ J. A. Gautier, M. Micocque, and C. Lafontaine, *Bull. Soc. Chim. Fr.*, **1960**, 1117.

⁴¹ M. Regitz and A. Liedhegener, *Chem. Ber.*, **99**, 2918 (1966).

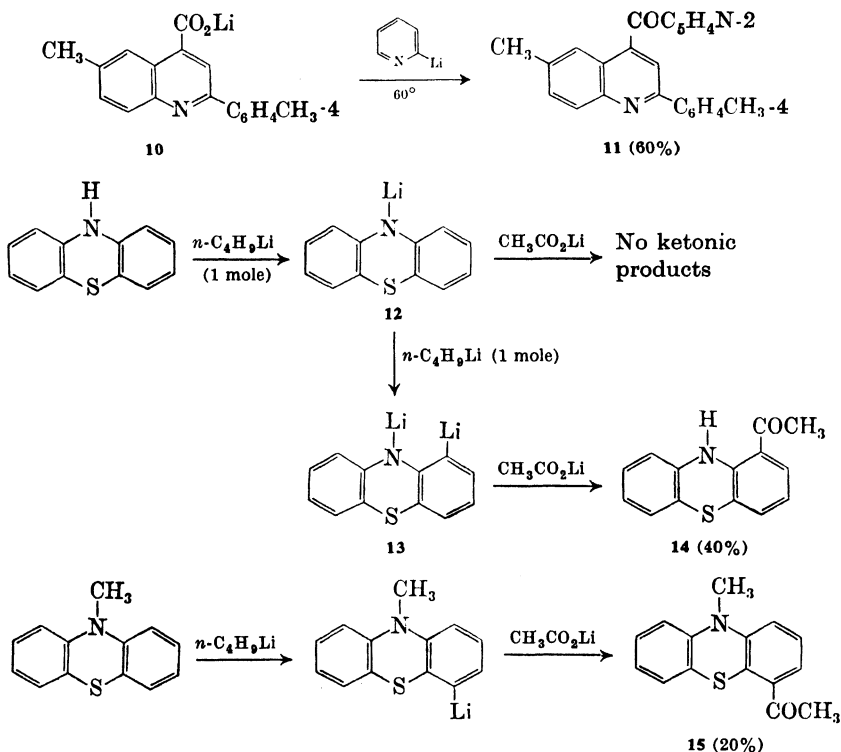
⁴² N. N. Goldberg and R. Levine, *J. Amer. Chem. Soc.*, **77**, 3647, 4926 (1955).

⁴³ C. S. Sheppard and R. Levine, *J. Heterocycl. Chem.*, **1**, 67 (1964).

⁴⁴ D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967).

⁴⁵ G. Cauquil, M. Casadevall, and E. Casadevall, *Bull. Soc. Chim. Fr.*, **1960**, 1049; *Compt. Rend.*, **243**, 590 (1956).

It is evident that 2 moles of butyllithium are required to convert phenothiazine, *via* **12**, to the productive dilithium reagent **13** because of the presence of an acidic hydrogen. The different direction of acylation in the two phenothiazines is striking. Minor amounts of the 3-acyl derivatives are also formed from the reaction of the lithiated 10-alkylphenothiazines.



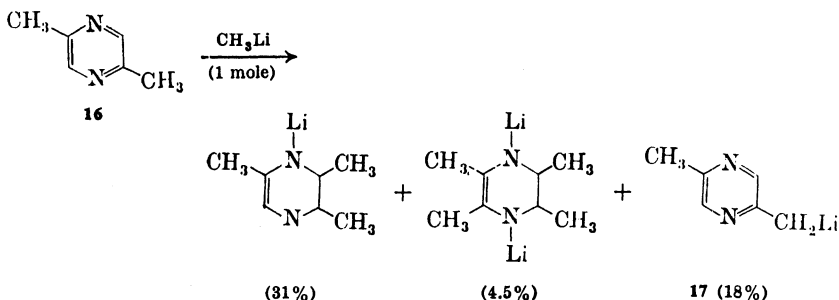
Attempted lithiation of heterocycles may lead to competitive side reactions. For example, reaction of the pyrazine **16** with methyllithium gave both the desired organolithium reagent **17** and substantial amounts of products derived from addition to the heterocyclic ring.⁴⁶ (See p. 12.)

Metalation of furan proceeds smoothly to form a lithio derivative which furnishes ketones on subsequent reaction with carboxylic acids (Eq. 10).⁴⁷ By contrast, the reaction of furyllithium with carboxylic acids yielded only tertiary alcohols.⁴⁸ Reaction of 2-thienyllithium and trifluoroacetic acid at -60° furnished trifluoromethyl 2-thienyl ketone in 87%

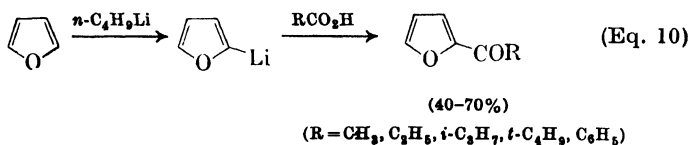
⁴⁶ G. P. Rizzi, *J. Org. Chem.*, **33**, 1333 (1968).

⁴⁷ C. H. Heathcock, L. G. Gulick, and T. Dehlinger, *J. Heterocycl. Chem.*, **6**, 141 (1969).

⁴⁸ V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1216 (1962).



yield.⁴⁹ Reactions with other perfluorocarboxylic acids gave lower yields of ketones, owing to the instability of the intermediates; this complicating side reaction is discussed under "Failures Due to Instability of the Dilithio Intermediate."



When a molecule possesses two readily metalated positions, the possibility of forming a dilithiated compound exists. In the presence of excess *n*-butyllithium, 9,10-dihydroanthracene reacted to form a mixture of lithiated compounds, including the 9,10-dilithio derivative; carbonation produced 9,10-dicarboxyanthracene.⁵⁰ The reaction with lithium carboxylates could take a similar course to yield the corresponding diketones.

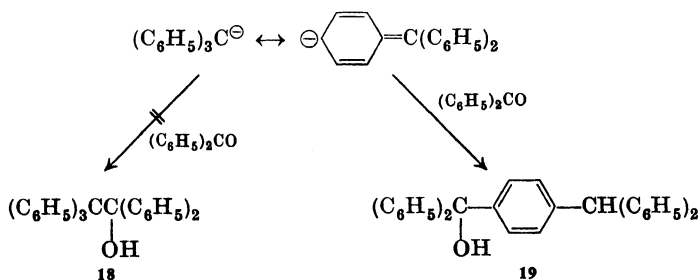
When metalation leads to a molecule in which the negative charge is delocalized, as in allyl-, benzyl- or cyclopentadienyl-lithium, complications arising from facile multisubstitution as in cyclopentadiene⁵¹ and from reactions occurring *via* canonically related lithium reagents can be expected. For example, trityllithium upon reaction with benzophenone did not yield the expected carbinol, **18**, but carbinol **19**,⁵² by contrast, carbonation proceeds normally to furnish triphenylacetic acid. Indirect evidence exists for a similar reaction course with triphenylacetic acid and lithium reagents (*cf.* Eq. 20, p. 27).

⁴⁹ E. Jones and I. M. Moodie, *J. Chem. Soc.*, **C**, 1968, 1195.

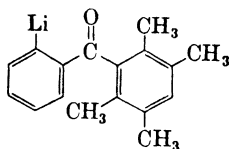
⁵⁰ H. Gilman and B. L. Bebb, *J. Amer. Chem. Soc.*, **61**, 109 (1939).

⁵¹ W. J. Linn and W. H. Sharkey, *J. Amer. Chem. Soc.*, **79**, 4970 (1957).

⁵² P. Tambouliau and K. Stehower, *J. Org. Chem.*, **33**, 1509 (1968); G. A. Olah, C. U. Pittman, Jr., E. Namanworth, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **88**, 5571 (1966).



The presence of methoxy, dimethylamino, or fluoro substituents in the benzene ring can be tolerated in the phenyllithium reagent. For the existence, ease of preparation, and stability of various organolithium reagents possessing other functional groups the reader is referred to the vast literature on this subject. The limitations arising from the presence in the organolithium molecule of functional groups that are reactive toward organolithium reagents are obvious. One curious exception is found in the stability and normal reactivity of *o*-duroylphenyllithium **20**, in which the carbonyl group is apparently too hindered to react.⁵³



20

Stereochemical Stability. The stereochemical behavior of carbanions has been reviewed and the conclusions reached apply to organolithium reagents.⁵⁴ With the possible exception of cyclopropyllithium reagents, optically active aliphatic organolithium reagents do not maintain their stereochemistry at ambient temperatures in diethyl ether. Consequently, the formation and the reaction of an optically active alkylolithium compound under these conditions with a carboxylic acid or with carbon dioxide to give an optically active ketone is not feasible. Since epimerization is expected during the formation of organolithium reagents from stereochemically pure cyclic halides,^{54a} the stereospecific transformation of such halides into ketones also is not possible. Recently 2-norbornyllithium was found to react with carbon dioxide or methyl chloroformate to give products in which retention of configuration prevailed.⁵⁵

⁵³ R. C. Fuson, W. C. Hammann, and W. E. Smith, *J. Org. Chem.*, **19**, 674 (1954).

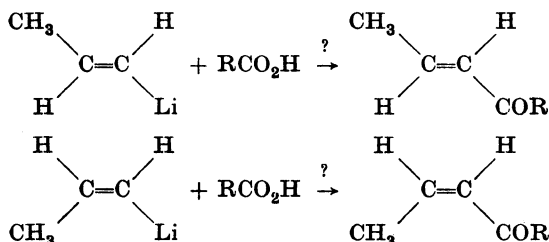
⁵⁴ D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York, 1965.

^{54a} W. H. Glaze and C. M. Selman, *J. Org. Chem.*, **33**, 1987 (1968).

⁵⁵ D. E. Applequist and G. N. Chmurny, *J. Amer. Chem. Soc.*, **89**, 875 (1967).

As a corollary it is expected that norbornyllithium reagents will react with lithium carboxylates with at least partial retention of geometry.

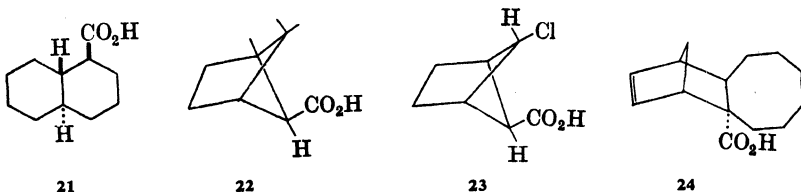
In contrast to alkylolithium compounds, simple alkenyllithium reagents do generally possess considerable stereochemical stability in boiling diethyl ether and react with carbon dioxide and carbonyl compounds with retention of configuration. On this basis, it would be expected that *cis*- and *trans*-propenyllithium, for example, would react with carboxylic acids without change in their geometry to give the *cis* and *trans* ketones, respectively. However, this reaction has not been carried out.



Finally, the geometric stability of allyllithium compounds deserves mention; this complex subject has been reviewed.⁵⁴ Stereochemical integrity is not preserved when the allyl carbanion is stabilized by additional conjugation. For example, the two isomeric 1,3-diphenylpropenes gave an identical mixture of organolithium reagents on metalation.⁵⁶

The Carboxylic Acid

Failures Due to Steric Effects. Steric factors present in the carboxylic acid appear not to be strongly dominating. However, a few examples exist where the carboxylic acid would not react with methylolithium. The bicyclic carboxylic acids **21**,⁵⁷ **22**,⁵⁸ **23**,⁵⁹ and **24**⁶⁰ could not



⁵⁶ H. H. Freedman, V. R. Sandel, and B. P. Thill, *J. Amer. Chem. Soc.*, **89**, 1762 (1967).

⁵⁷ W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

⁵⁸ J. Meinwald, A. Lewis, and P. G. Gassman, *J. Amer. Chem. Soc.*, **84**, 977 (1962).

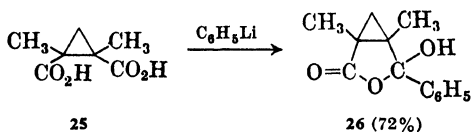
⁵⁹ J. Meinwald, C. B. Jensen, A. Lewis, and C. Swithenbank, *J. Org. Chem.*, **29**, 3469 (1964).

⁶⁰ P. E. Eaton and W. S. Hurt, unpublished observations.

be converted to methyl ketones in refluxing diethyl ether, and the acids **22** and **24** did not react even in refluxing tetrahydrofuran. By contrast, the *endo* isomers of **22**⁵⁸ and **23**⁵⁹ reacted normally with methyllithium.

Slow reactions may be caused by insolubility of the lithium carboxylate rather than by steric factors. The carboxylic acid **21** was reported to form a lithium salt which was insoluble in ether. The lack of reactivity of **21** is probably due to this factor. For acids **22**, **23**, and **24**, the steric factor appears to be real. The lack of reactivity of 2,6,6-trimethylcyclohexene-1-carboxylic acid in diethyl ether in the presence of a large excess of methyllithium over prolonged periods was ascribed to steric factors.^{60a} However, this may be just another example of the operation of solubility factors.

Other Structural Effects on Reactivity. A variety of carboxylic acids have been converted to ketones by reaction with organolithium reagents. Specific difficulties which arise during the reaction are treated under separate headings. Low yields have been reported for aliphatic acids of low molecular weight,³ but the poor yields or failures to obtain ketone are probably due to experimental difficulties in isolating the water-soluble ketones. For the simplest case, that of methyllithium reacting with acetic acid, for which no acetone was reported,² reinvestigation revealed that acetone was formed in at least 20% yield.²⁹ In reactions with organolithium reagents of higher molecular weight, acetic acid or lithium acetate has furnished yields of ketones up to 40% (see Table IA). From the higher-molecular-weight acids, hexanoic and dodecanoic, yields of 83 and 63%, respectively, of methyl ketones were isolated.³ No report of a successful use of this reaction with formic acid to furnish an aldehyde exists. Reaction of formic acid with isobutenyllithium³⁰ or 2-furyllithium⁴⁷ produced no carbonyl products. Only two reports of the reaction of a dicarboxylic acid could be located. One, that of perfluoroglutaric acid with 2-thienyllithium,⁴⁹ constitutes a special case due to the instability of the intermediate formed, a complication discussed in a later section. The other, the reaction of cyclopropanedicarboxylic acid **25** with phenyllithium, furnished compound **26** in good yield.⁶¹ Whether such complications will be general for dibasic acids possessing the two carboxyl groups in proximity remains to be determined.

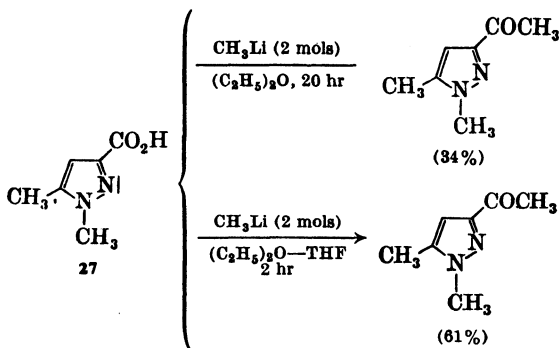


^{60a} H. B. Henbest and G. Woods, *J. Chem. Soc.*, **1952**, 1150.

⁶¹ G. Maier, *Chem. Ber.*, **98**, 2438 (1965).

Alicyclic carboxylic acids (*cf.* Table IB) furnish consistently high yields of ketones. With aralkanoic acids (Table IC), interference due to metalation at the reactive benzylic position frequently diminishes yields. This side reaction is discussed under "Competitive Metalation Reactions." With α,β -unsaturated acids (Table IIA), the possibility of conjugate addition and deconjugation reactions exists. These interfering reactions, together with addition to double bonds in nonconjugated unsaturated acids (Table IIB) are discussed under "Reactions at Multiple Bonds."

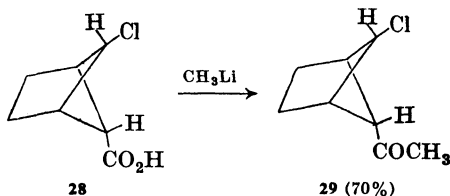
Metalation of the aromatic ring in aromatic acids, when the aromatic ring contains sufficiently powerful electron-withdrawing groups, or metalations at benzylic carbon atoms are the most serious side reactions for these acids. If these complicating features are not present, high yields of ketones are obtained in the conversion of benzoic and naphthoic acids (Table IIIA) with the more common organolithium reagents. Heterocyclic aromatic carboxylic acids (Table IIIB) pose a special problem due to very facile metalation of the heterocyclic ring, favored by electronic factors. However, when this side reaction is taken into account by employing a compensating amount of organolithium reagent, ketones can be obtained. Solubility problems can be particularly severe in these cases because of the formation of dilithio salts on metalation. But, if cognizance is taken of this difficulty, the problem can be surmounted by choosing better solvents. The pyrazolecarboxylic acid **27** offers a striking example of an insolubility problem with a heterocyclic acid.⁶² In diethyl ether a very slow reaction gives rise to only a 34% yield of the methyl ketone, while a white solid indicative of the presence of undissolved lithium carboxylate remains throughout the reaction. In a tetrahydrofuran-ether solvent mixture the reaction furnishes a 61% yield of methyl ketone in a 2-hour reaction period and, in contrast to the reaction in ether, the reaction mixture becomes homogeneous. Another example



⁶² C. Wynberger and C. L. Habraken, *J. Heterocycl. Chem.*, **6**, 545 (1969). This procedure is reproduced under "Experimental Procedures."

is furnished by β -phenylcinnamic acid.⁶³ A 24-hour reaction period in boiling diethyl ether furnished only a 15% yield of the expected methyl ketone, while a 30-minute reaction period in tetrahydrofuran resulted in 52% yield of the ketone. In the latter case the reaction mixture became homogeneous, whereas the heavy precipitate present when ether was the solvent never dissolved.

Halogenated carboxylic acids may be subject to two undesirable reactions. When the halogen is reactive, metalation can be expected to occur, particularly with the more reactive organolithium reagents. The reactions in which such acids have been used are too few to permit one to predict the seriousness of this interfering reaction. The bicyclic chlorinated acid **28** reacted with methyllithium to give a 70% yield of the ketone **29**.⁵⁹ Fluorine present in a number of aromatic acids remained intact during the conversion to ketones⁶⁴⁻⁶⁷ (cf. Table IIIA) and the yields of ketones were generally good. On the other hand, 4-chloro-3-pentenoic acid furnished only a 12% yield of a methyl ketone and a 15% yield of a phenyl ketone on reaction with methyllithium and phenyllithium, respectively.⁶⁸



The intermediates formed on reaction of α -halogenated carboxylic acids with organolithium reagents are unstable, decomposing to yield an array of undesired products. Specific illustrations are provided in the section entitled "Failures Due to Instability of Dilithio Intermediates."

Reactions at Multiple Bonds. Addition of reactive organolithium reagents to simple unconjugated double bonds have been observed.^{68a} When the double bond is conjugated with an aromatic ring, addition of

⁶³ M. J. Jorgenson, A. F. Thacher and T. Leung, unpublished observations. This procedure is reproduced under "Experimental Procedures."

⁶⁴ M. S. Newman, S. Swaminathan, and R. Chatterji, *J. Org. Chem.*, **24**, 1961 (1959).

⁶⁵ M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

⁶⁶ M. S. Newman and K. Naiki, *J. Org. Chem.*, **27**, 863 (1962).

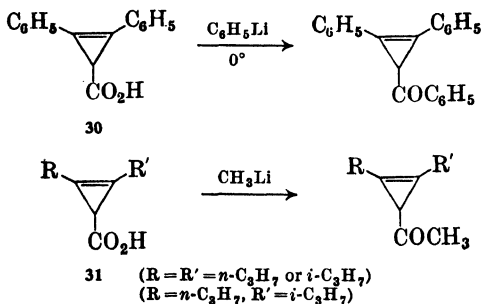
⁶⁷ M. S. Newman and S. Seshadri, *J. Org. Chem.*, **27**, 76 (1962).

⁶⁸ M. Julia and M. Fetizon, *Compt. Rend.* **240**, 1109 (1955); *Bull. Soc. Chim. Fr.* **1959**, 1378.

^{68a} P. D. Bartlett, S. J. Tauber and W. P. Weber, *J. Amer. Chem. Soc.* **91**, 6362 (1969); P. D. Bartlett, C. V. Goebel and W. P. Weber, *ibid.*, 7425 (1969); W. H. Glaze and C. H. Freeman, *ibid.*, 7198 (1969).

organolithium reagents to the double bond of 1,1-diphenylethylene,⁶⁸ 1-cyclopropyl-1-phenylethylene,^{69a} and *trans*-stilbene take place readily.^{69b} Among carboxylic acids related to such olefins, cinnamic acid reacts smoothly with methyl lithium to furnish benzalacetone in yields in the range 69–95%^{2,70} depending on conditions. The further activation of the double bond by an additional phenyl group, as in β -phenylcinnamic acid, however, diminished the yield of the ketone, 4,4-diphenyl-3-buten-2-one, to 52%.⁶³ This may have been the result of addition to the double bond, as evidenced by the appearance of a deep red color (probably due to the benzhydryl carbanion) during the reaction.

When the double bond is located in a strained ring, addition of lithium reagents occurs more readily, as illustrated by the addition of phenyllithium to cyclopropene.⁷¹ However, several cyclopropenecarboxylic acids have been reported to react normally; the acid **30** furnished the corresponding phenyl ketone,⁷² and a number of cyclopropenecarboxylic acids of structure **31** furnished the corresponding methyl ketones in



yields ranging from 50 to 70%.⁷³ Another acid, 2-*p*-anisyl-3-phenyl-2-cyclopropene-1-carboxylic acid, reacted with phenyllithium to give the phenyl ketone.⁷⁴

With nonconjugated unsaturated carboxylic acids, in which the unsaturated site is a normal double bond, the reaction of the carboxylate

⁶⁸ K. Ziegler, F. Crössmann, H. Kleiner, and O. Schäfer, *Ann.*, **473**, 1 (1929); A. G. Evans and D. B. George, *J. Chem. Soc.*, **1961**, 4653; R. Waack and M. A. Doran, *J. Amer. Chem. Soc.*, **91**, 2456 (1969).

^{69a} J. A. Landgrebe and J. D. Shoemaker, *J. Amer. Chem. Soc.*, **89**, 4465 (1967).

^{69b} Y. Okamoto, M. Kato, and H. Yuki, *Bull. Chem. Soc. Japan*, **42**, 760 (1969).

⁷⁰ J. Baddiley, G. Ehrensvald, and H. Nilsson, *J. Biol. Chem.*, **178**, 399 (1949).

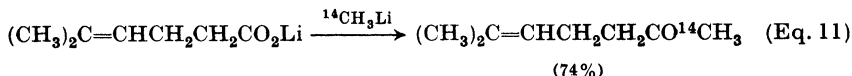
⁷¹ J. E. Mulvaney and Z. G. Garlund, *J. Org. Chem.*, **30**, 917 (1965); J. G. Welch and R. M. Magid, *J. Amer. Chem. Soc.*, **89**, 5300 (1967); R. M. Magid and J. G. Welch, *ibid.*, **90**, 5211 (1968).

⁷² R. Breslow, J. Brown, and J. J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967).

⁷³ M. Vidal, E. Chollet, and P. Arnaud, *Tetrahedron Lett.*, **1967**, 1073.

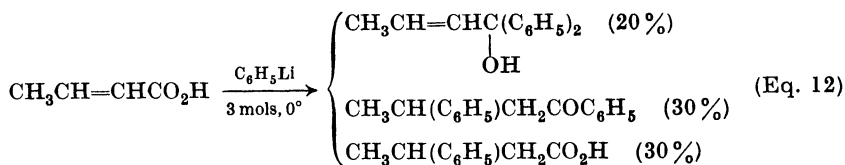
⁷⁴ R. Breslow and M. Douek, *J. Amer. Chem. Soc.*, **90**, 2698 (1968).

salt with methyllithium proceeds smoothly. Numerous examples are provided in Table IIB. An interesting preparation, illustrating the application of labeled methyllithium, has been described for the conversion of lithium 5-methyl-4-hexenoate to the methyl ketone (Eq. 11).⁷⁵ The examples given in Table IIB do not involve the use of highly reactive organolithium reagents. Addition to the double bond is more likely in these reactions if organolithium reagents such as isopropyllithium or



t-butyllithium are employed.¹⁶ Notice should also be taken of the ready addition of lithium reagents to double bonds in allylic alcohols⁷⁶ if carboxylic acids containing this feature are used.

Conjugate additions are known to be less general for organolithium reagents than for other organometallic reagents. (Comparison is offered in a later section.) Isolated examples of such reaction modes exist. Crotonic acid reacted with phenyllithium to furnish primarily products derived from conjugate addition (Eq. 12).²⁹ With methyllithium it has been reported to react normally to furnish methyl propenyl ketone (*cf.* Table IIA).



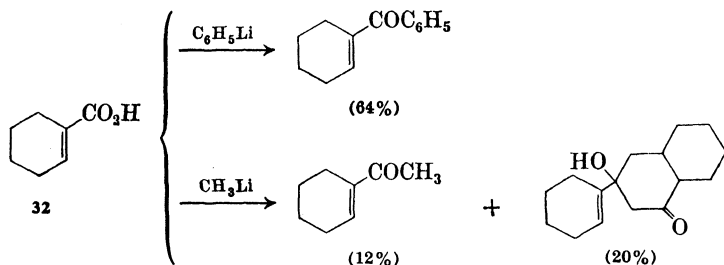
Reaction of the cyclohexenecarboxylic acid **32** with phenyllithium proceeded normally.⁷⁷ With methyllithium, however, the principal product was a tricyclic compound whose structure is probably that shown in the accompanying equation and whose formation from the expected methyl 1-cyclohexenyl ketone can be accounted for as the result of successive aldol and Michael condensations. (Equation on p. 20.)

In general conjugate addition is expected to yield a new carboxylic acid which would be revealed by the examination of the acidic products formed. Unfortunately, the acidic material has generally not been isolated and, when isolated, has generally been assumed to consist of the

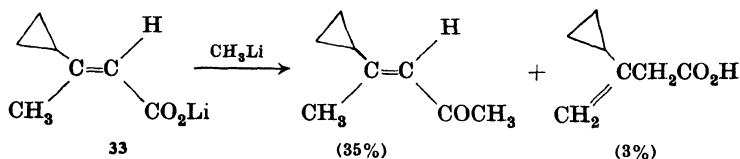
⁷⁵ J. Meinwald, *J. Amer. Chem. Soc.*, **77**, 1617 (1955). This procedure is reproduced under "Experimental Procedures."

⁷⁶ J. K. Crandall and A. C. Clark, *Tetrahedron Lett.*, **1969**, 325; H. Felkin, G. Swierczewski and A. Tambute, *ibid.*, **1969**, 707.

⁷⁷ J. Klein, *Tetrahedron*, **20**, 465 (1964).



unchanged starting acid. In the case of the cyclopropylbutenoic acid **33** examination of the acidic material (30% recovery) after reaction with methyl lithium revealed the absence of any 3-methyl-3-cyclopropylbutenoic acid, which would have formed had conjugate addition occurred.⁷⁸



From the data available in the literature, on the conjugate addition of organolithium reagents to α,β -unsaturated ketones,⁷⁹ nitriles,⁷⁹ and amides,^{77,77a} it is evident that the extent to which conjugate addition takes place in these systems depends on various factors, including the structure of the organolithium reagent and the structure of the unsaturated compound.

When allylic hydrogens are present in the α,β -unsaturated carboxylic acid, products may be formed in which deconjugation of the double bond has occurred. This reaction, since it involves metalation at the allylic site, is discussed under "Competitive Metalation Reactions."

Addition of organolithium reagents to acetylenic bonds occurs readily.⁸⁰ However, the unsaturated acid **34** was reported to furnish the methyl ketone **35** in 70% yield.⁸¹ Phenylpropionic acid does not furnish a ketone on reaction with phenyllithium²⁹ because of the instability of the intermediate, as discussed in a later section. Further examples of reactions of acetylenic carboxylic acids are lacking in the literature.

^{77a} G. Gilbert and B. F. Aycock, *J. Org. Chem.*, **22**, 1013 (1957).

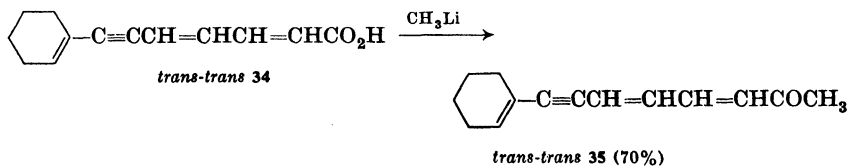
⁷⁸ M. J. Jorgenson, D. Dahlhauser, and T. Leung, unpublished observations.

⁷⁹ See, for example, H. Gilman and R. H. Kirby, *J. Amer. Chem. Soc.*, **63**, 2046 (1941).

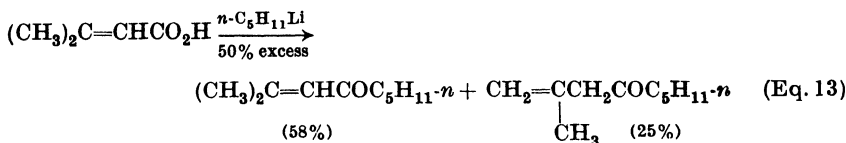
^{79a} W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1961).

⁸⁰ J. E. Mulvaney, Z. G. Gardlund, S. L. Gardlund, and D. J. Newton, *J. Amer. Chem. Soc.*, **88**, 476 (1966); J. E. Mulvaney, S. Groan, L. J. Carr, Z. G. Gardlund, and S. L. Gardlund, *ibid.*, **91**, 388 (1969).

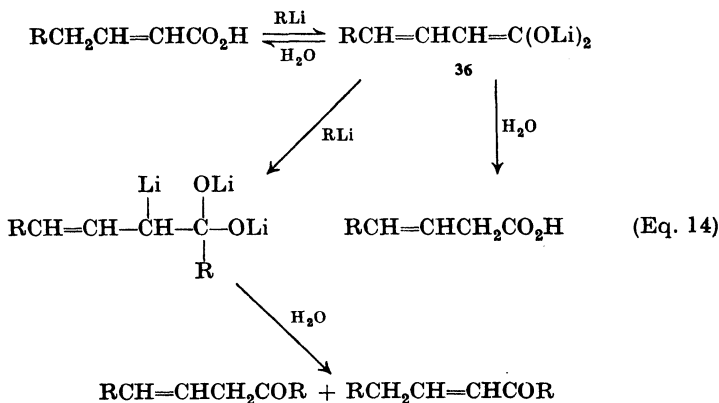
⁸¹ I. Heilbron, E. R. H. Jones, and R. W. Richardson, *J. Chem. Soc.*, **1949**, 287.



Competitive Metalation Reactions. Metalation at the double bond, when vinyl hydrogen atoms are present, does not occur with the less reactive organolithium reagents. Allylic hydrogen, on the other hand, can be metalated during the reaction of an α,β -unsaturated carboxylic acid with an organolithium reagent. The amount of recovered acid serves as a measure of the extent of this side reaction, particularly if double-bond isomerization to the β,γ -position has occurred. Thus in the case of the cyclopropylbutenoic acid **33** the recovered carboxylic acid was contaminated by the β,γ isomer to the extent of 10%.⁷⁸ No β,γ -unsaturated ketone was formed. With more reactive metalating agents, the extent of β,γ -isomerization appears to be more extensive. The reaction of 3,3-dimethylacrylic acid with excess *n*-pentyllithium gave, in 83% yield, a mixture of ketones containing only 70% of the α,β -unsaturated isomer, accompanied by the β,γ isomer (Eq. 13).²⁶



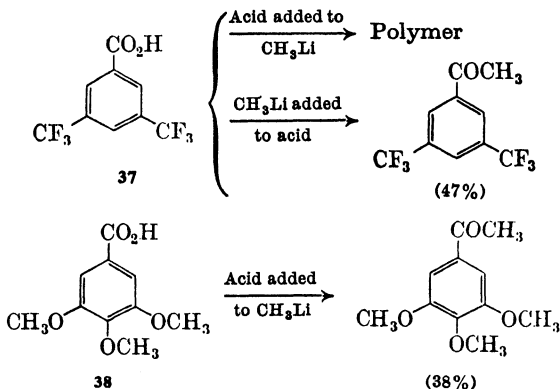
The course of such deconjugation reactions can be formulated as in Eq. 14. Protonation of the dilithiated acid **36** on hydrolysis will furnish a mixture of α,β - and β,γ -unsaturated acids. It is possible, as appears to be the case for the 3,3-dimethylacrylic acid (Eq. 13), that the dilithiated



acid reacts with the organolithium reagent to furnish a trilitio species which can hydrolyze to the α,β - and β,γ -unsaturated ketones. Alternatively, but less likely,* deconjugation could have occurred on generation of the ketone in the basic hydrolysis medium.

Deconjugated ketones may not always have originated during the course of the reaction, but during subsequent workup. For example, only α,β -unsaturated ketone was obtained from the reaction of 4-*t*-butylcyclohexylideneacetic acid with methyllithium;⁸² however, during conventional purification procedures it isomerized to the more stable β,γ isomer. Examination of the product composition after purification in such a case can be misleading. When isomerization is expected to be facile, it is particularly advisable to avoid acidic or basic conditions during the isolation of the product.

Metalation reactions at the aromatic ring have been found to occur when benzoic acids possessing strong electron-withdrawing substituents are employed. The bistrifluoromethyl-substituted benzoic acid **37** could not be converted to the methyl ketone when the acid was added to the methyllithium solution; only polymeric products were obtained.¹⁹ It is speculated that metalation followed by condensation had occurred. When methyllithium was added to the carboxylic acid, however, a fair yield of the ketone was realized. The low yield obtained in the reaction of the benzoic acid **38** might also be due to interfering metalation.⁸³ It should be possible to minimize these side reactions by the slow addition of a stoichiometric amount of lithium reagent to the carboxylic acid.

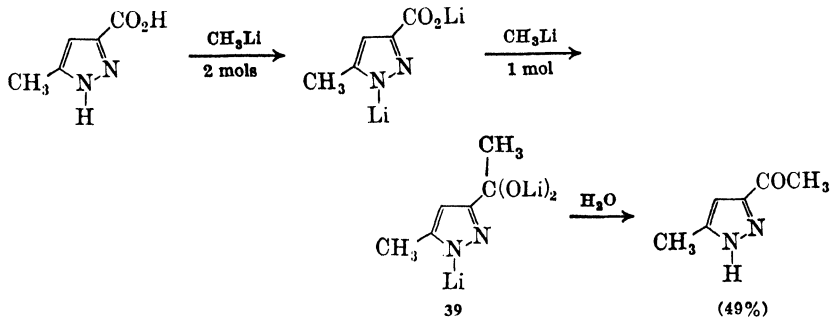


* Enolization of ketones does not appear to take place during the workup, as epimerization is not found to occur in labile ketones; cf. subsequent section, "Stereochemical Fate of the α -Carbon Atom."

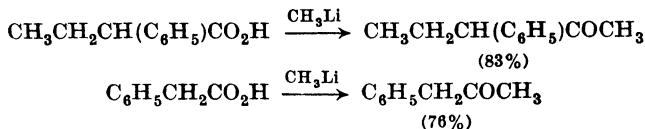
⁸² H. O. House, W. L. Respass, and G. M. Whitsides, *J. Org. Chem.*, **31**, 3128 (1966); H. O. House and R. Giese, unpublished observations. This procedure is reproduced under "Experimental Procedures."

⁸³ A. G. Anderson, Jr., and H. F. Greef, *J. Amer. Chem. Soc.*, **74**, 2923 (1952).

Competitive metalations are serious side reactions in ketone syntheses when more reactive organolithium reagents are employed. For example, even naphthalene is metalated at an appreciable rate by *n*-butyllithium and phenyllithium.³⁸ It is not certain, of course, that metalation on the aromatic ring is always harmful to the ketone yield. If the metalated intermediate does not undergo self-condensation, but reacts with the organolithium reagent at the carboxylate group, hydrolysis furnishes the desired ketone. The necessary precaution in such cases is to supply sufficient organolithium reagent to replace the lithium reagent consumed in the side reaction. The reaction of 5-methylpyrazole-3-carboxylic acid serves as a good illustration. With 3 moles of methyllithium (in tetrahydrofuran to effect solution of the metalated species **39**), a 49% yield of ketone could be obtained.⁶² The need for a large excess of methyllithium in the case of benzofuran-3-carboxylic acid could also be related to metalation at the α -carbon atom of the furan ring.⁸⁴



Alkanoic acids and aromatic acids possessing benzylic hydrogen undergo side reactions as a result of metalations at the activated benzylic position. With methyllithium this is not always serious, as attested by the high yields of ketones obtained from the reactions of 2-phenylbutanoic acid⁸⁵ and phenylacetic acid.² Diphenylacetic acid, however, is recovered



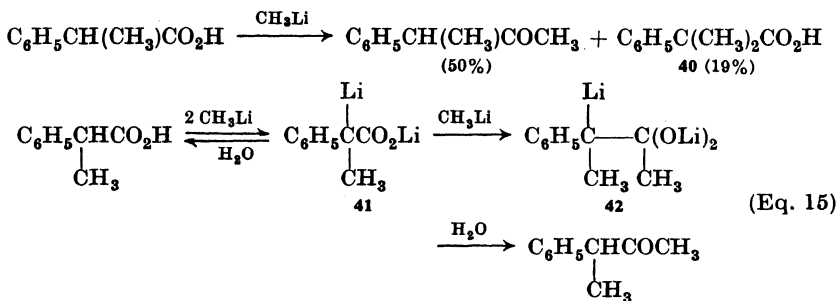
unchanged after treatment with 2 moles of methyllithium; evidence for dianion formation in this case comes from the formation of 2,2-diphenylpropanoic acid when methyl iodide is added to the reaction mixture.^{85a}

⁸⁴ D. W. Nichols and D. S. Noyce, unpublished observations.

⁸⁵ W. W. Leake and R. Levine, *J. Amer. Chem. Soc.*, **81**, 1169 (1959).

^{85a} S. Mackenzie and H. Abajian, unpublished results. R. Gencarelli, H. Abajian, P. Irving, and S. Mackenzie, 158th Meeting of the American Chemical Society, Div. Org. Chem., Paper No. 17, Sept. 1969, New York.

From 2-phenylpropanoic acid a lower yield of product was obtained and a 19% yield of a side product **40** was formed.⁸⁶ The acid **40** can be accounted for by metalation at the α -carbon atom, followed by reaction with methyl iodide remaining from the *in situ* generation of the methyllithium. In a more detailed study with 2-phenylpropanoic acid the yield of ketone, which ranged from 10 to 55% when a theoretical quantity of methyllithium was employed, was raised to 91% when at least a 100% excess of methyllithium was employed.^{23,87} The strong dependence of yield on the molar ratio of organolithium reagent employed suggests the consumption of some of the reagent in a reaction which produces the dilithio species **41** (Eq. 15). In the absence of excess methyllithium, this dilithio intermediate reverts to the starting material on hydrolysis. In the presence of excess methyllithium, however, it must react further to give the trilithiated species **42**, which furnishes ketone on hydrolysis. This scheme is in accord with the isolation of racemized ketone when optically active 2-phenylpropanoic acid is employed in this reaction.²³ The reactivity of dilithio species such as **41** toward organolithium reagents is also supported by the formation of both carboxylic acids and ketones derived from conjugate addition to α,β -unsaturated carboxylic acids (*cf.* Eq. 12, p. 19); the ketone formation is best accounted for by further reaction of dilithio intermediates similar to **41**.

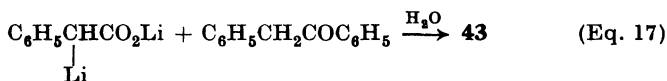
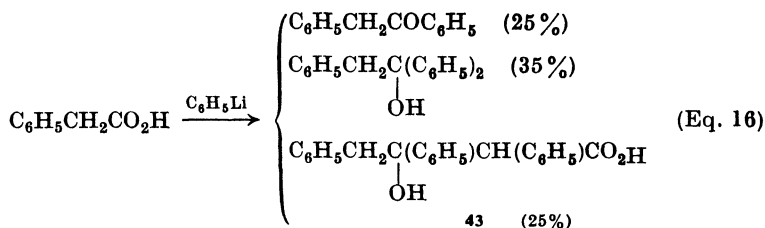


An interesting side reaction which is due to the intervention of the α -metalated carboxylic acid takes place when phenylacetic acid is treated with phenyllithium (Eq. 16).²⁹ The hydroxy acid **43** can be accounted for by reaction of the lithiated phenylacetic acid with benzyl phenyl ketone (Eq. 17), possibly during the workup, as the ketone is being generated. It should be noted that, by contrast, phenylacetic acid reacts normally with methyllithium (p. 23).²

The recovery of starting material in the reaction of phenylacetic acids with organolithium reagents could serve as an index of the extent of

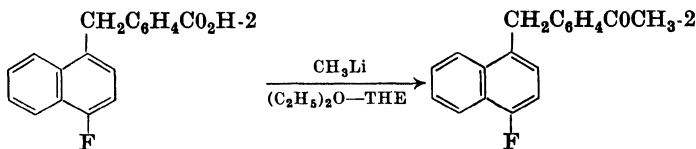
⁸⁶ L. M. Jackman and J. W. Lown, *J. Chem. Soc.*, **1962**, 3776.

⁸⁷ K. Mislow and J. Brenner, *J. Amer. Chem. Soc.*, **75**, 2318 (1953).



lithiation at the α -carbon atom. Unfortunately the amount of recovered acid in these transformations has rarely been noted, so that generalizations are not possible. For esters, nitriles, and ketones the factors which determine the ratio of α metalation to nucleophilic addition have been examined for various organolithium reagents.^{79a} Such studies remain to be carried out with carboxylic acid salts.

The presence of hydrogen atoms activated by two aryl groups,^{27,64-67} as in the acid **44**, does not impede the normal course of reaction with methyllithium.⁶⁶ However, the reported intense deep purple color of the reacting solutions suggests the formation of at least some of the diaryl carbanion during the reaction. For 2-(α -1-naphthylethyl)benzoic acid the yield of pure ketone formed on reaction with methyllithium was

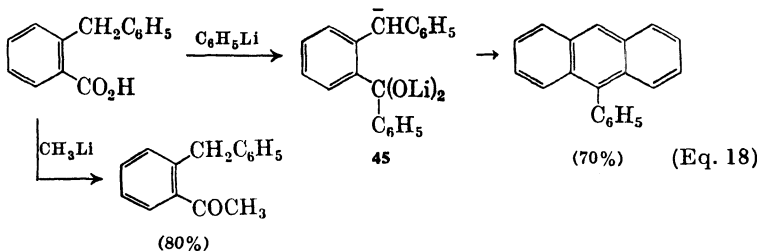


44

75%;⁶⁶ for various fluorine-substituted derivatives the yields of methyl ketones ranged from 34 to 79%.^{66,67} The modest yields in some of these cases suggest the incursion of side reactions due to metalation.

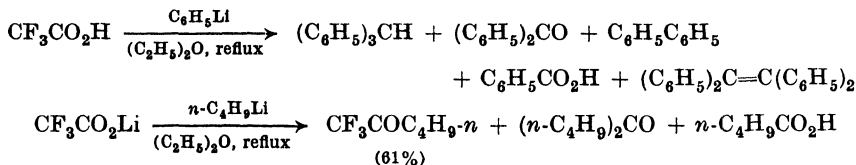
An interesting side reaction was observed with *o*-benzylbenzoic acid and phenyllithium. In the presence of excess reagent the reaction did not stop at the ketone product but proceeded to give 9-phenylanthracene.²⁷ It is postulated that the hydrocarbon is formed by way of the benzhydryl carbanion **45**, as shown in Eq. 18. (The formation of the anthracene during workup, *via* an anthranol intermediate formed from the free ketone corresponding to **45**, has not been excluded.) Analogous behavior was found for *m*- and *p*-tolyllithium with *o*-benzylbenzoic acid,²⁷ and for

phenyllithium with *o*-naphthylbenzoic and substituted *o*-benzylbenzoic acids.⁸⁸ However, the yields of the anthracenes were lower in these cases.



In striking contrast to the reaction of *o*-benzylbenzoic acid with phenyllithium, the reaction with excess methyllithium proceeds normally (Eq. 18).²⁷ It is evident from these data that *o*-benzylbenzoic, *o*-benzyl-naphthoic, and *o*-naphthylbenzoic acids are subject to serious metalation side reactions only if more reactive organolithium reagents are employed. Compare Table III.

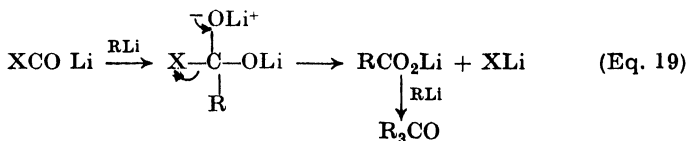
Failures Due to Breakdown of Dilithio Intermediates. When α -halogenated carboxylic acids are employed, reactions with organolithium reagents take an abnormal course. For example, when trifluoroacetic acid was treated with phenyllithium at room temperature, a number of products, primarily benzophenone, triphenylmethane, and biphenyl, were formed.⁸⁹ When lithium trifluoroacetate reacted with *n*-butyllithium, a 61% yield of the expected ketone was obtained, but di-*n*-butyl ketone and pentanoic acid were also produced.³ These side products



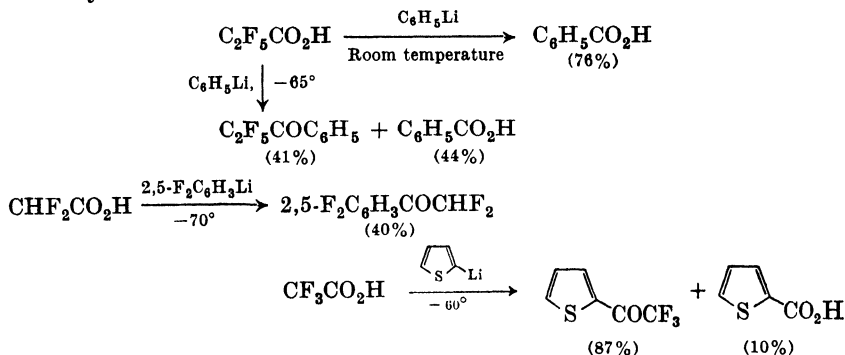
have been rationalized in terms of the breakdown of the intermediate, (X = α -haloalkyl) as illustrated in Eq. 19.³ Alternatively, a sequence involving decarboxylation of the lithium salt of the halogenated acid to give carbon dioxide, followed by the reaction of the carbon dioxide with the organolithium reagent, explains the formation of such products as benzophenone, di-*n*-butyl ketone, benzoic acid, and pentanoic acid.⁸⁹ The scheme of Eq. 19 finds analogy in the thermal decomposition of the dilithium salt of hexafluoropropane-2,2-diol.⁴

⁸⁸ C. K. Bradsher and S. T. Webster, *J. Org. Chem.*, **23**, 482 (1958).

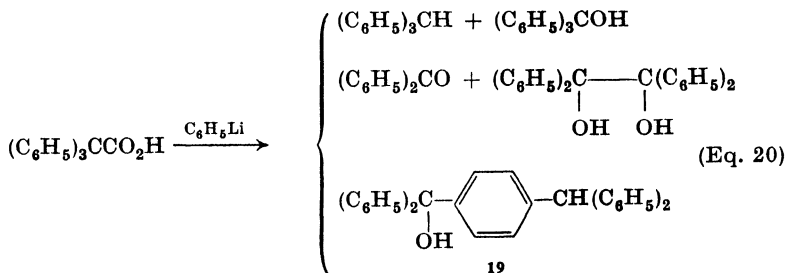
⁸⁹ T. F. McGrath and R. Levine, *J. Amer. Chem. Soc.*, **77**, 3634, 3656, 4168 (1955).



This reaction, shown in Eq. 19, appears to be common to all α -halogenated carboxylic acids which have been treated with *n*-butyl- or 2-thienyl-lithium (*cf.* Table IA). At low temperatures the breakdown of the intermediate has been partially arrested, so that good yields of ketones can be obtained; examples are given for pentafluoropropionic acid reacting with phenyllithium,⁴⁹ for difluoroacetic acid reacting with 2,5-difluorophenyllithium,²⁸ and for trifluoroacetic acid reacting with 2-thienyllithium.⁴⁹

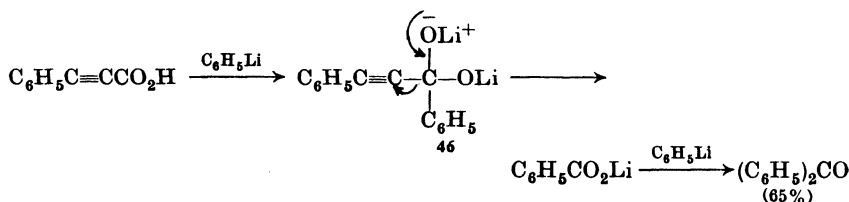


The fragmentation illustrated in Eq. 19 is not restricted to α -halogenated carboxylic acids. Since it occurs *via* the expulsion of a carbanion, decomposition of the intermediate should be expected when X corresponds to other stable anion species. The reported abortive reaction of phenyllithium with triphenylacetic acid (Eq. 20)⁵² can be rationalized by this mechanism. Dissociation of the intermediate in this reaction would provide lithium benzoate and lithium triphenylmethide [X = (C₆H₅)₃C in Eq. 19]. Lithium benzoate reacts with phenyllithium to give benzophenone and triphenylcarbinol, while the trityllithium appears to react



with benzophenone to furnish compound **19**, as outlined on p. 13. Products derived from a similar breakdown pattern have been reported for 2,2-diphenylpropanoic and 2,2-diphenyl-2-methoxyacetic acids, whereas benzoic acid reacted normally, probably because of its conversion under the reaction conditions to the dilithium salt, whose breakdown becomes electronically unfavorable.^{85a}

It was expected that similar complications would arise when X was $C\equiv CR$ in Eq. 19. The dilithio derivative **46** formed from the reaction of either phenylpropionic acid with phenyllithium or from the reaction of lithium phenylacetylide with benzoic acid might decompose according to Eq. 19, since the acetylenic anion is a favorable leaving group. Consonant with this interpretation, phenylpropionic acid was found not to yield the phenyl ketone on reaction with phenyllithium.²⁹ Instead, as expected, benzophenone was isolated in good yield. Successful conversions may, however, be brought about at low temperature.



Interference by Other Functional Groups. Methoxyl groups are not attacked by methyl-,^{2,64,83,90-95} phenyl-,⁷⁴ or isopropyl-lithium¹⁷ reagents in the synthesis of ketones from carboxylic acids possessing methoxyl substituents. Various other ether linkages also appear to be immune under these conditions.⁹⁶⁻⁹⁸ Because ethylene ketals or acetals do not react with methyllithium⁹⁹⁻¹⁰¹ or ethyllithium,²² protection of carbonyl groups in this form is feasible. An example of the use of this way of protecting a carbonyl group in a synthetic scheme is shown in Eq. 21.²²

⁹⁰ D. S. Noyce, G. L. Woo, and B. R. Thomas, *J. Org. Chem.*, **25**, 260 (1960).

⁹¹ C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 3753 (1968).

⁹² D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959).

⁹³ T. J. Leitereg and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 4019 (1968).

⁹⁴ J. Meinwald and J. C. Ripoll, *J. Amer. Chem. Soc.*, **89**, 7075 (1967).

⁹⁵ M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, **1957**, 4419.

⁹⁶ B. Sjöberg, *Ark. Kemi* **15**, 473 (1960) [*C.A.*, **55**, 4356 (1961)].

^{97a} H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961).

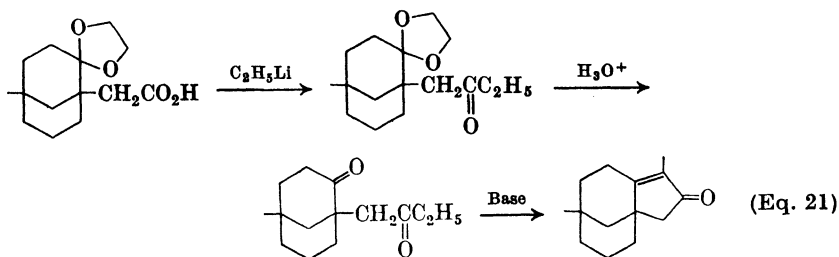
⁹⁷ M. Julia and C. Tchernoff, *Compt. Rend.*, **245**, 1246 (1957).

⁹⁸ M. Julia and M. Baillarge, *Compt. Rend.*, **249**, 2793 (1959).

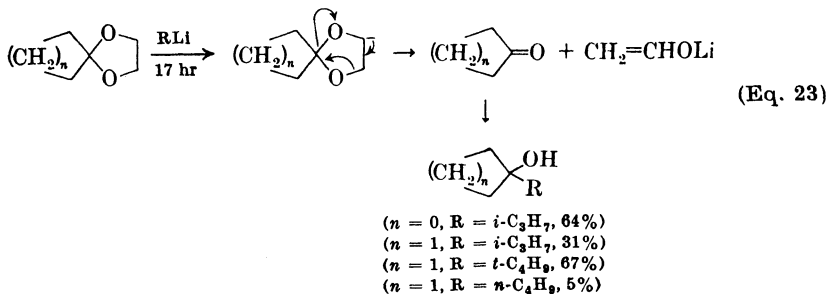
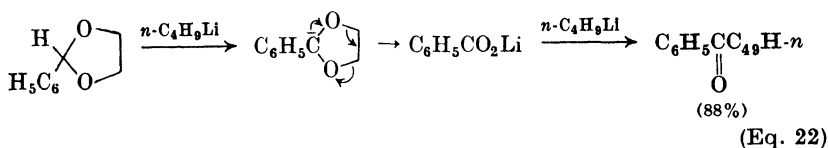
⁹⁹ C. K. Warren and B. C. L. Weedon, *J. Chem. Soc.*, **1958**, 3972.

¹⁰⁰ C. K. Warren and B. C. L. Weedon, *J. Chem. Soc.*, **1958**, 3986.

¹⁰¹ R. Anliker, M. Müller, M. Perelman, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **42**, 1071 (1959).



When more reactive organolithium reagents are employed, abstraction of a proton from the α -carbon atom of the acetal or ketal occurs. The ethylene acetal of benzaldehyde reacted with *n*-butyllithium to give *n*-butyl phenyl ketone in 88% yield (Eq. 22).¹⁰² The ethylene ketals of cyclopentanone and cyclohexanone were attacked by isopropyl- and *t*-butyl-lithium (Eq. 23).¹⁰³ The products derived from these reactions are those which formally arise from the reaction of cyclopentanone or cyclohexanone with the organolithium compound. Clearly the protection of a carbonyl group as an acetal or ketal is not feasible with the more reactive organolithium reagents which are capable of cleaving ethers by β -elimination. It is evident that ethoxyl and larger alkoxyl groups in the molecule are subject to degradation by reactive organolithium reagents for the same reason, in contrast to the stability of methoxyl substituents. The ketals formed from cyclopentanone and cyclohexanone with 1,3-propanediol, however, were stable to isopropyllithium and *t*-butyllithium,¹⁰³ so that these can be used for the protection of carbonyl groups, when the ethylene ketal protection mode fails.

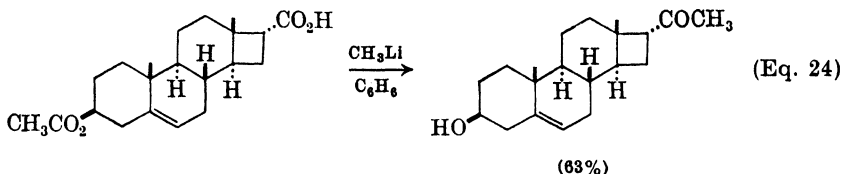


¹⁰² K. D. Berlin, B. S. Rathore, and M. Peterson, *J. Org. Chem.*, **30**, 226 (1965).

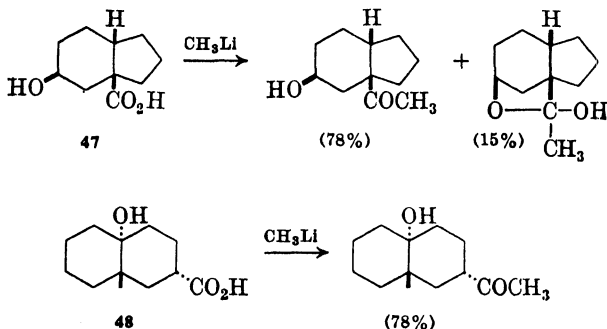
¹⁰³ C. H. Heathcock, J. E. Ellis, and R. A. Badger, *J. Heterocycl. Chem.*, **6**, 139 (1969).

If a ketonic carbonyl group in the carboxylic acid is not protected, it undergoes smooth transformation into tertiary alcohol. These concurrent transformations of the carbonyl group have been reported to take place in high yields.^{104,105} Esterified hydroxyl groups in the substrate are transformed into hydroxyl groups, concomitantly with the conversion of the carboxyl group to a ketone. An example is shown in Eq. 24.¹⁰⁶

The hydroxyl group generally does not interfere with the transformation of an acid into a ketone when a sufficient excess of organolithium reagent is present to allow for the consumption of 1 equivalent of the organolithium reagent per hydroxyl group (refs. 91, 92, 106a-111). However,



ketone formation may be very slow because of insolubility of the dilithium salt of the hydroxy carboxylic acid. Long heating⁹² and use of a more favorable solvent^{108a,110} have overcome this problem. When the hydroxyl



¹⁰⁴ D. B. Bigley, N. A. J. Rogers, and J. A. Barltrop, *Chem. Ind.* (London), 558 (1958).

¹⁰⁵ V. I. Gunar and S. I. Zav'yalov, *Dokl. Akad. Nauk., SSSR*, **132**, 829 (1960) [*C.A.*, **54**, 21180 (1960)].

¹⁰⁶ G. Müller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, **1962**, 296.

^{106a} R. A. Schneider and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 2023 (1967).

¹⁰⁷ Roussel-UCLAF, Fr. Pat. 1,473,892 [French Pat. Abstr., **7**, No. 17, p. 64, 3-4 (1967)].

¹⁰⁸ P. F. Vlad, G. V. Kryshchal', and G. V. Lazur'evskii, *J. Gen. Chem. (USSR)*, **37**, 2074 (1967).

¹⁰⁹ H. Heusser, J. Wohlfahrt, M. Müller, and R. Anliker, *Helv. Chim. Acta*, **42**, 2140 (1959).

¹¹⁰ N. Danieli, Y. Mazur, and F. Sondheimer, *J. Amer. Chem. Soc.*, **84**, 875 (1962); *Tetrahedron*, **22**, 3189 (1966).

¹¹¹ J. A. Marshall and M. T. Pike, *Tetrahedron Lett.*, **1966**, 4989.

^{111a} J. D. Billimoria and N. F. MacLagen, *J. Chem. Soc.*, **1951**, 3067.

and the carboxyl groups are in a favorable steric relationship to each other, as in the acid **47**, the lactol is formed along with the ketone.¹¹² The hydroxy acid **48**, on the other hand, though sterically capable of forming a lactol, gave only the ketone.⁹¹

The presence of an amino group does not interfere in the conversion of 3-anilino-3-phenylpropanoic acid to the methyl ketone.¹¹³ The presence of a nitro group, on the other hand, entirely precludes ketone formation. Thus *p*-nitrobenzoic acid after reaction for 24 hours with an excess of phenyllithium furnished only a polymeric product; approximately half of the starting material was recovered.²⁹

Stereochemical Fate of the α -Carbon Atom. In alicyclic carboxylic acids the absence of epimerization at the α -carbon atom has been rigorously demonstrated in the reaction with methyllithium of 3- β -carboxycholestane,¹¹⁴ of *cis*-2-methylcyclohexanecarboxylic acid,¹¹⁵ of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid,²⁰ and of *exo*-5,5-dimethylbicyclo[2.1.1]hexane-2-carboxylic acid.¹¹⁶ Since a driving force exists for epimerization in *cis*-2-methyl- and *cis*-4-*t*-butyl-cyclohexanecarboxylic acid, these two examples are particularly convincing evidence for the integrity of stereochemistry at the α -carbon atom. In two other examples, the bicyclic acid **49**¹¹⁷ and the etianic acid **50**,¹¹⁰ although the ketones formed are readily epimerized under basic conditions to the more stable isomeric ketones, the less stable ketones were isolated from the reaction. The stereospecific nature of the reaction of carboxylic acids with organolithium reagents has made this preparative scheme the method of choice for the synthesis of ketones to be used in subsequent Baeyer-Villiger reactions¹¹⁸ when it is desired to degrade carboxylic acids stereospecifically to alcohols (refs. 57, 58, 87, 115, 117, 119). Immunity of the α -carbon atom to epimerization may be less likely with more reactive organolithium reagents; examples of the use of isopropyllithium and *t*-butyllithium with epimerizable simple alicyclic carboxylic acid substrates are lacking.

The fate of an optically active α -carbon atom which is also benzylic, and therefore particularly activated, is less clear. Interference due to enolization in such reactions has been discussed under the heading

¹¹² H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965).

¹¹³ O. F. Zinkel, Ph.D. Thesis, Univ. of Wisconsin; *Diss. Abstr.*, **26**, 1359 (1965) [*C.A.*, **64**, 3330 (1966)].

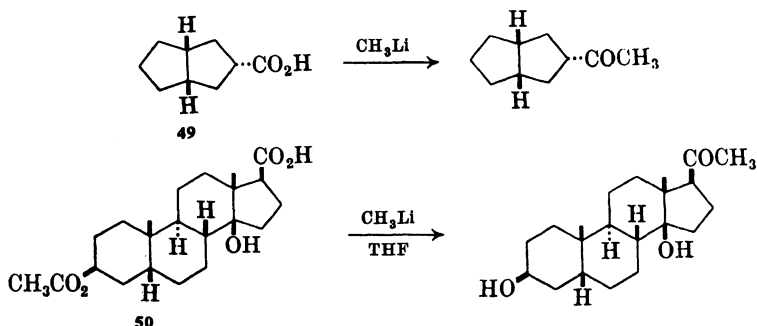
¹¹⁴ E. J. Corey and R. A. Sneed, *J. Amer. Chem. Soc.*, **75**, 6234 (1953).

¹¹⁵ W. G. Dauben and E. Hoerger, *J. Amer. Chem. Soc.*, **73**, 1504 (1951).

¹¹⁶ J. Meinwald and P. Gassman, *J. Amer. Chem. Soc.*, **82**, 5445 (1960).

¹¹⁷ R. Granger, P. F. G. Nau, and J. Nau, *Bull. Soc. Chim., Fr.* **1959**, 1811; *Compt. Rend.*, **247**, 479 (1958).

¹¹⁸ C. H. Hassal, *Org. Reactions*, **9**, 73 (1957).



"Competitive Metalation Reactions." In the reaction of a series of optically active α -aryl-substituted propionic acids and butyric acids with methyllithium, it has been reported that the ketones formed were optically active;⁹⁶ however, their optical purity was not ascertained. In more careful studies it has been established that the reaction of methyllithium with optically active 2-phenylpropanoic acid led to partial racemization, the extent varying from 10 to 70% in a series of runs.⁸⁷ Similar results were obtained for the reaction of 2-phenylbutanoic, 2-phenylpentanoic, and 2-phenylhexanoic acids with methyl-, ethyl-, or propyl-lithium.²³ The reason for these differences is obscure, but the chemical purity of the starting acid may be one factor which affects the degree of racemization. The amount of methyllithium employed was shown not to affect the amount of racemization, but it did affect the yields of ketone product profoundly.⁸⁷

The reaction of less than the theoretical amount of methyllithium with optically active 2-methylbutanoic acid led to an optically active methyl ketone,¹¹⁹ and the reaction of the lithium salt of this acid with phenyllithium gave an optically active phenyl ketone.¹²⁰ As optical purity of the ketones was not noted, it is not possible to generalize concerning the stability toward epimerization of these simple acyclic aliphatic carboxylic acids which possess less acidic α -hydrogen atoms than the α -phenyl-substituted carboxylic acids previously described.

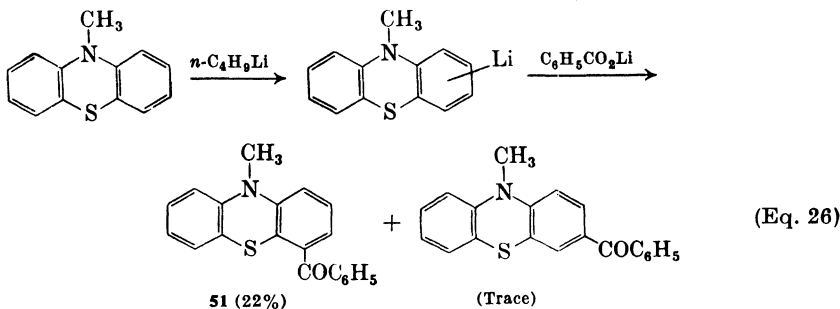
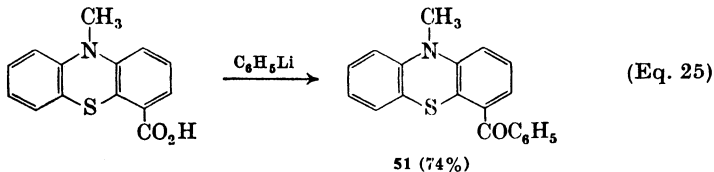
Design of Synthesis

Of the two pathways which could lead to an unsymmetrical ketone, the choice is generally dictated by the availability of the carboxylic acid and the lithium reagent. Since complex organolithium reagents are more difficult to prepare than are the corresponding carboxylic acids,

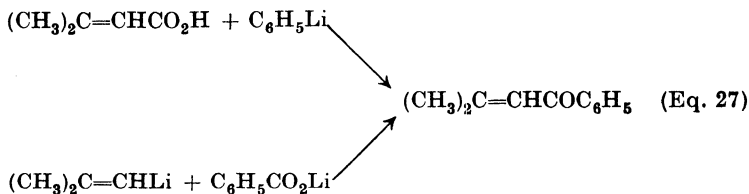
¹¹⁹ W. G. Dauben and J. Jiu, *J. Amer. Chem. Soc.*, **76**, 4426 (1954).

¹²⁰ C. Djerassi and L. E. Geller, *J. Amer. Chem. Soc.*, **81**, 2789 (1959).

the reaction of a simple organolithium reagent with a complex carboxylic acid is the most frequently utilized path. Structural features present in the organolithium reagent frequently limit its use in a synthesis. The synthesis of the ketone **51** (Eqs. 25 and 26) affords a direct comparison between the two approaches.⁴⁵ The synthesis *via* the 10-methylphenothiazinyl lithium reagent is inefficient, probably because of difficulties in the metalation step, and yields a mixture of isomers.

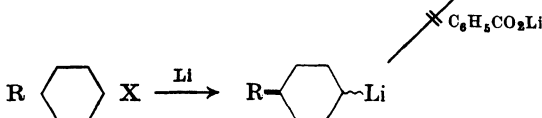
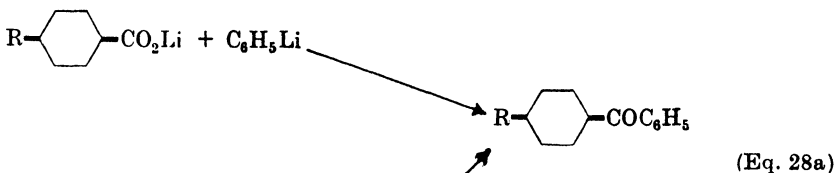
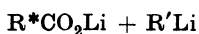
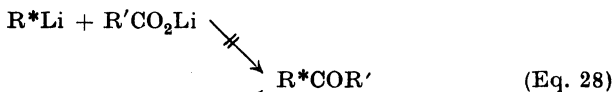
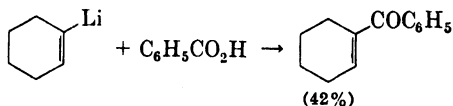
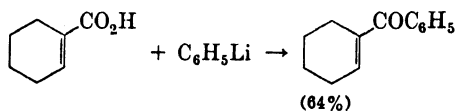


Side reactions also influence the choice of reagents. In the synthesis of isobutenyl phenyl ketone (Eq. 27) the first method may be complicated by addition of phenyllithium to the double bond²⁹ and by deconjugation,²⁶ while the second method will probably lead to low yield of ketone, typical for an alkenyllithium reacting with a carboxylic acid.^{30, 31}

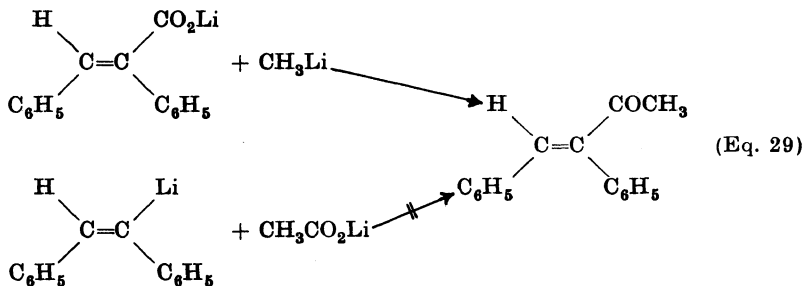


Support for the preceding expectation is found in the reported yields of cyclohexenyl phenyl ketone formed by both methods. The first gave a 64% yield,⁷⁷ the second only 42%.³⁰ (Equations on p. 34.)

The stereochemical limitations discussed in previous sections confine a stereospecific synthesis to one in which the center of asymmetry is at the α -carbon atom of the acid and not in the organolithium reagent (Eqs. 28 and 28a).



Similarly in the synthesis of one geometrical isomer of an unsaturated ketone, as for example in the synthesis of methyl *cis*-1,2-diphenylvinyl ketone (Eq. 29), it is advisable to employ the carboxylic acid rather than *cis*-1,2-diphenylvinyl lithium, because the latter is liable to isomerize during the reaction if not earlier during its preparation.^{121,122}



Finally, attention should be drawn to the economy achieved if the lithium salt of a carboxylic acid is employed in the reaction with a complex

¹²¹ U. Schöllkopf and W. Fabian, *Ann.*, **642**, 1 (1961).

¹²² A. N. Nesmeyanov, A. E. Borisov, *Tetrahedron*, **1**, 158 (1957); D. Y. Curtin and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **84**, 1967 (1962).

organolithium reagent. The use of lithium carboxylates requires only one half as much of the organolithium reagent and has the added advantage of avoiding contamination of the ketone with the hydrocarbon derived from the organolithium reagent. When such hydrocarbons are of high molecular weight, separation of the ketone may be difficult. Reactions such as the second step in Eq. 26 should obviously not be conducted on the free acid. Other advantages of using the lithium carboxylate rather than the free carboxylic acid are discussed in the next section.

FORMATION OF TERTIARY ALCOHOLS AS A SIDE REACTION

Formation of a tertiary alcohol is the most general side reaction during the conversion of an acid to a ketone with a lithium reagent. The amount of alcohol formed is seemingly erratic, unpredictable, and irreproducible, suggesting that inadequately controlled factors are responsible. In most reactions the presence of alcohol has not been specifically noted in the product and many of the high yields reported for the ketone do not take into account the presence of alcohol. When the product has been analyzed, the amounts of alcohol formed have varied from zero (refs. 20, 21, 58, 59, 62, 75, 83, 101) to as much as 35%,¹²³ 42%,⁴⁷ 45%,¹²⁴ 50%,⁷⁷ 54%,²¹ or even 75%⁶³ of the product. From the data in the literature it is not possible to correlate the ease of alcohol formation with the structure of the organolithium reagent. An excess of organolithium reagent can definitely be harmful. For example, with a theoretical amount of methyllithium no alcohol¹²⁵ was formed in the conversion of β -ionylidene-crotonic acid, but with a 300% excess of lithium reagent the product consisted of alcohol to the extent of 74%.¹²⁶ Similarly, whereas a theoretical amount of methyllithium produced only 10% of alcohol, a 300% excess furnished a product mixture containing 50% alcohol in the reaction with cyclohexenecarboxylic acid.⁷⁷ Two additional pieces of evidence shed light on the origin of alcohol. When benzoic acid was treated with the theoretical amount of phenyllithium, a 37% yield of ketone and a 14% yield of triphenylcarbinol were obtained; but, when the lithium salt of benzoic acid was used, benzophenone was formed in 70% yield and no alcohol was produced.¹ When 4-*t*-butylcyclohexanecarboxylic acid was treated with excess methyllithium or ethyllithium and hydrolysis was carried out carelessly the percentage of alcohol in the product ranged from 30 to 45%, but when special precautions were taken in the hydrolysis,

¹²³ F. J. Impastato and H. M. Walborsky, *J. Amer. Chem. Soc.*, **84**, 4838 (1962).

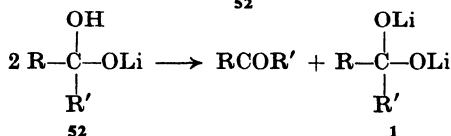
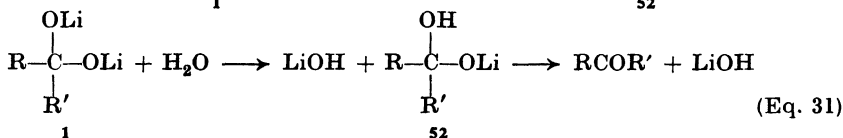
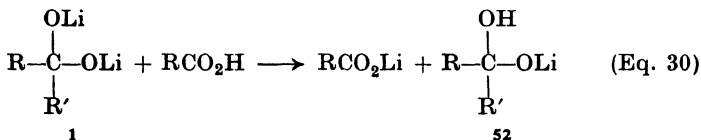
¹²⁴ D. J. Cram, A. Langemann, J. Allinger, and K. F. Kopecky, *J. Amer. Chem. Soc.*, **81**, 5740 (1959).

¹²⁵ D. A. van Dorp and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **65**, 338 (1946).

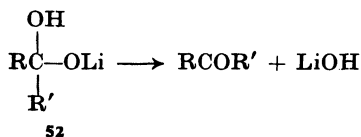
¹²⁶ P. Karrer and J. Benz, *Helv. Chim. Acta*, **31**, 1607 (1948).

by pouring the ethereal reaction solution very slowly into a large amount of aqueous hydrolyzing medium with efficient stirring, no alcohol was produced.²¹ When a theoretical amount of methyllithium was added to the carboxylic acid, "negligible" amounts of carbinol were formed, whereas addition of carboxylic acid to methyllithium produced a 74:26 ratio of ketone:alcohol.^{111a} Further examples of this phenomenon have been reported for benzilic^{95a} and 1,2,3,4-tetrahydro-1-naphthoic acids.^{126a}

The following interpretation of the origin of alcohol is offered.* The reaction of the lithium carboxylate with the organolithium reagent normally does not form a tertiary alcohol, consonant with the view that the dilithium salt **1** is inert toward further reaction. Alcohol is formed, instead, by way of the free ketone whose generation in the presence of organolithium reagent accounts for its formation. Two different reactions (Eqs. 30 and 31) produce the *mono* lithium salt **52**, whose decomposition or disproportionation gives rise to free ketone and **1** (Eq. 32). (The disproportionation sequence is supported by the report that the corresponding bistrifluoromethyl salt (**52**, $R = R' = CF_3$) disproportionates in an analogous manner.⁴) The first of these two reactions (Eq. 30) can occur during the addition, if the rate of mixing is not very much faster than the reaction of **1** with the free carboxylic acid and if the rate of reaction of the lithium carboxylate with the organolithium reagent to give **1** is not very much slower than the reaction of the carboxylic acid with the organolithium reagent.



or



(Eq. 32)

* Other interpretations have been advanced^{1,2} but are considered unlikely by the author.

^{126a} L. J. Ferrarini, Ph.D. Thesis, Univ. of Rhode Island, 1969.

In principle, the reaction of Eq. 30 could be arrested by assuring that free carboxylic acid and **1** not be present in the same medium, i.e., by the addition, with very efficient stirring, of the carboxylic acid to the organolithium reagent. However, since the rate of mixing is crucial in this operation, it would be impossible to suppress reaction 30 entirely, particularly as the rate of that reaction appears to be comparable to the rate with which the organolithium reacts with the carboxylic acid. Since the ketone formed in this manner would immediately react with the organolithium reagent, this addition mode must invariably lead to tertiary alcohol. For these reasons it is crucial that the reaction be carried out instead by the slow addition, with very efficient stirring, of the organolithium reagent to the carboxylic acid, so that all the carboxylic acid is converted to its lithium salt before any appreciable amount of the dilithium intermediate has been produced in the reaction mixture.

The reaction of Eq. 31 corresponds to the hydrolysis step and is also a potential source of tertiary alcohol. The precautionary measures in mixing the reagents must be followed by a careful workup procedure if the formation of tertiary alcohol is to be minimized. These precautions are always necessary if unchanged organolithium reagent remains, as it usually does, at the end of the reaction. The following specific precautionary measures have to be taken: the organic reaction mixture should be added slowly, dropwise, to a large volume of the hydrolyzing medium in order to cause the immediate hydrolysis of the organolithium reagent before it can react with the freed ketone, whose concentration in the organic layer is constantly increasing; and the rate of mixing of the two layers (the ethereal reaction medium and the aqueous hydrolysate) needs to be extremely rapid so that the organolithium reagent can be transported quickly out of the organic layer, where it may react with the free ketone, into the aqueous medium for hydrolysis. (The use of several portions of fresh hydrolyzing medium is desirable in order to decrease the likelihood of the organolithium reagent reacting with the free ketone.²¹)

When all these precautions were followed, it was shown that no alcohol was formed.²¹ Alternatively, the use of lithium salt obviates the need for the very careful mixing procedure of the two reagents; however, the careful workup procedure must be followed if optimum results are to be obtained. (Occasional reports that the use of lithium salts of carboxylic acids^{63, 78} or adherence to the recommended preventive measures⁴⁷ did not entirely eliminate alcohol formation are probably due to failures to adhere rigorously to all the necessary measures.) Detailed procedures, which eliminate the formation of tertiary alcohol in the reaction of *t*-butylcyclohexanecarboxylic acid²¹ and lithium cyclohexanecarboxylate¹²⁷

¹²⁷ T. M. Bare and H. O. House, *Org. Syntheses* **49**, 81 (1969). This procedure is reproduced under "Experimental Procedures."

with methyllithium are provided under "Experimental Procedures"; they incorporate most of the preventive measures enumerated above.

When methyllithium is employed, excess lithium reagent could be destroyed at completion of reaction before hydrolytic workup, by addition of ethyl acetate or ethyl formate, if the presence of *t*-butyl alcohol or isopropyl alcohol in the product can be tolerated. This could prove to be a useful general measure to prevent alcohol formation in reactions with methyllithium, but it has not been tried.

Solubility problems may be conducive to the formation of large amounts of alcohol, unless the hydrolysis is carefully carried out. For example, it was found that the lithium salt of β -phenylcinnamic acid was not appreciably soluble in ether, so that the reaction with methyllithium was very slow.⁶³ Conventional workup after 24 hours afforded a recovery of 75% of the carboxylic acid and furnished a neutral product mixture which contained 75% of the tertiary alcohol. Because of the harmful excess of lithium reagent remaining at the hydrolysis stage, the ketone liberated in this step reacted with the unreacted organolithium reagent. When tetrahydrofuran was employed, the solubility problems were overcome and little unreacted organolithium reagent remained; conventional workup afforded product which contained only 18% alcohol. Another favorable feature in the last reaction was probably the miscibility of the tetrahydrofuran with the aqueous hydrolyzing medium, which alleviates the problem of mixing two immiscible layers. Others have reported that, in contrast to ether media, no alcohol formation was encountered when tetrahydrofuran was used as a solvent.¹⁰⁹ In a procedure which led to no alcohol formation from the lithium salt of cyclohexanecarboxylic acid, the water-miscible 1,2-dimethoxyethane was employed as a cosolvent.¹²⁷ Alternatively, the use of an organic hydrolyzing medium, such as methanol, should prove advantageous in the workup.

In general the formation of some tertiary alcohol has been tolerated, since purification of the ketone was readily achieved by standard procedures. Whenever fractional crystallization or distillation has been impractical or ineffective, column chromatography (refs. 63, 78, 92, 96a, 112, 114, 120, 124, 128, 129, 129a) or vapor phase chromatography¹⁶ has been successful. Tertiary alkyl carbinols can be easily removed by dehydration during vapor phase chromatography^{78,82} or by chemical

¹²⁸ W. G. Dauben, V. M. Alhadeff, and M. Tanabe, *J. Amer. Chem. Soc.*, **75**, 4580 (1953).

¹²⁹ D. J. Cram and H. P. Fischer, *J. Org. Chem.*, **30**, 1815 (1965). This procedure is reproduced under "Experimental Procedures."

^{129a} T. D. Hoffman and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1001 (1969).

means; a readily separable mixture of ketone and olefin results. Preparation of the tosylate with or without subsequent elimination to the olefin has been employed as a separation process.¹²³ Ketones have been isolated from the crude reaction mixture *via* the bisulfite adduct,¹²⁰ the semicarbazone,^{87, 120, 124, 130} or by reaction with Girard P reagent.^{109, 126, 131} Purification of optically active ketones without loss of optical activity has been achieved by a special method of regeneration from the semicarbazones¹²⁴ or by column chromatography.^{123, 129a}

Alcohol formation does not appear to be significantly suppressed when a bulky organolithium reagent¹⁹ or a hindered carboxylic acid⁴⁷ is employed. It is quite possible that bulky but more nucleophilic organolithium reagents, such as *t*-butyl- or isopropyl-lithium, promote alcohol formation by increasing the rate of formation of the dilithium salt 1. p. 36; so that in the absence of an ideally fast rate of mixing, the reaction depicted in Eq. 30 is accelerated by these reagents.

It is significant that tertiary alcohols formed as by-products are formed stereospecifically, as in the reaction of *cis-t*-butylcyclohexanecarboxylic acid with methylolithium to give the *cis-t*-butylcyclohexyldimethylcarbinol.²¹ Consequently, it can be concluded that ketones are not epimerized in the basic medium before they are transformed into tertiary alcohols.

RELATED KETONE-FORMING REACTIONS

In this section, attention is drawn to reactions which are related to the reaction of organolithium reagents and carboxylic acids. They are organized into four families: the reaction of organolithium reagents with derivatives of carboxylic acids (esters, halides, amides, nitriles, lactones, and anhydrides); the reaction of carboxylic acids with organometallic reagents other than organolithium compounds; the reaction of organolithium reagents with carbon dioxide and dialkyl carbonates; and the reaction of derivatives of carboxylic acids with organometallic reagents other than organolithium reagents.

The reaction of organolithium reagents with carboxylic esters, though not a general reaction, is frequently reported to provide good yields of ketones. This is particularly true with esters of *t*-alkylcarboxylic acids (Eq. 33,¹²⁴ 34,¹³²) and other hindered esters such as methyl hecolate which yields 96% of phenyl ketone on reaction with phenyllithium,¹³³ or

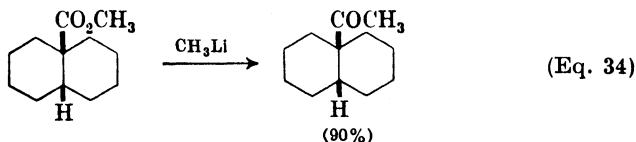
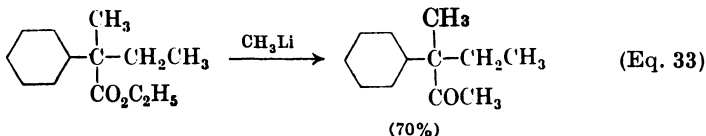
¹²⁰ J. F. Arens and D. A. van Dorp, *Rec. Trav. Chim. Pays-Bas*, **66**, 759 (1947).

¹³¹ P. Karrer, K. P. Karanth, and J. Benz, *Helv. Chim. Acta*, **32**, 1036 (1949).

¹³² F. D. Greene and N. N. Lowry, *J. Org. Chem.*, **32**, 875 (1967).

¹³³ P. Bladon and W. McMeekin, *J. Chem. Soc.*, **1961**, 3504.

reactions between heterocyclic lithium reagents and esters; pyridyllithium,^{40, 41} picolylithium,^{40, 41, 134-136} lutidyllithium,^{41, 137} quinolyl-lithium,⁴¹ isoquinolylithium,¹³⁸ and 9-acridinylmethylithium⁴³ have been reported to give ketones in high yields.



The reaction of *t*-butyllithium with hindered esters such as pivalates gave di-*t*-butyl ketone in 80% yield.¹³⁹ From less hindered esters, both alcohols and ketones were produced,¹⁴⁰ but improved yields of ketones were claimed at lower temperatures.¹⁴¹ The reaction of the bulky organolithium reagents fluorenyllithium,¹⁴² triphenylethenyllithium,¹⁴³ and 2,6-dimethoxyphenyllithium¹⁴⁴ with aromatic esters has been reported to produce ketones in good yields.

Isolated examples of the successful conversion of acid halides to ketones by reaction with organolithium reagents exist; they appear to be special cases of the use of particularly hindered acid halides and/or hindered organolithium reagents, as in the reaction of duroyl chloride with 2,6-dimethoxyphenyllithium,¹⁴⁵ and of *o*-duroylphenyllithium⁵³ or triphenylvinylithium¹⁴³ with various acid chlorides. Alternatively, these successful ketone syntheses use heterocyclic lithium reagents.^{40, 42, 45}

¹³⁴ T. Nakashima, *Yakugaku Zasshi*, **77**, 1298 (1957) [*C.A.*, **52**, 6345 (1958)].

¹³⁵ N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951).

¹³⁶ R. P. Zelinsky and M. Benilda, *J. Amer. Chem. Soc.*, **73**, 696 (1951).

¹³⁷ D. A. Dimmig, Ph.D. Thesis, Univ. of Pittsburgh; *Diss. Abstr.*, **25**, 6228 (1965) [*C.A.*, **63**, 8309 (1965)].

¹³⁸ R. B. Engl and L. L. Ingraham, *J. Org. Chem.*, **26**, 4933 (1961).

¹³⁹ J. E. Dubois, B. Leheup, F. Hennequin, and P. Bauer, *Bull. Soc. Chim. Fr.*, **1967**, 1150.

¹⁴⁰ A. D. Petrov, E. B. Sokolova, and K. Ching-lang, *J. Gen. Chem. (USSR)*, **30**, 1124 (1960), and previous papers.

¹⁴¹ A. D. Petrov, E. P. Kaplan, and Ya. Tsir, *Zh. Obshch. Khim.*, **32**, 693 (1962); E. P. Kaplan, S. V. Zakharova, and A. D. Petrov, *ibid.*, **33**, 2103 (1963) [*C.A.*, **58**, 6685 (1963); **59**, 12689 (1963)], and previous papers.

¹⁴² G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **39**, 1613 (1961).

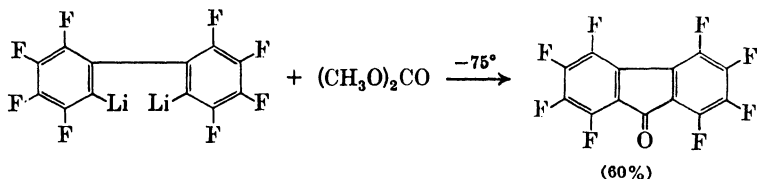
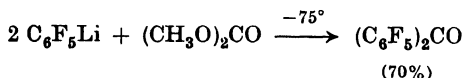
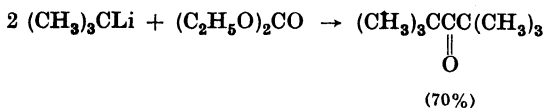
¹⁴³ D. Y. Curtin, H. W. Johnson, Jr., and E. C. Steiner, *J. Amer. Chem. Soc.*, **77**, 4566 (1955).

¹⁴⁴ J. R. Somers, Ph.D. Thesis, Univ. of Pittsburgh; *Diss. Abstr.*, [7] **B27**, 2262 (1967).

¹⁴⁵ R. C. Fuson and B. Vittimberga, *J. Amer. Chem. Soc.*, **79**, 6030 (1957).

In contrast to the facile reaction of organolithium reagents with carboxylic acids, the reaction of carboxylic acids with other organometallic reagents is usually not a satisfactory route to ketones. Isolated examples of the successful conversion to ketones with Grignard reagents exist,⁶ but this reaction does not appear to have preparative potential; the yields of ketones are low and much tertiary alcohol is formed. In the reaction of cyclohexenecarboxylic acid with phenyl- or benzyl-magnesium bromide, the principal products were derived from conjugate addition.⁷⁷ Similar results were noted for 2-norbornenecarboxylic acid and its methyl ester.^{158c}

The reaction of organolithium reagents with carbon dioxide under properly chosen conditions can lead to ketones¹ *via* the intermediate lithium carboxylate (Eqs. 1 and 2). A number of reports of high yields of ketones from this reaction have appeared in the literature (refs. 1, 15, 32, 50, 151). In a variant of this reaction, organolithium reagents have been shown to give good yields of ketones by reaction with dialkyl carbonates, as shown in the accompanying equations.^{139, 159} These reactions proceed by way of ester intermediates and, because esters generally give poor yields of ketones, they constitute special cases.



Among good ketone syntheses involving organometallic reagents are the reactions of dialkylcadmiums,¹⁶⁰ dialkylzincs, and Grignard reagents with acid halides. These reactions have been reviewed previously;¹⁶¹ a comparison of these reactions with the ketone synthesis from organolithium reagents and carboxylic acids is presented in the next section. The

^{158c} R. A. Finnegan and W. H. Mueller, *J. Organometal. Chem.*, **17**, 361 (1969).

¹⁵⁹ R. D. Chambers and D. J. Spring, *J. Chem. Soc.*, **C**, 1968, 2394.

¹⁶⁰ J. Cason, *Chem. Rev.*, **40**, 15 (1947).

¹⁶¹ D. A. Shirley, *Org. Reactions*, **8**, 28 (1954).

reaction of Grignard reagents with nitriles^{77, 123, 161a, 162a} and amides^{162, 162a, 163} also leads to good yields of ketones. Whereas the reaction with nitriles is an excellent general synthetic method, the reaction with amides appears to be limited to aromatic or highly hindered amides if high yields of ketones are to be obtained. Related ketone syntheses *via* Grignard reagents have been summarized.¹⁶⁴ Among them, the reaction of Grignard reagents with acetic anhydride at low temperatures is a particularly good method for methyl ketones (refs. 31, 81, 165, 166–170). The relative merits of these ketone syntheses have been discussed in a number of reviews (refs. 155, 160, 161, 164, 164a).

A number of successful ketone preparations from organoaluminum compounds and nitriles¹⁷¹ or acid halides¹⁷² are on record; yields of 80–90% were obtained from aromatic acid chlorides. Reactions of organopotassium reagents with carboxylic acid derivatives have been reported;^{35, 173} no examples of their reaction with carboxylic acids exist. The reaction of methylcopper, prepared *in situ*, with benzoyl chloride furnished a 56% yield of acetophenone.^{173a}

COMPARISON WITH OTHER KETONE SYNTHESSES

Ketone syntheses *via* organometallic reagents have been treated in the previous section. In this section a brief survey of other ketone syntheses will be made, with emphasis on new methods. Examples of direct comparison of various methods leading to the same ketone will be presented.

^{161a} R. Mohrbecher and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 401 (1957).

¹⁶² F. C. Whitmore, C. I. Noll, and V. C. Meunier, *J. Amer. Chem. Soc.*, **61**, 683 (1939).

^{162a} S. Mackenzie, S. F. Mavsoeci, and H. L. Lampe, *J. Org. Chem.*, **30**, 3328 (1965).

¹⁶³ S. S. Jenkins, *J. Amer. Chem. Soc.*, **55**, 703, 1618, 2896 (1933); **56**, 682 (1934); C. M. Suter and A. W. Weston, *ibid.*, **61**, 232 (1939).

¹⁶⁴ Reference 6, Chapters VIII to XII.

^{164a} R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, pp. 316–351, John Wiley and Sons, Inc., New York, 1953.

¹⁶⁵ M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948); M. S. Newman and W. T. Booth, *J. Amer. Chem. Soc.*, **67**, 154 (1945).

^{166a} C. G. Overberger and A. Lebovitz, *J. Amer. Chem. Soc.*, **76**, 2722 (1954).

^{166b} J. Rouzaud, G. Cauquil, and L. Giral, *Bull. Soc. Chim. Fr.*, **1964**, 2908.

¹⁶⁷ M. S. Newman and J. R. Mangham, *J. Amer. Chem. Soc.*, **71**, 3342 (1949).

¹⁶⁸ M. S. Newman and T. S. Bye, *J. Amer. Chem. Soc.*, **74**, 905 (1952).

¹⁶⁹ V. Theus and H. Schinz, *Helv. Chim. Acta*, **39**, 1290 (1956).

¹⁷⁰ B. D. Tiffany, J. B. Wright, R. B. Moffett, R. V. Heinzelman, R. E. Strube, B. D. Aspergren, E. H. Lincoln, and J. L. White, *J. Amer. Chem. Soc.*, **79**, 1682 (1959).

¹⁷¹ S. Pasynkiewicz, W. Kuran, and E. Soszynska, *Rocz. Chem.*, **38**, 1285 (1964) [*C.A.*, **62**, 14555 (1965)], and previous papers.

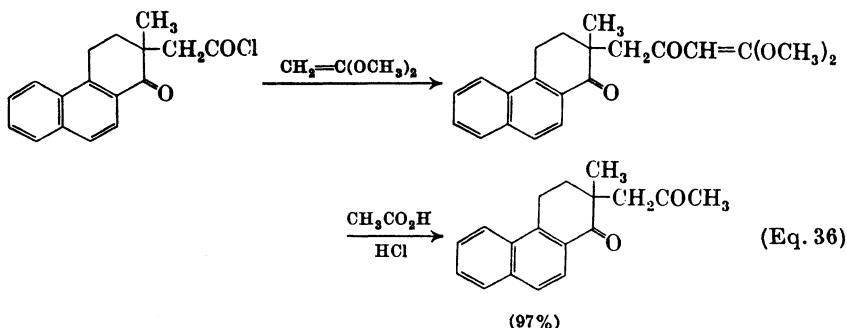
¹⁷² S. Pasynkiewicz, W. Dahlig, T. Wojnarowski, and T. Radziwonka, *Rocz. Chem.*, **37**, 293 (1963) [*C.A.*, **59**, 8640 (1963)], and previous papers in this series.

¹⁷³ G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **39**, 1613 (1961).

^{173a} H. Gilman and L. A. Woods, *J. Amer. Chem. Soc.*, **65**, 435 (1943).

Traditional ketone syntheses include the Friedel-Crafts acylation,¹⁷⁴⁻¹⁷⁶ the acetoacetic ester synthesis with alkyl halides or acyl halides^{164a, 167} and the malonic ester synthesis with acyl halides.^{166a, 177a-178} The scope and merits of these reactions have previously been discussed.^{160, 161} The Friedel-Crafts reaction is subject to strong directive effects and is frequently not applicable to the synthesis of aliphatic ketones, while enolate condensations require complex experimentation and generally provide inferior yields.

Newer synthetic methods include the reaction of acyl halides with ketene acetals (e.g., Eq. 36),¹⁷⁹ the reaction of diazoketones with hydrogen bromide followed by reduction¹⁸⁰ (Eq. 37), the addition of photochemically or thermally generated carbenes to olefins (Eq. 38),¹⁸¹ and the use of sulfur ylide reagents with carboxylic esters^{182, 183} and lactones,¹⁸⁴ followed by the reduction of the intermediates with aluminum amalgam^{182, 184} or zinc dust (Eqs. 39-41).¹⁸⁵ The keto sulfoxides have been alkylated to



¹⁷⁴ D. P. N. Satchell and R. S. Satchell, in *Chemistry of the Carbonyl Group*, S. Patai, Ed., p. 233, Interscience Publishers, New York, 1966.

¹⁷⁵ W. S. Johnson, *Org. Reactions* **2**, 114 (1944).

¹⁷⁶ H. O. House, *Modern Synthetic Reactions*, p. 282, and references therein, W. A. Benjamin Inc., New York, 1965.

^{177a} K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2251 (1966).

^{177b} H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1386 (1946).

¹⁷⁸ (a) R. E. Bowman, *J. Chem. Soc.*, **1950**, 325; (b) W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *J. Amer. Chem. Soc.*, **85**, 1409 (1963); (c) G. S. Fonken and W. S. Johnson, *ibid.* **74**, 831 (1952); (d) W. H. Hartung, *Org. Reactions*, **7**, 272 (1953).

¹⁷⁹ S. M. McElvain and G. R. McKay, Jr., *J. Amer. Chem. Soc.*, **78**, 6086 (1956); S. M. McElvain and D. G. Kundiger, *ibid.*, **64**, 254 (1942).

¹⁸⁰ A. K. Banerjee and M. Gut, *Tetrahedron Lett.*, **1969**, 51.

¹⁸¹ M. Jones, Jr. and W. Ando, *J. Amer. Chem. Soc.*, **90**, 2200 (1968).

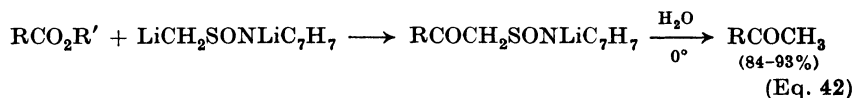
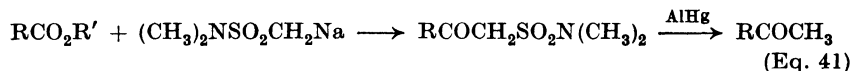
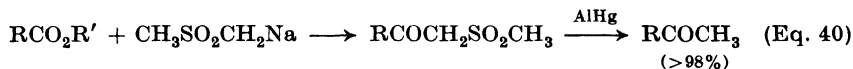
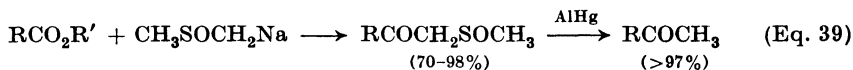
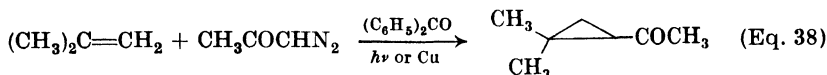
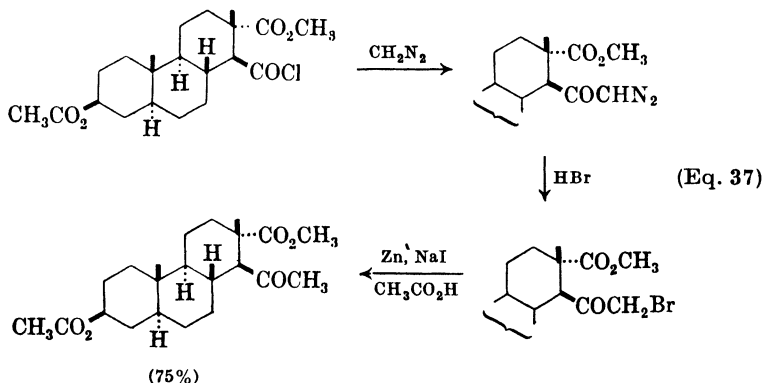
¹⁸² E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964); **87**, 1345 (1965).

¹⁸³ E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, **88**, 5656 (1966).

¹⁸⁴ H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1968).

¹⁸⁵ H. D. Becker, G. J. Mikol, and G. A. Russel, *J. Am. Chem. Soc.*, **85**, 3410 (1963); **88**, 5498 (1966).

furnish more complex ketones.¹⁸⁶ A related method utilizes the dilithium salt of a sulfonamide and yields methyl ketone directly on hydrolysis (Eq. 42).¹⁸³ Organoboranes have recently been employed to prepare ketones by reaction with carbon monoxide.¹⁸⁷



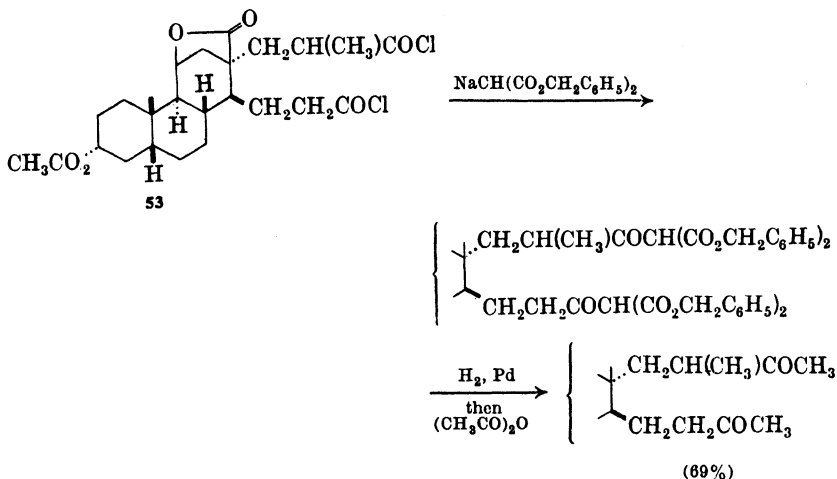
Each of these new synthetic methods finds a particular application. The sulfur ylide methods (Eqs. 39–42) are useful for the conversion of esters to ketones. The yields are excellent, but more steps are involved than in the organolithium reaction with carboxylic acids. The use of ketene acetal is a clever way of overcoming synthetic problems connected with organometallic synthesis when other carbonyl groups may react (Eq. 36), or with enolate condensations when the substrate is sensitive to base but not to mild acid. The diazoketone method finds application,

¹⁸⁶ P. D. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).

¹⁸⁷ H. C. Brown and M. W. Rathke, *J. Amer. Chem. Soc.*, **89**, 2737, 2738, 4528 (1967); H. C. Brown and E. Negishi, *ibid.*, **89**, 5477, 5478 (1967); M. E. D. Hillman, *ibid.*, **84**, 4715 (1962); H. C. Brown, *Acc. Chem. Res.*, **2**, 65 (1969).

as in Eq. 37, where the presence of another ester group prohibits the use of organometallic reagents. The carbene method of Eq. 38 is restricted to the synthesis of cyclopropanes and is limited to substrates that do not contain groups which react with carbenes or are altered photochemically.

An ingenious modification of the malonic ester synthesis obviates the alkaline hydrolysis with its attendant complications. Dibenzyl malonate is acylated and the acylated ester is hydrogenolyzed to furnish the ketone.¹⁷⁸ In this way the *bis* acid chloride **53** gave the diketone in 69% yield;^{178b} the lactone function in the molecule precluded the use of organometallic reagents. Di-*t*-butyl malonate has also been used to improve the hydrolysis-decarboxylation step.^{178c}



Because the preparation of α,β -unsaturated ketones from carboxylic acids and organolithium reagents may be accompanied by side reactions, the synthesis of these materials from Wittig reagents,¹⁸⁸ such as the anions derived from phosphonates, is a very attractive alternate pathway (Eq. 43). The reaction goes readily with aldehydes,¹⁸⁹ with longer reaction times and higher temperatures good yields are obtained from ketones.¹⁹⁰ Acetonylidenetriphenylphosphorane (**54**)^{191a} reacts with aldehydes^{191b} to furnish α,β -unsaturated methyl ketones.

New methods for the preparation of β,γ -allenic ketones and γ,δ -olefinic ketones have been reported.¹⁹²

¹⁸⁸ A. Maercker, *Org. Reactions* **14**, 270 (1965).

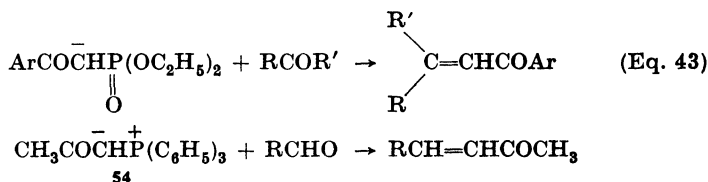
¹⁸⁹ W. S. Wadsworth, Jr., and W. S. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

¹⁹⁰ M. J. Jorgenson, S. Rhodes, and A. F. Thacher, unpublished observations.

^{191a} F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

^{191b} C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 731 (1969).

¹⁹² G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 1158, 2091. (1967); R. Marbet and G. Saucy, *ibid.*, **50**, 2095 (1967).



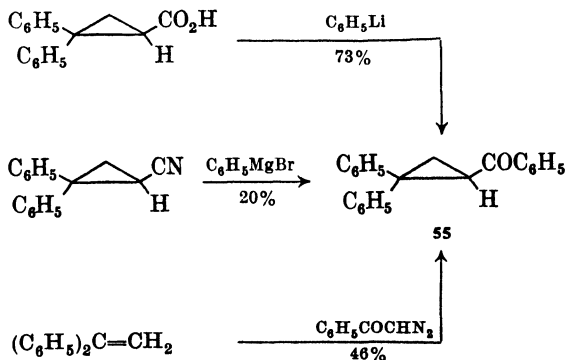
Various methods that have been employed in the formation of methyl cyclohexyl ketone are summarized in the accompanying formulation. The results attest to the superiority of the organolithium-carboxylic acid method over most of the other methods tried.

SYNTHESES OF METHYL CYCLOHEXYL KETONE

Reactants*	Conditions	Yield, %	Ref.
$\text{C}_6\text{H}_{11}\text{CO}_2\text{H} + \text{CH}_3\text{Li}$	—	83	169
$\text{C}_6\text{H}_{11}\text{CO}_2\text{Li} + \text{CH}_3\text{Li}$	—	93	127
$\text{C}_6\text{H}_{11}\text{MgBr} + (\text{CH}_3\text{CO})_2\text{O}$	-75°	62	166a
$\text{C}_6\text{H}_{11}\text{MgBr} + \text{CH}_3\text{COCl}$	-75°	"Poor"	166a
$\text{C}_6\text{H}_{11}\text{MgBr} + \text{CH}_3\text{COCl}$	0°	95	166b
$\text{C}_6\text{H}_{11}\text{MgCl} + (\text{CH}_3\text{CO})_2\text{O}$	-75°	61	70
$\text{C}_6\text{H}_{11}\text{COCl} + \text{CH}_3\text{MgI}$	—	60	193
$\text{C}_6\text{H}_{12} + \text{CH}_3\text{COCl}$	AlCl_3	50	194

* C_6H_{11} indicates cyclohexyl

Direct comparisons between two or more syntheses of the same ketone indicate that the organolithium-carboxylic acid reaction generally provides yields comparable to, if not higher than, the reaction of Grignard reagents with nitriles. One example is furnished by the three syntheses of phenyl 2,2-diphenylcyclopropyl ketone (55) shown in the accompanying equations.¹²³ A second example comes from two syntheses of phenyl 2-phenylcyclopropyl ketone. The reaction of phenyllithium with 2-phenylcyclopropanecarboxylic acid led to an 88% yield of the purified

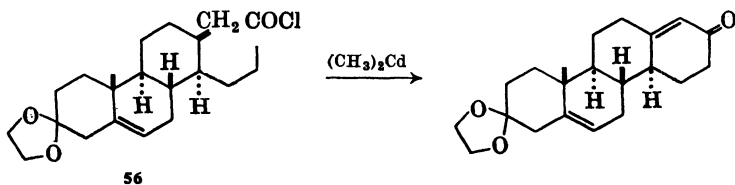


ketone,^{96a} whereas the yield from the corresponding nitrile and phenylmagnesium bromide was 85%.^{161a} In the synthesis of cyclohexenyl phenyl ketone, however, the best yields were obtained from the nitrile and the amide rather than from the carboxylic acid-organolithium reaction.⁷⁷ (Similarly, the reaction of methylmagnesium bromide with cyclohexenyl cyanide gave a 68% yield of the methyl ketone, whereas the corresponding carboxylic acid and methylolithium was complicated by the formation of the tricyclic ketone from **32** (see p. 20). In a comparison of the Friedel-Crafts acylation of olefins with the organolithium-carboxylic acid reaction, the latter reaction, even though involving an unfavorable alkenyl reactant, was found to provide a superior yield of pure product.³⁰ Thus cyclohexenyllithium and lithium benzoate furnished cyclohexenyl phenyl ketone in 42% yield, whereas the benzylation of cyclohexene led to the formation of only 30% of this ketone together with by-products which caused difficulties in separation. All the methods of formation of cyclohexenyl phenyl ketone are compared on p. 49, together with two reactions that gave none of the ketone.



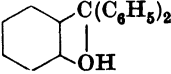




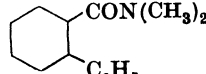



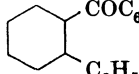
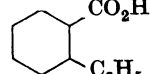

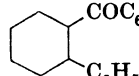
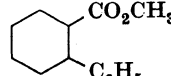




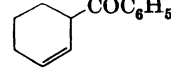
Excellent yields of ketones are generally obtained from the organolithium-nitrile reaction,^{21, 101} and this reaction is not plagued by the formation of alcohol. When the nitrile is available as starting material, this reaction is to be preferred to the carboxylic acid-organolithium reaction for these reasons. It should be noted, however, that isobutenyllithium, which with lithium acetate, lithium crotonate, and lithium benzoate furnishes ketones in 30–40% yields, does not with the corresponding nitriles afford "significant amounts" of ketones.³¹

Reports of comparable^{68, 120} and superior^{87, 117} yields of ketones from the reaction of organolithium reagents with carboxylic acids compared to organocadmium reagents reacting with the corresponding acid chlorides can be found in the literature. One report claims a very low yield of benzalacetone from cinnamonitrile and methylmagnesium iodide, a low yield from dimethylcadmium and cinnamoyl chloride, but a yield of 90–95% from lithium cinnamate and methylolithium.⁷⁰

The organocadmium reaction can be complicated by an intramolecular Friedel-Crafts type acylation when a double bond is suitably located in the molecule as in **56**.¹⁰¹ The reaction of methylolithium with the corresponding carboxylic acid proceeds normally, on the other hand.

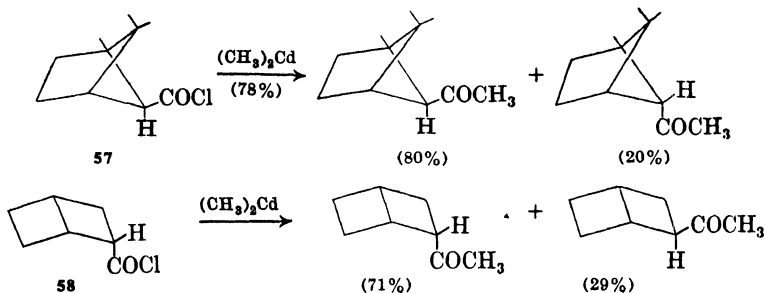


SYNTHESES OF CYCLOHEXENYL PHENYL KETONE

Reactants	Product(s) Yield(s) (%)	Ref.
 $\text{CO}_2\text{H} + \text{C}_6\text{H}_5\text{Li}$	 $+$  (64) (6)	77
 $\text{CONH}_2 + \text{C}_6\text{H}_5\text{Li}$	 (70)	77
 $\text{CON}(\text{CH}_3)_2 + \text{C}_6\text{H}_5\text{Li}$	 $+$  (35) (25)	77
 $\text{CN} + \text{C}_6\text{H}_5\text{MgBr}$	 (73)	77
 $\text{CO}_2\text{H} + \text{C}_6\text{H}_5\text{MgBr}$	 $+$  (45) (32)	77
 $\text{CO}_2\text{CH}_3 + \text{C}_6\text{H}_5\text{MgBr}$	 $+$  (83) (Small amounts)	77
 $\text{Li} + \text{C}_6\text{H}_5\text{CO}_2\text{H}$	 (42)	30
 $+ \text{C}_6\text{H}_5\text{COCl} + \text{AlCl}_3$	 $+$  (30) (45)	30

In one example, the reaction of 2-phenylpropanoyl chloride with dimethylcadmium, ethyl 2-phenylpropanoate was formed from the breakdown of the diethyl ether employed as solvent in the presence of the cadmium reagent.⁸⁷

Significant stereochemical differences exist among various methods of ketone synthesis. When the acid chlorides **57**⁶⁸ or **58**^{194a} reacted with dimethylcadmium, substantial epimerization occurred in the products. That loss of optical activity is generally higher for the organocadmium reaction than for the carboxylic acid-organolithium reaction has been noted also in acyclic systems;⁸⁷ the stereochemical outcome of the reactions with organocadmium reagents was found to be erratic. Other investigators have designated the organocadmium reaction as stereospecific.¹⁹⁵ It has been reported that acid chlorides undergo epimerization



and racemization on storage and during their preparation, and it was concluded that the organocadmium reaction in itself is stereospecific.¹⁹⁶ It is not clear at what stage epimerization of the chloride **57** occurred. The chloride **58**, however, was noted to be stereochemically pure.^{194a} Nonetheless, since the stereochemical purity of acid chlorides is difficult to control, the organocadmium reaction should not be used where epimerization or racemization is likely to occur.

The stereochemical instability of acid halides also limits the application of other synthetic methods in which they are employed as starting material. Thus the malonic ester synthesis with the stereochemically pure acid chloride **59** led to epimerization.^{177a} Because diethylzinc, on the other hand, was reported not to cause significant epimerization, the organozinc method has been designated superior to the organocadmium method.^{177a}

¹⁹³ G. Darzens and H. Rost, *Compt. Rend.*, **153**, 773 (1911) [*C.A.*, **6**, 227 (1912)].

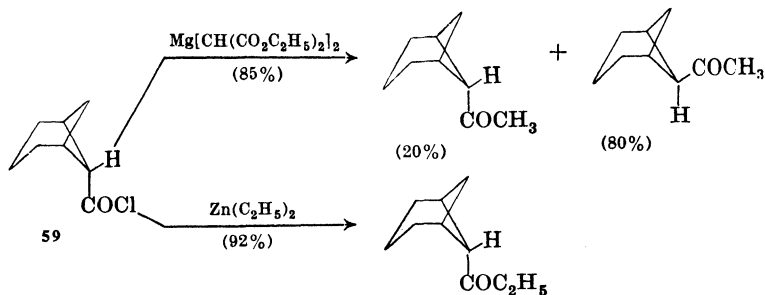
¹⁹⁴ C. D. Nenitzescu and E. Cioranescu, *Ber.*, **69**, 1820 (1936).

^{194a} R. N. McDonald and G. E. Davis, *Tetrahedron Lett.*, **1968**, 1448; *J. Org. Chem.*, **34**, 1916 (1969).

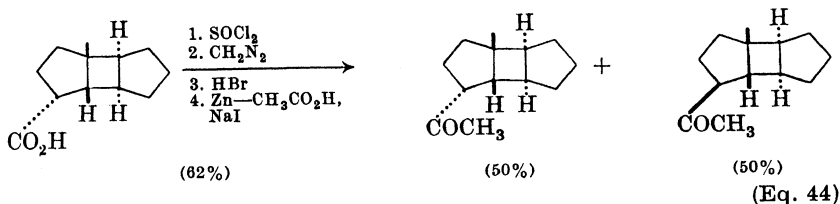
¹⁹⁵ A. Campbell and J. Kenyon, *J. Chem. Soc.*, **1946**, 25; F. A. A. Elhafez and D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 5846 (1952).

¹⁹⁶ J. Cason and F. J. Schmitz, *J. Org. Chem.*, **28**, 555 (1963).

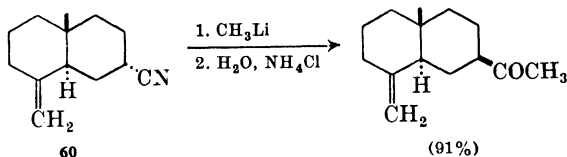
Although the reaction *via* the diazoketone shown in Eq. 37 was reported to be stereospecific, another example of the same synthetic method (Eq. 44) has been found by other investigators to give rise to a mixture of



stereoisomeric ketones, in contrast to the methyllithium-carboxylic acid synthesis which produced no epimerization.¹⁹⁷



The reaction of organolithium reagents with nitriles is also not immune to epimerization. The conversion of the nitrile **60** was accompanied by complete epimerization to the more stable ketone.¹⁹⁸ Neither is the reaction of esters with dimethylsulfinyl carbanion (Eq. 39) stereospecific. Reaction of the methyl ester corresponding to the acid chloride **58** by this method gave an *exo:endo* ratio of ketones of 62:38.¹⁹⁴



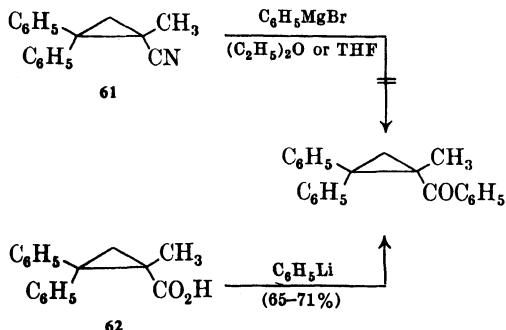
These reports stand in strong contrast to the established stereospecificity of the reaction of organolithium reagents with alicyclic carboxylic acids to give ketones.^{20, 110, 114, 115, 117}

Steric effects also come into play to different extents in syntheses of ketones utilizing different organometallic reagents. The organolithium-carboxylic acid reaction appears to be less subject to steric hindrance than

¹⁹⁷ C. H. Heathcock and R. A. Badger, unpublished observations.

¹⁹⁸ J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966).

the Grignard-nitrile synthesis. Thus the nitrile **61** failed to give the phenyl ketone in diethyl ether, probably because of steric hindrance, and the reaction in boiling tetrahydrofuran led only to an intractable polymer. By contrast, the carboxylic acid **62** smoothly furnished the phenyl ketone.¹²³



The organocadmium reaction, on the other hand, may be less sensitive to steric effects than the organolithium-carboxylic acid reaction. Whereas the bicyclic carboxylic acid **22** (p. 14) did not furnish the methyl ketone on reaction with methyl lithium, the corresponding acid chloride **57** (p. 50) did, albeit with epimerization, on reaction with dimethylcadmium.⁵⁸ Steric constraints are also operative to a lesser extent in other reactions involving acid halides. Thus, whereas the carboxylic acid **24** (p. 14) could not be converted to the methyl ketone with methyl lithium, the corresponding acid chloride furnished the methyl ketone on treatment with methyl lithium.⁶⁰

EXPERIMENTAL FACTORS

Preparation and Handling of Organolithium Reagents. Commercial preparations of organolithium reagents are available as filtered solutions, packaged in bottles capped with serum stoppers.* Aliquots are readily withdrawn by means of a hypodermic syringe.

Two major methods for the preparation of organolithium compounds, the direct metalation with organolithium compounds³⁸ and the halogen-metal interconversion reaction with organolithium reagents,⁸ have been reviewed in previous volumes. The direct metalation of organic halides with lithium is the more convenient and economical preparative method for the more common organolithium reagents. Detailed directions for the preparation, by this method, of various organolithium reagents have

* Suppliers in the United States: Foote Mineral, Lithium Corporation of America, Alpha Inorganics, Inc., and Columbia Organics; in Europe: Fluka Ltd.

been published: *e.g.*, for *n*-butyllithium,⁸ methyllithium from methyl iodide^{2, 125, 199} and, from methyl bromide,²⁰⁰ for *n*-amyllithium,²⁰¹ isopropyllithium,^{202, 203} *t*-butyllithium,^{204, 205} and phenyllithium.^{8, 199, 206} A detailed procedure for the generation of methyllithium in yields of 95 per cent has been published.² For the preparation of *t*-butyl- and isopropyl-lithium in pentane the presence of 1% of sodium in the lithium employed is necessary. Lithium preparations, containing 1 per cent of sodium, are now marketed for this purpose. The presence of magnesium in the lithium has also been shown to catalyze the reaction.^{204, 205} The preparation of salt-free phenyllithium from phenylmercury and lithium has been described.²⁰⁷ The best preparation of pure phenyllithium utilizes the reaction between *n*-butyllithium and iodobenzene.²⁰⁶

Directions for assay of organolithium reagents have appeared^{2, 125, 208-212} and have been summarized.²¹³ Methyllithium concentrations are most easily determined by titration with *sec*-butyl alcohol employing the charge transfer complex formed between methyllithium and bipyridyl or *o*-phenanthroline as the indicator.^{211, 212} For an accurate assay of methyllithium, a double titration method, employing ethylene dibromide or phenyldimethylsilyl chloride, is recommended.^{209, 210} Titrations of halide-free methyllithium that had been supplied by Foote Mineral Co. showed the concentration of three bottles to be 1.33–1.55 *M* in methyllithium by this procedure, and the halide content to be only 0.04–0.06 *M* by the Volhard method.²¹⁴

When a commercial preparation is not employed, the reagent is generally prepared *in situ*. An inert atmosphere is mandatory; because of the slow reaction of lithium with nitrogen, a helium or argon atmosphere is advisable, especially when the lithium reagent is being prepared at low

¹⁹⁹ H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Amer. Chem. Soc.*, **55**, 1252 (1933).

²⁰⁰ H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Amer. Chem. Soc.*, **71**, 1499 (1949).

²⁰¹ H. Gilman, F. W. Moore, and O. Baine, *J. Amer. Chem. Soc.*, **63**, 2479 (1941).

²⁰² H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem. Soc.*, **62**, 2327 (1940).

²⁰³ H. Gilman, E. A. Zoellner, W. M. Selby, and C. Boatner, *Rec. Trav. Chim. Pays-Bas*, **54**, 584 (1935).

²⁰⁴ P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, **77**, 2804 (1955).

²⁰⁵ P. D. Bartlett, C. G. Swain, and R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 3229 (1941).

²⁰⁶ M. Schlosser and L. Ladenberger, *J. Organometal. Chem.*, **8**, 193 (1967).

²⁰⁷ G. Wittig and E. Benz, *Chem. Ber.*, **91**, 873 (1958).

²⁰⁸ H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

²⁰⁹ H. Gilman and F. C. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

²¹⁰ H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

^{210a} R. L. Eppley and J. A. Dixon, *J. Organometal. Chem.*, **8**, 176 (1967).

²¹¹ W. Voskuil and J. F. Arens, *Org. Syntheses*, **43**, 47 (1968).

²¹² S. C. Watson and J. C. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

²¹³ A. G. Davies, *Ann. Rept.*, **64**, 219 (1967).

²¹⁴ H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).

temperatures or in nonvolatile solvents. Since most reactions leading to organolithium compounds do not take place quantitatively, assaying must be done if a specific concentration of the organolithium reagent in the subsequent reaction is desired. The usual precautions in handling organolithium reagents should be carefully heeded; isopropyllithium and *t*-butyllithium are especially pyrophoric and ignite when exposed to air. It is customary to employ the unfiltered solution directly after preparation. Various investigators have filtered the solution before use and have obtained consistently high yields of ketones.^{75, 96a, 215} Laboratory preparations of organolithium reagents will contain lithium halide and, if the reaction is not conducted quantitatively and carried to completion, the starting halide and unchanged lithium will remain. These substances can cause side reactions during the preparation of the ketone; variations in the outcome of reactions may be caused by their presence. Many of the commercial preparations appear to be almost halide-free.²¹⁴

When the carboxylic acid is added directly to the prepared organolithium reagent, the addition can be made to the original reaction vessel. This addition method, however, is conducive to alcohol formation. For optimum results the organolithium reagent should be added to the carboxylic acid. Since this calls for the additional operation of transferring the organolithium reagent *slowly* from the reaction vessel in which it was generated into the reaction vessel containing the carboxylic acid, special precautions should be taken with the very reactive organolithium reagents. A reaction vessel adapted for siphoning or filtering is convenient for such transfer.⁷⁵

More complex organolithium reagents are generally prepared by direct metalation with a reactive organolithium reagent such as *n*-butyllithium.³⁸ This reaction gives pure product if the reaction proceeds quantitatively. If unchanged reagent remains, products derived from the starting organolithium reagent (*e.g.*, *n*-butyllithium) may be obtained.

Solvents. The preparation of organolithium reagents is generally carried out in diethyl ether. Secondary and tertiary alkylolithium reagents are often prepared in pentane, hexane, or heptane because their solutions in diethyl ether are not stable at room temperature. Since these reagents are generally used immediately, deterioration of the reagent due to reaction with solvent is usually negligible. Over longer periods, even the less reactive aryl and primary alkyl organolithium reagents react appreciably with diethyl ether, tetrahydrofuran,¹¹ or 1,2-dimethoxyethane.²⁶ In these solvents the organolithium reagents can be generated and stored at low temperatures.^{11, 26, 167}

When commercial preparations are employed, part of the solvent

²¹⁵ C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

system in the reaction is determined by the medium in which the preparation is available, generally diethyl ether, benzene, hexane, pentane-tetrahydrofuran, or a mixture of any two. Some commercial preparations may also contain the mineral oil in which the lithium metal was originally dispersed. Since lithium carboxylates are not very soluble in hydrocarbon solvents, substantial dilution with diethyl ether to effect faster reaction is often recommended. If secondary or tertiary alkyl reagents are used, the reaction should be carried out at low temperatures to prevent reaction with diethyl ether.¹⁶ Solubility problems are frequently encountered even with diethyl ether; tetrahydrofuran solutions have been employed in some reactions (refs. 18, 63-65, 101, 109, 110) and benzene in others.^{94, 106} Complete solution of the carboxylic acid, however, does not appear to be crucial, for high yields of products have been reported when suspensions of the acid in diethyl ether¹²⁹ or dioxane⁸³ were utilized. Problems arising from insolubility are more frequently encountered when lithium carboxylates are employed. In such cases the choice of solvent may be critical. For example, the lithium salt of 3-hydroxy-2,2-dimethylpropionic acid was not converted to a ketone in diethyl ether over long reflux periods, whereas the same reaction in tetrahydrofuran was successful.^{106a} In this reaction, besides increasing the solubility of the lithium salt, substitution of tetrahydrofuran for diethyl ether may also have increased the nucleophilicity of the organolithium reagent; such solvent effects are known.¹¹ Tetrahydrofuran also permits a higher reaction temperature. Dioxane and 1,2-dimethoxyethane, because of even higher boiling points, should be attractive for the same reasons if the stability of the organolithium reagents is not impaired. Suspensions of the lithium carboxylates in tetrahydrofuran¹²⁰ or diethyl ether^{2, 75} have also led to successful reactions.

Ethyllithium has been employed in pentane²² and in benzene.²¹ When pentane was the solvent, low conversions to ketone occurred, but recycling the recovered acid led ultimately to a high yield of ketone.²² The choice of solvent may influence the amount of alcohol formed, as discussed in the section entitled "Formation of Tertiary Alcohols as a Side Reaction." In two examples, tetrahydrofuran has been claimed to suppress alcohol formation entirely.^{101, 109}

Selection of Experimental Conditions. When the free acid is employed, it is customary to carry out the highly exothermic mixing at low temperatures by very slow admixing of the two reagents. Efficient stirring is essential, since in diethyl ether the reaction mixture generally forms a thick mass due to the separation of the lithium salt. As the reaction progresses, the solid generally dissolves to form the dilithium salt 1. When filtered organolithium reagents are employed, the solution

often becomes clear on completion of the reaction, and this provides a visual index of the reaction progress. The completion of the reaction and the presence, if any, of excess organolithium reagent at the end of the reaction, is also indicated by standard tests for organolithium reagents performed on the reaction mixture.²¹⁶ Since the nature of the hydrolysis step is dictated by the presence or absence of unchanged organolithium reagent, such tests are advisable. When a higher temperature is desired than is permitted by the boiling point of the solvent in which the commercial preparation of organolithium reagent is supplied, the diethyl ether or hydrocarbon can be removed by distillation and replaced by higher-boiling solvents. Substitutions by benzene¹²⁹ and tetrahydrofuran²¹⁷ have been made.

Although it is advisable to limit the amount of organolithium reagent to the theoretical, this is difficult to achieve in practice because some reagent is lost in transfer and by reaction with water and other impurities in the solvents. A comfortable excess to compensate for these losses is generally employed. When the organolithium reagent is prepared *in situ*, a considerable excess of reagent is generated. If an excess is employed and the excess is not destroyed during the reaction, as by reaction with atmospheric moisture or by slow decomposition with solvent on prolonged heating, the hydrolysis must be carried out carefully. Because of the problem presented by excess organolithium reagent at the end of the reaction, it is often advisable to heat reactions longer than the minimum necessary period for completion in order to bring about destruction of the lithium reagent by reaction with the solvent; the intermediate 1 is stable to heat.

Hydrolysis is most frequently performed by reaction with ice water, since this procedure keeps the unchanged lithium carboxylate in the basic aqueous medium from which the organic acid can readily be recovered upon acidification. The neutral products can readily be isolated by extraction. Aqueous ammonium chloride solution (refs. 16, 23, 31, 82, 96a, 123, 215, 217a) and hydrochloric acid (refs. 3, 21, 26, 28, 89, 111a, 127), acetic acid,⁶⁸ and potassium carbonate^{106a} solutions have also been used for hydrolysis. For products sensitive to acid or base, the hydrolytic conditions should be carefully chosen.

The optimum procedure in the conversion of a carboxylic acid to a ketone with an organolithium reagent should include the following: efficient mechanical stirring; slow addition of reagents; use of an anhydrous inert solvent, of an inert atmosphere over the reaction solution, of filtered organolithium reagents, of a slight excess of organolithium

²¹⁶ H. Gilman and J. Swiss, *J. Amer. Chem. Soc.*, **62**, 1847 (1940).

²¹⁷ T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, **1961**, 2423.

^{217a} R. J. Stanaback, Ph.D. Thesis, Seton Hall Univ.; *Diss. Abstr.*, **27**, 4330B (1967).

reagent (determined by assay), of a prolonged reaction period, and a careful hydrolytic workup.

Preparation of Lithium Carboxylates. Yields can often be improved by converting the carboxylic acid to its lithium salt before addition of the lithium reagent.^{1, 127} However, if alcohol formation is not serious there is no advantage in using the lithium carboxylate, as it adds another step in the reaction sequence. It has been reported, for example, that comparable yields of ketones were obtained from the reaction of either cinnamic acid or the lithium cinnamate with methyllithium.²

There are obvious advantages in the use of a lithium carboxylate as the starting material when expensive organolithium reagents are employed or when the reaction of the organolithium reagent with the acid would lead to the formation of a hydrocarbon which contaminates the product. Lithium carboxylates were used to advantage in reaction with ¹⁴C-labeled methyllithium,⁷⁵ with cyclohexenyllithium,³⁰ and with lithio-phenothiazines.⁴⁵

The lithium salt can be prepared most simply from the interaction of powdered lithium hydride and the carboxylic acid in boiling 1,2-dimethoxyethane over a period of 2-3 hours as described in the preparation of methylcyclohexyl ketone under "Experimental Procedures."¹²⁷ (Because the conversion to the lithium carboxylate may be relatively slow, a generous time interval should be allowed.) An alternative procedure for the preparation of the pure lithium carboxylate is the titration of the carboxylic acid with lithium hydroxide, followed by drying the lithium carboxylate to constant weight at reduced pressure and elevated temperatures.⁷⁵ The resulting dried salt has been triturated with diethyl ether in order to dissolve unchanged acid.^{*75, 86} The pure dry salt should be powdered before use. Reactions of the carboxylic acid with the theoretical amount of lithium methoxide^{85, 121} or lithium carbonate² have also been employed to generate the lithium salt. The lithium salt from pivalolactone was prepared by its reaction with lithium hydroxide in isopropyl alcohol^{106a} or in ethanol.²¹⁸

EXPERIMENTAL PROCEDURES

The procedures are selected to take into account the variety of experimental problems encountered in this reaction. The first two are at present the best standard procedures for the reaction of methyllithium with a typical saturated carboxylic acid where formation of a tertiary

* This treatment presumes that the lithium salt is less soluble in ether than is the sodium salt. When a dilithium salt is prepared,⁷⁵ this assumption is safe; trituration with ether does not result in an unnecessary loss of lithium salt.

¹¹⁸ A. P. Meshcheryakov and I. E. Dolgii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 496 (1961) [*C.A.*, 55, 23370 (1961)].

alcohol may be a problem. The third procedure describes the use of *t*-butyllithium in an inert solvent, while the fourth should advantageously serve as a general model for reactions involving alkenyllithium reagents where Wurtz coupling is a serious side reaction. For reactions with α -halogenated carboxylic acids the special procedure for the preparation of α,α,α -trifluoroacetophenone should be followed.

Syntheses of α,β -unsaturated ketones should be patterned after the procedure for the preparation of 4-*t*-butylcyclohexylideneacetone where side reactions are avoided. The preparation and use of a lithium carboxylate as starting material are detailed in the second preparation and in the preparation of 6-methyl-5-hepten-2-one-1-¹⁴C: the latter procedure also describes the preparation of isotopically labeled methyl-lithium. The last three procedures embody particular difficulties which were overcome by proper selection of experimental conditions; they illustrate the types of modification sometimes necessary for a successful reaction.

Except for the first two, the procedures reproduced do not incorporate all measures for optimizing yields and minimizing alcohol formation. The precautionary measures outlined in the text, when closely followed, would probably result in higher yields of ketones than those reported.

4-*t*-Butylcyclohexyl Methyl Ketone²¹ (optimum procedure for minimizing alcohol formation). To a cold (0°), vigorously stirred solution of 7.24 g (37.9 mmols) of a mixture of stereoisomeric *t*-butylcyclohexanecarboxylic acids in 250 ml of diethyl ether was added, dropwise during 45 minutes, 60 ml of an ethereal solution containing 76.0 mmols of methyllithium. During the addition a voluminous white precipitate (the lithium salt of the acid) separated and then redissolved as the addition was continued. The resulting faintly turbid solution was stirred at room temperature for 4 hours and then 50-ml aliquots were removed from the reaction mixture and added, dropwise and with stirring, to fresh portions of ice and dilute aqueous hydrochloric acid. The combined ether layers were washed with aqueous sodium carbonate and with water and were dried and concentrated. Distillation of the residual liquid (6.59 g) separated 6.54 g (94.8% based on unrecovered acid) of the ketone as a colorless liquid, bp 67–72 (0.57 mm); n_D^{25} 1.4593. Acidification of the sodium carbonate washings afforded 0.24 g of starting material. No alcohol was detected by gas chromatography.

Cyclohexyl Methyl Ketone¹²⁷ (procedure employing a lithium carboxylate to minimize alcohol formation). A solution of 19.25 g (0.150 mol) of cyclohexanecarboxylic acid in 100 ml of 1,2-dimethoxyethane (dried by distillation from lithium aluminum hydride) was added

dropwise during 10 minutes to a vigorously stirred suspension of 1.39 g (0.174 mol) of powdered lithium hydride (Alpha Inorganics, Inc) in 100 ml of anhydrous 1,2-dimethoxyethane under a nitrogen atmosphere. (This part of the reaction should be carried out in the hood as hydrogen is liberated.) The resulting mixture was heated under reflux with stirring for 2.5 hours at which time hydrogen evolution ceased and the formation of lithium cyclohexanecarboxylate was complete. The suspension was cooled to approximately 10° and stirred vigorously while 123 ml of an ethereal solution containing 0.170 mol of methylolithium was added dropwise during 30 minutes. After the addition was complete, the ice bath was removed and the mixture was stirred at room temperature for 2 hours. The reaction flask was equipped with a rubber septum fitted with a glass tube, 4 mm o.d., of suitable dimensions to enable the reaction mixture to be siphoned from the flask when a slight positive nitrogen pressure was maintained in the flask.

The fine suspension in the reaction flask was agitated and siphoned into a vigorously stirred mixture of 27 ml (0.32 mol) of concentrated hydrochloric acid and 400 ml of water. The reaction flask was rinsed with an additional 100 ml of diethyl ether which was also added to the aqueous solution. After the resulting mixture had been saturated with sodium chloride, the organic phase was separated and the alkaline aqueous phase was extracted with three 150-ml portions of ether. The combined organic solutions were dried over anhydrous magnesium sulfate, the bulk of the ether was removed by distillation through a 40-cm Vigreux column, and the remaining solvent mixture was removed by distillation through a 10-cm Vigreux column. Distillation of the residual, pale yellow liquid afforded 17.53–17.69 g (92.7–93.5%) of methyl cyclohexyl ketone as a colorless liquid: bp 57–60° (8 mm); n_D^{25} 1.4488–1.4480. Less than 1% of the tertiary alcohol was present, as determined by vapor phase chromatography employing a column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P.

***t*-Butyl Phenyl Ketone (use of *t*-butyllithium in benzene).²⁰** In a 500-ml three-necked flask fitted with a mechanical stirrer, nitrogen inlet tube, condenser, and pressure-equalizing funnel was placed 150 ml (0.23 mol) of a pentane solution which was 1.54 *M* in *t*-butyllithium (Alfa Inorganics, Inc). A solution of 10.0 g (0.082 mol) of benzoic acid in 200 ml of dry benzene was added dropwise during 40 minutes to the rapidly stirred lithium reagent. The reaction mixture was stirred overnight and the orange-brown reaction mixture was hydrolyzed by pouring it slowly into 200 ml of water. The organic phase was separated, and the aqueous layer was extracted with one 100-ml portion and two 50-ml

portions of diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride (200 ml) and dried over anhydrous sodium carbonate.

Evaporation of the solvent under reduced pressure left 13.4 g (theory 13.3 g) of a clear yellow liquid. Distillation of the crude product gave 6.96 g (52.5%) of *t*-butyl phenyl ketone, bp 101–103° (10 mm), judged to be pure by vapor phase chromatographic analysis and from its nmr spectrum. Higher-boiling fractions (104–107°/10 mm and 108–110°/10 mm) furnished an additional 1.592 g of product whose *t*-butyl phenyl ketone content was greater than 95%. The combined yields from these fractions and the fore-run amounted to 66–67%. Some product remained in the pot residue. The infrared spectrum of the major fraction exhibited no absorption in the hydroxyl region.

Isobutenyl Phenyl Ketone (generation of an organolithium reagent in the presence of the lithium carboxylate to minimize Wurtz coupling).³¹ To a suspension of lithium benzoate (65 g, 0.5 mol) and lithium (6.9 g, 0.5 g atom) in diethyl ether (1 l), a solution of isobutenyl bromide (68.5 g, 0.54 mol) was added during 30 minutes. After the reaction mixture had been stirred for 24 hours, it was cooled in a solid carbon dioxide (Dry Ice)-methanol bath and treated with excess saturated aqueous ammonium chloride solution (500 ml).^{*} Isolation of the product in the usual way afforded phenyl isobutenyl ketone (32 g, 40%) as a pale yellow liquid: bp 120–121° (4 mm); n_D^{20} 1.5598.

From a similar procedure for the preparation of mesityl oxide, a 26% yield of 2,5-dimethyl-2,4-hexadiene was also isolated. The use of larger molar quantities of isobutenyllithium should, therefore, compensate for this loss of reagent and lead to higher yields of ketone.

α,α,α -Trifluoroacetophenone (procedure for α -halogenated acids employing low temperatures).³⁹ Trifluoroacetic acid (22.8 g, 0.20 mol) dissolved in 50 ml of anhydrous diethyl ether was added to a rapidly stirred ether solution of phenyllithium (0.4 mol) cooled to –65° by immersion in a solid carbon dioxide (Dry Ice)-acetone bath. The mixture was stirred for an additional 2 hours at –65°, allowed to warm to room temperature, and poured onto a mixture of ice and excess concentrated hydrochloric acid. The layers were separated and the aqueous layer was extracted with several portions of ether. The combined ether extracts were dried, the solvent was removed, and the residue was distilled first at atmospheric pressure to give 22.5 g (75%) of trifluoroacetophenone,

^{*} This hydrolysis procedure is conducive to formation of tertiary alcohol; the reaction mixture should have been added to the aqueous ammonium chloride.

bp 150–152°, and then at reduced pressure to give 3.1 g (13%) of benzoic acid.*

4-*t*-Butylcyclohexylideneacetone.⁸² To a cold (10°) solution of 25.0 g (0.13 mol) of 4-*t*-butylcyclohexylideneacetic acid in 100 ml of diethyl ether was added, dropwise and with vigorous stirring over 1.5 hours, a solution of 0.27 mol of methyllithium in 140 ml of ether. The resulting solution was stirred for an additional 11 hours and then added to cold, aqueous ammonium chloride. The organic layer was separated, combined with the ether extracts of the aqueous phase, dried, and concentrated to leave 24.19 g (96%) of the crude ketone as a pale yellow liquid.

The gas chromatogram of this product indicated that it was composed of 4-*t*-butylcyclohexylideneacetone contaminated with 2–3% of tertiary alcohol. The tertiary alcohol underwent dehydration on the gas chromatograph to a mixture of two or more dienes. Since attempts to purify the product by fractional distillation or gas chromatography resulted in partial isomerization of the product to the unconjugated isomer, a pentane solution of the crude ketone was cooled to solid carbon dioxide (Dry Ice) temperature to separate the ketone as fine white needles that remelted below room temperature. The low-temperature recrystallization was repeated several times and then the sample was dried under reduced pressure to give 7.95 g (ca. 32%) of the pure ketone as a colorless liquid, n_D^{26} 1.4895. Alternatively, the crude product may be recrystallized from methanol at solid carbon dioxide (Dry Ice) temperatures to improve recovery of product. Material purified in this way may be distilled in a short-path still (100° at 3.2 mm) to separate the product from residual methanol.

6-Methyl-5-hepten-2-one-1-¹⁴C.⁷⁵ (a) The lithium salt of 5-methyl-4-hexenoic acid was prepared as follows. A mixture of 13.2 g of 5-methyl-4-hexenoic acid (containing about 20% of the corresponding lactone) and a small amount of water was neutralized with aqueous lithium hydroxide using phenolphthalein as an indicator. The resulting solution was evaporated to dryness, the white residue washed several times with diethyl ether to remove the lactone, and finally dried to constant weight at 100°. The theoretical yield of salt (11 g) was obtained.

(b) Methyllithium-¹⁴C was prepared in the following way. A three-necked, round-bottomed flask, equipped with an exit stopcock at its base, was provided with a mechanical stirrer, reflux condenser, and dropping funnel. A small plug of glass wool was placed in the exit tube above the

* An extraction of the ether solution with aqueous base before distillation would have been preferable for the isolation of benzoic acid.

stopcock so that the product could be filtered as it was drawn out at the end of the reaction. The entire system was swept with anhydrous nitrogen.

Approximately 25 g of lithium ribbon, cut into small pieces, was placed in the flask and covered with about 50 ml of dry diethyl ether. A small portion of the solution of 17 g of methyl iodide- ^{14}C ($108 \pm 5 \text{ m}\mu\text{c/mg C}$) in 150 ml of dry ether was then added and stirring was started. Refluxing began in about a minute. The remainder of the methyl iodide solution was then added at a rate which maintained refluxing. When the addition was complete, the mixture was stirred for an additional hour and then filtered into a dropping funnel.

(c) Dry ether (200 ml) was used to suspend 16.5 g of lithium 5-methyl-4-hexenoate in a round-bottomed flask swept by anhydrous nitrogen. The filtered solution of methyllithium- ^{14}C was added slowly with stirring. After the addition, the mixture was heated under reflux for 6 hours and the resulting clear solution was poured onto ice. The ether layer was separated, washed with water until neutral and dried over magnesium sulfate. The ether was evaporated and the residue was distilled to separate 10.1 g (74%) of 6-methyl-5-hepten-2-one-1- ^{14}C , bp $81-84^\circ$ (36 mm).

4,4-Diphenyl-3-buten-2-one.⁶³ To a stirred solution of 16.78 g (0.075 mol) of β -phenylcinnamic acid in 200 ml of anhydrous tetrahydrofuran was added, dropwise, a solution of 0.164 mol (10% excess) of methyllithium in 93 ml of diethyl ether. The initially formed white precipitate dissolved to furnish a deep red solution which was heated in a $40-50^\circ$ water bath for 30 minutes.

The reaction mixture was cooled and hydrolyzed by dropwise addition of water.* The reaction mixture was extracted twice with 250-ml portions of ether. The combined ether extracts were washed with water three times and dried over anhydrous sodium sulfate. The solvent was evaporated on the steam bath, leaving a yellow liquid which contained (nmr analysis) 82% of the ketone and 18% of the corresponding tertiary alcohol. The crude product was dissolved in benzene and chromatographed on a column packed with Merck alumina. This procedure gave the desired ketone in the early fractions eluted with benzene, while the alcohol was retained on the column. The yield of pure 4,4-diphenyl-3-buten-2-one, obtained as a colorless, viscous oil after evaporation of the benzene, was 8.56 g (52%), bp $135-137^\circ$ (0.6 mm)

* This hydrolysis procedure is conducive to formation of tertiary alcohol; the reaction mixture should have been added to the aqueous ammonium chloride.

(-)-1-Methyl-1-benzoyl-2,2-diphenylcyclopropane.¹²³ This procedure was employed to obtain pure product, since standard procedures gave 30–35% of the carbinol which could not be separated by crystallization.

A solution of 0.1 mol of phenyllithium in 250 ml of anhydrous diethyl ether was added during 5 minutes to a stirred solution of 12.2 g (0.049 mol) of 1-methyl-2,2-diphenylcyclopropanecarboxylic acid ($[\alpha]_D^{23} + 34^\circ$) in 500 ml of anhydrous diethyl ether. Stirring was continued for 5 minutes after the addition, and then the mixture was hydrolyzed by pouring it into aqueous ammonium chloride.

The ether layer was separated and washed with 50-ml portions of saturated aqueous sodium chloride until the washings were neutral to litmus. The ether solution was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to leave an oil which did not solidify. The infrared spectrum indicated that the crude product was the desired ketone contaminated with a small amount of carbinol.

The oil was dissolved in 20 ml of pyridine and heated on a steam bath with excess *p*-toluenesulfonyl chloride (5 g) for 2 hours. The solution was poured onto 100 g of cracked ice and the organic product was extracted with ether. The ether was dried and the solvent was evaporated, leaving an oily residue. Chromatography of the oil on an alumina column yielded a small amount of 1,1,4,4-tetraphenyl-2-methylbutadiene and 5 g of the desired ketone as a colorless oil which solidified on standing. The yield of ketone (mp 75.5–77°, $[\alpha]_D^{23} - 33^\circ$) based on unrecovered acid was 64%. By acidification of the aqueous layer, 6 g of the starting acid was recovered.

(-)-4-Benzoyl-2,2-paracyclophane.¹²⁹ To a solution of phenyllithium prepared from 0.030 g of lithium and 0.194 g of bromobenzene in 5 ml of dry diethyl ether was added a suspension of 0.14 g of (-)-4-carboxy[2,2]paracyclophane, $[\alpha]_{546}^{25} - 212^\circ$, in 2 ml of absolute ether under dry nitrogen at 20°. After 15 minutes, 20 ml of dry benzene was added and the ether was evaporated. The resulting benzene solution was refluxed for 24 hours (bath 110°) and then cooled to 0°. Water (5 ml) was added,* the layers were separated, and the organic layer was washed with water, dried, and concentrated. The residue was chromatographed on neutral aluminum oxide. Elution with a 1:1 mixture of pentane and dichloromethane separated 0.163 g (94%) of the (-) ketone, mp 140–145°. Recrystallization of this material from acetone gave 0.105 g (61%) of pure material: mp 145–146°; $[\alpha]_{589}^{25} - 163^\circ$.

* This is a poor hydrolysis procedure; the benzene solution should have been added slowly to the water to minimize alcohol formation.

3-Acetyl-5-methylpyrazole.⁶² To a solution of 3.8 g of 5-methylpyrazole-3-carboxylic acid (0.030 mol) in 50 ml of tetrahydrofuran was added 50 ml of 2.0 *M* methyllithium in ether (Fluka Ltd.) (0.10 mol). The reaction was followed by hydrolyzing small aliquots of the reaction mixture with water and analyzing the solution by thin-layer chromatography (chloroform:methanol ratio of 9:1). When no unchanged carboxylic acid remained (after 2 hours), the reaction mixture was poured into a large volume of ice water. The water-soluble acetylpyrazole was isolated from the aqueous hydrolysate by continuous extraction with ether over a period of 20 hours. Concentration of the ether extracts furnished 1.85 g (49%) of 3-acetyl-5-methylpyrazole, contaminated by less than 2% of carbinol. Crystallization from ethyl acetate gave colorless crystals, mp 92°; after sublimation, the mp was 97°.

TABULAR SURVEY

This survey of reactions of carboxylic acids with organolithium reagents covers the literature through 1968 and includes some references to work published in 1969. Although the attempt has been made to present an exhaustive list of examples of this reaction, difficulties in searching the literature make it likely that some examples were overlooked.

The table entries are grouped according to the structure of the carboxylic acid as saturated, unsaturated, or aromatic. Within each category, acids are listed by increasing number of carbon atoms.

Reaction conditions are not specified in the survey. Unless otherwise stated, diethyl ether was the solvent and ambient or reflux temperature was used. The reader is referred to the original literature for proportions of reagents employed, reaction times, mode of mixing of reagents, and workup procedures. Since precautionary measures, now known to influence profoundly the product yield, were not routinely taken in these examples, the reported yields are not optimal. Because in many cases the presence of alcohol was not determined, the yields of ketone recorded may not be accurate.

CHAPTER 2

THE SMILES AND RELATED REARRANGEMENTS OF AROMATIC SYSTEMS

WILLIAM E. TRUCE, EUNICE M. KREIDER, AND
WILLIAM W. BRAND

Purdue University, Lafayette, Indiana

CONTENTS

	PAGE
INTRODUCTION	100
MECHANISM	101
SCOPE AND LIMITATIONS	102
Activation in the Aromatic Ring	102
The Nature of the Leaving Group X and the Nucleophilic Group YH.	104
Early Studies on Diaryl Compounds	104
Alkyl Aryl Rearrangements	106
Examples Where the Leaving Group X and Nucleophilic Group YH are Joined by Three Atoms	107
Reverse Smiles Rearrangements	108
Rearrangement in Reducing Media	110
The Truce-Smiles Rearrangement	112
The Smiles Rearrangement of Phosphonium Zwitterions	114
Summary of Variations in the Leaving Group X and the Nucleophilic Group YH	115
Acidity of the YH Function	116
Electronic Effects of Substituents in the Aromatic Nucleus Bonded to the Groups X and YH	117
Steric Effects	118
Phenazine, Phenothiazine, and Phenoxazine Formation	120
Smiles Rearrangements of Pyridyl Systems	123
Pyridyl Phenyl Systems	123
Dipyridyl Systems	125
RELATED REARRANGEMENTS	127
EXPERIMENTAL CONDITIONS	128

EXPERIMENTAL PROCEDURES	129
Rearrangement of N-Acetyl-2-nitro-2'-aminodiphenyl Sulfide	129
Rearrangement of 2-Nitrophenyl 2-Hydroxy-5-methylphenyl Sulfone	129
Rearrangement of <i>o</i> -(2,4-Dinitrophenoxy)benzamide	129
Rearrangement of Mesityl Phenyl Sulfone	130
Rearrangement of N-(<i>p</i> -Nitrophenoxy carbonyl)hydrazobenzene	130
Rearrangement of 2-Acetamidophenyl 5-Chloro-2-nitrophenyl Sulfide	130
Rearrangement of 2-Acetamidophenyl 3-Nitro-4-pyridyl Sulfide	131
Rearrangement of 3-Amino-2-pyridyl 3-Nitro-2-pyridyl Sulfide	131
TABULAR SURVEY OF SMILES-TYPE REARRANGEMENTS	132
Table VI. Alkyl Aryl Systems	133
Table VII. Diphenyl Sulfides	144
Table VIII. Diphenyl Sulfoxides	147
Table IX. Diphenyl Sulfones	148
Table X. Diphenyl Esters	157
Table XI. Diphenyl Ethers	158
Table XII. Phenyl Naphthyl Systems	167
Table XIII. Dinaphthyl Systems	170
Table XIV. Phenyl- and Naphthyl-sulfonylanthraquinone Systems	172
Table XV. Phenazines Produced by Smiles Rearrangements in Reducing Media	173
Table XVI. Syntheses of Phenoxazines Involving Smiles Rearrangements	180
Table XVII. Phenothiazines Formed by Smiles Rearrangements	182
Table XVIII. Pyridyl Phenyl Sulfides	192
Table XIX. Azaphenothiazines Formed by Smiles Rearrangements	197
Table XX. Dipyridyl Sulfides	200
Table XXI. Dipyridyl Sulfones	208
Table XXII. Dipyridothiazines Formed by Smiles Rearrangements	209
Table XXIII. Smiles Rearrangements of Phosphonium Zwitterions	210
Table XXIV. Smiles Rearrangements of Iodonium Compounds	212
Table XXV. Aryl Sulfonamides	214
References to Tables VI-XXV	215

INTRODUCTION

In 1894 Henriques reported that bis-(2-hydroxy-1-naphthyl) sulfide was converted to an isomeric dibasic substance by treatment with alkaline ferricyanide and subsequent reduction of the intermediate obtained.¹ Hinsberg carried out a similar sequence of reactions with bis-(2-hydroxy-1-naphthyl) sulfone.²⁻⁴ The structures of the isomeric products in the two series (shown in Fig. I) were established by Smiles, who, during the

¹ R. Henriques, *Ber.*, **27**, 2993 (1894).

² O. Hinsberg, *J. Prakt. Chem.*, **90**, 345 (1914).

³ O. Hinsberg, *J. Prakt. Chem.*, **91**, 307 (1915).

⁴ O. Hinsberg, *J. Prakt. Chem.*, **93**, 277 (1916).

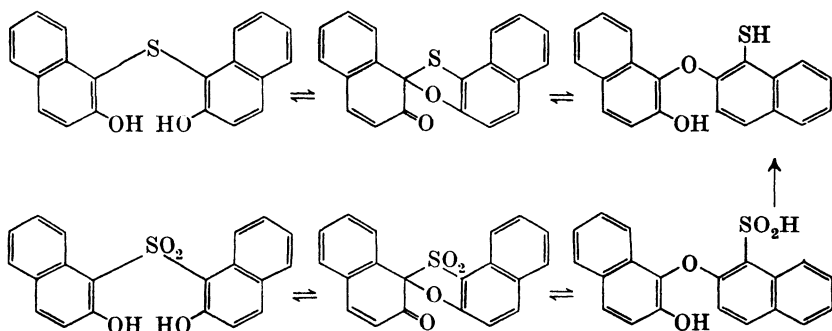


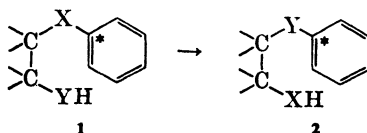
FIGURE I

course of this work, recognized the occurrence of a novel intramolecular nucleophilic rearrangement.⁵

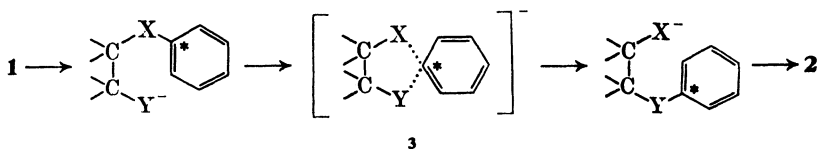
This chapter surveys the reactions which, because of the extensive work of Smiles, have frequently been identified as Smiles rearrangements. They may be characterized as intramolecular displacements at aromatic rings initiated by nucleophilic centers located two or three atoms distant from the functional group which is displaced.

MECHANISM

The rearrangement may be represented in overall form as follows. The two carbon atoms joining groups X and Y may be aliphatic or part of an aromatic ring; in a few cases hetero atoms have replaced one of these carbon atoms.

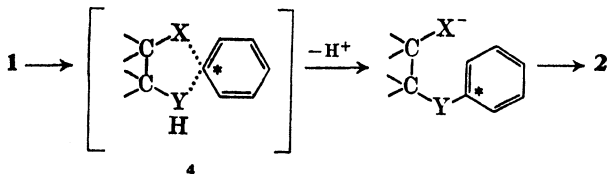


Several pathways are possible for the conversion of 1 to 2; for example, the nucleophilic function, YH, may be ionized with substitution occurring *via* the transition state 3. On the other hand, prior ionization is not

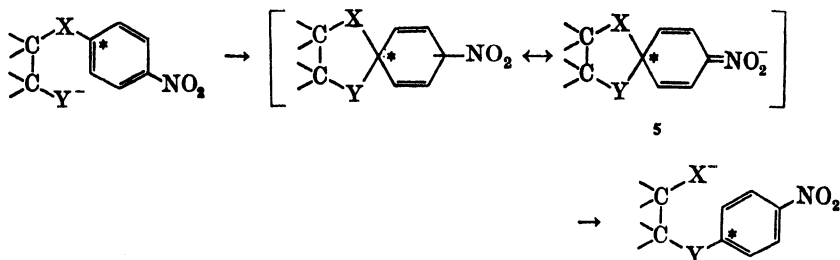


⁵ L. A. Warren and S. Smiles, *J. Chem. Soc.*, **1930**, 956, 1327.

always required, and the rearrangement may proceed in a more concerted fashion through transition state 4. There is also the possibility



that in certain systems the rearrangement proceeds through a stabilized intermediate such as 5, as opposed to a transition state.



SCOPE AND LIMITATIONS

The scope and limitations of the Smiles rearrangement are best discussed in terms of the four factors which Smiles considered the most important: (a) activation in the aromatic ring; (b) replaceability of the leaving group, X; (c) nucleophilicity of the entering group, Y⁻ (or YH); and (d) acidity of the nucleophilic function, YH.

Activation in the Aromatic Ring

Most Smiles rearrangements require electronic activation in the migrating aromatic ring. The most common activating group is nitro in the *ortho* or *para* position, with or without additional substituents, but a *p*-sulfonyl group is effective under more vigorous conditions.⁶ Ironically, the first examples of the rearrangement were the dinaphthyl sulfides in which the naphthalene nucleus contained only an additional *o*-hydroxyl group.⁷ More recently rearrangements have been obtained with *o*-halogen substituents.^{8, 9} When a 2-pyridyl group is the migrating

⁶ L. A. Warren and S. Smiles, *J. Chem. Soc.*, **1932**, 1040.

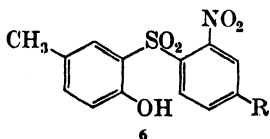
⁷ L. A. Warren and S. Smiles, *J. Chem. Soc.*, **1931**, 914.

⁸ G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 4272 (1962).

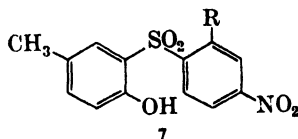
⁹ E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **29**, 2453 (1964).

aromatic nucleus, acid-catalyzed rearrangement (p. 125) can occur with an *o*-amino group or with no activating substituent, although the rate is slower than with the corresponding nitro compounds.^{10, 11} Examples in which an *o*-nitroso function is the probable activating group have been reported by Grundon.¹²⁻¹⁶ When the leaving group is sulfinate ($X = SO_2$), and the nucleophilic group is a carbanion ($YH = CH_3$), with strong bases used to induce rearrangement, no activating group is required.¹⁷ In the system just described, the influence exerted on the reaction rate by substituents in the migrating aromatic nucleus has been studied.¹⁸ Substituents which have been unsuccessful in promoting rearrangement in the more usual Smiles reactions are: *o*-OH in the benzene series,¹⁹ *p*-CH₃S,⁶ *o*-CO₂H,²⁰ and *m*-NO₂.²¹

Galbraith and Smiles made an extensive study of the effect of activation on the rate of rearrangement of typical compounds prepared in Smiles' studies.²⁰ By a rough colorimetric method they determined the time necessary for complete rearrangement of a number of sulfones of types 6 and 7. The following order of reactivity was observed: 2,4-(NO₂)₂ > 2-NO₂ > 4-NO₂. When R was a second electron-withdrawing substituent, the compounds of type 6 reacted faster than those of type 7; i.e., the nitro group is more effective in the 2 position than in the 4 position.



Relative rates:
 R = NO₂ (very rapid) >
 C₆H₅CO (0.5 min) >
 CO₂Na (50 min) > Cl (70 min) >
 H (255 min)



Relative rates:
 R = NO₂ (very rapid) >
 C₆H₅CO (12 min) >
 CO₂Na (450 min) >
 H (very slow)

In the same study it was shown that sulfone 8 underwent rearrangement more slowly than any of the sulfones represented by structures 6 and 7. The three *p*-sulfonyl substituents (SO₂CH₃, SO₂NH₂, and SO₂NHCH₃)

¹⁰ O. R. Rodig, R. E. Collier, and R. K. Schlatter, *J. Org. Chem.*, **29**, 2652 (1964).

¹¹ O. R. Rodig, R. E. Collier, and R. K. Schlatter, *J. Med. Chem.*, **9**, 116 (1966).

¹² M. F. Grundon and B. T. Johnston, *J. Chem. Soc., B*, **1966**, 255.

¹³ M. F. Grundon and W. L. Matier, *J. Chem. Soc., B*, **1966**, 266.

¹⁴ M. F. Grundon, B. T. Johnston, and A. S. Wasfi, *J. Chem. Soc.*, **1963**, 1436, 1962.

¹⁵ M. F. Grundon, B. T. Johnston, and W. L. Matier, *Chem. Commun.*, **1965**, 67.

¹⁶ M. F. Grundon, B. T. Johnston, and W. L. Matier, *J. Chem. Soc., B*, **1966**, 260.

¹⁷ W. E. Truce, W. J. Ray, Jr., O. L. Norman, and D. B. Eickemeyer, *J. Amer. Chem. Soc.*,

80, 3625 (1958).

¹⁸ W. E. Truce and M. M. Guy, *J. Org. Chem.*, **26**, 4331 (1961).

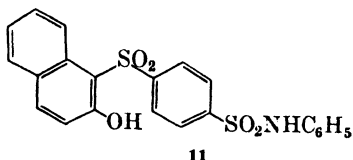
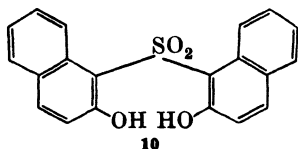
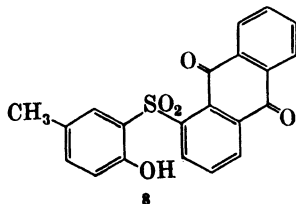
¹⁹ L. A. Warren and S. Smiles, *J. Chem. Soc.*, **1931**, 2207.

²⁰ F. Galbraith and S. Smiles, *J. Chem. Soc.*, **1935**, 1234.

²¹ B. A. Kent and S. Smiles, *J. Chem. Soc.*, **1934**, 422.

illustrated in structure 9 provide about the same degree of activation as the anthraquinone carbonyl functions in structure 8.^{6, 20}

The importance of activating substituents in the migrating aromatic nucleus is illustrated by the retarding effect of a large excess of base on the rearrangement of compounds 10 and 11.^{6, 19} At high alkali concentrations



the second hydroxyl function in structure 10 and the sulfonamide function in structure 11 are converted to the corresponding anions. These negatively charged groups reduce the positive character of the ring atom at which substitution occurs, thus depressing the rate of rearrangement. In support of this explanation, the rates of rearrangement of analogous compounds containing *para* substituents [$\text{SO}_2\text{N}(\text{CH}_3)\text{C}_6\text{H}_5$ and SO_2CH_3] which cannot form such anions are not decreased by high alkali concentrations.

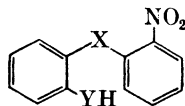
The Nature of the Leaving Group X and the Nucleophilic Group YH

Factors (b) and (c), the replaceability of the leaving group X and the nucleophilicity of the group YH are interrelated in their effects on the rearrangement, as was recognized by Smiles.²² The nature of the carbon chain joining X and Y, and the influence of substituents if the chain is part of an aromatic ring, are also important in their effects on the nature of X and Y. Some of these influences are electronic and some are steric.

Early Studies on Diaryl Compounds. Examples from Smiles' studies showed that, if X is a good leaving group, even a sulfinate anion formed by displacement of a sulfone function, or if Y⁻ is a strong nucleophile, rearrangement occurs readily. As X becomes less replaceable or as Y⁻ becomes a weaker nucleophile, rearrangement is more difficult.

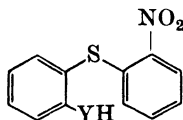
²² A. Levi, L. A. Warren, and S. Smiles, *J. Chem. Soc.*, **1933**, 1490.

The importance of the nature of X was demonstrated in several studies.^{23, 24} For the *o*-nitro diaryl system **12** where X was a sulfonyl group and YH was a hydroxyl group, rearrangement occurred; however, when X was a sulfoxide or a sulfide function, the compound **12** failed to rearrange. Similarly the compound **12** where X was a sulfonyl group

**12**

and YH was an amino group rearranged, whereas rearrangement failed with the compound where X was a sulfide function and YH was an amino group. The ease of rearrangement thus was found to depend on X in the order $\text{SO}_2 > \text{SO}$ or S, which is the general order for the base-catalyzed β -elimination of these groups as anions from aliphatic compounds.²⁵

An example of a more complex interrelationship of these two factors is provided by the series of N-substituted *o*-amino sulfides **13** in which YH is NHCH_3 , NH_2 , NHCOCH_3 , $\text{NHCOC}_6\text{H}_4\text{NO}_2$ -2, $\text{NHC}_6\text{H}_2(\text{NO}_2)_3$ -2,4,6,

**13**

and $\text{NHSO}_2\text{C}_6\text{H}_5$.²³ These derivatives form a series in which the electron-donating capacity of the nitrogen atom decreases and the acidity of the NH bond increases. When these compounds **13** were treated with hot ethanolic sodium hydroxide, only the acetyl and the *o*-nitrobenzoyl derivatives rearranged, the latter much slower than the former. The benzenesulfonyl and picryl derivatives formed sodium salts and were recovered unchanged, indicating that the anions from these compounds were too weakly nucleophilic to attack the ring. The amino and methyl-amino derivatives **13** represent the other extreme, where the groups YH are too weakly acidic to provide a sufficient concentration of anions under the conditions used. However, when the related series of N-substituted *o*-amino sulfones, in which YH is NHCH_3 , NH_2 , NHCOCH_3 , or $\text{NHSO}_2\text{C}_6\text{H}_5$, was subjected to hot aqueous sodium hydroxide, the amino and acetamido derivatives rearranged rapidly, the benzenesulfonamido

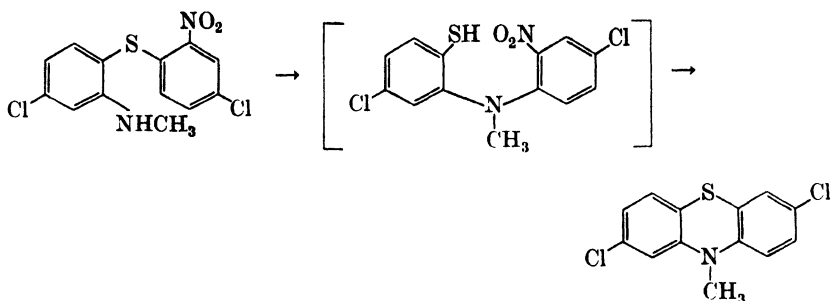
²³ W. J. Evans and S. Smiles, *J. Chem. Soc.*, **1935**, 181.

²⁴ L. A. Warren and S. Smiles, *J. Chem. Soc.*, **1932**, 2774.

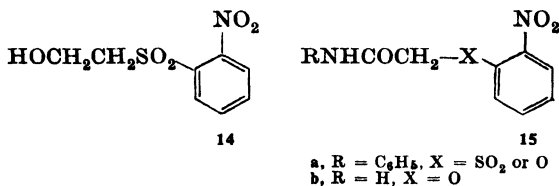
²⁵ J. E. Hofmann, T. J. Wallace, P. A. Argabright, and A. Schriesheim, *Chem. Ind. (London)*, **1963**, 1243; T. J. Wallace, J. E. Hofmann and A. Schriesheim, *J. Amer. Chem. Soc.*, **85**, 2739 (1963).

derivative rearranged slowly, and the methylamino derivative required more concentrated alkali. Under these conditions where X is a better leaving group, maximum reactivity has been shifted toward compounds with less acidic YH groups.

An interesting variation in the reaction conditions was found to induce rearrangement of N-alkylamino sulfides; when these compounds were heated for 3–4 hours in boiling aniline or quinoline (temperature $> 170^\circ$), fair yields of 10-alkylphenothiazines were obtained.²⁶ Yields could be increased by the addition of sodium phenoxide. The intermediacy of the Smiles product has been demonstrated in a number of phenothiazine syntheses (see p. 120).



Alkyl Aryl Rearrangements. The evident importance of the nucleophilicity of the displacing group Y^- (or YH) in Smiles studies suggested that an aliphatic hydroxyl group should be able to make rearrangement possible. This was indeed the case. Treatment of sulfone **14** with aqueous sodium hydroxide induced rearrangement at a rate too fast to measure by the colorimetric procedure used.²¹ The corresponding sulfoxide also rearranged on heating, but the sulfide did not. A variation in the aliphatic chain joining X and Y, found in compound **15a**, also permitted rearrangement.^{27, 28} However, the ether **15b** did not rearrange, presumably because of its lower acidity relative to **15a**.

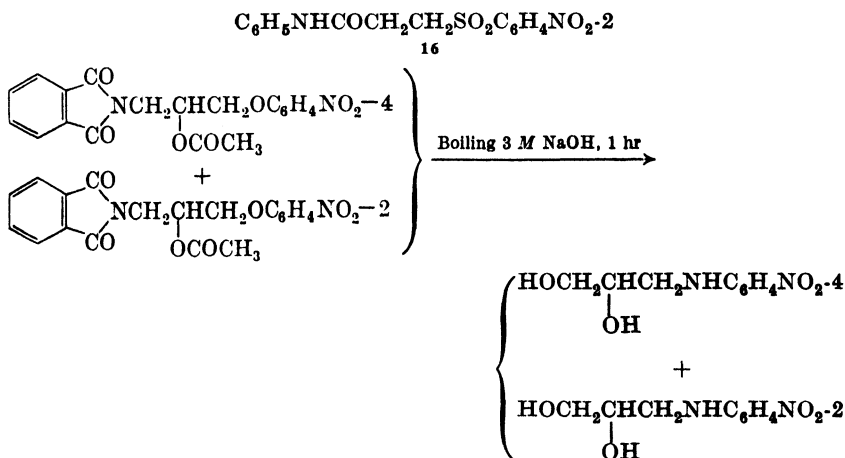


²⁶ K. Fujii, *J. Pharm. Soc. Japan.*, **77**, 3 (1957) [*C.A.*, **51**, 8756 (1957)].

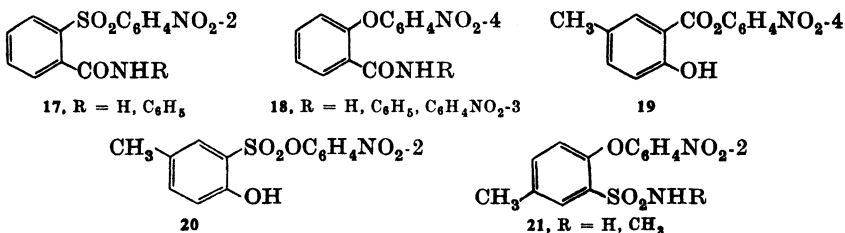
²⁷ W. J. Evans and S. Smiles, *J. Chem. Soc.*, **1936**, 329.

²⁸ B. T. Tozer and S. Smiles, *J. Chem. Soc.*, **1938**, 2052.

Examples Where the Leaving Group X and the Nucleophilic Group YH Are Joined by Three Atoms. Smiles was unsuccessful in obtaining rearrangement of the sulfone **16** in which three carbon atoms intervene between the groups X and Y,²⁷ but Caldwell has demonstrated rearrangement under Smiles conditions of the mixture of phenoxypropyl phthalimides shown in the accompanying equation.²⁹



Other examples of the rearrangement of compounds in which the groups X and Y are separated by three atoms were reported subsequently.^{27, 28, 30, 31} Compounds **17–21** all undergo rearrangement, whereas compounds **22–26** do not; again presumably owing to counterbalancing influences in the replaceability of the group X, the nucleophilicity of the group Y⁻, and steric influences. Rearrangement of

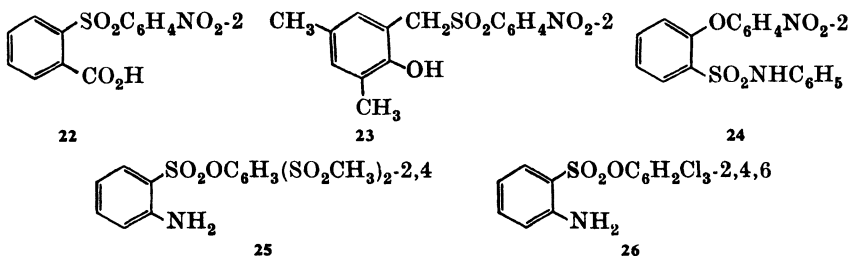


compounds **17**, **18**, and **21** is undoubtedly facilitated by the fact that acylation or sulfonation of an amine increases the acidity of the NH function, whereas alkylation increases the nucleophilicity of the amide

²⁹ W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, **74**, 5187 (1952).

³⁰ E. A. Shearing and S. Smiles, *J. Chem. Soc.*, **1937**, 1348.

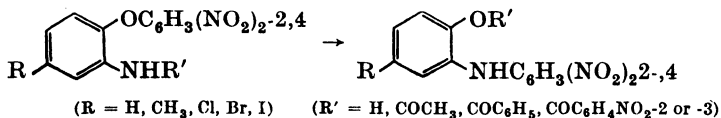
³¹ B. T. Tozer and S. Smiles, *J. Chem. Soc.*, **1938**, 1897.



anion formed. However, the $\text{C}_6\text{H}_5\text{NSO}_2\text{Ar}$ anion from **24** is too weakly nucleophilic to rearrange. The same is true for the carboxylate ion from **22**.

Reverse Smiles Rearrangements. A related reaction, which has been designated the reverse Smiles rearrangement, was explored by Coats and Gibson, who found that many of the sulfinic acids obtained from the Smiles rearrangement of *o*-hydroxy sulfones could be reconverted to the original sulfones.³² The reverse reactions took place readily when the sulfinic acids were buffered in solution to a pH at which the sulfinic acid but not the product phenol was in its ionized form. The optimum pH was usually between 2 and 6. In general, the reverse rearrangements followed the same rate order as did the original rearrangements but were somewhat slower. The aliphatic sulfinic acid derived from sulfone **14** was exceptional in that no reversal could be obtained.

A similar reaction which can be classed as a reverse Smiles rearrangement was discovered and investigated by Roberts.³³⁻³⁸ The most favorable conditions for the rearrangement, in contrast to the Smiles reaction, are basic or hydroxylic solvents, particularly with water present,



without ionic base added. The rearrangements often proceed at room temperature or at 50° ; caustic soda at 100° can also be used. Rearrangement does not take place in nonpolar or polar un-ionizable solvents, *e.g.*, benzene or acetone. Possibly these reactions occur without prior ionization, but require solvents which sustain ionization,³⁸ *i.e.*, the mechanism

³² R. R. Coats and D. T. Gibson, *J. Chem. Soc.*, **1940**, 442.

³³ K. C. Roberts, *J. Chem. Soc.*, **1932**, 2358.

³⁴ K. C. Roberts and H. B. Clark, *J. Chem. Soc.*, **1935**, 1312.

³⁵ K. C. Roberts and J. A. Rhys, *J. Chem. Soc.*, **1937**, 39.

³⁶ K. C. Roberts and C. G. M. deWorms, *J. Chem. Soc.*, **1934**, 727.

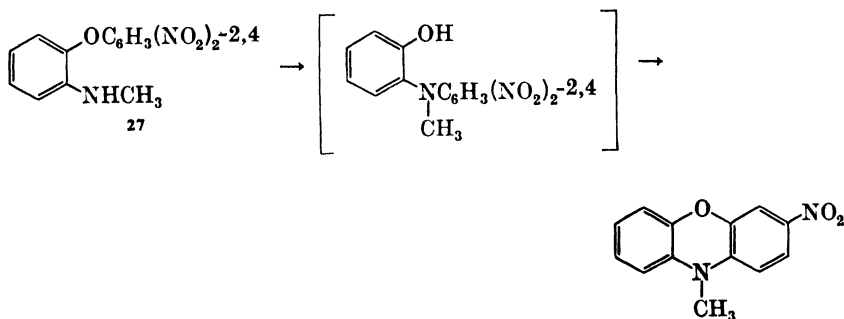
³⁷ K. C. Roberts and C. G. M. deWorms, *J. Chem. Soc.*, **1935**, 1309.

³⁸ K. C. Roberts, C. G. M. deWorms, and H. B. Clark, *J. Chem. Soc.*, **1935**, 196.

may involve the transition state 4 (p. 102). An additional variation is thermal rearrangement in a melt with no solvent.

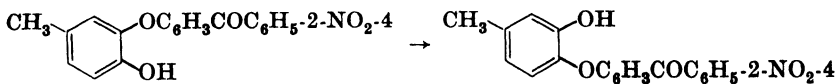
The N-acyl derivatives rearrange more slowly than the free amino compounds, the rate falling off with increasing strength of the acid corresponding to the acyl group present. This order of reactivity is also the order of the decreasing nucleophilicity of the acylamido group. The increased acidity of the group —NHCOR is apparently of secondary importance. The requirement for solvents with high dielectric constants is a characteristic of nucleophilic substitution reactions.

When the *o*-methylaminodiphenyl ether **27** was rearranged, a phenoxazine was isolated,³⁴ a result which was to become useful later in syntheses of phenoxazines and related heterocyclic structures.^{13, 39}



In the rearrangement of *o*-aminodiphenyl ethers, an *o*-halogen atom provides sufficient activation to induce rearrangement with sodium amide in benzene or potassium carbonate in dimethylformamide.^{8, 13}

Certain *o*-hydroxy ethers activated by a nitro group rearrange to isomeric *o*-hydroxy ethers on treatment with dilute aqueous potassium hydroxide at room temperature.^{40, 41} If the methyl group is replaced by



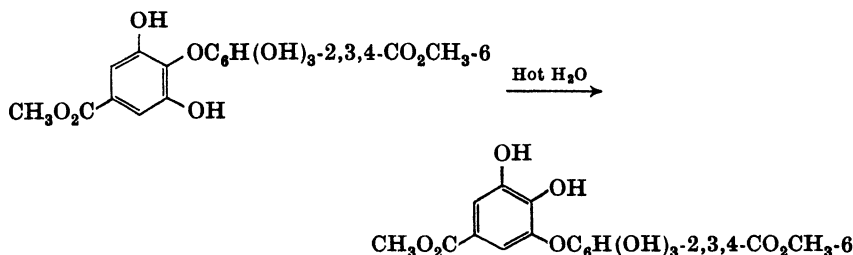
a phenyl group, the rearrangement is much faster but, if the methyl group is moved to the 6 position, rearrangement is incomplete and a saturated alcoholic solution containing a trace of sodium hydroxide must be used.⁴¹ A related rearrangement is shown in the equation on p. 110.⁴²

³⁹ B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, **1953**, 1499.

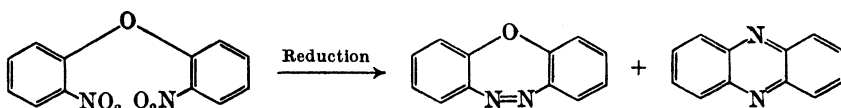
⁴⁰ J. D. Loudon, J. R. Robertson, J. N. Watson, and S. D. Aiton, *J. Chem. Soc.*, **1950**, 55.

⁴¹ J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, **1953**, 265.

⁴² W. Mayer and H. Scheuermann, *Angew. Chem.*, **71**, 382 (1959).



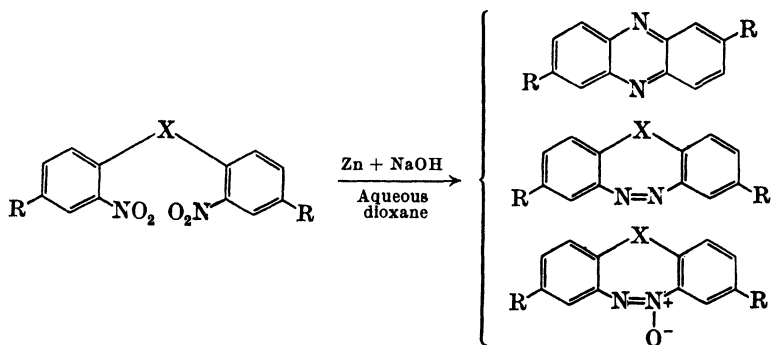
Rearrangement in Reducing Media. A Smiles rearrangement has been suggested as one step in the reduction of 2,2'-dinitrodiphenyl ethers from which phenazines and related compounds containing three hetero atoms are obtained.¹⁴ The amounts of the two products vary with the reducing agent and temperature as shown in Table I. When 2,2'-dinitrodiphenyl sulfones were reduced with zinc and sodium hydroxide in



aqueous dioxane, or were treated with sodium hydroxide in aqueous dioxane, the corresponding two products were observed.¹² In addition, a small amount of phenazine-5-oxide was sometimes found.¹² Similarly, the sulfoxide also produced the phenazine, whereas the sulfide gave mostly the thiadiazepine and thiadiazepine-5-oxide (see Table II). Thus the propensity for formation of a phenazine follows the order $\text{SO}_2 > \text{SO} > \text{S}$, the same order of reactivity found for the Smiles rearrangement. Treatment of 4,4'-dichloro-2,2'-di(hydroxylamino)diphenyl sulfone with zinc and alkali at 20° gave in 20% yield the phenazine in which the halogens appeared at positions requiring rearrangement at some point in the reduction.^{15, 16} The possibility of the hydroxylamino group functioning as the nucleophilic group YH has received some justification thereby.

TABLE I.¹⁴ REDUCTION OF 2,2'-DINITRODIPHENYL ETHER

Reducing Agent, Temperature	Yield, %	
	Oxadiazepine	Phenazine
LiAlH_4 , 20°	25	2
LiAlH_4 , 66°	4	18
Zn , NaOH , 20°	13	15
Zn , NaOH , 78°	0	50



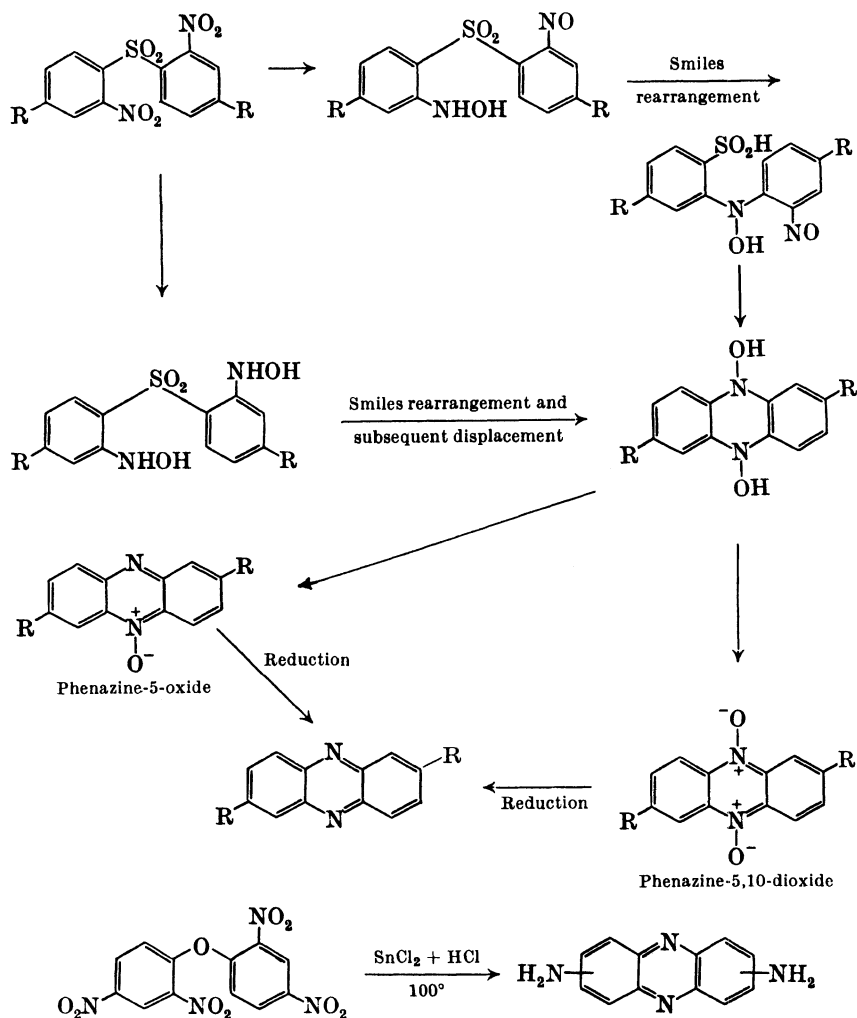
The mechanism postulated by Grundon involves partial reduction of the dinitro compound to a hydroxylamino, nitroso, or nitro intermediate which undergoes Smiles rearrangement and further steps leading to ring closure. Since alternative sequential steps in the reduction of the two nitro groups can be postulated, the activation for the rearrangement cannot be assigned with certainty to the nitroso group; one nitro group could still be present at the stage of rearrangement. Grundon suggests that an earlier reduction of a dinitrodiphenyl ether leading to a phenazine (with stannous chloride and hydrochloric acid) may also have involved a Smiles rearrangement.^{43, 14} (Equations on p. 112.)

TABLE II.¹² REDUCTION OF 2,2'-DINITRODIPHENYL SULFONE, SULFOXIDE, AND SULFIDE^a

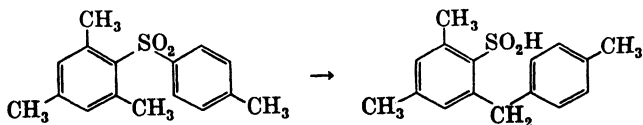
Substrate/ Temperature	Time (hr)	Yield, %		
		Phenazine	Diazepine	Diazepine-5-oxide
Sulfone				
20°	2	18	6	0
100°	0.5	14	0	Trace
100°	13	16	2	0
Sulfoxide				
20°	2	13	—	—
Sulfide				
20°	2	0	6-13	12
100°	3	Trace	0	0

^a Presumably some of the acidic Smiles rearrangement product is also formed, but in most reactions it was not isolated.¹²

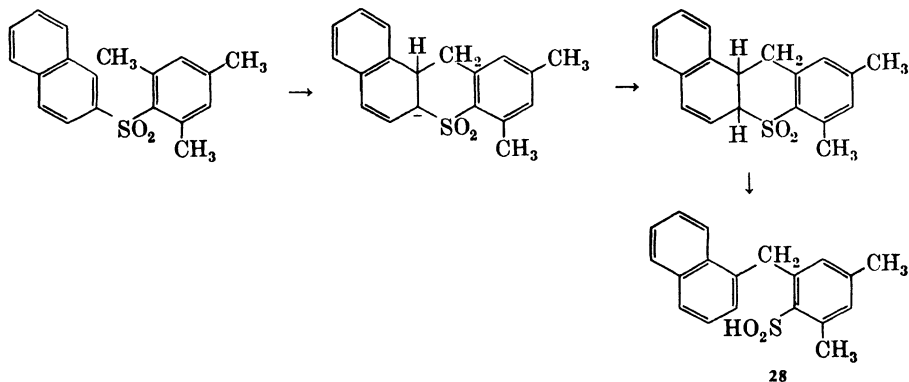
⁴³ K. Matsumura, *J. Amer. Chem. Soc.*, **52**, 3199 (1930).



The Truce-Smiles Rearrangement. In 1958 an unusual variation of the Smiles rearrangement of sulfones was reported which utilized a methyl group as the nucleophilic group YH.¹⁷ Treatment of *o*-methyl-diaryl sulfones with *n*-butyllithium in diethyl ether then produced the rearranged *o*-benzylbenzenesulfinic acids in high yield. Only compounds with *o*-methyl groups underwent this rearrangement in which strong bases were required to form the initial benzylic carbanion. Later work showed that potassium *t*-butoxide in dimethyl sulfoxide was also capable of effecting this reaction.⁴⁴ A similar rearrangement occurs when the methyl group is bonded to a naphthalene nucleus.⁴⁵ However, where the



naphthalene nucleus would have to migrate, a Smiles rearrangement does not take place with potassium *t*-butoxide in dimethyl sulfoxide. Instead nucleophilic addition across the 1,2 bond of naphthalene is followed by β -elimination to produce the product **28**. It should be pointed out that no examples are known of Smiles rearrangements on systems where the migrating group is an α - or β -naphthyl group with a free β or α position.



Smiles rearrangement in the diphenyl sulfone series has been confirmed and, in addition, a structure of the type **29**, which resembles the intermediate in an addition- β -elimination sequence, has been trapped.⁴⁶⁻⁴⁸ Apparently the adduct is the product of a side reaction because rearrangement of mesityl *p*-tolyl sulfone gives a product with the *para* orientation maintained as is required by a Smiles rearrangement. In fact, further treatment of protonated **29** with *n*-butyllithium gave the same product **30**. However, when the same protonated **29** was treated with ethanolic sodium ethoxide, 2-(3'-methylbenzyl)-4,6-dimethylbenzenesulfinic acid was obtained in analogy with the naphthalene compounds.⁴⁹

The pyrolysis of sulfones to give diarylmethanes could be considered a Truce-Smiles rearrangement.⁵⁰ Dimesityl sulfone at 375–400° for 20

⁴⁴ W. E. Truce, C. R. Robbins, and E. M. Kreider, *J. Amer. Chem. Soc.*, **88**, 4027 (1966).

⁴⁵ W. E. Truce and D. C. Hampton, *J. Org. Chem.*, **28**, 2276 (1963).

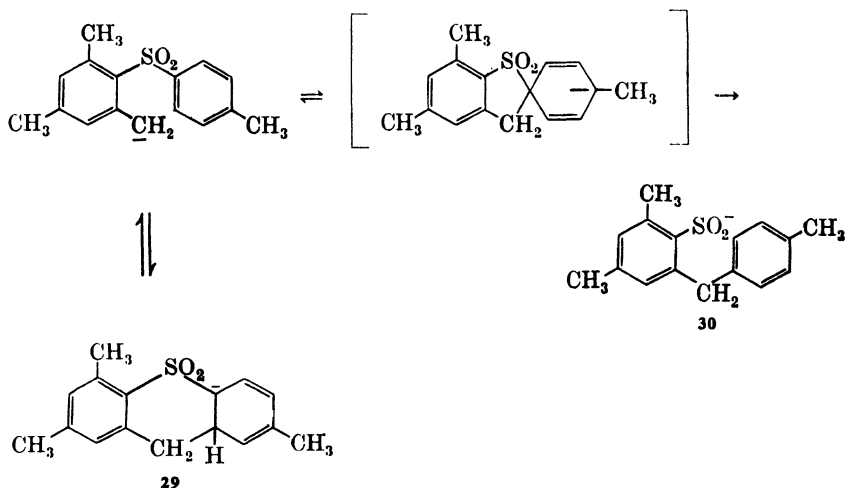
⁴⁶ V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **189**, 107 (1966) [*C.A.*, **65**, 13646 (1966)].

⁴⁷ V. N. Drozd and T. Y. Frid, *Zh. Org. Khim.*, **3**, 373 (1967) [*C.A.*, **67**, 2586 (1967)].

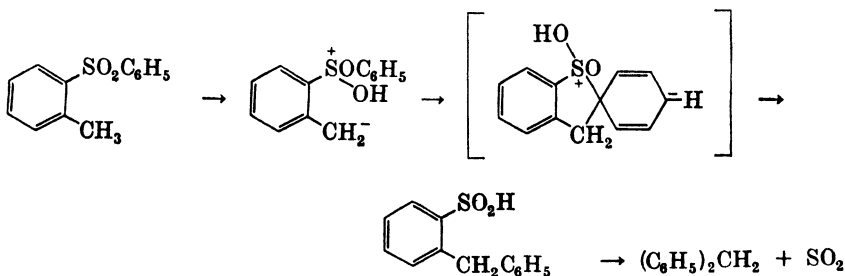
⁴⁸ V. N. Drozd and V. I. Sheichenko, *Zh. Org. Khim.*, **3**, 554 (1967) [*C.A.*, **67**, 10965 (1967)].

⁴⁹ W. W. Brand, Ph.D. Thesis, Purdue University, 1970.

⁵⁰ H. Drews, E. K. Fields, and S. Meyerson, *Chem. Ind. (London)*, **1961**, 1403.



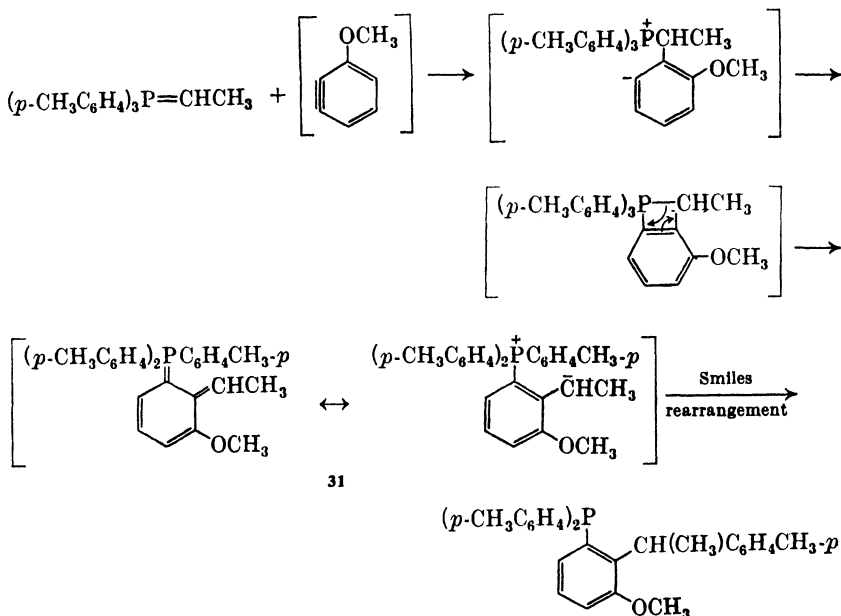
hours produced pentamethyldiphenylmethane in 95% yield. Several other *o*-methyldiphenyl sulfones were pyrolyzed similarly, giving lower yields of hydrocarbons.



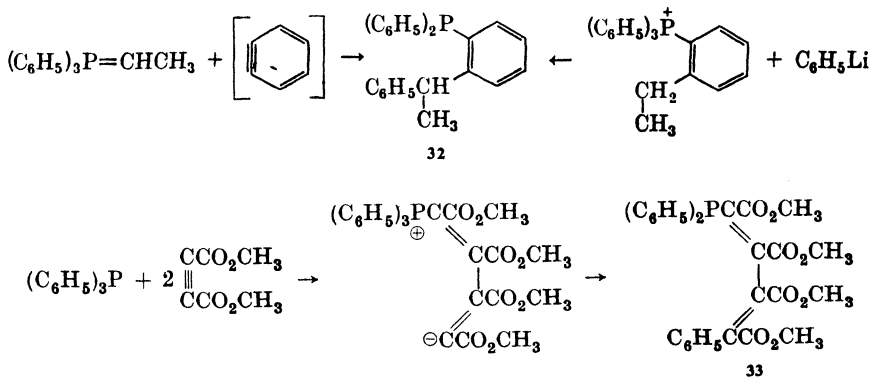
The Smiles Rearrangement of Phosphonium Zwitterions. One of the most unusual variations of the Smiles rearrangement involves the addition of an aryne to an alkylidene triarylphosphorane to form a product in which one of the aryl groups initially bound to phosphorus has migrated to a neighboring benzylic position.^{51, 52} The mechanism postulated is shown in the accompanying equations. Evidence supporting the zwitterion intermediate **31**, and thus the occurrence of a Smiles rearrangement in this reaction, was obtained by isolating the product **32** from metalation of *o*-ethylphenyl-triphenylphosphonium bromide and from the addition sequence.⁵¹ A number of alkylidenephosphoranes have

⁵¹ E. Zbiral, *Monatsh. Chem.*, **95**, 1759 (1964).

⁵² E. Zbiral, *Tetrahedron Lett.*, **1964**, 3963.



been added to several different arynes (see Table XXIII) to form comparable rearranged products. Phenyl migration from a phosphonium salt to a neighboring anion to form the adduct **33** was reported earlier.⁵³



Summary of Variations in the Leaving Group X and the Nucleophilic Group YH. The dependence of the Smiles rearrangement on the nature of the groups X and YH is summarized in Table III.

⁵³ A. W. Johnson and J. C. Tebby, *J. Chem. Soc.*, **1961**, 2126.

TABLE III. SUMMARY OF REARRANGEMENTS

Activating Group	YH ^a	X	Failed when X was:
<i>o</i> - and/or <i>p</i> -NO ₂	NHCOR	SO ₂ , SO, S, O	
	NHR	SO ₂ , O	
	NHAr (alkyl)	O	
	NH ₂	SO ₂ , (SO ?)	S, NH
	CONHAr (alkyl)	SO ₂ , O	
	CONHAr	SO ₂ , O	
	CONH ₂	SO ₂ , O	
	CH ₂ NH ₂ (alkyl)	O	
	SO ₂ NHR	O	
	SO ₂ NH ₂	O	
	SH	O	
	OH (alkyl)	SO ₂ , SO	S
	OH	SO ₂ , CO ₂ ⁻ , SO ₂ O ⁻ , O, NHSO ₂	SO, S, CH ₂ SO ₂
<i>o</i> -NO or NO ₂ ^b	NHOH	SO ₂ , SO, S, O	
<i>o</i> -Halogen	NHR	O	
	NH ₂	O	
H	CH ₃	SO ₂ , P ⁺	
	CH ₂ R	SO ₂ , P ⁺	
	CH ₂ Ar	SO ₂	
	CHAr ₂	SO ₂	
	=CHCO ₂ CH ₃	P ⁺	
	CO ₂ H (alkyl)	I ⁺	
	CO ₂ H	I ⁺	

^a YH is a substituent on an aryl ring unless indicated by the designation (alkyl).

^b The nature of the intermediate undergoing rearrangement is uncertain.

Acidity of the YH Function

This factor has already been mentioned in the discussion of the nature of the groups X and Y, particularly the effects of N-acylation and N-alkylation on the rate of rearrangement. When *o*-hydroxy sulfones activated by an *o*-nitro group were treated with various bases in the corresponding hydroxylic solvents, the rate of rearrangement decreased in the order: NaOCH(CH₃)₂ > NaOC₂H₅ > NaOCH₃ > NaOH.²¹ This is also the order observed for the basicity of these reagents as determined by rates of isomerization of olefins.⁵⁴

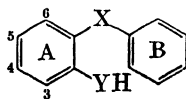
The acidity of the YH function is not always an independent factor in the rearrangement, since substituents which enhance the acidity of the

⁵⁴ G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, **1929**, 1269.

group YH may decrease the nucleophilicity of the anion Y^- . The net effect on the rearrangement must be the resultant of these two counterbalancing effects. This is particularly obvious in the case where YH is an arylsulfonamido group $-SO_2NHAr$. This function is sufficiently acidic to ionize, but the negative charge in the resulting anion is too weakly nucleophilic to effect rearrangement. Additional examples of opposing influences are provided by electron-withdrawing substituents *para* to the YH group.

Electronic Effects of Substituents in the Aromatic Nucleus Bonded to the Groups X and YH

The effects of substituents in the aromatic ring joining X and Y are much more complex than those in the ring sustaining the nucleophilic attack. Most of the systems studied were of the structural type **34**. It is readily seen that any substituent in ring A will be able to influence the reaction both by its effect on the group YH and the corresponding anion Y^- , and also by its effect on the transition state leading to the rearranged product. Thus an electron-withdrawing substituent at position 4 or 6



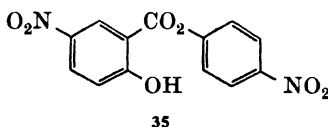
34

may by induction increase the acidity of the group YH and may by induction or resonance stabilize the charge appearing on X as the reaction proceeds. These effects appear to be favorable for rearrangement unless the group YH is sufficiently acidic to be able to ionize readily. Then the influence of such a substituent at the 4 position or any other position in the ring may serve to reduce the nucleophilicity of the anion Y^- to the detriment of the rearrangement. Electron-releasing groups would have the opposite effect.

An example in which a nitro group at position 4 greatly increases the rate is the case where $X = S$ and $YH = NHCOCH_3$.²³ The electron-withdrawing nitro group serves to increase the acidity of the nucleophilic group YH by induction but, more important, the nitro group stabilizes the sulfhydryl anion in the product by resonance. Similarly, in the same acetamido sulfide, a sulfonamido in position 4 is more effective in promoting rearrangement than the same substituent in position 5.⁵⁵

⁵⁵ G. Pappalardo, *Gazz. Chim. Ital.*, **90**, 648 (1960).

The opposite situation with a nitro group is seen in compound **35** where the leaving group would be a carboxylate anion and the nucleophile a hydroxyl group.³¹ The ester **35** does not rearrange, presumably because



of the excessive charge delocalization in the phenoxide anion. If the nitro group is replaced by hydrogen, methyl, or chlorine, rearrangement occurs.

The following order of reactivity has been observed for 2-hydroxy-2'-nitrodiphenyl sulfones: 5-Cl > 5-OH > 5-CH₃ > 4-OH.²¹ The rate of rearrangement of the 5-hydroxy compound was increased sixfold by the use of 2 equivalents of base, whereas the rate of rearrangement of the 4-hydroxy compound was increased only by a factor of 2. Clearly the combined effects of the 5-substituent on both of the groups X and YH are much more favorable than are the effects of the 4-substituent.

TABLE IV.³⁵ TIME FOR COMPLETE REARRANGEMENT OF 2-AMINO-2',4'-DINITRODIPHENYL ETHERS AT 50°

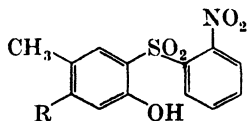
	Substituent							
	NH ₂	OCH ₃	CH ₃	H	I	Br	Cl	CO ₂ H
4-Series time (min)	50	13	7	5	15	30	60	No reaction
5-Series time (min)	—	No reaction	90	5	7	—	No reaction	—

In the rearrangement of *o*-aminodiphenyl ethers, where ionization of the group YH to Y⁻ is not required, substituents may facilitate reaction by increasing the basicity of the amino group and by stabilizing the phenoxide anion formed. The opposite influences would retard rearrangement. A study of the 4- and 5-substituted series of amino ethers showed that a maximum rate of reaction was achieved with substituents of intermediate electronic character (Table IV).^{35, 38} Again the 5-substituent had the greater effect, in this case inhibitory, when the electronic nature of the substituent became unfavorable.

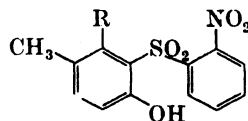
Steric Effects

In 1937 Smiles observed that *o*-hydroxy sulfones having a methyl group in the 6 position rearranged much faster than the corresponding

unsubstituted compounds.⁵⁶ Similarly bis-(2-hydroxy-1-naphthyl) sulfides and sulfones rearranged rapidly. The rate increase was attributed to an inductive effect. Bunnett, however, showed that this rate increase could also be explained on steric grounds⁵⁷ and later provided evidence for this argument. A series of compounds **36** and **37** were



36, R = H, CH₃, Cl, Br



37, R = CH₃, Cl, Br

synthesized⁵⁸ and the kinetics of their rearrangements determined titrimetrically or polarographically.⁵⁹ First-order kinetics was observed, and in all cases compounds **37** with a 6-substituent rearranged much faster than the compounds **36** lacking a substituent in this position (Table V). The 6-halogen substituents had the retarding effect expected of electron-withdrawing substituents, but the decrease was small in comparison with the rate increase resulting from the presence of a substituent in the 6 position (compounds **37**) rather than elsewhere. Bunnett's suggestion, the predominance of steric over electronic factors in 6-substituted compounds, runs as follows. Conformation **A**, with the migrating ring perpendicular to the plane of the other aromatic ring and with the nucleophilic group adjacent to rather than away from the migrating ring, is required for rearrangement, whereas other conformations such as **B** or **C** would be favored in the absence of a 6-substituent.

TABLE V.⁵⁹ REARRANGEMENT IN 50% AQUEOUS DIOXANE WITH 1.25 M SODIUM HYDROXIDE

	Substituent R	<i>k</i> (min ⁻¹) ^a	
		46.0°	0.0°
36	H	1.94 × 10 ⁻²	—
	CH ₃	1.6 × 10 ⁻²	(3.6 × 10 ⁻⁵)
	Cl	1.44 × 10 ⁻³	(1.8 × 10 ⁻⁶)
	Br	1.23 × 10 ⁻³	—
37	CH ₃	—	>3
	Cl	—	0.92
	Br	—	2.1

^a The numbers in parentheses were obtained by extrapolation.

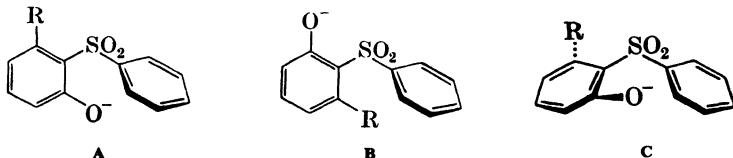
⁵⁶ C. S. McClement and S. Smiles, *J. Chem. Soc.*, **1937**, 1016.

⁵⁷ J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 362 (1951).

⁵⁸ T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5357 (1956).

⁵⁹ J. F. Bunnett and T. Okamoto, *J. Amer. Chem. Soc.*, **78**, 5363 (1956).

In order to rearrange, a free-energy barrier due to steric compression must be overcome to convert conformation **B** or **C** to **A**. When a 6-substituent

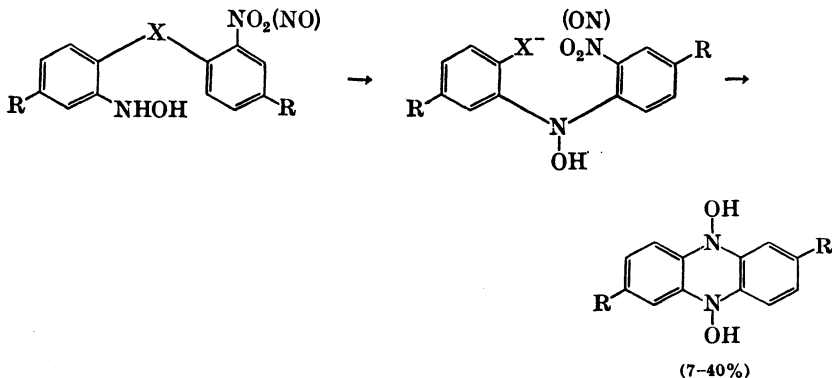


is present, however, conformation **B** is no longer so favorable, and conformation **C** is limited in that now one *ortho* group must oppose the *o'*-nitro group in the second ring. Therefore conformation **A** has become statistically much more probable, the ground state free energy of the starting material has been raised, and the size of the free-energy barrier to rearrangement has been reduced. This produces the faster rate of rearrangement when the 6-substituent is present.

Truce and Ray also observed some acceleration of the rate of rearrangement of *o*-methyldiaryl sulfones when a methyl group was also present in the 6-position, although in these cases the rates differed only by a factor of approximately 15.⁶⁰ Dimesityl sulfone is an exception in which, in spite of the *o*-methyl groups, rearrangement is slower even than for *o*-tolyl phenyl sulfone.

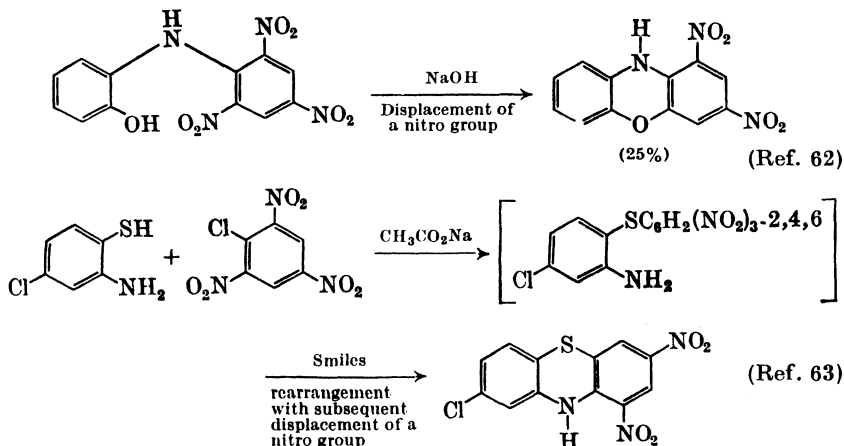
Phenazine, Phenothiazine, and Phenoxazine Formation

The formation of phenazine derivatives was mentioned in the previously discussed reduction of dinitrodiaryl sulfones, sulfoxides, sulfides, and ethers with zinc and alkali (p. 110).



⁶⁰ W. E. Truce and W. J. Ray, Jr., *J. Amer. Chem. Soc.*, **81**, 484 (1959).

More frequently observed is the opposite reaction, the displacement of a nitro group by the group X^- . This reaction was developed for syntheses of phenoxazines and phenothiazines which had commercially or medicinally interesting properties. The syntheses of phenothiazines reported before 1954 have been reviewed.⁶¹



The products from several rearrangements of *o*-acylamido sulfides were found to be phenothiazines.^{64, 65} Sometimes the uncyclized Smiles rearrangement product could be isolated and then cyclized; at other times the intervention of the Smiles rearrangement had to be inferred from the orientation of the substituents in the phenothiazine products. Furthermore, concurrent deacylation occurred in some reactions while in others the *N*-acyl phenothiazine was isolated. Usually the Smiles product could be isolated after rearrangement of mononitrodiaryl sulfides, whereas cyclization generally occurred with dinitro- and trinitro-diaryl sulfides.

The combination of Smiles rearrangement and ring closure has been given a great deal of study in the interest of synthesizing specific substituted phenoxazines and phenothiazines. The variety of substituents used in either aromatic nucleus may be observed in Tables XVI and XVII. In almost all cases, *N*-acyl amines are used, in particular formamido derivatives. Heating under reflux for several hours in acetone with 2 or more equivalents of sodium or potassium hydroxide is found by many

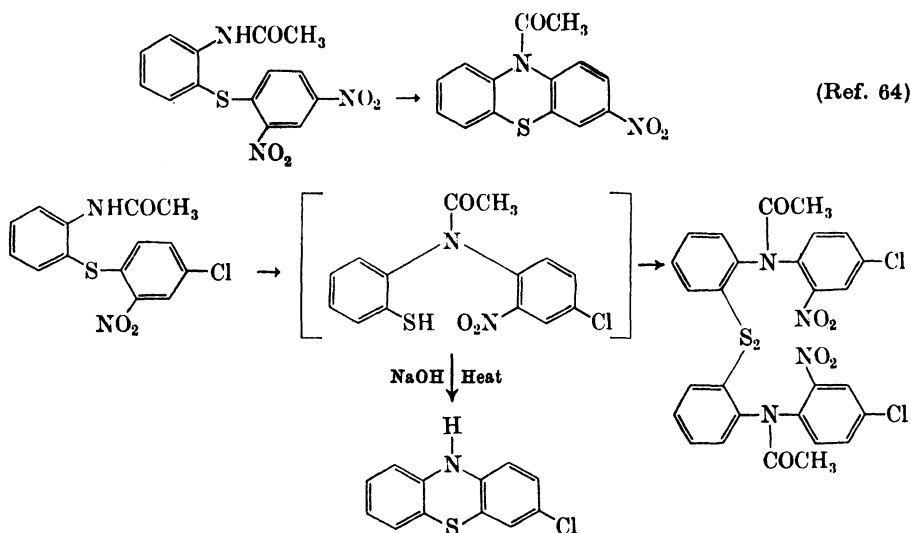
⁶¹ S. P. Massie, *Chem. Rev.*, **54**, 797 (1954).

⁶² G. S. Turpin, *J. Chem. Soc.*, **59**, 714 (1891).

⁶³ J. Pollak, E. Riesz, and Z. Kahane, *Monatsh. Chem.*, **49**, 213 (1928).

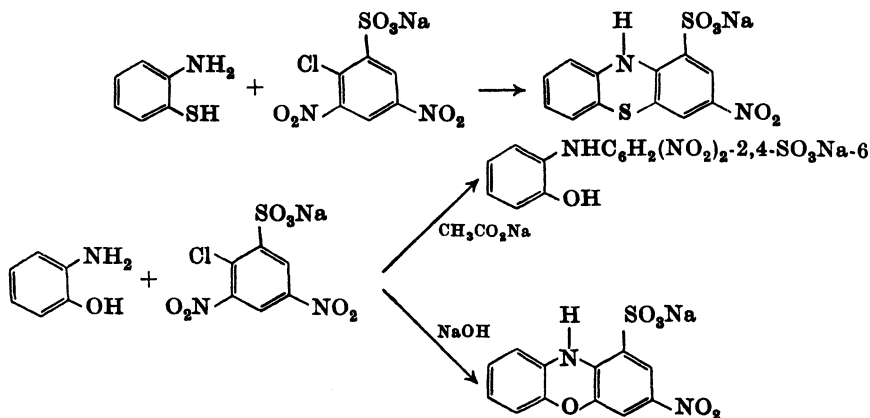
⁶⁴ W. J. Evans and S. Smiles, *J. Chem. Soc.*, **1935**, 1263.

⁶⁵ C. F. Wight and S. Smiles, *J. Chem. Soc.*, **1935**, 340.



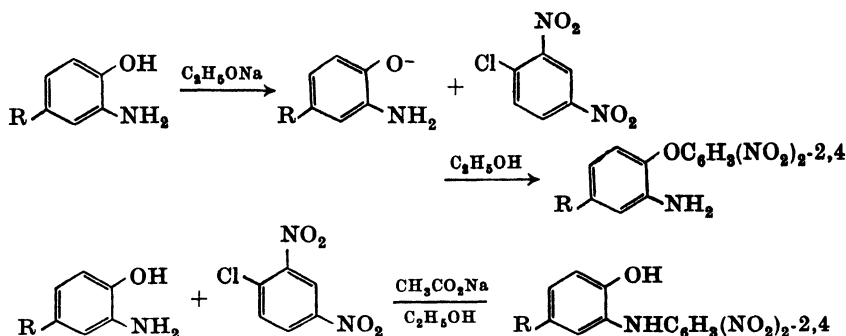
workers to give deacylated rearranged cyclic products in optimum yield (typically 43–70%). Phenothiazines were also obtained from Smiles rearrangement of *o*-acylamido-*o'*-halodiphenyl sulfides by heating under reflux in dimethylformamide with potassium carbonate with⁹ or without¹³ a copper-bronze catalyst.

When the two aromatic moieties are condensed and cyclized in one step, it is sometimes difficult to decide whether Smiles rearrangement has occurred because the initial condensation may occur either at the hydroxyl or the sulfhydryl group or at the amino group, depending on the reaction conditions. For example, in a review,⁶¹ Massie lists as preparations of



phenothiazines *via* Smiles rearrangements a number of reactions which were thought by the authors to be direct condensations at nitrogen followed by ring closure. The amine, not the ether, was isolated from a similar reaction.⁶⁶

To answer the question whether the intermediates are formed directly or by a Smiles rearrangement, Roberts in his work on Smiles rearrangement of *o*-aminodiaryl ethers prepared both the diaryl ethers and the diaryl amines. His method of synthesis of the two types of compounds is illustrated in the following equations.³⁸



We have used Roberts' reaction conditions, *i.e.*, the use of ethoxide to form diaryl ethers and the use of sodium acetate to form diaryl amines, as a criterion for deciding whether to include ambiguous cases in the tables for phenoxazine and phenothiazine formation *via* Smiles rearrangements.

Smiles Rearrangements of Pyridyl Systems

Takahashi reported the first Smiles rearrangement in a heterocyclic system.⁶⁷ Since that time a number of rearrangements of *o*-aminopyridine derivatives have been reported.

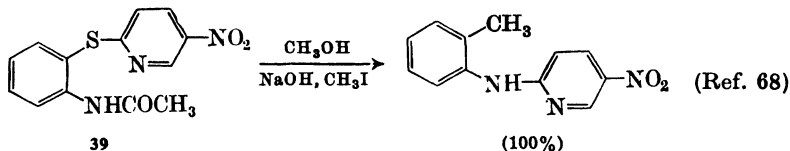
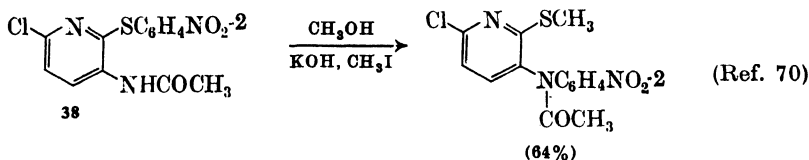
Pyridyl Phenyl Systems. Although both types of mixed pyridyl phenyl systems have been found to rearrange, the migration of the phenyl nucleus is more common with only a few examples of pyridyl migration known.^{68, 69}

⁶⁶ F. Ullmann, *Ann.*, **366**, 79 (1909).

⁶⁷ T. Takahashi and E. Yoshii, *Pharm. Bull. (Japan)*, **2**, 383 (1954) [*C.A.*, **50**, 13032 (1956)].

⁶⁸ Y. Maki, K. Kawasaki, and K. Sato, *Gifu Yakka Daigaku Kiyo*, **13**, 34 (1963) [*C.A.*, **60**, 13220 (1964)]. The Chemical Abstracts report is incomplete.

⁶⁹ Y. Maki, M. Sato, and K. Yamane, *Yakugaku Zasshi*, **85**, 429 (1965) [*C.A.*, **63**, 5477 (1965)].

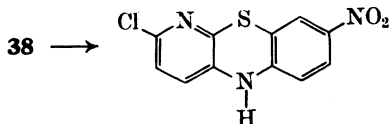


The only nucleophilic functions YH studied were the amino and acetamido groups; the group X was usually a sulfide, but in one case it was a sulfone.⁷¹

The substituents present on the pyridine ring of the 2-pyridyl phenyl sulfides have included 6-chloro, 4-chloro, and 6-ethoxy groups. When the sulfide group was in the 4 position of the pyridine ring, rearrangement occurred without additional substituents on the pyridine nucleus. Usually an *o*'- or a *p*'-nitro group or both have been the only substituents present on the migrating phenyl nucleus, but occasionally an additional chloro substituent has been present.⁶⁹

Although both the amino and the acetamido derivatives of pyridyl phenyl sulfides rearrange, the product is formed more rapidly⁷² and in better yields when the acetamido derivative is used.⁷¹ For example, the amino derivative corresponding to the acetamide 38 rearranged when a methanol solution was heated in a sealed tube for 5 hours without base.⁷³ This rearrangement, like the rearrangements of *o*-aminodiphenyl ethers, appears to be thermal rather than solvent-assisted since rearrangement did not occur in some of the solvents found effective for other solvent-assisted reactions.

As with the diphenyl sulfides, the migrating dinitrophenyl and trinitrophenyl groups of pyridyl aryl sulfides often underwent ring closure after



⁷⁰ Y. Maki, *Yakugaku Zasshi*, **77**, 485 (1957) [*C.A.*, **51**, 14738 (1957)].

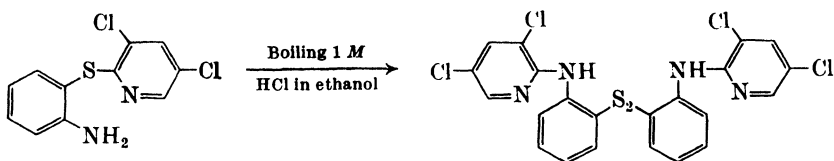
⁷¹ Y. Maki, Y. Okada, Y. Yoshida, and K. Obata, *Gifu Yakka Daigaku Kiyo*, **12**, 54 (1962) [*C.A.*, **59**, 11479 (1963)].

⁷² Y. Maki, *Yakugaku Zasshi*, **77**, 862 (1957) [*C.A.*, **52**, 1174 (1958)].

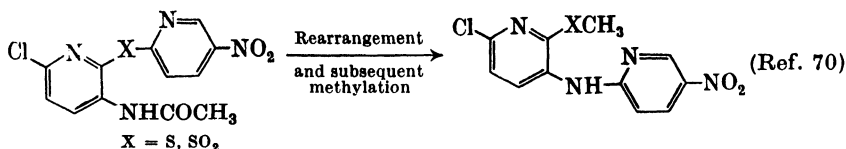
⁷³ T. Takahashi and Y. Maki, *Chem. Pharm. Bull.* (Tokyo), **6**, 369 (1958) [*C.A.*, **53**, 9228 (1959)].

rearrangement, giving azaphenothiazines. Potassium hydroxide with either boiling acetone or an alcohol-acetone mixture gave predominantly the cyclized product.

The pyridine systems are unique in their ability to undergo an acid-catalyzed Smiles rearrangement. This capability was discovered in the dipyridyl systems and has been extended to only two mixed systems, both of them having the pyridyl nucleus as the migrating group. One of these compounds is also the only example yet found of rearrangement with only halogen activation.⁷⁴



Dipyridyl Systems. Many more Smiles rearrangements have been reported for dipyridyl sulfides than for pyridyl phenyl sulfides. In addition, several sulfones have been studied.



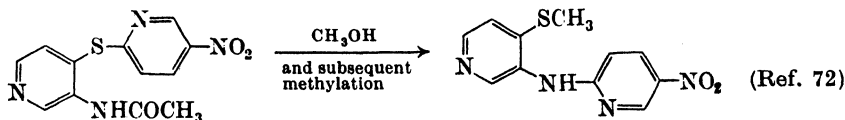
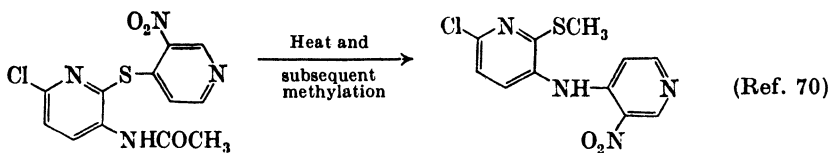
The chlorine atom in position 6 may be replaced by methoxyl, ethoxyl, hydrogen, or a chlorine atom in the 5 position. The migrating ring usually contains a 3'- and/or a 5'-nitro group for activation; in addition a chlorine atom in the 3' or 5' position or a methoxyl group in the 3' position may be present. An unusual case of acid-catalyzed rearrangement of bis-(3-amino-2-pyridyl) sulfide has been reported in which the only activation for reaction is provided by an *o*-amino group and the ring nitrogen atom.¹¹

The different nucleophilic functions YH studied in these sulfides include methylamino, amino, and acylamido groups. The alkylated amine rearranged more slowly than the corresponding acetamide.⁷⁰ In general, the unalkylated amines also rearrange more slowly than the amides.^{72, 75}

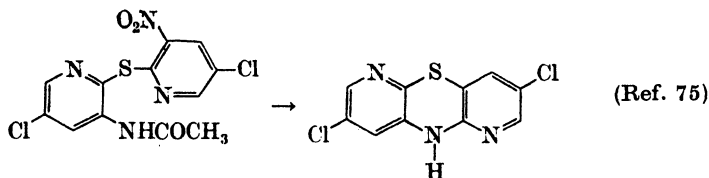
Rearrangement of one of the two possible 4-pyridyl isomers was induced by heat alone.

⁷⁴ Y. Maki, K. Yamane, and M. Sato, *Yakugaku Zasshi*, **86**, 50 (1966) [*C.A.*, **64**, 11165 (1966)].

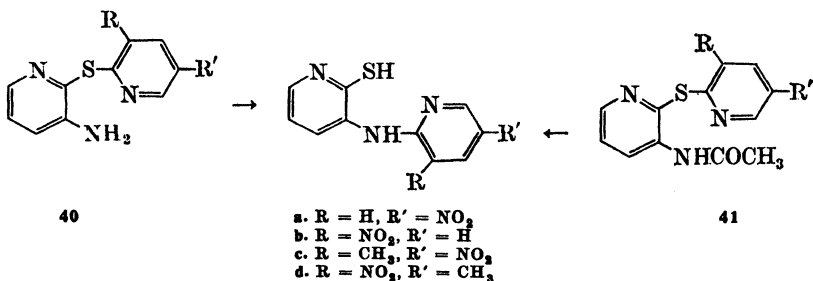
⁷⁵ T. Takahashi and Y. Maki, *Yakugaku Zasshi*, **78**, 417 (1958) [*C.A.*, **52**, 14622 (1958)].



Dipyridyl sulfides can undergo ring closure to form dipyridothiazine derivatives when treated with potassium hydroxide in boiling alcohol or acetone, the same conditions that effect ring closure in other systems.



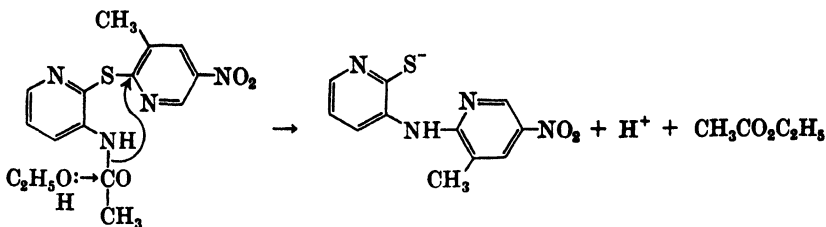
The only systematic study of Smiles rearrangements under conditions other than with base catalysis suggested that the scope of this reaction may be much broader than previously envisioned. The eight compounds of structures **40** and **41** all rearrange in yields of 67–99% when treated with aqueous 5% hydrochloric acid at 100° for an hour or less.¹⁰ Compounds **40a** and **40b** also were shown to rearrange in 95% yield in concentrated hydrochloric acid at room temperature in 7 minutes. The catalytic effect of acid can be explained by protonation on either ring



nitrogen atom. If ring B is protonated, carbon atom 2 is made more positive and thus more susceptible to nucleophilic attack. If ring A is protonated, the sulfide anion leaving group is stabilized.

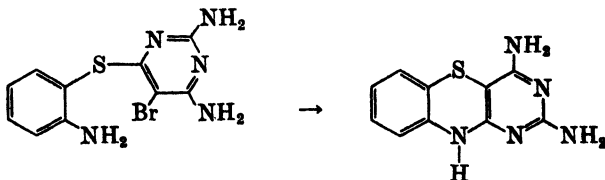


The thermal rearrangement of a number of the same sulfides in various solvents was examined.¹⁰ It was found that thermal rearrangement occurred relatively rapidly in refluxing ethanol, more slowly in water, and not at all in benzene or in dimethyl sulfoxide. The amino compounds rearranged more slowly than the corresponding acetamides. These facts suggested solvent participation for which the following mechanism was offered.



Sulfides 40a-c were also shown to rearrange completely when heated dry at 110° for 9 days.

Analogous to the acid-catalyzed rearrangements of pyridyl systems is the sole example of rearrangement in a pyrimidine system.⁷⁶



RELATED REARRANGEMENTS

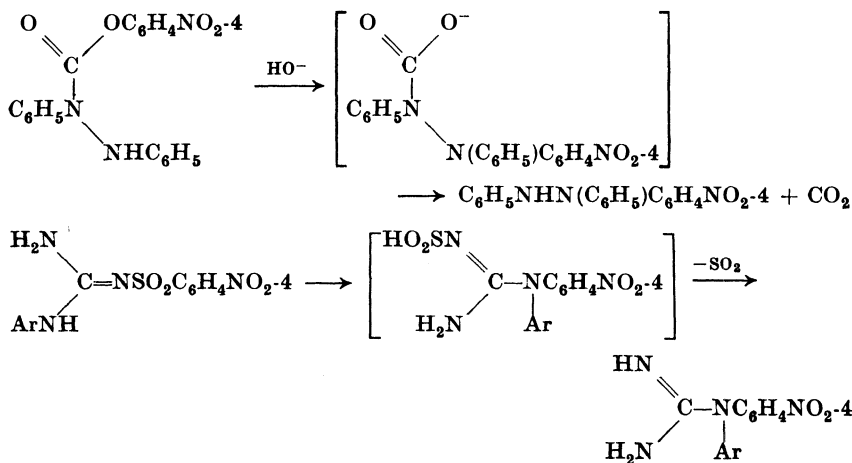
A recent variation in the aliphatic chain joining the leaving group X and the nucleophilic group YH was found where the group $-C-YH$ was replaced by the grouping $-N(C_6H_5)NHC_6H_5$.⁷⁷ Another system which undergoes base-catalyzed rearrangement in a reaction analogous to the Smiles is that reported by Backer.^{78, 79} (Equations on p. 128.)

⁷⁶ A. P. Phillips, N. B. Mehta, and J. Z. Strelitz, *J. Org. Chem.*, **28**, 1488 (1963).

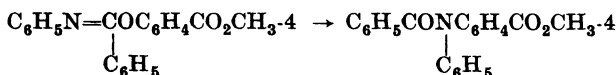
⁷⁷ P. Baudet, M. Calin, and E. Cherbuliez, *Helv. Chim. Acta*, **47**, 1047 (1964).

⁷⁸ H. J. Backer and H. D. Moed, *Rec. Trav. Chim. Pays-Bas*, **66**, 689 (1947).

⁷⁹ H. J. Backer and S. K. Wadman, *Rec. Trav. Chim. Pays-Bas*, **68**, 595 (1949).



The extension of the Smiles rearrangement implied by the discoveries of acid-catalyzed and thermal rearrangements in a few systems has not been fully explored. Obviously a very large number of rearrangements might be considered formally analogous to the Smiles rearrangement when these variations are taken into consideration. For example, the thermal rearrangement of aryl imidates known as the Chapman rearrangement⁸⁰ bears some resemblance to the thermal rearrangements of *o*-aminodiphenyl ethers and of the sulfides **40**. This review does not



include all the rearrangements which on this basis would appear to be related to the Smiles rearrangement.

EXPERIMENTAL CONDITIONS

Most Smiles rearrangements are base catalyzed because the initial function YH is converted to the more nucleophilic anion Y⁻. The bases used depend on the acidity of the group YH; in the rearrangements of *o*-substituted sulfones reported by Smiles, sodium or potassium hydroxide, normally in slight excess, sufficed. The choice of solvent is governed by the solubility of the compound being rearranged. The customary solvent systems used are: water, ethanol, acetone, aqueous ethanol, or aqueous acetone. Usually the reaction mixtures are heated at 50° or 100° or under reflux for the length of time required for complete rearrangement.

⁸⁰ J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).

Less activated or less acidic substances require special conditions. Rearrangements of *o*-bromo-*o*'-amino ethers have been effected with sodium amide in benzene⁸ or with potassium carbonate in dimethylformamide.¹³ Reverse Smiles rearrangements of activated *o*-aminodiphenyl ethers can be induced by heating in basic solvents such as pyridine, aniline, piperidine, ethanol, or glycerol, or occur at room temperature in aqueous solutions of pyridine, acetic acid, or propionic acid.³⁴⁻³⁸ Reverse Smiles rearrangements of substituted *o*-phenoxybenzenesulfinic acids have been obtained in aqueous acetic acid-sodium acetate solutions buffered to pH 2-6.³² Rearrangements in reducing media have been run in aqueous dioxane with zinc and sodium hydroxide, or in tetrahydrofuran with lithium aluminum hydride.¹²⁻¹⁶ For Truce-Smiles rearrangements, *n*-butyllithium in diethyl ether and potassium *t*-butoxide in dimethyl sulfoxide are effective reagents. Several cases of acid-catalyzed^{10, 69, 74} and thermal^{10, 70, 73, 75} rearrangements of pyridyl sulfides have been reported, various concentrations of aqueous hydrochloric acid being used for the acid-catalyzed reactions.

EXPERIMENTAL PROCEDURES

Rearrangement of N-Acetyl-2-nitro-2'-aminodiphenyl Sulfide.²³

A solution of 2 g (0.007 mol) of the sulfide in a 1:1 (v/v) mixture of acetone and ethanol which contained 1.25 equivalents of aqueous 0.5 *M* sodium hydroxide was boiled for 15 min; excess methyl iodide was added to the solution which discharged the red color. After most of the solvent had been evaporated, the product, methyl N-acetyl-2-(2'-nitrophenylamino)phenyl sulfide, separated as 1.4 g (67%) of yellow needles, mp 151°. Hydrolysis with ethanolic sodium hydroxide gave methyl 2-(2'-nitrophenylamino)phenyl sulfide, mp 98°.

Rearrangement of 2-Nitrophenyl 2-Hydroxy-5-methylphenyl Sulfone.⁸¹ A solution of 0.8 g (1.2 equivalents) of sodium hydroxide in 50 ml of water was added to a suspension of the sulfone (5 g, 0.017 mol) in 150 ml of water. The initially red solution was heated at 50-60° for 45 min, by which time the color had faded to a very pale yellow. The sulfinic acid, 2-nitrophenyl 2-sulfinyl-4-methylphenyl ether, was liberated in almost theoretical yield by acidification of the cooled solution. After purification by recrystallization from aqueous acetone, the product separated as needles, mp 132-133°. It was soluble in aqueous ammonium carbonate and gave a blue solution in sulfuric acid.

Rearrangement of *o*-(2,4-Dinitrophenoxy)benzamide.²⁸ Rearrangement of this amide was effected in 2 min at 18° by dissolving it

⁸¹ A. A. Levy, H. C. Rains, and S. Smiles, *J. Chem. Soc.*, **1931**, 3264.

in a solution containing 1.25 equivalents of 0.2 *M* sodium hydroxide in aqueous acetone (1:4 v/v). The progress of the reaction was followed by the change in color of the solution from yellow to red. On completion of the reaction, the mixture was diluted with water and the product liberated by acidification with dilute aqueous sulfuric acid. N-(2,4-Dinitrophenyl)salicylamide crystallized from benzene as yellow needles, mp 213°.

The same product, mp 213°, was obtained by heating the molten amide at 200–210° until it solidified.

Rearrangement of Mesityl Phenyl Sulfone.¹⁷ A well-stirred solution of 2.0 g (7.7 mmols) of mesityl phenyl sulfone in 100 ml of anhydrous diethyl ether was brought to a boil and treated rapidly with 7.9 ml of an ether solution containing 8.1 mmols of *n*-butyllithium. After the solution had been heated under reflux for 2 hr, it was hydrolyzed with 100 ml of water and the layers were separated. Acidification of the aqueous layer with hydrochloric acid followed by extraction with ether and evaporation of the solvent left 1.96 g (98%) of the crude product as an almost colorless solid. A solution of the crude product in 100 ml of aqueous sodium bicarbonate was decolorized with charcoal and then acidified. The product, isolated as previously described, was recrystallized from aqueous acetone. The colorless 2-benzyl-4,6-dimethylbenzenesulfinic acid melts with decomposition at 92.5–94.7°.

Rearrangement of N-(*p*-Nitrophenoxycarbonyl)hydrazobenzene.⁷⁷ A solution of 0.482 g (5.73 mmols) of sodium bicarbonate in 10 ml of water was added to 30 ml of dioxane containing 2 g (5.73 mmols) of the hydrazobenzene derivative. The mixture was heated under reflux for 24 hr, the solvent was removed under reduced pressure, and the residual oil was crystallized from a mixture of ethyl acetate and petroleum ether. The product, N-(*p*-nitrophenyl)-N,N'-diphenylhydrazine, weighed 1.05 g (60%) and melted at 131°.

Rearrangement of 2-Acetamidophenyl 5-Chloro-2-nitrophenyl Sulfide.⁸² To 888 ml of acetone was added a solution of 6.8 g (0.103 mol) of 85% potassium hydroxide in 51 ml of 95% ethanol. The mixture was stirred and nitrogen bubbled through for 15 min. Then 16.1 g (0.05 mol) of crude 2-acetamidophenyl 5-chloro-2-nitrophenyl sulfide (mp 143–150°) was added and the solution was heated under reflux for 3 hr. Approximately 600 ml of acetone was removed by distillation and then 500 ml of petroleum ether (bp 90–120°) and 700 ml of water were added. The small amount of insoluble material present was removed by filtration, and the two layers were separated.

⁸² R. J. Galbreath and R. K. Ingham, *J. Org. Chem.*, **23**, 1804 (1958).

The aqueous layer was washed with an additional 200-ml portion of petroleum ether and the organic layer was washed with 200 ml of water. The combined petroleum ether solutions were dried over magnesium sulfate and concentrated to a volume of 60 ml. After this solution had been cooled, the resulting precipitate was collected and washed with cold petroleum ether (bp 20–40°) to leave 5.5 g of crude product as a brown solid which melted at 180–193° with prior softening. A solution of this material in boiling xylene was decolorized with charcoal (Norit) and cooled to separate 4.3 g (37%) of 2-chlorophenothiazine as pale yellow crystals, mp 194.5–196°. Another recrystallization from xylene gave 3.6 g of the phenothiazine as almost colorless crystals, mp 196–197°.

Rearrangement of 2-Acetamidophenyl 3-Nitro-4-pyridyl Sulfide.⁸³ To a stirred, boiling solution of 32.5 g (0.089 mol) of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide in 2.5 l of acetone under a nitrogen atmosphere was added 14.5 g (0.26 mol) of powdered potassium hydroxide in small portions during a 30-min period. The stirring and heating under nitrogen were continued for 1 hr, and then the acetone was distilled from the mixture during 1.5 hr. Reduced pressure was employed in the final stages of this distillation. Ice water (about 1 l) was added to the residue, the mixture was stirred and the solid collected, washed well with water, and dried. The product, 3-azaphenothiazine, was isolated as a light yellow solid; 13.8 g (62%), mp 243–244° dec. Several recrystallizations from ethanol or acetone raised the melting point to 246–248° dec.

Rearrangement of 3-Amino-2-pyridyl 3-Nitro-2-pyridyl Sulfide.¹⁰ (A) *Acid-Catalyzed Rearrangement.* A mixture of the sulfide (881 mg, 3.55 mmol) in 10 ml of aqueous 5% hydrochloric acid was heated at 100° for 1 hr. After the mixture had been cooled, the N-(3-nitro-2-pyridyl)-2-mercapto-3-pyridylamine, separated by filtration, amounted to 873 mg (99%), mp 235° dec. Repeated recrystallization from benzene raised the melting point to 242–244° dec.

Rearrangement in concentrated hydrochloric acid was accomplished by dissolving 39 mg (0.157 mmol) of the dipyridyl sulfide with shaking in 3 ml of concentrated hydrochloric acid at room temperature. After 7 min the solution was poured onto crushed ice, whereupon the red product precipitated. Filtration separated 37.0 mg (95%) of N-(3-nitro-2-pyridyl)-2-mercapto-3-pyridylamine, mp 228–235° dec. Recrystallization from acetone-benzene raised the melting point to 239–243° dec.

⁸³ F. Clarke, G. Silverman, C. Watnick, and N. Sperber, *J. Org. Chem.*, **26**, 1126 (1961).

(B) *Thermal Rearrangement.* When the same dipyridyl sulfide (mp 167–168°) in the solid state was heated to 110° in an oven for 9 d, the product obtained was identified from its infrared spectrum as N-(3-nitro-2-pyridyl)-2-mercapto-3-pyridylamine. Recrystallization gave the pure product in 88% yield.

TABULAR SURVEY

In the following tables an attempt has been made to include all the Smiles rearrangements reported through May 15, 1969. Tables VI–XIV, XVIII, XX, XXI, and XXIII–XXV are organized by the type of compound undergoing rearrangement, *e.g.*, diphenyl sulfides. Tables XV–XVII list phenazines, phenoxazines, and phenothiazines formed by Smiles rearrangements; these reactions are not included in the tables of rearrangements of sulfides and ethers. Similarly Table XXII lists dipyridyl sulfides that have been rearranged to form dipyridothiazines; these compounds are not included in Table XX. However, although Table XIX lists azaphenothiazines formed from pyridyl phenyl sulfides, most of these reactions are also included in Table XVIII to indicate that changes of the conditions or reagents used can result in the formation of different products.

Internally the tables are organized by increasing complexity of the migrating group, *e.g.*, according to the number of substituents in the migrating group. This ordering is applied to each system undergoing rearrangement in order of increasing complexity of the nonmigrating portion of the structure. In reactions for which more than one reference is cited, the experimental data are taken from the first reference and the remaining references are listed in numerical order. Mixed solvents are reported in volume ratios.

CHAPTER 3

THE REACTIONS OF DIAZOACETIC ESTERS WITH ALKENES, ALKYNES, HETEROCYCLIC AND AROMATIC COMPOUNDS

VINOD DAVE AND E. W. WARNHOFF
University of Western Ontario, London, Canada

CONTENTS

	PAGE
INTRODUCTION	218
MECHANISM	220
STEREOCHEMISTRY	223
SCOPE AND LIMITATIONS	230
Alkenes, Alkadienes, and Allenes	231
Alkynes and Alkenynes	236
Heterocyclic Compounds	238
Benzene and Benzene Derivatives	239
Polynuclear Aromatic Compounds	242
Miscellaneous Reactions	244
STRUCTURE AND STEREOCHEMISTRY OF PRODUCTS	246
EXPERIMENTAL CONDITIONS	249
PREPARATION AND PROPERTIES OF DIAZOACETIC ESTERS	253
EXPERIMENTAL PROCEDURES	258
Catalysts	258
Reactions	259
Ethyl <i>trans</i> -2,3-Di- <i>n</i> -propylcyclopropane-1-carboxylate	259
Methyl <i>cis</i> -2,3-Dimethylcyclopropane-1- <i>cis</i> (and 1- <i>trans</i>)-carboxylate	259
Ethyl <i>cis</i> -Bicyclo[4.1.0]heptane-7-carboxylate (<i>exo</i> and <i>endo</i>)	259
7-Carbethoxy- Δ^3 -norcarene (<i>exo</i> and <i>endo</i>)	260
2-Methyl-2-isopropenyl-1-carbethoxycyclopropane (<i>cis</i> and <i>trans</i>)	260
Ethyl 2,2-Dimethyl-3-isopropylidenecyclopropane-1-carboxylate	261

Ethyl <i>cis</i> - and <i>trans</i> -2-Phenylcyclopropanecarboxylate	261
<i>cis</i> -2,3-Diphenylcyclopropane- <i>trans</i> -1-carboxylic Acid	261
Methyl 2,3-Dimethyl-2-cyclopropene-1-carboxylate	262
2,3-Di- <i>n</i> -propyl-2-cyclopropene-1-carboxylic Acid	262
Ethyl 2,3-Di- <i>n</i> -butyl-2-cyclopropene-1-carboxylate	263
Ethyl 2-Thiabicyclo[3.1.0]hex-3-ene-6-carboxylate	263
2,4,8-Trimethylazulene	263
Ethyl Diazoacetate and Acenaphthene	264
 TABULAR SURVEY	 265
Table I. Reactions with Monoalkenes	267
Table II. Reactions with Polyalkenes	289
Table III. Reactions with Alkenes Containing Aromatic Rings	301
Table IV. Reactions with Alkynes and Alkenynes	319
Table V. Reactions with Heterocyclic Compounds	328
Table VI. Reactions with Compounds Containing One Aromatic Ring . .	338
Table VII. Reactions with Compounds Containing More than One Aromatic Ring	354
Table VIII. Reactions with Miscellaneous Compounds	368

INTRODUCTION

After the first unsuccessful attempt of Curtius in 1884 to effect the reaction of ethyl diazoacetate with toluene,¹ Buchner and Curtius in 1885,^{2,3} and later Buchner and his school,⁴⁻²⁴ treated several aromatic, olefinic, and acetylenic compounds with diazoacetic esters to form

¹ T. Curtius, *Ber.*, **17**, 953 (1884).

² E. Buchner and T. Curtius, *Ber.*, **18**, 2371 (1885).

³ E. Buchner and T. Curtius, *Ber.*, **18**, 2377 (1885).

⁴ E. Buchner, *Ann.*, **273**, 214 (1893).

⁵ E. Buchner and A. Papandieck, *Ann.*, **273**, 233 (1893).

⁶ E. Buchner, *Ber.*, **27**, 3250 (1894).

⁷ E. Buchner, *Ber.*, **29**, 106 (1896).

⁸ E. Buchner, *Ber.*, **30**, 632 (1897).

⁹ E. Buchner and F. Lingg, *Ber.*, **31**, 402 (1898).

¹⁰ E. Buchner, *Ber.*, **31**, 2241 (1898).

¹¹ W. Braren and E. Buchner, *Ber.*, **33**, 684 (1900).

¹² W. Braren and E. Buchner, *Ber.*, **33**, 3453 (1900).

¹³ W. Braren and E. Buchner, *Ber.*, **34**, 982 (1901).

¹⁴ E. Buchner and L. Lehmann, *Ber.*, **35**, 35 (1902).

¹⁵ E. Buchner and S. Hediger, *Ber.*, **36**, 3502 (1903).

¹⁶ E. Buchner and L. Feldmann, *Ber.*, **36**, 3509 (1903).

¹⁷ E. Buchner and J. Geronimus, *Ber.*, **36**, 3782 (1903).

¹⁸ E. Buchner and K. Scheda, *Ber.*, **37**, 931 (1904).

¹⁹ E. Buchner and K. Delbruck, *Ann.*, **358**, 1 (1907).

²⁰ E. Buchner and P. Schulze, *Ann.*, **377**, 259 (1910).

²¹ E. Buchner and W. Weigand, *Ber.*, **46**, 759 (1913).

²² E. Buchner and W. Weigand, *Ber.*, **46**, 2108 (1913).

²³ E. Buchner and K. Rehorst, *Ber.*, **46**, 2680 (1913).

²⁴ E. Buchner and K. Schottenhammer, *Ber.*, **53**, 865 (1920).

cyclopropanes. Since then the reactions of diazoacetates with various unsaturated compounds have been studied under thermal,* catalytic, and photochemical conditions. In recent years there has been an added impetus to these investigations because of current interest in carbenes. The carbalkoxy carbenes ($:\text{CHCO}_2\text{R}$), which are believed to be intermediates in higher-temperature thermal and photochemical reactions of diazoacetates, together with various other aspects of carbene chemistry have been subjects of numerous reviews in recent years.²⁵⁻⁴⁴ Although there are also reviews of the chemistry of diazo compounds,⁴⁵⁻⁴⁸ no review has appeared in which the reactions of diazoacetic esters to form cyclopropanes and cyclopropenes are treated as useful synthetic methods.

* The term *thermal* is understood to include any reaction not carried out with irradiation or a deliberately added catalyst; it includes reactions run at and above room temperature although most reactions have been carried out above 80–100°.

²⁵ J. Hine, *Divalent Carbon*, The Ronald Press Co., New York, 1964.

²⁶ W. Kirmse, *Carbene Chemistry*, Academic Press, New York, 1964.

²⁷ J. Leitich, *Osterr. Chemiker-Ztg.*, **61**, 164 (1960).

²⁸ G. Herzberg, *Proc. Roy. Soc.*, **A262**, 291 (1961).

²⁹ W. Kirmse, *Angew. Chem.*, **73**, 161 (1961).

³⁰ H. W. Wanzlick, *Ang. Chem. Int. Ed. Engl.*, **1**, 75 (1962).

³¹ P. Miginiac, *Bull. Soc. Chim. Fr.*, **1962**, 2000.

³² E. Chinoporos, *Chem. Rev.*, **63**, 235 (1963).

³³ W. E. Parham and E. E. Schweizer, *Org. Reactions*, **13**, 55 (1963).

³⁴ A. Ledwith, *Royal Inst. Chem. Lectures (London)*, No. 5, 1964.

³⁵ W. Kirmse, *Progr. Org. Chem.*, **6**, 164 (1964).

³⁶ H. M. Frey in G. Porter, Ed., *Progress in Reaction Kinetics*, Vol. 2, p. 131, The Macmillan Co., New York, 1964.

³⁷ J. A. Bell in S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Eds., *Progr. Phys. Org. Chem.*, **2**, 1 (1964).

³⁸ W. B. DeMore and S. W. Benson, *Advan. Photochem.*, **2**, 219 (1964).

³⁹ C. W. Rees and C. E. Smithen in A. R. Katritzky, Ed., *Advan. Heterocycl. Chem.*, **3**, 57 (1964).

⁴⁰ W. Kirmse, *Ang. Chem. Int. Ed. Engl.*, **4**, 1 (1965).

⁴¹ G. G. Rozantsev, A. A. Fainzil'berg, and S. S. Novikov, *Russ. Chem. Rev.*, **34**, 69 (1965).

⁴² B. J. Herold and P. P. Gaspar, *Fortschr. Chem. Forsch.*, **5**, 89 (1965).

⁴³ (a) B. Capon, M. J. Perkins, and C. W. Rees, *Organic Reaction Mechanisms-1965*, p. 222, Interscience Publ. New York, 1966; (b) p. 279, 1967; (c) p. 278, 1968; (d) p. 319, 1969.

⁴⁴ (a) G. L. Closs in E. L. Eliel and N. L. Allinger, Eds., *Topics in Stereochemistry*, Vol. 3, p. 193, Interscience Publishers, New York, 1968. (b) R. A. Moss, *Chem. Eng. News*, June 16, 1969, p. 60; June 30, 1969, p. 50; see also Feb. 23, 1970, p. 8. (c) D. Bethell, *Advan. Phys. Org. Chem.*, **7**, 153 (1969). (d) T. L. Gilchrist and C. W. Rees, *Carbenes, Nitrenes, and Arynes*, Thomas Nelson and Sons, Ltd., London, 1969. (e) W. Kirmse, *Carbene, Carbenoide und Carbenanalogue*, Verlag Chemie, Weinheim, 1969.

⁴⁵ I. A. D'yakonov, *Aliphatic Diazo Compounds* (in Russian), Leningrad, Gosudarst. Univ., 1958 [*C.A.*, **53**, 2088 (1959)].

⁴⁶ H. Zollinger, *Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds*, Interscience Publishers, New York, 1961.

⁴⁷ E. Müller, H. Kessler, and B. Zeeh, *Fortschr. Chem. Forsch.*, **7**, 128 (1966).

⁴⁸ (a) B. Eistert, M. Regitz, G. Heck, and H. Schwall, *Methoden der Organischen Chemie (Houben-Weyl)*, 10/4, p. 473, Georg Thieme Verlag, Stuttgart, 1968. (b) G. W. Cowell and A. Ledwith, *Quart. Rev. (London)*, **24**, 119 (1970).

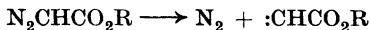
The current interest in strained ring systems and the chemistry of cyclopropanes⁴⁹ and cyclopropenes^{50, 51} makes such a review timely.

This chapter includes the reactions of ethyl and methyl diazoacetate with olefinic, acetylenic, heterocyclic, and aromatic compounds, but excludes (except for illustrative examples) reactions with α,β -unsaturated carbonyl, imino, and nitrilic compounds. In the discussion that follows, the terms diazoacetate(s) and diazoacetic ester(s) refer specifically to methyl and ethyl diazoacetate, the two compounds that have been used almost exclusively. In the future, *t*-butyl diazoacetate which is now readily available^{51a} will probably be used frequently.

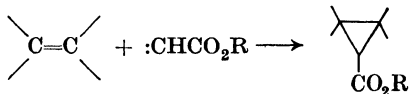
MECHANISM

Because systematic mechanistic studies of the reactions of diazoacetates with unsaturated compounds are only now beginning, the following discussion represents only the current tentative views on the subject. Diazoacetates, when allowed to react with olefins or acetylenes, give products containing three-membered carbocyclic rings. This result could occur in any of the following three ways.

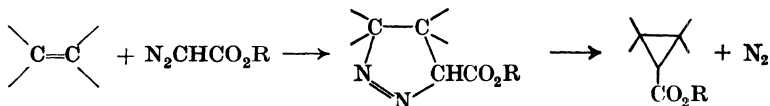
The diazoacetic ester might lose nitrogen under the influence of heat or light to produce a carbalkoxy carbene which adds to the olefin (or acetylene) giving a cyclopropane (or cyclopropene) carboxylate.



(Path 1)



Alternatively, the diazoacetic ester molecule might react with the olefin to form a pyrazoline which loses nitrogen to produce the cyclopropanecarboxylate.



(Path 2)

Finally, bond formation might take place between the α -carbon atom of the diazoacetate and one carbon atom of the olefin. Closure of the

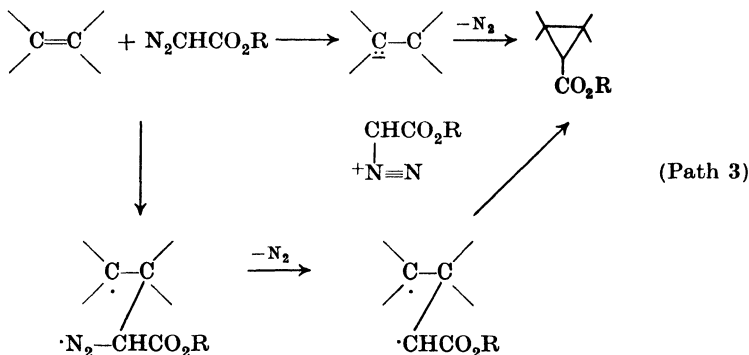
⁴⁹ M. Yu Lukina, *Russ. Chem. Rev.*, **31**, 419 (1962).

⁵⁰ F. L. Carter and V. L. Frampton, *Chem. Rev.*, **64**, 497 (1964).

⁵¹ G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 53 (1966).

^{51a} M. Regitz, J. Hocker, and A. Leidhegener, *Org. Syntheses*, **48**, 36 (1968).

resulting diradical or zwitterionic intermediate with loss of nitrogen would form the second bond of the cyclopropane.



In nonphotochemical reactions of double or triple bonds conjugated with carbonyl, imino, or nitrile groups, 1,3-dipolar addition of the diazo group (Path 2) usually occurs to give a pyrazoline or pyrazole which is stable under the reaction conditions. In a few of these reactions, cyclopropane formation occurs, presumably by Path 3. These olefins conjugated with C=O or C=N multiple bonds will not be considered further here.^{52, 53} Carbalkoxy carbenes are involved in higher-temperature thermal (above 80–100°) and photochemical reactions (Path 1). The reaction of carbethoxycarbene, an electrophile, with monosubstituted benzenes exhibited $\rho = -0.38$.⁵⁴

Metals and metal salts catalyze the decomposition of diazoacetic esters.^{55–57} For reactions with olefins and acetylenes the catalysts most frequently used are copper and copper salts. In these catalyzed reactions the reaction path is probably different from those discussed previously. The related copper-catalyzed decomposition of diazo ketones is believed to involve an organocopper complex.⁵⁸ The systematic studies by Moser of reactions of diazoacetic esters catalyzed by soluble phosphite ester-copper(I) chloride complexes demonstrated that changes occur in product stereoisomer ratios with variation in the phosphite ligands.⁵⁹ Nozaki,

⁵² T. L. Jacobs in R. C. Elderfield, Ed., *Heterocyclic Compounds*, Vol. 5, p. 70, John Wiley and Sons, New York, 1957.

⁵³ (a) R. Fusco in R. H. Wiley, Ed., *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*, Interscience Publishers, New York, 1967. (b) C. J. Jarboe, *ibid.*

⁵⁴ J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **89**, 1886 (1967).

⁵⁵ O. Silberrad and C. S. Roy, *J. Chem. Soc.*, **89**, 179 (1906).

⁵⁶ A. Loose, *J. Prakt. Chem.*, [2] **79**, 505 (1909).

⁵⁷ K. Lorey, *J. Prakt. Chem.*, [2] **124**, 185 (1930).

⁵⁸ P. Yates, *J. Amer. Chem. Soc.*, **74**, 5376 (1952).

⁵⁹ W. R. Moser, *J. Amer. Chem. Soc.*, **91**, 1135, 1141 (1969), and personal communication.

Noyori, and coworkers have obtained optically active cyclopropane-carboxylates from olefins by decomposition of methyl and ethyl diazoacetate with an optically active copper complex **8** (p. 251).⁶⁰ These data show that the catalyst is not serving merely to liberate a free carbene before reaction (Path 1); instead the catalyst must be bound in some way to the diazoacetic ester⁶¹⁻⁶⁵ or carbene derived from it.^{60, 66-70} In several cyclopropane-forming reactions where catalysts or reactants such as zinc-copper couples (Simmons-Smith reaction), dialkylaluminum halides, alkylolithiums, and zinc halides are used, the presence of organometallic complexes has been strongly indicated,⁷¹⁻⁷⁴ and in a few cases complexes have been isolated.^{75, 76} The term *carbenoid*, signifying a qualitative similarity between the reactions of these organometallic intermediates and those of free carbenes, has been accepted for these organometallic complexes.^{73, 77} Thus the evidence favors a carbenoid intermediate in the metal-catalyzed reactions of diazoacetic esters with olefins and acetylenes. The reactivity of these carbenoid intermediates is reduced since products resulting unambiguously by direct C-H insertion are rarely found.*⁷⁸ In the copper(II) chloride-catalyzed decomposition of diazomethane, copper(I) chloride, formed in the reaction mixture by reduction, is believed to be the active catalyst.^{75, 80} Whether this holds true for the other copper salt-catalyzed decompositions is uncertain. The copper mirror formed in some copper(II) sulfate-catalyzed reactions led D'yakonov

* For an exception see ref. 79.

⁶⁰ H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968).

⁶¹ E. Buchner, *Ber.*, **28**, 215 (1895).

⁶² P. Yates and F. X. Garneau, *Tetrahedron Lett.*, **1967**, 71.

⁶³ F. Gerhart, U. Schöllkopf, and H. Schumacher, *Ang. Chem. Int. Ed. Engl.*, **6**, 74 (1967).

⁶⁴ U. Schöllkopf and N. Rieber, *Ang. Chem. Int. Ed. Engl.*, **6**, 261 (1967).

⁶⁵ H. Kwart and A. A. Kahn, *J. Amer. Chem. Soc.*, **89**, 1950, 1951 (1967).

⁶⁶ (a) T. DoMinh, H. E. Gunning, and O. P. Strausz, *J. Amer. Chem. Soc.*, **89**, 6785 (1967).

(b) O. P. Strausz, T. DoMinh, and J. Font, *J. Amer. Chem. Soc.*, **90**, 1930 (1968).

⁶⁷ D. O. Cowan, M. M. Couch, K. R. Kopecky, and G. S. Hammond, *J. Org. Chem.*, **29**, 1922 (1964).

⁶⁸ R. Huisgen, G. Binsch, and L. Ghosez, *Chem. Ber.*, **97**, 2628 (1964).

⁶⁹ R. K. Armstrong, *J. Org. Chem.*, **31**, 618 (1966).

⁷⁰ H. Werner and J. H. Richards, *J. Amer. Chem. Soc.*, **90**, 4976 (1968).

⁷¹ H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Amer. Chem. Soc.*, **86**, 1347 (1964), and previous papers in the series.

⁷² W. T. Miller, Jr., and D. M. Whalen, *J. Amer. Chem. Soc.*, **86**, 2089 (1964).

⁷³ G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).

⁷⁴ R. A. Moss, *J. Org. Chem.*, **30**, 3261 (1965).

⁷⁵ G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961).

⁷⁶ H. Hoberg, *Ann.*, **656**, 1 (1962).

⁷⁷ G. Köbrich, *Ang. Chem. Int. Ed. Engl.*, **6**, 41 (1967); *Bull. Soc. Chim. Fr.*, **1969**, 2712.

⁷⁸ W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **78**, 4947 (1956).

⁷⁹ H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 53 (1968).

⁸⁰ R. G. R. Bacon and H. A. O. Hill, *Quart. Rev. (London)*, **19**, 95 (1965).

to suggest that the actual catalyst is colloidal copper.^{81, 82} However, the soluble phosphite ester-copper(I) chloride catalysts apparently do catalyze the reactions of diazoacetates with olefins.⁵⁹ Whether the active catalytic species in these reactions is in solution remains to be decided. Successful decompositions at room temperature with these phosphite ester-copper(I) catalysts are always accompanied by the immediate appearance of a dark-colored, apparently insoluble, colloidal material,^{82a} and it remains to be determined whether this colloidal material catalyzes the reaction.

Carbalkoxy carbenes produced photochemically are less selective than the intermediates produced by catalytic or thermal decomposition of diazoacetic esters since larger amounts of C—H insertion products are formed in the photochemical reactions.⁸³ Even the intermediates produced by catalytic decomposition discriminate only slightly between pairs of differently substituted olefins. The observed order of reactivity in copper(II) sulfate-catalyzed decompositions of ethyl diazoacetate is tetramethylethylene (1.8) \sim trimethylethylene (1.8) > cyclohexene (1.1) > 1-hexene (1.0).⁸⁴ In the few studies of competitive reactions between double and triple bonds, the results are contradictory; this point is discussed more fully on p. 237. Aromatic rings are noticeably less reactive than double or triple bonds.

STEREOCHEMISTRY

The reaction to form cyclopropanes is a stereospecific or highly stereoselective *cis* addition to the multiple bond. With *cis*- and *trans*-2-butene, neither of which undergoes geometrical isomerization under the reaction conditions, *photochemically* produced carbalkoxy carbene adds in a stereospecifically *cis* manner.⁸⁵ Thus Doering and Mole showed that methyl diazoacetate and *cis*-2-butene gave a mixture of the two *meso* cyclopropanecarboxylic esters, whereas *trans*-2-butene gave only the corresponding racemic mixture. Other carbene additions are not completely stereospecific; for example, the addition of phenylcarbene (formed by photolysis of phenyldiazomethane) to the *cis*- and *trans*-2-butenes gave 2–3% of cyclopropane product in which apparent *cis-trans* isomerization of the olefin had occurred during the addition.⁸⁶

⁸¹ M. I. Komendantov, I. A. D'yakonov, and T. S. Smirnova, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 561 (1966) [*C.A.*, **65**, 7124 (1966)].

⁸² M. I. Komendantov, I. A. D'yakonov, I. Gokhmanova, and R. R. Kostikov, *J. Org. Chem. USSR (Engl. Transl.)*, **1**, 201 (1965) [*C.A.*, **62**, 16168 (1965)].

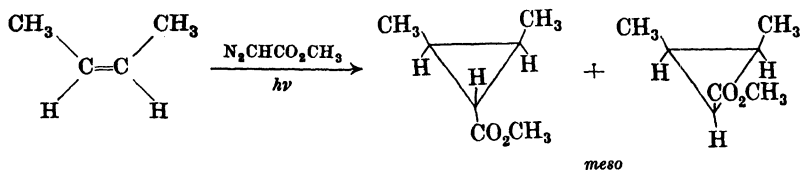
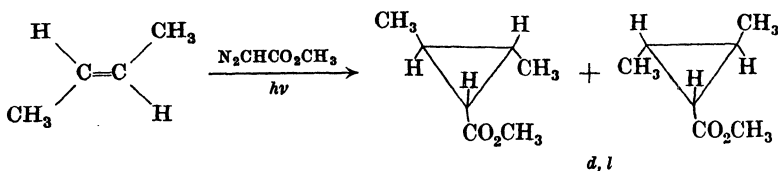
^{82a} H. O. House and C. J. Blankley, personal communication.

⁸³ P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, **1961**, 443.

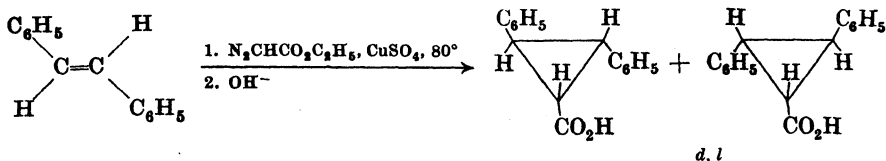
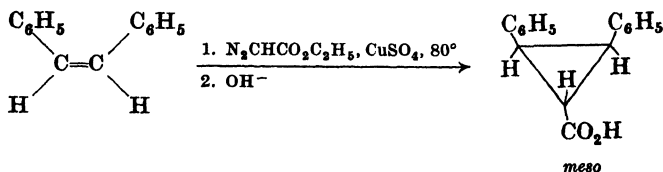
⁸⁴ P. S. Skell and R. M. Etter, *Chem. & Ind. (London)*, **1958**, 624.

⁸⁵ W. von E. Doering and T. Mole, *Tetrahedron*, **10**, 65 (1960).

⁸⁶ W. von E. Doering and M. Jones, Jr., *Tetrahedron Lett.*, **1963**, 791; M. Jones, Jr., A. M. Harrison, and K. R. Rettig, *J. Amer. Chem. Soc.*, **91**, 7462 (1969).



Stereospecific *cis* addition has also been found in *catalyzed* reactions. D'yakonov and his coworkers treated *cis*- and *trans*-stilbene with ethyl diazoacetate in the presence of copper(II) sulfate at 80°. The acid obtained by saponification of the product from *trans*-stilbene could be resolved into its optical antipodes, but the *meso* acid obtained from *cis*-stilbene could not. This result requires the addition to be *cis*.⁸⁷



Cis addition has also been found for the copper-catalyzed reactions of diazoacetic esters with *cis*-2-butene,^{85, 88} *trans*-3-hexene,⁸⁹ *cis*- and *trans*-4-octene,^{87, 90} *cis*- and *trans*-5-decene,^{89, 91} and *cis*- and *trans*-*p,p'*-dimethoxystilbene.⁹² Under noncatalytic *thermal* conditions, *cis* addition has been demonstrated in the reaction of ethyl diazoacetate with *cis*- and

⁸⁷ I. A. D'yakonov, M. I. Komendantov, Fu Gui-siya, and G. L. Korichev, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 917 (1962) [*C.A.*, **58**, 2375 (1963)].

⁸⁸ P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.*, **78**, 4496 (1956).

⁸⁹ J. M. Walbrick, J. W. Wilson, Jr., and W. M. Jones, *J. Amer. Chem. Soc.*, **90**, 2895 (1968).

⁹⁰ I. A. D'yakonov and R. R. Kostikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **34**, 3894 (1964) [*C.A.*, **62**, 6376 (1965)].

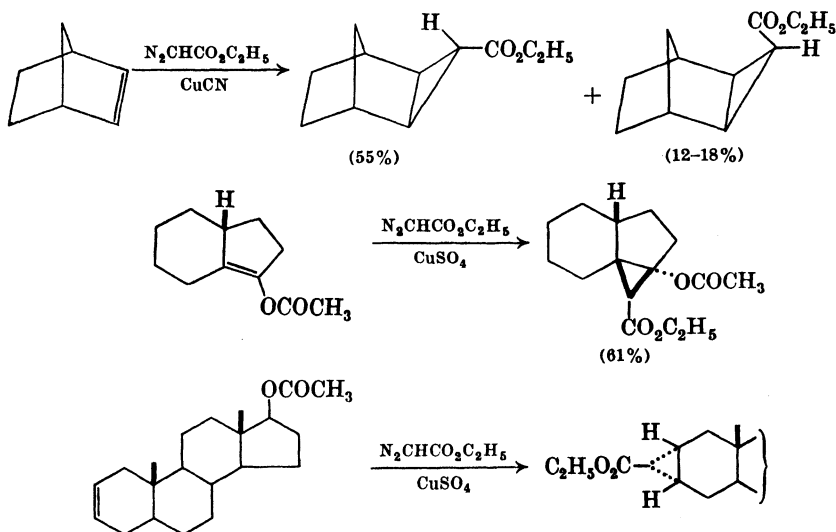
⁹¹ I. A. D'yakonov and R. R. Kostikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **34**, 1385 (1964) [*C.A.*, **61**, 5523 (1964)].

⁹² J. K. Blatchford and M. Orchin, *J. Org. Chem.*, **29**, 839 (1964).

trans-stilbene at 180–200°. ⁹³ No isomerization of the stilbenes was observed under the catalytic or thermal conditions used in these experiments.

Stereospecific *cis* addition of a carbalkoxy carbene to a double bond could be the consequence of a concerted reaction of a singlet carbene with a double bond, but this has not been established. ⁵⁴ Two stereochemical observations argue against the importance of a pyrazoline intermediate (Path 2) in these apparently stereospecific reactions of diazoacetic ester. First, pyrazoline formation can be nonstereospecific ^{94, 95} and, second, the long assumed stereospecificity in cyclopropane formation from conjugated olefins *via* a pyrazoline ⁹⁶ has recently been disproved by pyrolytic studies on pyrazolines which show the decomposition to cyclopropanes to be nonstereospecific in some cases. ^{97–99}

There are two other stereochemical aspects to consider. In the few olefins with different degrees of steric hindrance above and below the plane of the double bond, the expected preference for addition to the less



⁹³ W. M. Jones, *J. Amer. Chem. Soc.*, **81**, 3776 (1959).

⁹⁴ C. G. Overberger, N. Weinshenker, and J-P. Anselme, *J. Amer. Chem. Soc.*, **87**, 4119 (1965).

⁹⁵ C. G. Overberger, J-P. Anselme, and J. G. Lombardino, *Organic Compounds with Nitrogen-Nitrogen Bonds*, p. 57, The Ronald Press Co., New York, 1966.

⁹⁶ K. von Auwers and F. Konig, *Ann.*, **496**, 252 (1932).

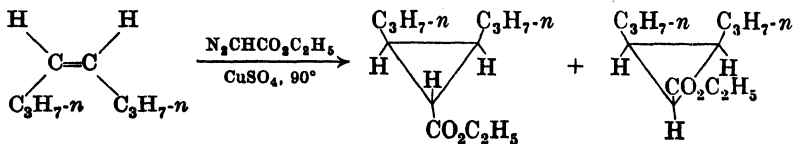
⁹⁷ W. M. Jones and W. T. Tai, *J. Org. Chem.*, **27**, 1324 (1962), and preceding papers in the series.

⁹⁸ D. E. McGreer and W-S. Wu, *Can. J. Chem.*, **45**, 461 (1967), and earlier papers in the series including references cited therein.

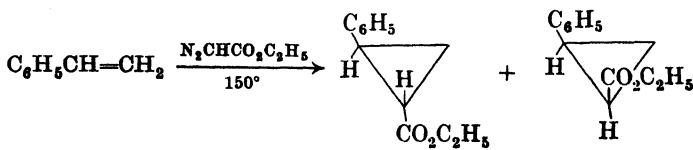
⁹⁹ R. J. Crawford and L. H. Ali, *J. Amer. Chem. Soc.*, **89**, 3908 (1967), and earlier papers.

shielded side of the double bond is found as is illustrated by reactions with norbornene,¹⁰⁰ hexamethylbicyclo[2.2.0]hexadiene,¹⁰² 1-hydrindanone enol acetate,¹⁰³ and 17 β -hydroxyandrost-2-ene acetate.¹⁰⁴

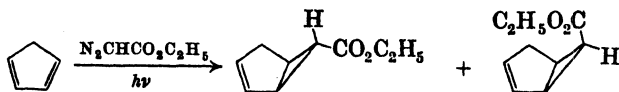
When two geometrically isomeric cyclopropanecarboxylates are possible from the *cis* addition of diazoacetate to one side of an olefin, that isomer in which the carbalkoxyl group is subject to fewer repulsive nonbonded interactions usually predominates. This generalization is based on reactions with *cis*-stilbene,^{87, 92, 93, 105} *cis*-2-butene,⁸⁵ vinylene carbonate,¹⁰⁶



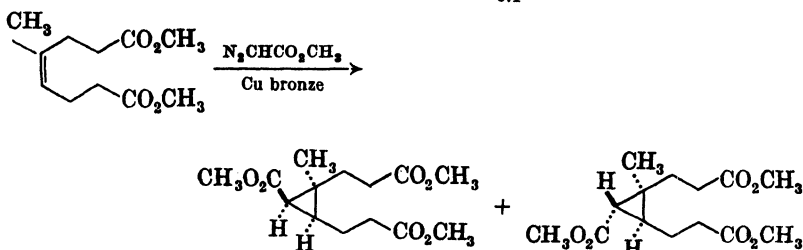
2:1



65:35



3:1



1:3

¹⁰⁰ R. R. Sauers, S. B. Schlosberg, and P. E. Pfeffer, *J. Org. Chem.*, **33**, 2175 (1968).

¹⁰¹ R. R. Sauers and P. E. Sonnet, *Tetrahedron*, **20**, 1029 (1964).

¹⁰² H. Prinzbach and E. Druckrey, *Tetrahedron Lett.*, **1968**, 4285.

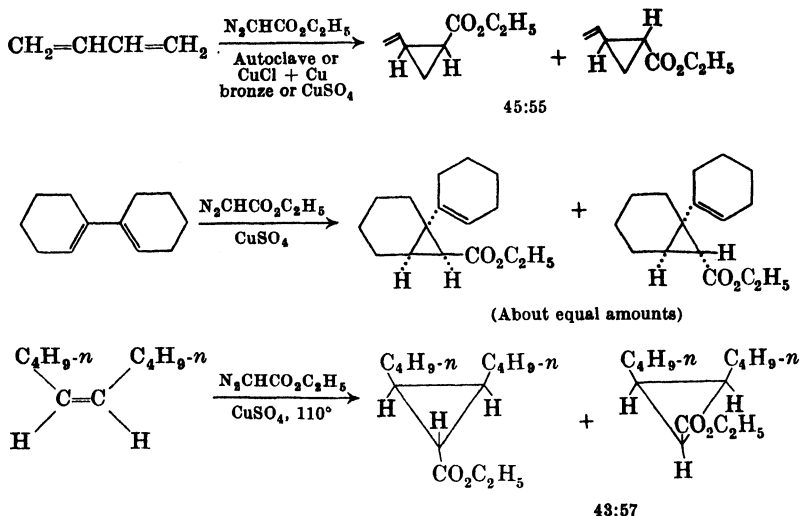
¹⁰³ H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 47 (1968).

¹⁰⁴ M. E. Wolff, S.-Y. Cheng, and W. Ho, *J. Med. Chem.*, **11**, 864 (1968).

¹⁰⁵ A. Burger, D. G. Marquees, W. R. Nes, and W. L. Yost, *J. Amer. Chem. Soc.*, **71**, 3307 (1949).

¹⁰⁶ F. W. Breitbeil, D. T. Dennerlein, A. E. Fiebig, and R. E. Kuznicki, *J. Org. Chem.*, **33**, 3389 (1968).

cis-4-octene,^{87, 90} cyclohexene,^{59, 83, 107-110} 1,3-cyclohexadiene,^{109, 111} 1,4-cyclohexadiene,^{107, 111} styrene,^{59, 60, 112-121} cyclopentene,^{59, 108, 122} cyclopentadiene,¹²³ phenanthrene,^{124, 124a} 4-vinylpyridine,¹²⁵ dimethyl *cis*-4-methyl-4-octenedioate,¹²⁶ and many other examples that can be found in the tables. Exceptions to this generalization are known in which the two isomers are



¹⁰⁷ H. Musso and U. Biethan, *Chem. Ber.*, **97**, 2282 (1964).

¹⁰⁸ W. Kirmse and K-H. Pook, *Chem. Ber.*, **98**, 4022 (1965).

¹⁰⁹ I. A. D'yakonov, T. V. Domareva-Mandel'shtam, and V. V. Razin, *J. Gen. Chem. USSR (Engl. Transl.)*, **33**, 3365 (1963) [*C.A.*, **60**, 4023 (1964)].

¹¹⁰ S. A. Konstas, *Chim. Chronika* (Athens, Greece), **29**, 13 (1964) [*C.A.*, **60**, 10566 (1964)].

¹¹¹ J. A. Berson and E. S. Hand, *J. Amer. Chem. Soc.*, **86**, 1978 (1964).

¹¹² C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

¹¹³ A. Burger and W. L. Yost, *J. Amer. Chem. Soc.*, **70**, 2198 (1948).

¹¹⁴ D. G. Markees and A. Burger, *J. Amer. Chem. Soc.*, **70**, 3329 (1948).

¹¹⁵ H. Veldstra and C. Van De Westeringh, *Rec. Trav. Chim., Pays-Bas*, **70**, 1127 (1951).

¹¹⁶ H. L. de Waal and G. W. Perold, *Chem. Ber.*, **85**, 574 (1952).

¹¹⁷ E. N. Trachtenberg and G. Odian, *J. Amer. Chem. Soc.*, **80**, 4015 (1958).

¹¹⁸ J. W. McFarland, *J. Org. Chem.*, **30**, 3298 (1965).

¹¹⁹ H. Nozaki, H. Takaya, and R. Noyori, *Tetrahedron*, **22**, 3393 (1966).

¹²⁰ J. Farkaš, P. Kouřim, and F. Šorm, *Collect. Czech. Chem. Commun.*, **24**, 2460 (1959).

¹²¹ R. E. Tedeschi, U.S. Pat. 2,997,422 [*C.A.*, **56**, 1392 (1962)].

¹²² K. B. Wiberg and A. J. Ashe, III, *J. Amer. Chem. Soc.*, **90**, 63 (1968).

¹²³ J. Warkentin, E. Singleton, and J. F. Edgar, *Can. J. Chem.*, **43**, 3456 (1965).

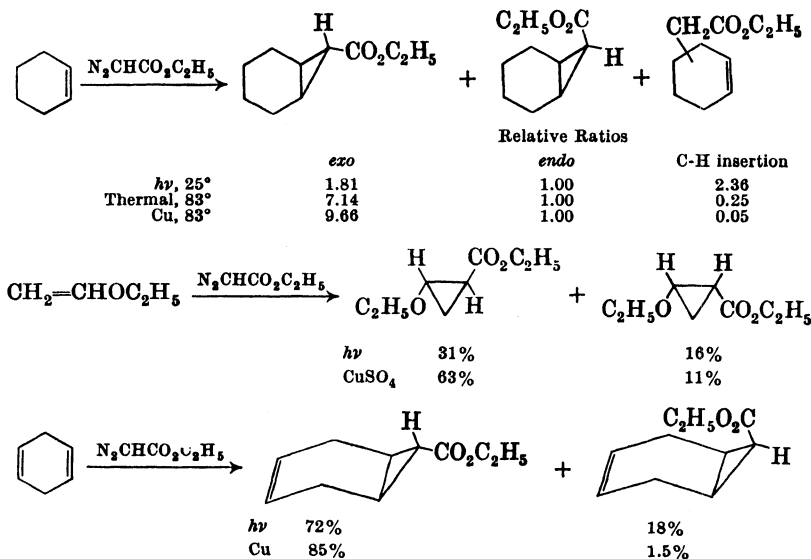
¹²⁴ G. E. Hall and J. P. Ward, *Tetrahedron Lett.*, **1965**, 437.

^{124a} S. H. Graham, D. M. Pugh, and A. J. S. Williams, *J. Chem. Soc., C*, **1969**, 68.

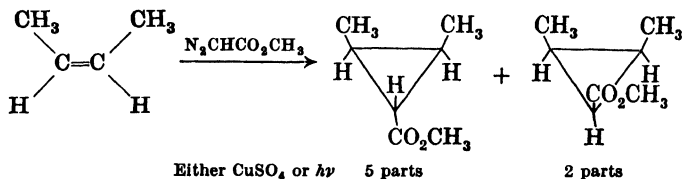
¹²⁵ G. L. Krueger, F. Kaplan, M. Orchin, and W. H. Faul, *Tetrahedron Lett.*, **1965**, 3979.

¹²⁶ W. H. Nutting, H. Rapoport, and L. Machlis, *J. Amer. Chem. Soc.*, **90**, 6434 (1968).

obtained in nearly equal amounts. Examples include the products from butadiene,¹²⁷⁻¹²⁹ bicyclohexenyl,¹³⁰ and *cis*-5-decene.⁹¹ (Equations on p. 227.) The ratio of the two isomers formed also depends on the experimental conditions. The tendency toward formation of the less hindered product is more pronounced in metal-catalyzed and thermal reactions than in photolytic reactions, as illustrated by reactions with cyclohexene,⁵⁹



vinyl ether,⁸³ and 1,4-cyclohexadiene.¹⁰⁷ The ratios of cyclopropane isomers obtained from *cis*-2-butene⁸⁵ and from butadiene¹²⁷⁻¹²⁹ seem to be unaffected by changes in conditions.



The effect of catalyst structure on product configuration has been examined in Moser's study of hydrocarbon-soluble complexed copper(I) catalysts.⁵⁹ It was found that the size and electronic effect of the complexing agent influenced the stereochemical outcome of the reaction of

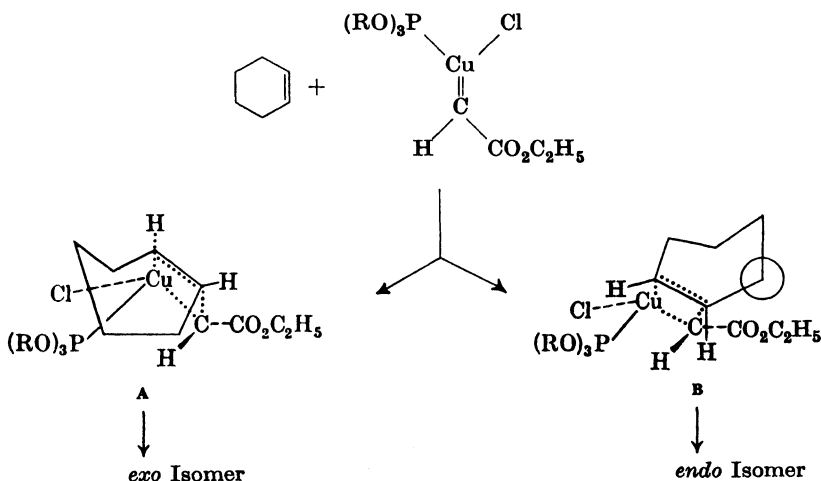
¹²⁷ E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Ann.*, **682**, 1 (1965).

¹²⁸ I. S. Lishanskii, A. G. Zak, I. A. D'yakonov, and T. G. Alieva, *J. Org. Chem. USSR (Engl. Transl.)*, **1**, 1199 (1965) [*C.A.*, **63**, 13093 (1965)].

¹²⁹ J. A. Landgrebe and L. W. Becker, *J. Org. Chem.*, **33**, 1173 (1968).

¹³⁰ P. Besinet, R. Fraisse, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, **1960**, 1377.

diazoacetic ester with cyclohexene. For a series of soluble trialkyl and triaryl phosphite-copper(I) chloride complexes it was found that an increase in the bulk of the alkyl groups in the trialkyl phosphite, $(RO)_3P$, resulted in a highly reproducible decrease in the *exo/endo* ratio as follows: R = methyl (8.18), ethyl (6.45), *n*-propyl (6.60), isopropyl (6.86), *n*-butyl (6.55), neopentyl (6.25), *t*-butyl (5.72), *t*-amyl (5.52), phenyl (4.87). For comparison, uncomplexed copper(I) chloride gave a ratio of 3.54. This trend was tentatively rationalized in terms of the following assumed transition-state geometries in each of which steric interaction between the trialkyl phosphite ligand and the carbethoxyl function has been minimized by arranging these groups *trans* to each other. Other things being equal,



the steric interaction of the carbethoxyl group and hydrogen in structure A would give a lower-energy transition state than the interaction of the carbethoxyl group with the encircled methylene group of the cyclohexene ring in structure B, thus favoring formation of the *exo* isomer. However, as the size of the $(RO)_3P$ group increases, interaction with the cyclohexene ring would raise the energy of A (but not of B), and decrease the rate of formation of the *exo* isomer. This hypothesis obviously requires further experimental test.

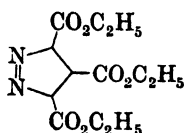
In a series of *p*-substituted triaryl phosphite-copper(I) chloride complexes in which the steric effect at the copper atom was kept constant and only the electronic effect of the aryl group changed, the *exo/endo* ratio in the reaction with cyclohexene was decreased by electron-withdrawing substituents.⁵⁹ Further work with soluble catalysts would seem to be the most promising approach to control of the stereochemistry of diazoacetic ester additions.

SCOPE AND LIMITATIONS

The reactions with diazoacetic esters have found general utility as a synthetic procedure for the preparation of cyclopropanes, cyclopropenes, cycloheptatrienes, azulenes, and tropolones. The reaction may eventually prove to be useful for preparing bicyclobutane derivatives. The carbalkoxy group in the reaction products can be transformed into a variety of other functions, and therefore the reaction constitutes an alternative to the Simmons-Smith reaction or the reaction of other carbenes or carbenoids with double, triple, and aromatic bonds to form substituted cyclopropanes.

Before the introduction of spectroscopic methods, the diazoacetic ester reaction was frequently used to determine the substitution pattern of double bonds. For instance, Buchner used the reaction of ethyl diazoacetate with camphene followed by hydrolysis and oxidation of the initial product to yield 1,1,2-cyclopropanetricarboxylic acid as a proof for the presence of the $R_2C=CH_2$ group.²¹ This use of the reaction has also been made in chlorophyll chemistry.¹³¹

Unsaturated compounds usually react with diazoacetic esters to give cyclopropane derivatives unless a faster side reaction intervenes. The most common side reaction in catalyzed reactions is the formation of maleate and fumarate esters from 2 molecules of diazoacetic ester. These by-products, diethyl maleate and diethyl fumarate, react with ethyl diazoacetate to give triethyl pyrazoline-3,4,5-tricarboxylate.^{70, 132}



In both photochemical¹³³ and catalytic reactions,^{134, 135} tetramers of carbalkoxy carbenes are also formed. Compounds containing OH, SH, NH, or $C\equiv CH$ groups often undergo alkylation, either by reaction of the diazo compound with an acidic hydrogen atom or by an insertion reaction of a carbalkoxy carbene, rather than addition (see, for example, allyl

¹³¹ (a) A. Stoll and E. Wiedemann in L. Zechmeister, Ed., *Progress in Chemistry of Organic Natural Products*, Vol. 1, p. 159, Springer-Verlag, Vienna, 1938. (b) H. J. Callot and A. W. Johnson, *Chem. Commun.*, **1969**, 749.

¹³² T. Curtius and E. Bourcart, *J. Prakt. Chem.*, [2] **91**, 47 (1915).

¹³³ G. O. Schenck and A. Ritter, *Tetrahedron Lett.*, **1968**, 3189.

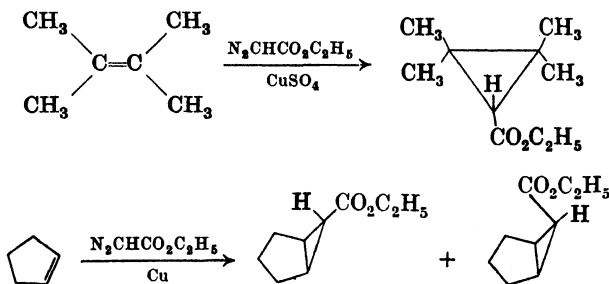
¹³⁴ J. Owen and J. L. Simonsen, *J. Chem. Soc.*, **1932**, 1424.

¹³⁵ J. Owen and J. L. Simonsen, *J. Chem. Soc.*, **1933**, 1225.

alcohol,^{136, 137} benzyl alcohol,¹³⁶ thiophenol,¹³⁸ phenol,¹³⁹ and 1-octyne¹⁴⁰). Allylic or benzylic halides (e.g., allyl chloride,¹⁴¹ bromide,¹⁴¹⁻¹⁴³ and iodide,^{143, 144} crotyl chloride,¹⁴³ benzyl bromide,¹⁴⁵ benzal chloride,¹⁴⁶ 9-phenyl-9-bromofluorene,¹⁴⁷ triphenylmethyl bromide,¹⁴⁵ and others listed in the tables) give carbon-halogen insertion products some of which rearrange.^{145, 147} In thermal reactions, pyrazolines or pyrazoles may be formed by addition of the diazo group to the unsaturated center. In the following discussion it should be borne in mind that optimum conditions for most of the reactions have not been determined.

Alkenes, Alkadienes, and Allenes

Most simple olefins react with diazoacetic esters to give moderate to good yields of cyclopropanecarboxylates. Examples are *cis*-2-butene (39%),⁸⁵ 2-methyl-2-butene (32%),¹⁴⁸ cyclopentene (30%),¹⁰⁸ tetramethylethylene (57%),¹⁴⁹ 1-hexene (50%),¹⁴⁹ cyclohexene (66%),¹⁰⁸ 1-heptene



¹³⁶ T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and T. Shimizu, *J. Org. Chem.*, **33**, 544 (1968).

¹³⁷ I. A. D'yakonov and N. D. Pirogova, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 2201 (1951) [*C.A.*, **46**, 6590 (1952)].

¹³⁸ E. Müller and A. Freytag, *J. Prakt. Chem.*, [2] **146**, 56 (1936).

¹³⁹ E. Baltazzi, *Compt. Rend.*, **241**, 321 (1955).

¹⁴⁰ V. K. Jones and A. J. Deutschman, Jr., *J. Org. Chem.*, **30**, 3978 (1965).

¹⁴¹ I. A. D'yakonov and N. B. Vinogradova, *J. Gen. Chem. USSR (Engl. Transl.)*, **22**, 1393 (1952) [*C.A.*, **47**, 4293 (1953)].

¹⁴² I. A. D'yakonov and N. B. Vinogradova, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 933 (1951) [*C.A.*, **46**, 440 (1952)].

¹⁴³ D. D. Phillips, *J. Amer. Chem. Soc.*, **76**, 5385 (1954).

¹⁴⁴ I. A. D'yakonov and N. B. Vinogradova, *J. Gen. Chem. USSR (Engl. Transl.)*, **23**, 63 (1953) [*C.A.*, **48**, 1256 (1954)].

¹⁴⁵ I. A. D'yakonov and N. B. Vinogradova, *J. Gen. Chem. USSR (Engl. Transl.)*, **23**, 255 (1953) [*C.A.*, **48**, 3318 (1954)].

¹⁴⁶ C. D. Gutsche and M. Hillman, *J. Amer. Chem. Soc.*, **76**, 2236 (1954).

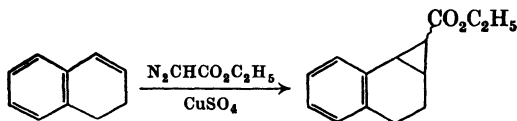
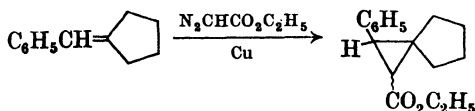
¹⁴⁷ I. A. D'yakonov and T. V. Domareva, *J. Gen. Chem. USSR (Engl. Transl.)*, **29**, 3064 (1959) [*C.A.*, **54**, 14211 (1960)].

¹⁴⁸ P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **30**, 1681 (1965).

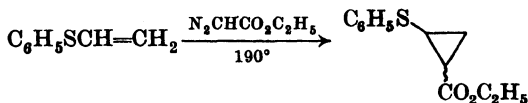
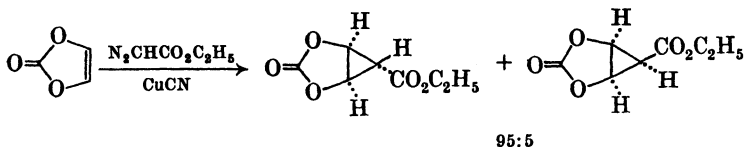
¹⁴⁹ A. P. Meshcheryakov and I. E. Dolgii, *Bull. Acad. Sci. USSR (Engl. Transl.)*, **1960**, 864 [*C.A.*, **54**, 24436 (1960)].

(67%),¹⁴⁹ norbornene (70%),^{100, 101} *trans*-4-octene (62%),^{87, 90} and camphene (73%).²¹

The yields are equally good if the double bond is conjugated with an aromatic ring as in styrene (79%),¹¹² α -methylstyrene (86%),¹⁵⁰ 1,2-dihydronaphthalene (48%),¹⁵¹ β,β -dimethylstyrene (63%),¹²⁰ benzylidene-cyclopentane (46%),¹⁵² vinylferrocene (67%),¹⁵³ *trans*-stilbene (81%),⁹² 1,1-diphenylethylene (46%),¹⁵⁴ and 1-vinylnaphthalene (47%).¹⁵⁰



Heteroatoms may be attached to the double bond as in vinyl acetate (67%),¹⁵⁵ vinylene carbonate (5%),¹⁰⁶ trimethylvinylsilane (12%),¹⁵⁶ butyl vinyl ether (84%),¹⁵⁷ phenyl vinyl ether (84%),¹⁵⁸ and phenyl vinyl sulfide (76%).¹⁵⁰



¹⁵⁰ C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.*, **5**, 1243 (1962).

¹⁵¹ R. Huisgen and G. Juppe, *Chem. Ber.*, **94**, 2332 (1961).

¹⁵² J. Šmejkal and J. Farkaš, *Collect. Czech. Chem. Commun.*, **28**, 1557 (1963).

¹⁵³ H. Mechtler and K. Schlögl, *Monatsh. Chem.*, **97**, 754 (1966).

¹⁵⁴ H. M. Walborsky and F. M. Hornyak, *J. Amer. Chem. Soc.*, **77**, 6026 (1955).

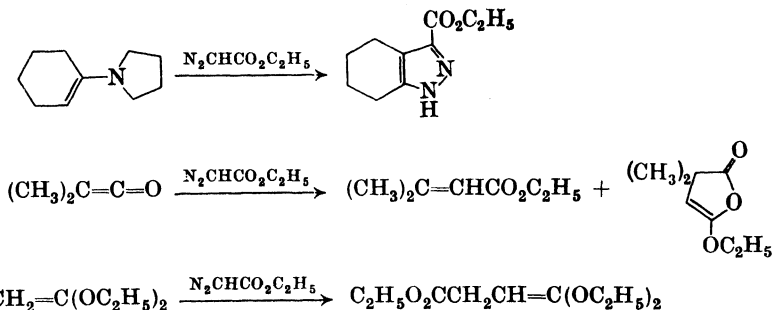
¹⁵⁵ K. B. Wiberg and R. K. Barnes, *J. Org. Chem.*, **23**, 299 (1958).

¹⁵⁶ I. A. D'yakonov, G. V. Golodnikov, and I. B. Repinskaya, *J. Gen. Chem. USSR (Engl. Transl.)*, **35**, 2169 (1965) [*C.A.*, **64**, 11238 (1966)].

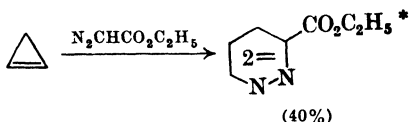
¹⁵⁷ I. A. D'yakonov, *J. Gen. Chem. USSR (Engl. Transl.)*, **19**, a-355 (1949) [*C.A.*, **44**, 1916 (1950)].

¹⁵⁸ J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965).

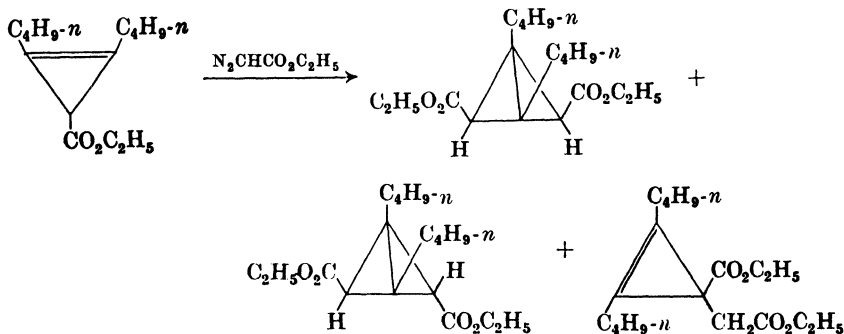
Some heteroatom substituted olefins, such as enamines,¹⁵⁹ ketenes,¹⁶⁰ and ketene acetals,¹⁶¹ give products other than cyclopropane derivatives.



Although cyclopropene itself does not yield a bicyclobutane carboxylate,¹⁶² cyclopropenes derived from the reaction of alkynes with diazo-



acetic ester usually do react to give bicyclobutane derivatives.¹⁶³



If strongly electron-withdrawing groups are attached to the double bond, cyclopropane formation may be too slow to compete successfully

* The structure of this compound is uncertain.

¹⁵⁹ F. Piozzi, A. Umami-Ronchi, and L. Merlini, *Gazz. Chim. Ital.*, **95**, 814 (1965) [*C.A.*, **64**, 725 (1966)].

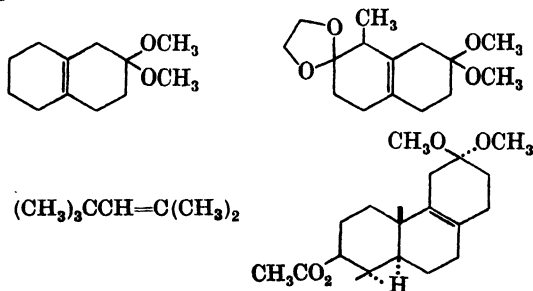
¹⁶⁰ A. S. Kende, *Chem. & Ind. (London)*, **75**, 1053 (1956).

¹⁶¹ M. F. Dull and P. G. Abend, *J. Amer. Chem. Soc.*, **81**, 2588 (1959).

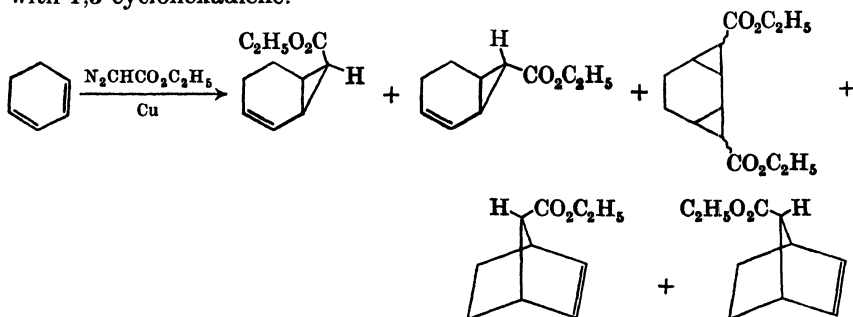
¹⁶² K. B. Wiberg and W. J. Bartley, *J. Amer. Chem. Soc.*, **82**, 6375 (1960).

¹⁶³ I. A. D'yakonov, V. V. Razin, and M. I. Komendantov, *Dokl. Akad. Nauk SSSR (Engl. Transl.)*, **177**, 1027 (1967) [*C.A.*, **68**, 49163y (1968)].

with maleate and fumarate formation or addition to produce nitrogen-containing products. 2-Trifluoromethylpropene,¹⁶⁴ β -chlorostyrene,¹⁶⁵ β,β -dichlorostyrene,¹⁶⁵ and $\text{CH}_2=\text{CHPO}(\text{OC}_2\text{H}_5)_2$ ¹⁶⁶ fall into this category. There are even examples in which steric interactions have presumably made the normal cyclopropane formation too slow to be observed as in the four compounds below.^{167, 168}



From polyolefinic compounds it is possible to isolate either mono or bis adducts. Reactions with conjugated dienes usually give 1,2-addition products, although small amounts of 1,4 addition have been obtained with 1,3-cyclohexadiene.¹¹¹



In dienes with nonequivalent double bonds, the effect of electronic and steric factors is apparently finely balanced. The vinyl group, being least hindered, reacts more readily than more highly substituted double bonds^{167, 169} but, if neither of the double bonds is mono-substituted, then electronic factors apparently determine the major product.¹⁷⁰

¹⁶⁴ F. Misani, L. Speers, and A. M. Lyon, *J. Amer. Chem. Soc.*, **78**, 2801 (1956).

¹⁶⁵ J. Farkaš and J. J. K. Novák, *Collect. Czech. Chem. Commun.*, **25**, 1815 (1960).

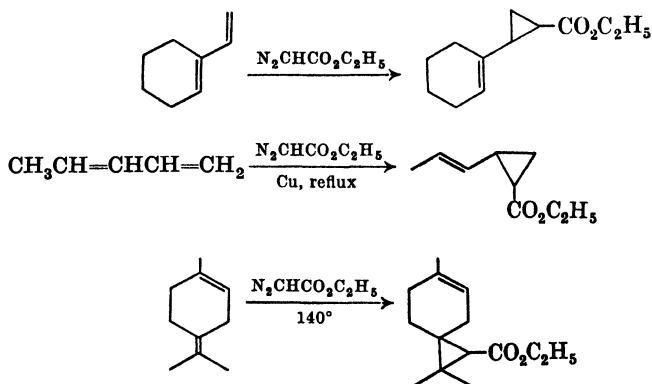
¹⁶⁶ A. N. Pudovik and R. D. Gareev, *J. Gen. Chem. USSR (Engl. Transl.)*, **33**, 3370 (1963) [*C.A.*, **60**, 4178 (1964)].

¹⁶⁷ F. B. LaForge, W. A. Gersdorff, N. Green, and M. S. Schechter, *J. Org. Chem.*, **17**, 381 (1952).

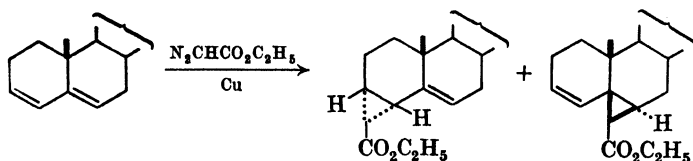
¹⁶⁸ R. D. Stipanovic and R. B. Turner, *J. Org. Chem.*, **33**, 3261 (1968).

¹⁶⁹ G. Stork, *Abstr. Org. Chem. Symposium*, Tempe, Ariz., 1965, p. 35.

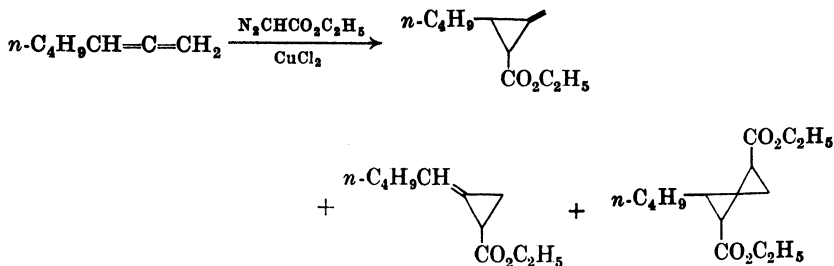
¹⁷⁰ H. Staudinger, O. Muntwyler, L. Ruzicka, and S. Seibt, *Helv. Chim. Acta*, **7**, 390 (1924).



The reactions of $\Delta^{3,5}$ -steroid dienes have been claimed to be highly stereoselective.¹⁷¹⁻¹⁷⁴



Allenes react to give methylenecyclopropanes and spirocyclopentane derivatives.¹⁷⁵



An interesting possibility for stereochemical control and increased yields is to make the alkene addition an intramolecular reaction by building the diazoacetic ester into the molecule. A few reactions of this

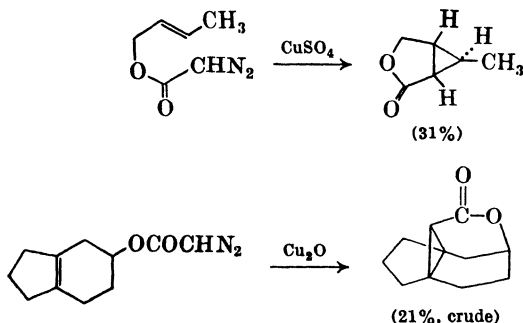
¹⁷¹ L. H. Knox, U.S. Pat. 3,079,406 [*C.A.*, **59**, 2910 (1963)].

¹⁷² L. H. Knox, U.S. Pat. 3,080,385 [*C.A.*, **59**, 14086 (1963)].

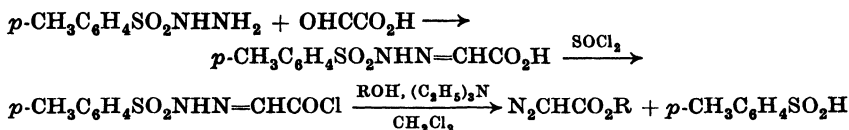
¹⁷³ L. H. Knox, U.S. Pat. 3,080,386 [*C.A.*, **60**, 626 (1964)].

¹⁷⁴ L. H. Knox, U.S. Pat. 3,080,387 [*C.A.*, **60**, 626 (1964)].

¹⁷⁵ Y. Vo-Quang, L. Vo-Quang, G. Emptoz, and P. Savignat, *Compt. Rend., Ser. C*, **262**, 220 (1966).

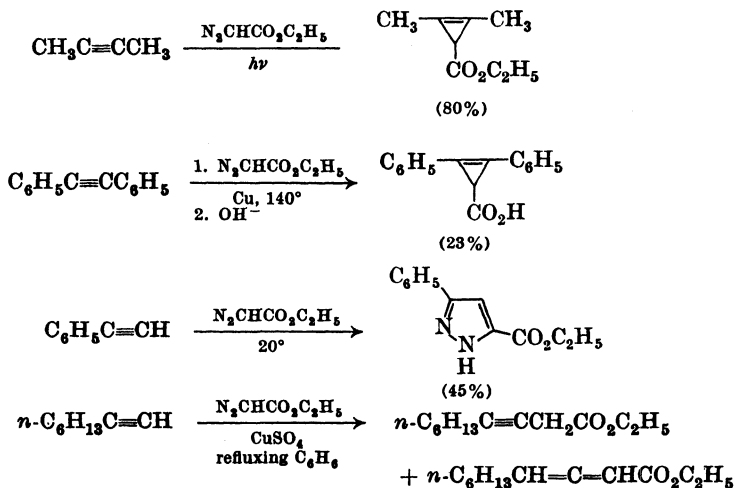


type have been carried out,^{79, 176} and House has developed a general synthesis for introducing the diazoacetic ester grouping into an alkenol.⁷⁹



Alkynes and Alkenynes

In the presence of a catalyst or light, nonterminal acetylenes give poor to moderate yields of cyclopropenecarboxylic esters with diazoacetic esters.^{85, 177} 4-Octyne, either in the presence of a copper catalyst or when heated without a catalyst, gives the cyclopropene derivative.⁸² However, in the absence of a catalyst or light, pyrazoles are often formed instead

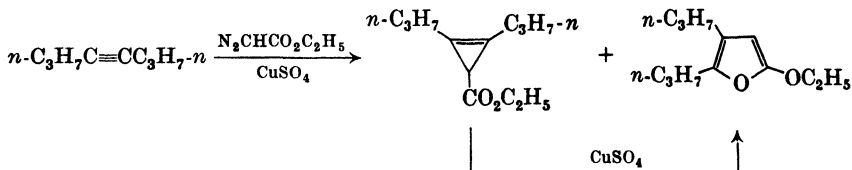


¹⁷⁶ W. Kirmse and H. Dietrich, *Chem. Ber.*, **98**, 4027 (1965).

¹⁷⁷ R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).

of cyclopropenes.¹⁷⁸ Terminal acetylenes can also give by-products from insertion of a carbalkoxy carbene.¹⁴⁰

In the reactions catalyzed by copper(II) sulfate a second product is often formed which, after some confusion, was found to be a furan derivative¹⁷⁹ resulting from isomerization of the initially formed cyclopropenecarboxylate.⁸¹ In separate experiments, D'yakonov showed that



the cyclopropenecarboxylate from 4-octyne is isomerized to the furan by copper(II) sulfate.⁸¹ The same alkyne under photochemical conditions gave no furan, but did give insertion products in addition to the cyclopropenecarboxylate.¹⁸⁰ Presumably the furan derivatives produced from other alkynes also arise by copper(II) sulfate-catalyzed rearrangement of an initially formed cyclopropenecarboxylate. The amount of copper(II) sulfate used is critical in determining the extent of rearrangement and, consequently, the course of the reaction. For instance with 1-phenylpropyne, whereas 0.001 mole of copper(II) sulfate per mole of diazoacetic ester gave almost exclusively the cyclopropenecarboxylate, only 0.008 mole of the catalyst was required for exclusive formation of the furan derivative. Mixtures of cyclopropenecarboxylate and furan were formed with 0.004 mole of catalyst.¹⁸¹

With the few alkenynes which have been studied, catalytic reactions take place at both multiple bonds, preference being shown for addition to the double bond.^{182, 183} However, in some competitive experiments with mixtures of alkenes and alkynes (*cis*-2-hexene + 2-hexyne, *trans*-2-hexene + 2-hexyne, *trans*-4-octene + 4-octyne), alkynes were observed to react faster in catalytic reactions and slower in photochemical reactions.^{183a}

¹⁷⁸ W. Kirmse and L. Horner, *Ann.*, **614**, 1 (1958).

¹⁷⁹ R. Breslow and D. Chipman, *Chem. & Ind.* (London), **1960**, 1105.

¹⁸⁰ H. Lind and A. J. Deutschman, Jr., *J. Org. Chem.*, **32**, 326 (1967).

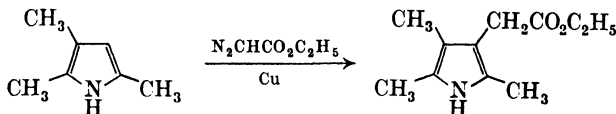
¹⁸¹ I. A. D'yakonov, M. I. Komendantov, and S. P. Korshunov, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 912 (1962) [*C.A.*, **58**, 2375 (1963)].

¹⁸² L. P. Danilkina and I. A. D'yakonov, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 1 (1966) [*C.A.*, **64**, 14101 (1966)].

¹⁸³ I. A. D'yakonov and L. P. Danilkina, *J. Gen. Chem. USSR (Engl. Transl.)*, **34**, 738 (1964) [*C.A.*, **60**, 15745 (1964)].

^{183a} I. A. D'yakonov, M. I. Komendantov, L. P. Danilkina, R. N. Gmyzina, T. S. Smirnova, and A. F. Vitenberg, *J. Org. Chem. USSR (Engl. Transl.)*, **5**, 368 (1969) [*C.A.*, **70**, 105633 g (1969)].

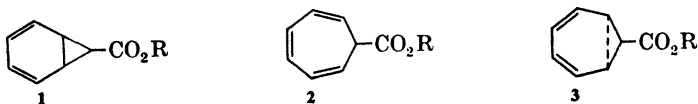
presence of copper(I) bromide to give cyclopropane derivatives. (See Table V.) Pyrroles normally undergo α substitution,¹⁸⁶ while indoles yield β -substitution products.¹⁸⁷ If some positions in the pyrrole ring are occupied by alkyl groups, the acetic acid side chain is introduced at an unblocked position.¹⁸⁶



Benzene and Benzene Derivatives

Although the reaction of diazoacetic esters with aromatic hydrocarbons was a subject of early investigation, it has recently attracted renewed interest as a means of synthesis of azulenes^{188, 189} and tropolones¹⁹⁰ and as one aspect of the norcaradiene-cycloheptatriene valence tautomer problem.¹⁹¹ Most of the reactions with aromatic compounds have been thermal or photochemical rather than catalytic, and therefore presumably involve carbene intermediates. The structure of the products and the nature of the bonding in them have been subjects of continuing investigation, and the difficulties may be illustrated with benzene.

Buchner originally assigned the structure 1 to the product from diazoacetic ester and benzene³ but later found that the product gave five acids on hydrolysis.¹⁰ (Much later Doering pointed out that one of the acids was a mixture of two others.¹⁹²) One acid was assigned the structure corresponding to 1 while the others were assigned cycloheptatriene carboxylic acid structures. The structures of the methyl esters of the four acids were reinvestigated by means of the Diels-Alder reaction with



¹⁸⁶ C. D. Nenitzescu and E. Solomonica, *Ber.*, **64**, 1924 (1931).

¹⁸⁷ S. S. Nametkin, N. N. Mel'nikov, and K. S. Bokarev, *Zh. Prikl. Khim.*, **29**, 459 (1956) [*C.A.*, **50**, 13867 (1956)].

¹⁸⁸ (a) E. Heilbronner in D. Ginsburg, Ed., *Non-benzenoid Aromatic Compounds*, p. 171, and references cited therein, Interscience publishers, New York, 1959. (b) W. Keller-Schierlein and E. Heilbronner, *ibid.*, p. 277, and references cited there.

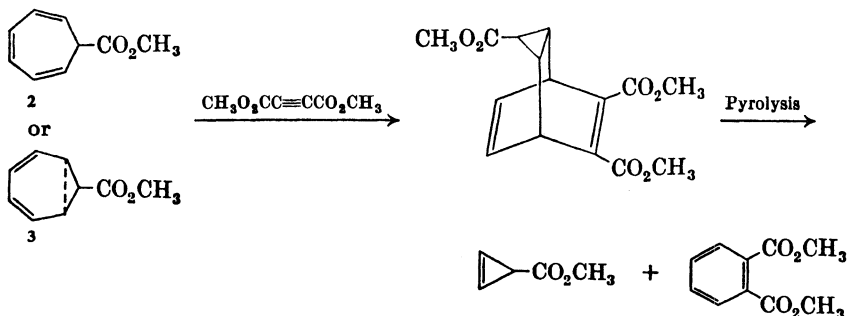
¹⁸⁹ W. Treibs, W. Kirchhof, and W. Ziegenbein, *Fortsch. Chem. Forsch.*, **3**, 334 (1955).

¹⁹⁰ T. Nozoe in L. Zechmeister, Ed., *Progress in the Chemistry of Organic Natural Products*, Vol. 13, p. 232, Springer-Verlag, Vienna, 1956.

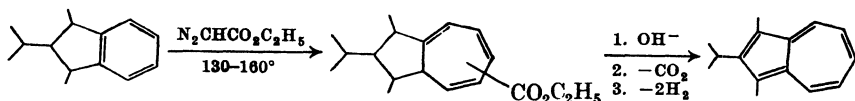
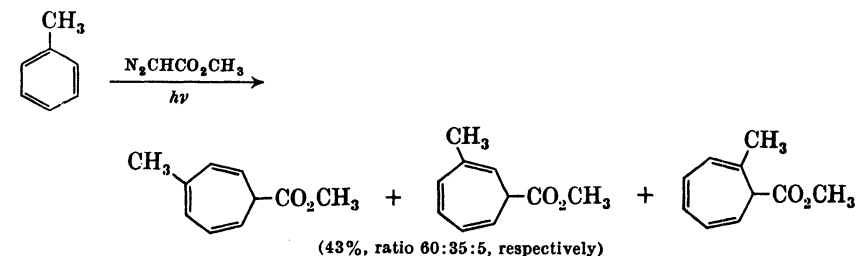
¹⁹¹ G. Maier, *Ang. Chem. Int. Ed. Engl.*, **6**, 402 (1967).

¹⁹² W. von E. Doering, G. Lafer, R. Vonderwahl, N. F. Chamberlain, and R. B. Williams, *J. Amer. Chem. Soc.*, **78**, 5448 (1956).

dimethyl acetylenedicarboxylate,^{192, 193} a reaction which is generally used for determining the relative positions of substituents in products from diazoacetic esters and aromatic compounds.*^{193, 194} Each of the four esters gave a single adduct differing from the others and each containing a cyclopropane ring. Pyrolysis of each adduct gave a phthalate ester from which the structure of the adduct could be deduced. The reaction is illustrated for one of the esters.



However, the nmr spectra of the methyl esters excluded the presence of a cyclopropane-containing norcaradiene structure 1, and suggested either the planar pseudoaromatic structure 3 or the nonplanar cycloheptatriene structure 2. For some of the simpler alkylbenzenes (*e.g.*, toluene, ethylbenzene, the xylenes), the relative positions of the substituents in the products have been determined by the acetylenedicarboxylate procedure.*



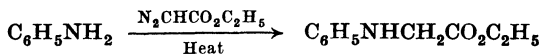
* The validity of this method depends on there being no tautomerization involving hydrogen shifts after the initial reaction of diazoacetic ester and the aromatic compound.

¹⁹³ K. Alder, H. Jungen, and K. Rust, *Ann.*, **602**, 94 (1957).

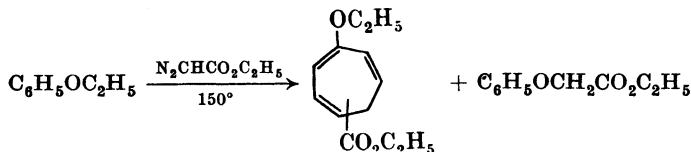
¹⁹⁴ K. Alder, R. Muders, W. Krane, and P. Wirtz, *Ann.*, **627**, 59 (1959).

All possible substitution products have been found with steric effects apparently influencing the relative yields. The reaction with toluene illustrates this point.¹⁹⁴ With other substituted benzene derivatives the relative positions of the carbalkoxyl group and the substituents have not been determined. In many azulene syntheses^{188, 189} the products of the diazoacetic ester reaction have been dehydrogenated without investigation of the structures of intermediates.¹⁹⁵

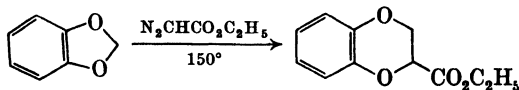
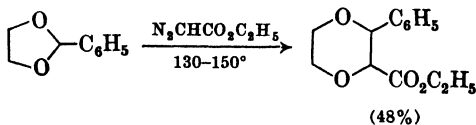
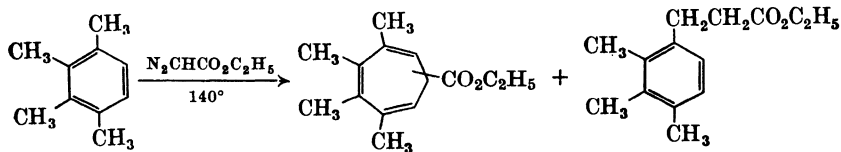
There are several important side reactions with benzene derivatives. Hydroxyl, amino, or sulfhydryl groups are normally alkylated by the diazoacetic ester as shown for aniline.¹⁹⁶



With phenolic ethers the O-alkyl group is often exchanged for the grouping $\text{O}-\text{CH}_2\text{CO}_2\text{R}$.¹⁹⁷



Insertion reactions also are responsible for side products,¹⁹⁸ or for the major product from substrates containing the $-\text{O}-\text{C}-\text{O}-$ group.^{146, 199}



¹⁹⁵ B. R. Pai, P. S. Santhanam, and M. Srinivasan, *Tetrahedron*, **22**, 3417 (1966).

¹⁹⁶ T. Curtius, *J. Prakt. Chem.*, [2] **38**, 396 (1888).

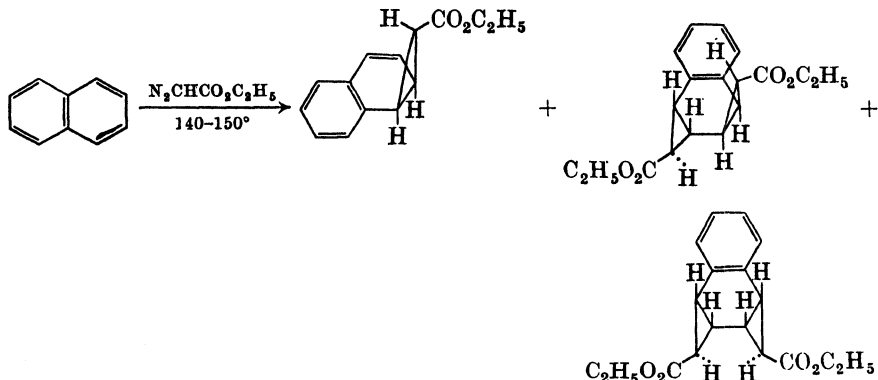
¹⁹⁷ G. B. R. de Graaff, J. H. van Dijk-Rothuis, and G. van de Kolk, *Rec. Trav. Chim.*, *Pay-Bas*, **74**, 143 (1955).

¹⁹⁸ L. I. Smith and C. L. Agre, *J. Amer. Chem. Soc.*, **60**, 648 (1938).

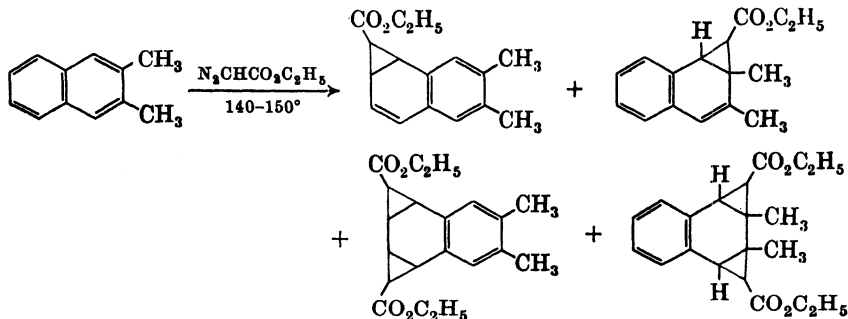
¹⁹⁹ A. W. Johnson, A. Langemann, and J. Murray, *J. Chem. Soc.*, **1953**, 2136.

Polynuclear Aromatic Compounds

In contrast to benzene, naphthalene reacts with ethyl diazoacetate to give stable cyclopropanecarboxylates: one mono- and two di-adducts are found.¹⁵¹



The configuration of the monoadduct was determined by oxidation studies, and the configurations of the diadducts were established by the successful resolution of one adduct. The isomer which could be resolved was assigned the *trans* configuration (all carboxymethyl groups were assumed to be *exo* in the diadducts). Substituted naphthalenes give mixtures of products in which both rings have been attacked.²⁰⁰

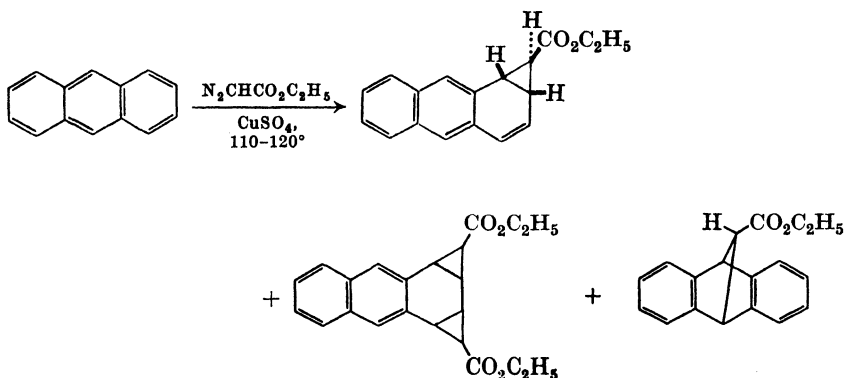


Whereas thermal decomposition of ethyl diazoacetate in the presence of anthracene gave only the monoadduct **4**,^{124a, 201} the copper(II) sulfate-catalyzed reaction gave three products including the compound derived from 1,4 addition.²⁰²

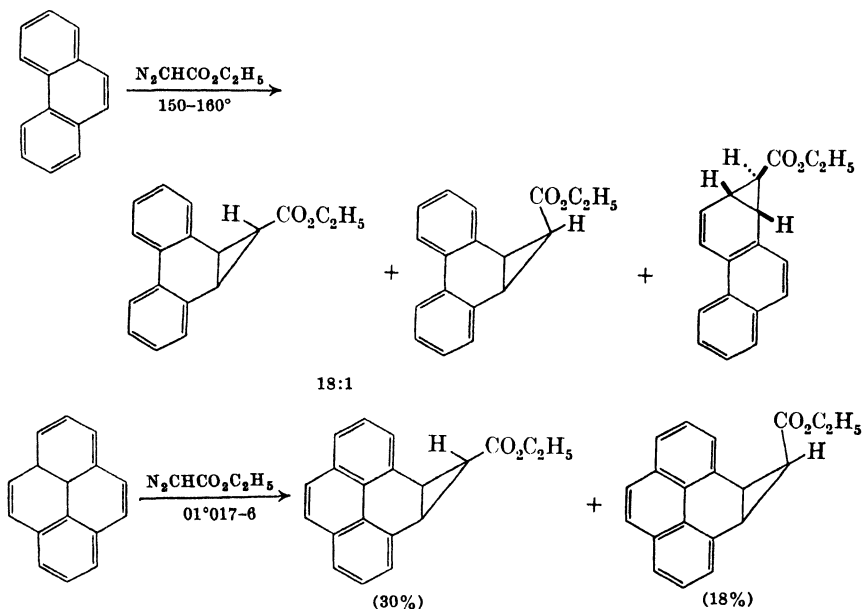
²⁰⁰ G. Juppe and R. Huisgen, *Ann.*, **646**, 1 (1961).

²⁰¹ G. M. Badger, J. W. Cook, and A. R. M. Gibb, *J. Chem. Soc.*, **1951**, 3456.

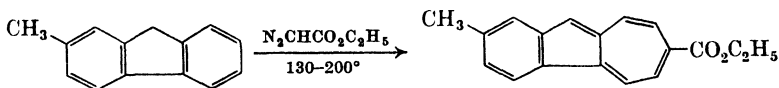
²⁰² T. V. Domareva-Mandel'shtam, I. A. D'yakonov, and L. D. Kristol, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 2223 (1966) [*C.A.*, **66**, 75833v (1967)]; I. A. D'yakonov, T. V. Domareva-Mandel'shtam, and K. K. Preobrazhenskii, *J. Org. Chem. USSR (Engl. Transl.)*, **5**, 1095 (1969) [*C.A.*, **71**, 70368r (1969)].



Thermal reactions of ethyl diazoacetate with phenanthrene^{124a} and pyrene²⁰³ gave the cyclopropanecarboxylates shown.



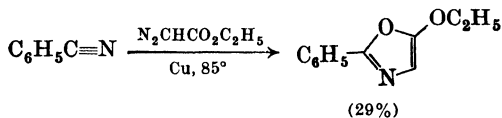
The reaction with fluorenes leads to benzazulene derivatives even if no dehydrogenating agent is added.²⁰⁴



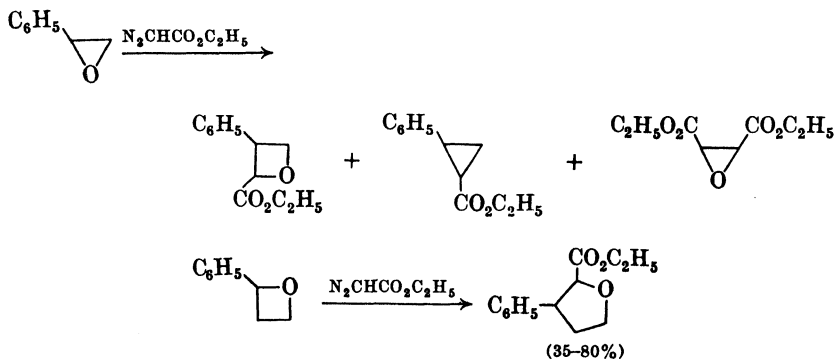
²⁰³ R. Munday and I. O. Sutherland, *J. Chem. Soc., C*, **1969**, 1427.

²⁰⁴ W. Treibs and C. Kurpjun, *Ann.*, **603**, 145 (1957).

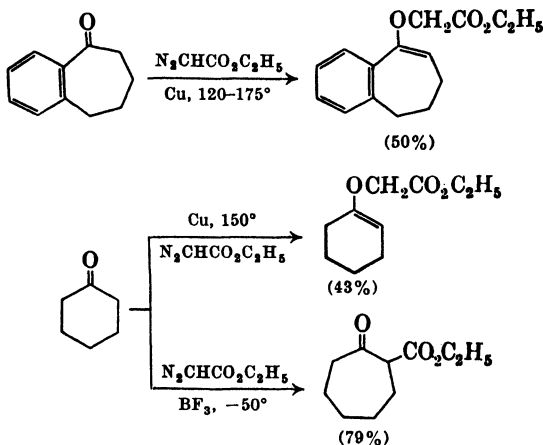
Nitriles can react to produce oxazoles.²⁰⁸



1,2-Epoxydes and oxetanes often react to give ring expanded products.¹¹⁹



Ketones can react to give enol ethers^{146, 209} or, in the presence of Lewis acids, β -keto esters.²¹⁰



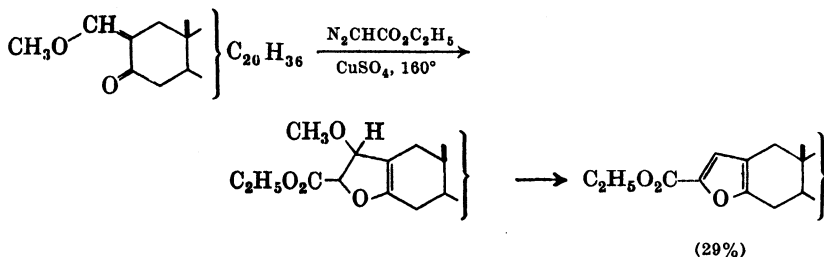
The addition of ethyl diazoacetate to α -methoxymethylene ketones gives furoic acid derivatives which can be hydrolyzed and decarboxylated to furnish furans.²¹¹

²⁰⁸ R. Huisgen, H. J. Sturm, and G. Binsch, *Chem. Ber.*, **97**, 2864 (1964).

²⁰⁹ M. S. Kharasch, T. Rudy, W. Nudenberg, and G. Büchi, *J. Org. Chem.*, **18**, 1030 (1953).

²¹⁰ W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

²¹¹ D. L. Storm and T. A. Spencer, *Tetrahedron Lett.*, **1967**, 1865.



STRUCTURE AND STEREOCHEMISTRY OF PRODUCTS

When the reaction with diazoacetic esters is used to form cyclopropane or cyclopropene derivatives, there are the problems of proving that the ring has been formed, locating the ring in polyunsaturated substrates, and determining the stereochemistry at the newly formed ring. The presence of a three-membered ring can often be detected spectroscopically. In the infrared region the cyclopropane C—H stretching frequency near 3090 cm^{-1} ,²¹² the ring deformation near 1020 cm^{-1} ,²¹² and the $3040\text{--}3055\text{ cm}^{-1}$ peak characteristic of a methylene group within a cyclopropane²¹³ are often useful. Peaks near 1008 and 1885 cm^{-1} have been attributed to the cyclopropene ring.^{85, 214, 215} In the near infrared region the first overtone at $\sim 6250\text{ cm}^{-1}$ and the combination peak at $\sim 4545\text{ cm}^{-1}$ of the C—H stretching vibration have often been used for identification of the cyclopropane ring.^{216–218} Although this spectral correlation is general,^{150, 216–218} cyclopropane derivatives not containing a methylene group may not exhibit a recognizable peak in the near infrared region.^{212, 217, 219} In the far infrared region, bands near $540\text{--}500$ and $471\text{--}464\text{ cm}^{-1}$ have been assigned to cyclopropane absorption.²¹⁸

The nmr spectra of cyclopropane derivatives frequently show high field absorption at $\delta -0.5$ to 1 ppm ^{220, 221} as well as the absence of low

²¹² H. E. Simmons, E. P. Blanchard, and H. D. Hartzler, *J. Org. Chem.*, **31**, 295 (1966).

²¹³ A. R. H. Cole, *J. Chem. Soc.*, **1954**, 3807, 3810.

²¹⁴ P. K. Faure and J. C. Smith, *J. Chem. Soc.*, **1956**, 1818.

²¹⁵ I. A. D'yakonov and M. I. Komendantov, *J. Gen. Chem. USSR (Engl. Transl.)*, **33**, 2387 (1963) [*C.A.*, **59**, 15210 (1963)].

²¹⁶ (a) W. H. Washburn and M. J. Mahoney, *J. Amer. Chem. Soc.*, **80**, 504 (1958). (b) P. G. Gassman and W. M. Hooker, *J. Amer. Chem. Soc.*, **87**, 1079 (1965), and references cited therein. (c) P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966). (d) P. G. Gassman, F. J. Williams, and J. Seter, *J. Amer. Chem. Soc.*, **90**, 6893 (1968).

²¹⁷ H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964).

²¹⁸ J. P. Phillips, *Spectra-Structure Correlation*, Academic Press, New York, 1964.

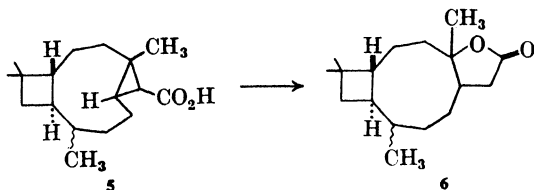
²¹⁹ E. W. Warnhoff and V. Dave, *Can. J. Chem.*, **44**, 621 (1966).

²²⁰ N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, p. 190, Holden-Day, Inc., San Francisco, Calif., 1964.

²²¹ R. R. Kostikov, V. B. Lebedev, and I. A. D'yakonov, *Dokl. Akad. Nauk SSSR (Engl. Transl.)*, **166**, 253 (1966) [*C.A.*, **64**, 18729 (1966)].

field absorption due to olefinic or aromatic hydrogen atoms which were present in the starting materials.

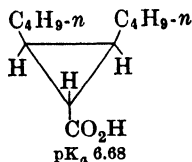
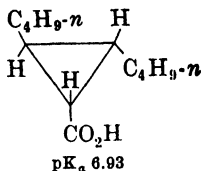
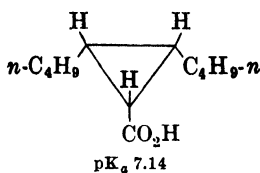
Chemical methods can also be of use if spectroscopic methods are inconclusive. Cyclopropanecarboxylates are transformed into γ -lactones by treatment with strong acids such as hydrobromic acid in acetic acid.^{101, 153, 219, 222} Thus the caryophyllene derivative **5** gave the lactone



6.²¹⁹ Vigorous oxidation of a cyclopropane compound to form a readily identifiable carboxyl derivative of cyclopropane has also been used.¹¹⁶

A number of general methods have been used to assign stereochemistry about the cyclopropane ring.

1. Acidity Measurements. The accumulation of bulky substituents in the vicinity of a carboxyl group has a pronounced weakening effect on the acidity of the carboxyl function, presumably due to steric hindrance to solvation of the carboxylate anion.²²³ This fact has been used to assign configurations to isomeric cyclopropanecarboxylic acids for which the various isomers are available and differ in steric hindrance.^{91, 92, 118, 224, 225} On the basis of their acidities⁹¹ the acids obtained from *cis*- and *trans*-5-decene have been assigned the configurations shown.



2. Esterification and Hydrolysis Rates. Another result of the steric effect mentioned above is the more rapid formation and saponification of the less hindered *trans* cyclopropanecarboxylic ester compared to the more crowded *cis* isomer.^{83, 116, 148, 226}

²²² J. Meinwald, A. Lewis, and P. G. Gassman, *J. Amer. Chem. Soc.*, **84**, 977 (1962).

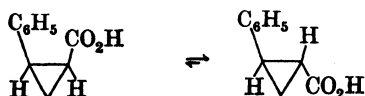
²²³ G. S. Hammond in M. S. Newman, Ed., *Steric Effects in Organic Chemistry*, p. 426, John Wiley & Sons, New York, 1956.

²²⁴ R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962).

²²⁵ T. Šmejkal, J. Jonáš, and J. Farkaš, *Collect. Czech. Chem. Commun.*, **25**, 1746 (1960).

²²⁶ J. A. van Auken and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962).

3. Epimerization. A third consequence of different degrees of steric hindrance arises when a carboxyl derivative can be epimerized *via* its enol to form a mixture of epimers in which the predominant stereoisomer will be the sterically less crowded one. The acid chloride or the ester is the most convenient carboxyl derivative for epimerization (refs. 113, 114, 120, 181, 215, 219). *cis*-2-Phenylcyclopropanecarboxylic acid is readily converted to the less crowded *trans* acid through the acid chloride.^{113, 227} When this method is used, care must be taken to use conditions that will ensure that enolization and consequent equilibration have occurred.^{91, 150}



4. Ultraviolet Spectroscopy. A fourth consequence of the differing steric environments is seen in the ultraviolet spectra of appropriate cyclopropane derivatives. For cyclopropanes bearing substituents which absorb ultraviolet light, the isomer with the more crowded substituents (more *cis* substituents) is less able to assume the most favorable arrangement for electronic interaction of the substituents with the cyclopropane ring. Hence the more crowded epimer will have a lower extinction coefficient and the absorption maximum will be shifted to shorter wavelength. This method has been used successfully for products from substituted styrenes.^{115, 117, 120}

5. Physical Properties. Certain other less reliable differences in stereoisomers also depend on the steric environment of the isomers. In chromatography the stereoisomer with the carboxyl group more shielded by *cis* substituents is usually eluted more rapidly.⁸³ The conformational rule²²⁸ has been invoked on occasion to support stereochemical assignment. The isomer having the greater enthalpy and hence higher density and refractive index usually has the more compact *cis* configuration.¹¹⁸

6. Resolution. If the alkene used in the diazo ester reaction is symmetrically substituted, the *cis* olefin isomer will give two *meso* acids while the *trans* isomer will give a *racemic* acid which can be resolved.⁸⁷

7. Nuclear Magnetic Resonance Spectroscopy. Occasionally there may be a predictable difference in the chemical shift of the protons of the carbalkoxyl group and/or the proton α to the carbalkoxyl group which allows configurational designation.^{92, 125, 221, 229} In the two epimeric

²²⁷ J. Šmejkal and J. Farkaš, *Collect. Czech. Chem. Commun.*, **28**, 481 (1963).

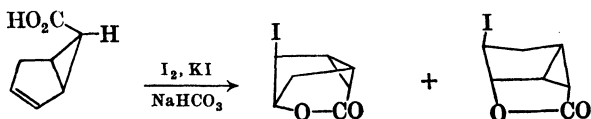
²²⁸ (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, p. 173, John Wiley & Sons, New York, 1965. (b) M. Hanack, *Conformation Theory*, p. 143, Academic Press, New York, 1965.

²²⁹ D. T. Longone and A. H. Miller, *Chem. Commun.*, **1967**, 447.

cyclopropanecarboxylates from phenanthrene mentioned on p. 243, the epimer in which the proton α to the carbalkoxyl function is held over the aromatic rings exhibits a marked upfield shift for this proton.¹²⁴ The carbomethoxyl protons in *cis*-phenyl substituted cyclopropanecarboxylates are usually shifted upfield with respect to the *trans*-phenyl isomers.¹²⁵

Coupling constants of the cyclopropane hydrogens can be useful since the *cis* vicinal coupling constants ($J \sim 4-9$ Hz) are larger than the corresponding *trans* coupling constants ($J \sim 3-5$ Hz).^{125, 217}

8. Lactonization. If the cyclopropanecarboxylic acid is unsaturated, lactonization may allow assignment of configuration. Either lactonization or halolactonization^{230-233, 111, 123 130.} may be used, the latter being useful for separating stereoisomers since the unsaturated acid can be regenerated by reduction of the halo lactone with zinc.^{111, 233} Thus the *endo* acid shown gives two iodolactones whereas the corresponding *exo* acid does not react.¹²³



9. Oxidation. Finally, oxidative degradation of the cyclopropane derivative to a simple substituted cyclopropanecarboxylic acid of known structure and stereochemistry can be used when other methods fail.^{116, 137}

EXPERIMENTAL CONDITIONS

The experimental technique for diazoacetic ester reactions is quite simple. In most cases merely mixing and then heating or irradiating suffices. The evolution of nitrogen serves as a convenient reaction indicator. However, the ratio of diazoacetic ester to substrate, the catalyst, and the temperature can have a profound influence on the yield and stereochemistry of the product. Unfortunately, systematic studies are few and often more than one variable has been changed at a time.

The ratio of diazoacetic ester to unsaturated compound can have a marked effect on yield. Thus, with equimolar quantities of 2,3-dimethyl-1-butene and diazoacetic ester in the presence of copper(II) sulfate catalyst, the yield of cyclopropanecarboxylate was only 4%, but when an

²³⁰ H. O. House, *Modern Synthetic Reactions*, p. 143, Benjamin, New York, 1965.

²³¹ (a) J. Kallos and P. Deslongchamps, *Can. J. Chem.*, **44**, 1239 (1966). (b) J. E. Baldwin and W. D. Foglesong, *Tetrahedron Lett.*, **1966**, 4089. (c) A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, **23**, 87 (1967).

²³² B. Föhlich, *Chem. Ber.*, **97**, 88 (1964).

²³³ J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963).

8:1 molar ratio of olefin to ester was used the yield was 47%.¹⁴⁹ Thus for maximum yield it is best to have the nonlimiting reagent (unsaturated compound or diazoacetic ester) present in considerable excess.

Most alkenes, alkynes, and aromatic compounds (e.g., 2-methyl-1-penten-3-yne,²³⁴ styrene,⁴ *cis*-stilbene,⁴ and diphenylacetylene⁴) do not give cyclopropanes or cyclopropenes with diazoacetic esters at room temperature in the absence of a catalyst or light. For the reaction to proceed at a reasonable rate, a temperature above 80° is required and a reaction temperature between 100 and 200° is commonly used. Light-catalyzed reactions can be done at or below room temperature. With catalysis by copper or a copper salt, some increase in temperature (50–100°) is usually needed to obtain a convenient reaction time. Soluble copper catalysts are exceptional since they are often effective at room temperature or lower. Even with copper salt catalysis the reaction temperature can affect the yield appreciably.

In the copper(II) sulfate-catalyzed reactions of 1-decene under identical conditions except for temperature, the yield of cyclopropanecarboxylate varied from 34% at 60–65° to 59% at 100–110° and decreased to 45% at 160–170°. ²³⁵ Meshcheryakov and Dolgii believe that most diazoacetic ester reactions catalyzed by copper(II) sulfate have a rather sharply defined temperature range in the vicinity of 90–100° for optimum yield.²³⁵ In the reactions of alkyl aryl ethers with diazoacetic esters, if temperatures much below 140–150° were used, the yields of the desired products were poorer regardless of whether the reaction was photochemical, thermal, or catalytic.¹⁹⁷

The manner of mixing the reactants (and perhaps the rate of heating) can also affect the yields. The addition of a mixture of olefin and diazoacetic ester to refluxing xylene has given much better yields with substituted styrenes and vinylpyridines than mixing the olefin and diazo ester at 0° and then gradually heating to 100–170°. ¹⁵⁰

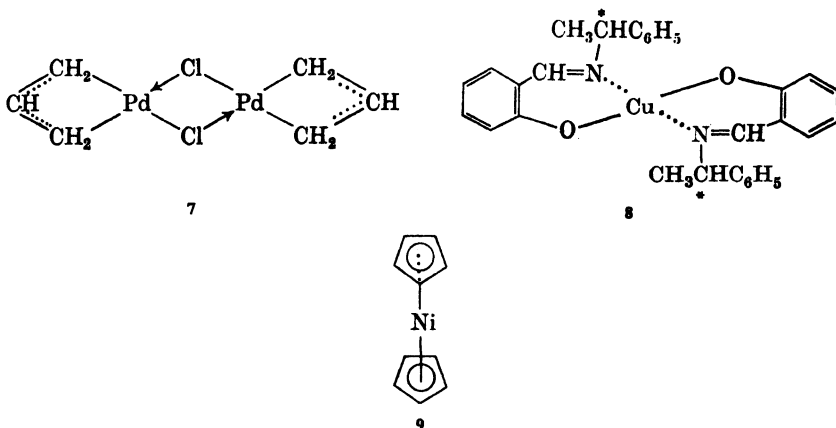
It is reported that reactions of diazoacetic ester with alkynes give different products depending on whether the reaction is run under an inert atmosphere or not.¹⁸⁰ Some workers routinely run diazoacetic ester reactions under an inert atmosphere.

In the past the common catalysts have been copper metal in various forms and copper salts such as copper(II) sulfate, copper(II) and copper(I) chloride, and copper(I) cyanide. They are all heterogeneous catalysts, and reactions in which they are used require heat for a convenient reaction rate. Recently some soluble complexes of copper, nickel, and palladium have been found to act as homogeneous catalysts at room temperature or

²³⁴ L. Vo-Quang, *Compt. Rend., Ser. C*, **266**, 642 (1968).

²³⁵ A. P. Meshcheryakov and I. E. Dolgii, *Bull. Acad. Sci. USSR (Engl. Transl.)*, **1960**, 1745 [*C.A.*, **55**, 13331 (1961)].

lower. The π -allylpalladium chloride dimer **7** catalyzes the reaction of diazoacetic ester with alkenes and alkynes at 0° although the yields at present are poor.^{69, 82a} In a separate experiment it has recently been shown that ethyl diazoacetate does not react with π -allylpalladium

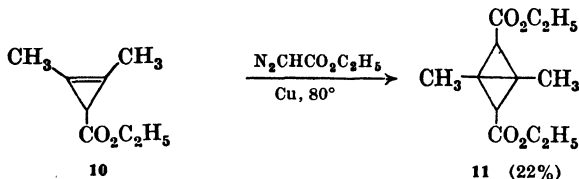


chloride. However, π -allylnickel bromide does react with ethyl diazoacetate giving butadiene derivatives. (See Table VIII.) Japanese workers have used the optically active copper complex **8** at 60° to produce optically active cyclopropanecarboxylates.⁶⁰ Nickelocene (**9**) catalyzes the reaction of diazoacetic esters with cyclohexene at room temperature.⁷⁰ By far the most extensive investigation yet of soluble catalysts is Moser's study of copper(I) chloride complexes at room temperature.⁵⁹ Variations in stereoisomer ratio are obtainable by changing the complexing agent as described in the section on stereochemistry. The phosphite ester-copper(I) chloride complexes are tetrameric in solution; they may be dissociated by the diazoacetic ester. These catalysts are most active when the alkene is peroxide-free and has been degassed to remove oxygen.⁵⁹

For unknown reasons one particular catalyst may give appreciably better yields in a reaction. For instance in the reaction of 1-hydrindanone enol acetate with diazoacetic ester, anhydrous copper(II) sulfate gave higher yields of cyclopropanecarboxylate than did copper bronze, the acetonylacetate-copper(II) complex, the tri-*n*-butylphosphine-copper(I) iodide complex, or the π -allylpalladium chloride dimer.¹⁰³ In the reaction with indole, catalysis by copper metal, copper(I) chloride, or copper(I) thiocyanate gave good yields of ethyl 3-indoleacetate, whereas copper(II), cobalt(II), and nickel(II) chlorides were ineffective.¹⁸⁷

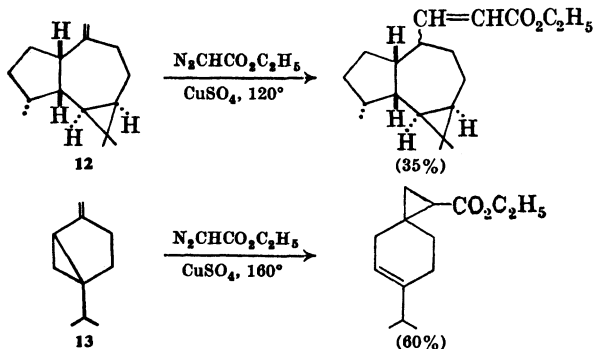
On the other hand, different catalysts or the use of light or heat may give different products from the same substrate. The cyclopropenecarboxylate **10** would not react with a fivefold excess of diazoacetic ester

in the presence of π -allylpalladium chloride dimer **7** even at 75° , but with powdered copper at 80° the bicyclobutane **11** and other products were



formed.⁶⁹ 4-Octyne in the presence of copper at 90° gave the cyclopropenecarboxylate in 51% yield as the only product isolated.⁸² However, with copper(II) sulfate as catalyst the corresponding alkoxy furan is also formed by the previously described (p. 237) copper(II) sulfate-catalyzed rearrangement of the cyclopropenecarboxylate.⁸¹ Other copper salts apparently catalyze the rearrangement also.⁸² If, instead of a catalyst, light is used to promote the reaction with 4-octyne, no furan derivative is found but three products from insertion into C—H bonds are formed along with the cyclopropenecarboxylate.¹⁸⁰

Rearrangements catalyzed by copper(II) sulfate are presumably responsible for the reported abnormal course of the reactions of allo-aromadendrene **12**²³⁶ and sabinene **13**.²³⁷ Furans, such as 2-methylfuran



and 2,5-dimethylfuran, give the monocyclopropanecarboxylate derivatives in light-catalyzed reactions,¹⁸⁴ but when copper(II) sulfate and/or copper metal is used as catalyst, ring-opened products are obtained.^{238–240} In contrast, the copper(II) sulfate-catalyzed reaction with Δ^2 -steroidal olefins

²³⁶ M. I. Goryaev and F. S. Sharipova, *J. Gen. Chem. USSR (Engl. Transl.)*, **34**, 3464 (1964) [*C.A.*, **62**, 4064 (1965)].

²³⁷ M. I. Goryaev and G. A. Tolstikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 303 (1962) [*C.A.*, **57**, 16771 (1962)].

²³⁸ Y. Noichi, I. Moritani, N. Obata, H. Fujita, and I. Kawanishi, *Kogyo Kagaku Zasshi*, **69**, 1491 (1966) [*C.A.*, **66**, 94585g (1967)].

²³⁹ J. Novák and F. Šorm, *Collect. Czech. Chem. Commun.*, **23**, 1126 (1958).

²⁴⁰ J. Novák and F. Šorm, *Chem. Listy*, **51**, 1693 (1957).

proceeds normally to give the cyclopropanecarboxylate,^{104, 171} but the use of light or temperatures up to 180° gave no reaction with the double bond of the steroid.¹⁰⁴

Solvents are frequently used to regulate reaction temperature,²⁴¹ to give a homogeneous liquid if the unsaturated reactant is a solid at room temperature, or, with substrates that sublime readily, to wash the reactant back into the reaction mixture.⁹² Commonly used solvents are petroleum ether, cyclohexane, saturated ethers, benzene, and xylene.

The best guide in the initial choice of conditions for a new reaction would appear to be the obvious one of using the most closely analogous successful reaction as a model.

PREPARATION AND PROPERTIES OF DIAZOACETIC ESTERS

Caution! Diazoacetic esters are toxic and potentially explosive. All reactions involving the formation or reaction of these substances should be performed in a well-ventilated fume hood and behind a safety shield. The chemist should wear a suitable face shield.

Extensive safety tests have been carried out on *ethyl* diazoacetate in the Explosives Department of the duPont Company: "It was found that *ethyl* diazoacetate was insensitive to impact and static charge, and failed as a base charge in a blasting cap, but that it did decompose on a copper block heated to 130° in 6 min. During the course of this work, 5 lb of *ethyl* diazoacetate was distilled without incident in 100-g batches at 35° (5–6 mm)." ⁶⁹ Nevertheless, *methyl* diazoacetate has been reported to "detonate with extreme violence" on heating.²⁴² All diazo esters should be considered potentially explosive and should be handled with care. Diazoacetic esters are prone to cause development of specific sensitivity.

Six general methods for the preparation of aliphatic diazoesters are described briefly below.²⁴³ Currently *ethyl* diazoacetate is available commercially from at least two sources (Aldrich Chemical Co. and Columbia Organic Chemicals). The method of House and Blankley⁷⁹ for converting alcohols (ROH) to the corresponding diazoacetic esters (RO₂CCHN₂) was outlined earlier on p. 236. The application of this method to crotyl alcohol is described in *Organic Syntheses*.^{243a}

The first and oldest of these methods, the diazotization of a glycine ester (method 1), is still the best for large-scale preparations because of the low cost of the reagents. For convenience in a small-scale preparation

²⁴¹ I. A. D'yakonov and N. A. Lugovtsova, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 921 (1951) [*C.A.*, **46**, 439 (1952)].

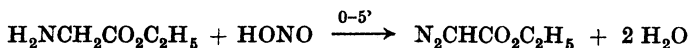
²⁴² N. E. Searle, *Org. Syntheses*, **36**, 25 (1956); *Coll. Vol.*, **4**, 424 (1963).

²⁴³ W. Ried and H. Mengler, *Fortschr. Chem. Forsch.*, **5**, 1 (1965).

^{243a} C. J. Blankley, F. J. Sauter, and H. O. House, *Org. Syntheses*, **49**, 22 (1969).

the use of carbethoxymethylenephosphorane (method 4) is advantageous because of its simplicity, nonaqueous conditions and workup, and the commercial availability of the reagent. For the preparation of *t*-butyl diazoacetate, which should be useful when an acid labile ester is desired in a product, the *Organic Syntheses* preparation from *t*-butyl acetoacetate (method 6) is the method of choice.^{51a}

1. Diazotization of Glycine Ethyl Ester. By far the most common method for the preparation of ethyl diazoacetate is that of Curtius in which glycine ethyl ester or one of its salts is diazotized.^{244, 196} Convenient



laboratory procedures for this method have long been available,^{242, 245} but more recently a number of modifications have been described. Better results have been claimed if 2 *N* rather than 4 *N* acid is used,¹⁵⁷ if the diazotization is carried out at about 20°, ¹⁶⁷ if the pH of the solution is controlled,²⁴⁶ if the crude product is steam-distilled under reduced pressure from barium hydroxide,⁸⁷ and if the reaction is carried out in an externally cooled separatory funnel and the solvent is evaporated under reduced pressure with a rotary evaporator.⁹²

The diazotization of glycine ethyl ester in the presence of halogenated aliphatic hydrocarbons provides protection for the diazo ester from further action of acids.²⁴² It is estimated that the ethyl diazoacetate made from glycine ethyl ester hydrochloride contains about 10% of ethyl chloroacetate.¹⁹⁹ Procedures for making ethyl diazoacetate free from this chloro ester are available.^{59, 247}

Detailed convenient procedures for preparing ethyl diazoacetate in 85% yield by this method starting with glycine ethyl ester hydrochloride are given in *Organic Syntheses*.^{242, 245} Below is given one procedure for preparing ethyl diazoacetate that contains relatively little ethyl chloroacetate.⁵⁹

To a solution of 279 g (2.00 mols) of glycine ethyl ester hydrochloride and 1.4 g of sodium acetate in 550 ml of water cooled to -15° was added 800 ml of petroleum ether (bp 30-60°). A solution of nitrous acid was prepared by adding 70 ml of 2 *N* sulfuric acid to 220 g (3.2 mols) of sodium nitrite dissolved in 300 ml of water. This nitrous acid solution was cooled to 10° and added dropwise and with stirring to the glycine ester solution as rapidly as possible while the reaction temperature was kept below 10°. Stirring was continued for 10 min after the addition was complete. The petroleum ether layer was separated and washed

²⁴⁴ T. Curtius, *Ber.*, **16**, 2230 (1883).

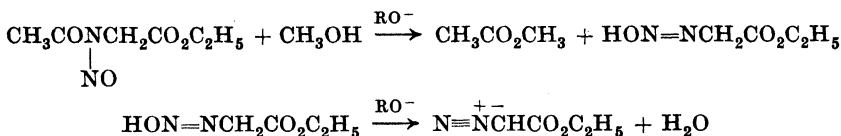
²⁴⁵ E. B. Wornack and A. B. Nelson, *Org. Syntheses*, **24**, 56 (1944); *Coll. Vol.*, **3**, 392 (1955).

²⁴⁶ C. Grundmann and G. Ottmann, *Ann.*, **582**, 163 (1953).

²⁴⁷ G. S. Skinner, *J. Amer. Chem. Soc.*, **46**, 731 (1924).

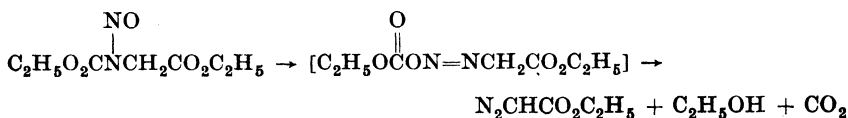
with portions of aqueous sodium bicarbonate until the bicarbonate wash remained basic. The petroleum ether layer was then washed twice with water and dried over anhydrous magnesium sulfate. The petroleum ether was removed under reduced pressure, and the residue distilled under reduced pressure to yield 70% of ethyl diazoacetate, bp 34° (7.8 mm), n_D^{20} 1.4634, which contained only 1–1.5% of ethyl chloroacetate.

2. From N-Nitroso-N-acetyl glycine Ethyl Ester. This nitrosoamide, made by nitrosation of N-acetyl glycine ethyl ester,²⁴⁸ is decomposed by barium oxide in methanol at –15° to give ethyl diazoacetate in 84% yield.^{248, 249} If potassium hydroxide is substituted for barium oxide the yield is only 30%.²⁴⁸ Sodium ethoxide has also been used as the base.²⁵⁰



The diazo ester can also be obtained in 50–75% yield by adding N-nitroso-N-acetyl glycine ethyl ester to an excess of tetraethylenepentamine [$\text{H}_2\text{N}(\text{CH}_2\text{CH}_2\text{NH})_3\text{CH}_2\text{CH}_2\text{NH}_2$] under reduced pressure and distilling the ethyl diazoacetate as it is formed.²⁵⁰

3. From N-Nitroso-N-carbethoxy glycine Ethyl Ester. Pyrolysis of this nitrosoamide at 125–140° (50–100 mm) gives ethyl diazoacetate in 74% yield.²⁵⁰



4. From Carbethoxymethylenephosphorane. Phosphorus ylides react with organic azides to give α -diazocarbonyl compounds.²⁵¹ Thus, when carbethoxymethylenetriphenylphosphorane is allowed to react with *p*-toluenesulfonyl azide in methylene chloride at 0°, ethyl diazoacetate is obtained in 70% yield. The other product of the reaction, N-*p*-toluenesulfonyl triphenylphosphinimine, is a solid which is easily separated from the diazo ester.²⁵¹ The advantages of the method include low temperature and use of an aprotic medium.

²⁴⁸ H. Reimlinger and L. Skattebøl, *Chem. Ber.*, **93**, 2162 (1960).

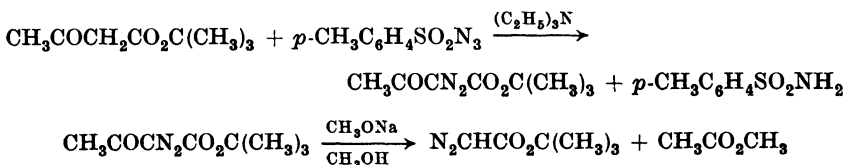
²⁴⁹ H. K. Reimlinger, U.S. Pat. 3,038,929 [C.A., **58**, 6702 (1963)].

²⁵⁰ E. H. White and R. J. Baumgarten, *J. Org. Chem.*, **29**, 2070 (1964).

²⁵¹ (a) G. R. Harvey, *J. Org. Chem.*, **31**, 1587 (1966). (b) U.S. Pat. 3,440,239 [C.A., **71**, 30046c (1969)].

9.92 g (84%) of crude N-*p*-nitrophenylazoglycine ethyl ester, mp 80–95°. The crude triazene was dissolved in 100 ml of methylene chloride and stirred for 20 hours with 100 ml of aqueous 6% acetic acid solution which was saturated with sodium chloride. The methylene chloride layer was separated, washed with saturated aqueous sodium carbonate solution, dried over potassium carbonate and filtered. Removal of methylene chloride under reduced pressure and distillation of the residual oil at 20–50 mm gave 3.20 g (66%) of ethyl diazoacetate.

6. From 1,3-Dicarbonyl Compounds. Sodium salts of β -keto or β -formyl esters when treated with sulfonyl azides at room temperature or lower give high yields of α -diazoesters.^{51a, 253–255} The preparation of *t*-butyl diazoacetate from *t*-butyl acetoacetate is described in *Organic Syntheses*:^{51a}



Similar procedures may be used to prepare ethyl diazoacetate from either ethyl α -formylacetate or ethyl acetoacetate.

(a) To an ice-cooled suspension of 7.0 g (0.05 mol) of the sodium salt of ethyl α -formylacetate²⁵⁶ in 125 ml of anhydrous acetonitrile was added with stirring 10 g (0.05 mol) of *p*-toluenesulfonyl azide (**Caution! Explosive**), the temperature being kept below 5°. The red reaction mixture was stirred at 0° for 2 hours, and then the solvent was removed at 30° and 12 mm pressure. A mixture of the residue with 2.5 ml of aqueous 2 *N* sodium hydroxide was extracted with 500 ml of diethyl ether. The ether was removed at reduced pressure from the washed and dried (sodium sulfate) organic layer to leave 4.8 g (85%) of crude ethyl diazoacetate which gave on distillation 3.8 g (69%) of pure diazo ester, bp 45° (12 mm).²⁵³

(b) *p*-Carboxybenzenesulfonazide²⁵⁵ (**Caution! Explosive**) (131 mg, 0.55 mmol) was suspended in a stirred solution of 72 mg (0.55 mmol) of ethyl acetoacetate in 1 ml of acetonitrile. The mixture was cooled in an ice bath, and 174 mg (1.73 mmol) of triethylamine was added, whereupon the azide dissolved. The reaction mixture was slowly warmed to room temperature, stirred for 2 hours, filtered, and poured with stirring into 8 ml of aqueous 1 *N* sodium hydroxide solution. After 5 minutes the

²⁵³ M. Regitz and F. Menz, *Chem. Ber.*, **101**, 2622 (1968).

²⁵⁴ M. Regitz, *Ang. Chem. Int. Ed. Engl.*, **6**, 733 (1967).

²⁵⁵ J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968).

²⁵⁶ W. Deuschel, *Helv. Chim. Acta*, **35**, 1587 (1952).

aqueous solution was extracted with methylene chloride to yield 44 mg (69%) of crude ethyl diazoacetate.²⁵⁵

Properties. Ethyl diazoacetate is a yellow oily liquid, mp -22° ; bp $29-31^{\circ}$ (5 mm), 42° (10 mm), 84° (61 mm), 141° (720 mm, slight decomp); n_D^{25} 1.4616, d_4^{24} 1.083.^{242, 256a} Methyl diazoacetate is also a yellow liquid, bp 73° (80 mm), 129° (721 mm), d_4^{21} 1.139.^{196, 256a} *t*-Butyl diazoacetate is a yellow-orange liquid, bp $51-53^{\circ}$ (12 mm), n_D^{20} 1.4551.^{51a}

EXPERIMENTAL PROCEDURES

Caution! Diazoacetic esters are toxic and potentially explosive. Observe the precautions described on p. 253.

Catalysts

Copper. Copper bronze can be freshly prepared by precipitating copper from aqueous copper(II) sulfate solution with zinc.²⁵⁷ Commercially available purified copper can be washed with dilute hydrochloric acid to obtain a more active catalyst.²⁵⁸ The activated Ullmann catalyst prepared by washing copper powder with ethylenediaminetetraacetic acid may prove to be useful in diazoacetic ester reactions.^{258a}

Copper(II) Sulfate. Freshly dehydrated copper(II) sulfate should be used in diazoacetic ester reactions. The pentahydrate is dehydrated at $120-180^{\circ}$.

Triisopropyl Phosphite-Copper(I) Chloride Complex.²⁵⁹ To a solution of 10.4 g (0.05 mol) of triisopropyl phosphite in 50 ml of benzene (or petroleum ether, bp $30-60^{\circ}$) was gradually added with stirring 4.9 g (0.05 mol) of copper(I) chloride. The temperature rose gradually, and the copper(I) chloride dissolved. After 1 hour a trace of insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure to leave 95% of the crude crystalline complex, mp 117° .

Trimethyl Phosphite-Copper(I) Iodide Complex.^{259a} To a solution of 1.24 g (10.0 mmols) of trimethyl phosphite in 20 ml of benzene was added 1.90 g (10.0 mmols) of copper(I) iodide and the mixture was

^{256a} I. Heilbron, A. H. Cook, H. M. Bunbury, and D. H. Hey, *Dictionary of Organic Compounds*, Eyre and Spottiswoode Ltd., London, 1965.

²⁵⁷ J. E. Hodgkins and R. J. Flores, *J. Org. Chem.*, **28**, 3356 (1963).

²⁵⁸ R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **86**, 4068 (1964).

^{258a} A. H. Lewin, M. J. Zovko, W. H. Rosewater, and T. Cohen, *Chem. Commun.*, **1967**, 80.

²⁵⁹ Y. Nishizawa, *Bull. Chem. Soc. Jap.*, **34**, 1170 (1961).

^{259a} H. O. House and W. Fischer, unpublished work.

heated at reflux for 8 hours. The hot suspension was filtered from the remaining insoluble 0.141 g of copper(I) iodide. The filtrate was concentrated to leave 2.63 g of a white solid mp 175–185°. Recrystallization from ether-chloroform gave 2.02 g (63%) of white needles, mp 192–193° (lit^{259b} mp 175–177°).

Reactions

Ethyl *trans*-2,3-Di-*n*-propylcyclopropane-1-carboxylate.⁸⁷ [Alkene and copper(II) sulfate.] Ethyl diazoacetate (19.38 g, 0.18 mol) was added slowly with mechanical stirring to a mixture of 38.08 g (0.36 mol) of *trans*-4-octene and 0.5 g of anhydrous copper(II) sulfate heated to 90° in an oil bath. The nitrogen evolved in the reaction was collected (3350 ml at 0° and 760 mm, or 88% of the calculated amount). After the reaction was complete, the mixture was filtered to remove the catalyst and the filtrate was distilled under reduced pressure to separate 21 g of *trans*-4-octene, bp 68–70° (150 mm), d_4^{20} 0.7145, n_D^{20} 1.4118, and 20.8 g of a mixture of ethyl *trans*-2,3-di-*n*-propylcyclopropane-1-carboxylate and diethyl fumarate. To remove the contaminating fumaric ester, the second fraction was extracted in the cold with 2% aqueous potassium permanganate until the aqueous solution retained a permanent purple color. A total of 1.2 g of the permanganate, corresponding to 0.98 g of diethyl fumarate, was consumed. The remaining cyclopropyl ester was redistilled under reduced pressure to separate 19 g (62%) of product, bp 89–90° (6 mm), d_4^{20} 0.8945, n_D^{20} 1.4353.

Methyl *cis*-2,3-Dimethylcyclopropane-1-*cis*-(and 1-*trans*)-carboxylate.⁸⁵ [Alkene and light.] After it had been irradiated for 40 hours with three 275-watt General Electric sunlamps, a cold solution of 8 g (0.08 mol) of methyl diazoacetate in 40 ml (0.43 mol) of liquid *cis*-2-butene had become colorless. Distillation of the mixture afforded 4.0 g (39%) of material, bp 50–60° (50 mm). Gas chromatographic analysis with a 4-m didecyl phthalate column at 130° indicated that the product consisted mainly of a mixture of two substances, methyl *cis*-2,3-dimethylcyclopropane-1-*cis*-carboxylate (r.t. 42 minutes, n_D^{20} 1.4308), and methyl *cis*-2,3-dimethylcyclopropane-1-*trans*-carboxylate (r.t. 47 minutes, n_D^{20} 1.4306), with small quantities of at least four other substances with shorter retention times. The ratio of *trans* to *cis* ester was about 5:2.

Ethyl *cis*-Bicyclo[4.1.0]heptane-7-carboxylate (*exo* and *endo*).⁵⁹ [Alkene and trimethyl phosphite-copper(I) chloride.] Trimethyl phosphite-copper(I) chloride complex (5.0 mmols) was dissolved in 20 ml of

degassed peroxide-free cyclohexene at 30°. A solution of ethyl diazoacetate (20 mmols) in 20 ml of degassed, peroxide-free cyclohexene was added from a dropping funnel at a rate of 5 drops/minute. Nitrogen evolution began within 1–2 minutes and was quantitative. The initial solution became a dark-brown color after *ca.* 1 ml of the diazoalkane solution had been added, suggesting the possible formation of a colloidal suspension. Ten to fifteen minutes after the addition was complete, the product was distilled at reduced pressure. Gas chromatographic analysis of the crude product indicated the yield to be 40–60% of a stereoisomeric mixture of ethyl *cis*-bicyclo[4.1.0]heptane-7-carboxylates in which the *exo/endo* ratio was 8.18/1. The remainder of the product was mainly diethyl fumarate and maleate.

7-Carbethoxy- Δ^3 -norcarene (*exo* and *endo*).¹¹¹ [Diene and metallic copper.] A mixture of 15 g (0.19 mol) of 1,4-cyclohexadiene (Aldrich), 0.35 g (0.0055 g-atom) of copper powder, and 2 ml of ethyl diazoacetate in a three-necked, 250-ml flask equipped with a dropping funnel and a solid carbon dioxide (Dry Ice)-acetone condenser was heated to boiling (bath at 85°). Foaming began, and the bath was kept at 85–90° while more ethyl diazoacetate (a total of 24 g, 0.21 mol) was added dropwise during 25 minutes. After an additional 5 minutes, gas evolution ceased, whereupon the mixture was cooled, filtered through glass wool, and distilled, first at atmospheric pressure to remove unchanged 1,4-cyclohexadiene, and then under reduced pressure. The major fraction, 9.7 g, bp 118–120° (25 mm), was a clear, colorless liquid which consisted of a mixture of *exo*- and *endo*-7-carbethoxy- Δ^3 -norcarene (in the ratio of about 7:1), diethyl maleate, and diethyl fumarate.

2-Methyl-2-isopropenyl-1-carbethoxycyclopropane (*cis* and *trans*).²⁶⁰ [Diene and light.] To 60 ml (44.7 g, 0.545 mol) of pure 2,3-dimethylbutadiene in a 250-ml round-bottomed flask was added 40 g (0.35 mol) of ethyl diazoacetate. The flask was equipped with a water-cooled reflux condenser and a bubble counter for evolved gas. The flask was irradiated with a 275-watt General Electric sunlamp placed approximately 2 cm below the flask. The heat from the lamp caused the reaction mixture to reflux at a moderate rate. Irradiation was continued until the reaction mixture became deep orange in color (approximately 30 hours). If irradiation was continued until nitrogen was no longer evolved, the reaction mixture became very black and viscous, and greatly reduced yields of the desired product were obtained after distillation. The combined product of two such irradiations was fractionally distilled through a 20-cm vacuum-jacketed Podbielniak Heli-Pak column. A

²⁶⁰ P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965).

fraction, collected at 39–50° (2.3 mm), amounted to 58.6 g of a nearly colorless oil. The nmr spectrum of this fraction indicated that the material was a mixture of *cis*- and *trans*-2-methyl-2-isopropenyl-1-carbethoxycyclopropane in the ratio 1:2 or 2:1. The overall yield was 68% after correction for recovered ethyl diazoacetate.

Ethyl 2,2-Dimethyl-3-isopropylidenecyclopropane-1-carboxylate.²⁶¹ [Allene and copper(II) chloride.] To a suspension of anhydrous copper(II) chloride (1.40 g, 0.01 mol) in tetramethylallene (63 g, 0.65 mol) contained in a 200-ml flask fitted with a mechanical stirrer, an addition funnel, and a condenser topped with a drying tube was added ethyl diazoacetate (22 g, 0.2 mol). The rate of addition was such that the reaction mixture did not boil. After the addition, which required 1.5 hours, was complete, the mixture was stirred for another hour, filtered, diluted with diethyl ether, washed successively with aqueous 6 *M* ammonium hydroxide and with water, and then dried over sodium sulfate. Ether and tetramethylallene were removed under reduced pressure with a rotary evaporator. The residual crude ester weighed 14.6 g (40%).

Ethyl *cis*- and *trans*-2-Phenylcyclopropanecarboxylate.¹¹² [Allene with aromatic ring and heat.] A mixture of styrene (167 g, 1.61 mols) and ethyl diazoacetate (183 g, 1.61 mols), cooled to 0°, was added dropwise to styrene (83.5 g, 0.8 mol) which was heated at 150° under a nitrogen atmosphere. The exothermic reaction was complete in 3 hours. After the excess styrene was removed under reduced pressure, the residue was distilled to yield 242 g (79%) of a mixture containing 65% *trans* and 35% *cis* ester, bp 79–92° (0.1 mm).

Distillation of the mixture of *cis* and *trans* esters through a spinning-band column yielded fractions boiling between 65.5° and 95.5° (0.35–0.65 mm). The pure ethyl *trans*-2-phenylcyclopropanecarboxylate had bp 94–95.5° (0.65 mm), mp 35–36° (from pentane), n_D^{25} 1.5191 (supercooled). The pure ethyl *cis*-2-phenylcyclopropanecarboxylate could be obtained in good yield by redistillation of the lower-boiling fractions through the spinning-band column. The pure liquid *cis* isomer had bp 88.5–89° (0.7 mm), n_D^{25} 1.5131.

***cis*-2,3-Diphenylcyclopropane-*trans*-1-carboxylic acid.**⁹² [Alkene with aromatic rings and copper(II) sulfate.] *trans*-Stilbene (35 g, 0.19 mol), 2 g of freshly dehydrated copper(II) sulfate, and 75 ml of reagent grade benzene were placed in a 500-ml four-necked, round-bottomed flask fitted with a mechanical stirrer having a Teflon blade, a thermometer, and two condensers. On top of one of the condensers was mounted a

pressure-equalized dropping funnel, and the top of the other condenser was connected to a bubbler filled with toluene for monitoring the evolution of nitrogen.

The mixture was heated to 75° with stirring, and 45 ml (0.43 mol) of ethyl diazoacetate was added from the dropping funnel over a period of 6.75 hours. The mixture was stirred for an additional 0.5 hour, and then allowed to stand overnight. Sodium hydroxide (25 g) and 200 ml of 95% ethanol were added, and the mixture was refluxed with stirring for 6 hours. The ethanol and the benzene were removed by distillation, and 200 ml of water was added. The aqueous mixture was heated to 90° and filtered. The recovered *trans*-stilbene, extracted from the water-insoluble residue with dichloromethane, weighed 14.5 g. The crystals of the insoluble sodium salt which separated from the aqueous filtrate on cooling overnight were filtered and redissolved in hot water. The solution was filtered, and the filtrate was acidified with aqueous 10% hydrochloric acid. The precipitate of *cis*-2,3-diphenylcyclopropane-*trans*-1-carboxylic acid obtained from the filtrate weighed 22.0 g (81% conversion), mp 157–158°. Recrystallization from methanol-water gave pure colorless acid, mp 157–158°.

Methyl 2,3-Dimethyl-2-cyclopropene-1-carboxylate.⁸⁵ [Alkyne and light.] A mixture of 23 g (0.43 mole) of 2-butyne, 7 g (0.07 mol) of methyl diazoacetate and 25 g of isobutane (used as solvent to prevent the 2-butyne from crystallizing on the condenser surface) was placed in a flask fitted with a solid carbon dioxide (Dry Ice) condenser. At the end of 30 hours of irradiation with three 275-watt General Electric sunlamps, all of the diazoacetic ester was decomposed. Distillation afforded 3.5 g of material, bp 45–60° (2 mm). Separation by gas chromatography with a 4-m didecyl phthalate column at 130° gave pure methyl 2,3-dimethyl-2-cyclopropene-1-carboxylate, n_D^{20} 1.4412, in 32% yield.

2,3-Di-*n*-propyl-2-cyclopropene-1-carboxylic Acid.^{86,2} [Alkyne and copper.] A mixture of 60 g (0.55 mol) of dry 4-octyne and 0.5 g of copper powder was stirred under a nitrogen atmosphere at 155° (oil-bath temperature) while 63 g (0.55 mol) of ethyl diazoacetate was added dropwise at the rate of 4 drops/minute. After the addition was complete, the stirring was continued for 2 hours. The mixture was cooled and 70 g of potassium hydroxide in 200 ml of 1-propanol was added.* The mixture

* If the cyclopropene resulting from the addition of diazoacetic ester to an alkyne has a benzylic hydrogen atom adjacent to the ring, alkaline hydrolysis causes double-bond isomerization to form a benzylidenecyclopropane derivative.^{348–349}

^{86,2} R. Breslow, H. Höver, and H. W. Chang, *J. Amer. Chem. Soc.*, **84**, 3168 (1962).

^{86,3} N. A. Ampilogova, I. A. D'yakonov, and R. R. Kostikov, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 1863 (1966) [*C.A.*, **66**, 55121h (1967)].

⁸⁴⁴ A. W. Herriott and W. M. Jones, *Tetrahedron Lett.*, **1967**, 2387.

⁸⁴⁵ A. W. Herriott, E. P. Olavarria, and W. M. Jones, *J. Org. Chem.*, **33**, 3804 (1968).

was refluxed for 4 hours, then cooled and worked up in the usual fashion. Distillation of the acidic fraction gave 48 g (52%) of the product, bp 101° (0.7 mm).

Ethyl 2,3-Di-*n*-butyl-2-cyclopropene-1-carboxylate.⁸² [Alkyne and copper(II) sulfate.] To 30 g (0.22 mol) of 5-decyne (bp 177–178°, n_{D}^{20} 1.4334) and 0.05 g of anhydrous copper(II) sulfate heated to 90° was added 12 g (0.11 mol) of ethyl diazoacetate dropwise with stirring, the rate of addition being 4 g/hour. The reaction was conducted under an atmosphere of nitrogen. After the reaction was complete as indicated by the absence of nitrogen evolution, the catalyst was removed by filtration. Filtration and all subsequent operations were likewise performed under a nitrogen atmosphere. The filtrate was fractionally distilled to separate three fractions: 5-decyne, 21 g (70%), bp 58–60° (10 mm), n_{D}^{20} 1.433; diethyl maleate, 1.1 g (12%), bp 80–85° (10 mm), n_{D}^{20} 1.4412; and the ethyl ester of 2,3-di-*n*-butyl-2-cyclopropene-1-carboxylic acid, 9.2 g (39%), bp 89–90° (3 mm), d_4^{20} 0.8965, n_{D}^{20} 1.44786.

Ethyl 2-Thiabicyclo[3.1.0]hex-3-ene-6-carboxylate.¹⁸⁴ [Heterocyclic compound and light.] A solution of 20 g (0.18 mol) of ethyl diazoacetate in 100 ml (1.3 mols) of thiophene was irradiated under nitrogen at room temperature with a mercury high-pressure lamp (Philips HPK, 125 W) in a water-cooled Solidex immersion lamp fitting. After 50 hours, 2.75 l of nitrogen had been evolved. The dark-brown oil remaining after removal of excess thiophene was distilled to give 4.8 g (15%) of ethyl 2-thiabicyclo[3.1.0]hex-3-ene-6-carboxylate, mp 36.5°.

2,4,8-Trimethylazulene.²⁸⁶ [Aromatic compound and heat.] In a flask fitted with a reflux condenser and immersed in an oil bath 50.5 g (0.32 mol) of 2,4,7-trimethylindane was heated to 130°. Ten grams (0.09 mol) of ethyl diazoacetate was added dropwise and the temperature was raised gradually to 165°. After 2 hours the mixture was fractionally distilled under reduced pressure. The fraction boiling above 120° (3 mm) was allowed to remain in the distilling flask and the recovered trimethylindane (44.5 g) in the distillate was again subjected to the reaction with diazoacetic ester. After the recovered indane had been recycled five times, 23.5 g of unchanged trimethylindane remained accompanied by 37 g of a red, viscous liquid boiling in the range 120–160° (2.5 mm).

The dark-red oil was dissolved in 150 ml of ethanol and 40 ml of water and saponified with 20 g of potassium hydroxide. Water was added and the alcohol was removed by distillation. The unsaponified material (1.7 g) was separated by extraction with diethyl ether, and the aqueous layer was acidified. The liberated green oil was extracted with ether. After

²⁸⁶ W. Herz, *J. Amer. Chem. Soc.*, **73**, 4923 (1951).

the ether extract had been dried, distillation yielded 4 g of fore-run (bp up to 165° at 3 mm) and 15.5 g of a dark-green, viscous oil boiling at 165–170° (3 mm).

The product was transferred to a small distilling flask, mixed with 2 g of a 10% palladium-on-charcoal catalyst, and slowly distilled over an open flame. The violet distillate was redistilled using a modified Claisen flask to give the following fractions: 2.8 g of a fairly mobile liquid, bp to 105° (1.5 mm); 3.1 g of a deeply colored and more viscous liquid, bp 105–140° (1.5 mm). The higher-boiling residue could be subjected to a second dehydrogenation.

Fraction 2 was dissolved in 20 ml of ethanol and treated with 4 g of 1,3,5-trinitrobenzene in 125 ml of warm ethanol. The purple 1,3,5-trinitrobenzene complex that separated immediately weighed 4.1 g. The derivative was dissolved in a minimum volume of a hexane-benzene mixture (2:1) and decomposed by chromatography on alumina. The violet eluate was concentrated and distilled, the fraction boiling at 110–115° (1.5 mm) being collected. The 2,4,8-trimethylazulene weighed 1.55 g. On prolonged chilling, it crystallized and remelted at 29°.

Ethyl Diazoacetate and Acenaphthene.²⁶⁷ [Polynuclear aromatic compound and heat.] To 462 g (3 mols) of molten acenaphthene held at 160° there was added dropwise with stirring 57 g (0.5 mol) of ethyl diazoacetate over a period of 8 hours. The dark-brown mixture was stirred for an additional 0.5 hour or until nitrogen evolution ceased. The excess acenaphthene was removed by distillation under reduced pressure (40 mm), and the residue was then subjected to distillation from a Claisen flask. This gave 95 g of crude oil (monoadduct), bp 155–165° (1 mm), and 15 g of a higher-boiling fraction (diadduct), bp 180–200° (1 mm). The crude monoadduct was then redistilled using a spinning-band column to give four fractions: (1) 21.3 g, bp 94–96° (0.05 mm); (2) 5.0 g, bp 96–97° (0.05 mm); (3) 50.2 g, bp 97–99° (0.05 mm); and (4) 13.3 g, bp 99–101° (0.05 mm).

Fractions 1 and 2 solidified to white crystals of ethyl 1a,8a-dihydro-1H-cyclopropa[c]acenaphthene-1-carboxylate, which melted at 81–82° after recrystallization from ethanol.

Fractions 3 and 4 were combined and dissolved in 250 ml of ethanol. When the solution was allowed to stand in the cold overnight, 47 g of ethyl 1a,7b-dihydro-1H-cyclopropa[c]acenaphthene-1-carboxylate separated as white crystals, mp 71–72°.

The mother liquor from the crystallization of ethyl 1a,7b-dihydro-1H-cyclopropa[c]acenaphthene-1-carboxylate was chromatographed on

²⁶⁷ V. Boekelheide and C. D. Smith, *J. Amer. Chem. Soc.*, **88**, 3950 (1966).

alumina (Woelm, activity 1) to give more of the above product and also ethyl 1,2-dihydro-8H-benz[cd]azulene-9-carboxylate, mp 62–63° after recrystallization from petroleum ether, bp 30–60°.

The crude diadduct fraction was chromatographed on alumina (Woelm, activity 1) to give in early fractions 1.5 g of diethyl *cis*-1,1a,1b,2,2a,7b-hexahydrodicyclopropa[ce]acenaphthene-1,2-dicarboxylate, mp 88–89.5°. The later fractions from chromatography of the diadduct gave 3.0 g of diethyl *trans*-1,1a,1b,2,2a,7b-hexahydrodicyclopropa[ce]acenaphthene-1,2-dicarboxylate, mp 120–120.5°.

TABULAR SURVEY

The following eight tables list the reactions of diazoacetic ester. The first seven tables include reactions with alkenes, alkynes, heterocyclic and aromatic compounds. The last table contains the reactions of diazoacetic ester with miscellaneous compounds including some conjugated alkenes and alkynes, quinones, aromatic compounds containing carbonyl, thio-carbonyl, and oxide groups, and some related aromatic compounds, including pyridones. Most of the reactions listed in the last table are of recent research interest and give products which are otherwise difficult to obtain. Literature coverage is through March 1970.

Entries are arranged in the order of increasing number of carbon atoms in the substrate. The first reference listed for an entry gives the best experimental procedure. Other references are arranged in numerical order. Although most of the reactions tabulated were carried out using *ethyl* diazoacetate, in a few reactions *methyl* diazoacetate was used. When the structure of the product does not indicate which diazoacetic ester was utilized, the use of the *methyl* ester is denoted by a footnote. In a few instances the particular diazoacetic ester used was not specified but was presumably the ethyl ester. *No reaction* indicates reported unreactivity of diazoacetic ester with the compound, though maleate and fumarate esters may have been formed during the attempted reaction. Maleate and fumarate esters are not tabulated as products.

Products formed by the reaction of alkenes and alkynes with diazoacetic ester to give cyclopropane derivatives with loss of nitrogen are simply listed as cyclopropyl ester (acid) or cyclopropenyl ester (acid), respectively. In reactions of olefins with diazoacetic ester in which the presence of a stereoisomeric mixture is proved or suspected, the product is tabulated as cyclopropyl esters or acids. In other cases where such a mixture of products is expected but not reported, the product is tabulated as cyclopropyl ester or acid, and is probably a stereoisomeric mixture. Among polyalkenes, products obtained by reaction of diazoacetic ester with more

than one double bond, and whose structures are not determined, are indicated as a mixture of cyclopropyl esters (acids). The stereochemistry of substituents on a cyclopropane ring is indicated as *cis* and *trans* with respect to the carboxyl group.

A yield followed by a class name indicates the form in which the product was isolated; *e.g.*, $\text{C}_6\text{H}_5\text{OCH}_2\text{CO}_2\text{C}_2\text{H}_5$ (7, amide) means that the product isolated was $\text{C}_6\text{H}_5\text{OCH}_2\text{CONH}_2$.

The diverse ways in which the reactions of diazoacetic ester are reported and abstracted make omission of some examples unavoidable; it is hoped that such omissions are few. In classifying polyfunctional compounds for the tables, a measure of arbitrariness was inescapable; *Caveat lector*.

CHAPTER 4

THE BASE-PROMOTED REARRANGEMENTS OF QUATERNARY AMMONIUM SALTS

STANLEY H. PINE

*California State College, Los Angeles, California**

CONTENTS

	PAGE
INTRODUCTION	404
THE STEVENS REARRANGEMENT	405
Mechanistic Considerations	406
Scope	407
THE SOMMELET-HAUSER REARRANGEMENT	416
Mechanistic Considerations	416
Scope	419
Table I. Competitive Sommelet-Hauser Reactions	420
COMPETITIVE STEVENS AND SOMMELET-HAUSER REARRANGEMENTS	424
Table II. The Importance of Solubility in Competitive Stevens and Sommelet-Hauser Rearrangements	425
EXPERIMENTAL CONSIDERATIONS	426
EXPERIMENTAL PROCEDURES	427
2,N,N-Trimethylbenzylamine and/or α ,N,N-Trimethylbenzylamine	427
2,N,N-Trimethylbenzhydrylamine	428
N,N-Dimethyl-1,2-diphenylethylamine	429
2-Benzyl-N,N-dimethylbenzylamine and N,N-Dimethyl-2,2-diphenyl- ethylamine	429
N,N-Dimethyl-1,2,2-triphenylethylamine	429
1,2-Dimethyl-3-(dimethylaminomethyl)pyrrole	430
β -Ferrocenylethylidimethylamine	430

* I thank the College for a creative research leave in the spring quarter, 1969, during which the major portion of this manuscript was written. I also thank Janice L. Romstad, du Pont Experimental Station, for assistance in searching the chemical literature.

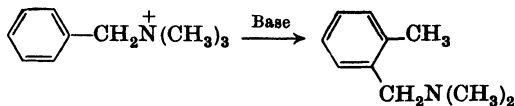
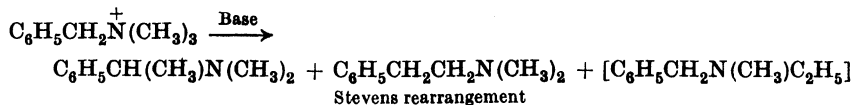
2,3,4,5,6,7-Hexahydro-2-methyl-1H-2-benzazonine	430
9-Dimethylamino-4,5-dimethyl-9,10-dihydrophenanthrene	431
3,4,5,6,9,10,11,12-Tetrabenzo-1-azabicyclo[6.5.0]3,5,9,11-tridecatetraene	431

TABULAR SURVEY	431
--------------------------	-----

Table III. Rearrangements of Quaternary Ammonium Salts with Alkyl, β -Aralkyl, or Aryl Groups Attached to Nitrogen	433
Table IV. Rearrangements of Benzyl Quaternary Ammonium Salts	434
Table V. Rearrangements of Arylmethyl Quaternary Ammonium Salts in Which the Aryl Group Contains Two or More Fused Aromatic Rings	442
Table VI. Rearrangements of Arylmethyl Quaternary Ammonium Salts in Which the Aryl Group Is Heterocyclic or Ferrocenyl	444
Table VII. Rearrangements of Allylic Quaternary Ammonium Salts	446
Table VIII. Rearrangements of Acetylenic Quaternary Ammonium Salts	448
Table IX. Rearrangements of Phenacyl and Related Quaternary Ammonium Salts	449
Table X. Rearrangements of Cyclic Quaternary Ammonium Salts in Which the Ammonium Nitrogen Atom Is a Ring Member	452

INTRODUCTION

The base-promoted rearrangements of quaternary ammonium salts can be divided into two categories. In the Stevens rearrangement one alkyl group migrates from the quaternary nitrogen atom to the *alpha* carbon atom of a second alkyl group.¹ The Sommelet-Hauser rearrangement involves migration to the *ortho* position of a benzyl quaternary ammonium salt.^{2, 3} When structurally feasible, both rearrangements may occur simultaneously although experimental conditions markedly affect the competing pathways.



Sommelet-Hauser rearrangement

In general, rearrangements occur in those quaternary ammonium salts that do not contain a *beta* hydrogen atom and thus are not capable of undergoing the Hofmann elimination. The latter important reaction of

¹ T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, **1928**, 3193.

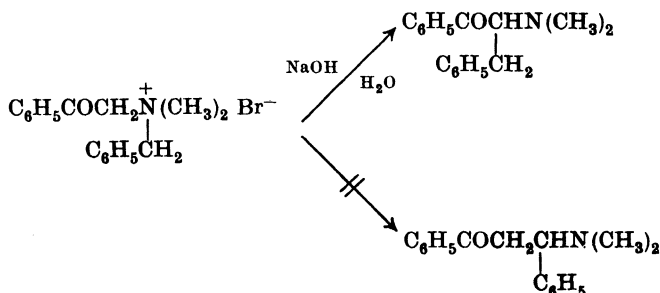
² S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.* **73**, 4122 (1951).

³ M. Sommelet, *C.R.*, **205**, 56 (1937).

quaternary ammonium salts is the subject of a chapter in an earlier volume of this series.⁴ Since reviews of earlier work on the Stevens and Sommelet-Hauser rearrangements are available,⁵⁻¹⁰ more recent contributions are emphasized here.

THE STEVENS REARRANGEMENT

In a study initially intended to explore suitable amine-protecting groups, Stevens, Creighton, Gordon, and McNicol in 1928 observed the migration of a benzyl group from a quaternary nitrogen atom to an adjacent carbon atom under the influence of base.¹ In this first example of the Stevens rearrangement, phenacylbenzyltrimethylammonium bromide treated with 10% sodium hydroxide over steam for 1 hour furnished α -dimethylamino- β -phenylpropiophenone in 90% yield. The alternative product that would arise from a migration of the phenacyl group was shown not to be present. In a subsequent series of papers,



Stevens and coworkers extended their studies to include various phenacyl¹¹⁻¹³ as well as acetyl-ammonium¹⁴ systems. They also established (as have many subsequent workers) that salts not containing a

⁴ A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

⁵ H. E. Zimmerman in *Molecular Rearrangements*, P. de Mayo, Ed., pp. 378-391, Interscience Publishers, New York, 1963.

⁶ D. J. Cram, *Fundamentals of Carbanion Chemistry*, pp. 223-229, Academic Press, New York, 1965.

⁷ H. J. Shine, *Aromatic Rearrangements*, pp. 316-326, Elsevier Publishing Co., New York, 1967.

⁸ T. S. Stevens, *Prog. Org. Chem.*, **7**, 48-54 (1968).

⁹ D. V. Banthorpe in *The Chemistry of the Amino Group*, S. Patai, Ed., pp. 612-622, Interscience Publishers, New York, 1968.

¹⁰ I. Iwai in *Mechanisms of Molecular Migrations*, Vol. 2, B. S. Thyagarajan, Ed., pp. 105-111, Interscience Publishers, New York, 1969.

¹¹ T. S. Stevens, *J. Chem. Soc.*, **1930**, 2107.

¹² J. L. Dunn and T. S. Stevens, *J. Chem. Soc.*, **1932**, 1926.

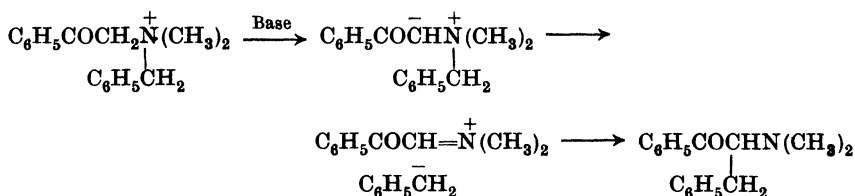
¹³ J. L. Dunn and T. S. Stevens, *J. Chem. Soc.*, **1934**, 279.

¹⁴ T. S. Stevens, W. W. Snedden, E. T. Stiller, and T. Thomson, *J. Chem. Soc.*, **1930**, 2119.

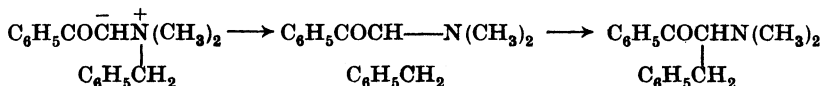
carbonyl or other electron-withdrawing group will undergo the rearrangement.¹⁵ Their studies of the influence of substituents on the rearrangement provided a basis for mechanistic considerations which are still pertinent.^{12-14, 16}

Mechanistic Considerations

Stevens considered three possible mechanisms for the rearrangement. He concluded, on the basis of substituent effects, that a dissociation-recombination ion-pair pathway following initial ylide formation best explained the data.^{11, 16} However, the high stereospecificity¹⁷⁻¹⁹



and intramolecularity^{11, 20-22} of the rearrangement led subsequent workers to propose a front-side nucleophilic displacement mechanism.^{18, 23} (The latter pathway was considered and rejected by Stevens.¹¹)



The front-side nucleophilic displacement mechanism is unlikely. The analogy to the often quoted S_Ni reaction of thionyl chloride with alcohol as a front-side displacement is misleading because this reaction actually appears to involve an ion-pair mechanism.²⁴ From a molecular orbital viewpoint, the front-side displacement mechanism requires the incoming electrons to enter an antibonding orbital of the migrating group, an

¹⁵ T. Thomson and T. S. Stevens, *J. Chem. Soc.*, **1932**, 1932.

¹⁶ T. Thomson and T. S. Stevens, *J. Chem. Soc.*, **1932**, 55.

¹⁷ A. Campbell, A. H. J. Houston, and J. Kenyon, *J. Chem. Soc.*, **1947**, 93.

¹⁸ J. H. Brewster and M. W. Kline, *J. Amer. Chem. Soc.*, **74**, 5179 (1952).

¹⁹ B. J. Millard and T. S. Stevens, *J. Chem. Soc.*, **1963**, 3397.

²⁰ E. Grovenstein, Jr., and G. Wentworth, *J. Amer. Chem. Soc.*, **89**, 1852 (1967).

²¹ M. G. Indzhikyan and A. T. Babayan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauk*, **10**, 411 (1957) [*C.A.*, **52**, 16256f (1958)].

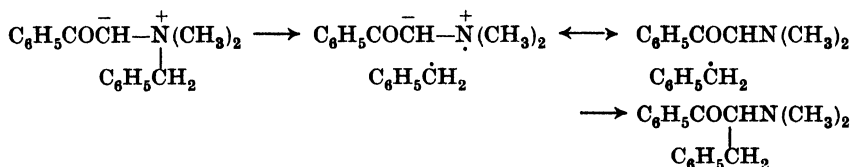
²² R. A. W. Johnstone and T. S. Stevens, *J. Chem. Soc.*, **1955**, 4487.

²³ C. R. Hauser and S. W. Kantor, *J. Amer. Chem. Soc.*, **73**, 1437 (1951).

²⁴ A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, pp. 158-160, McGraw-Hill Book Co., New York, 1962.

energetically unfavorable process.²⁵ The application of orbital symmetry arguments also suggests that such front-sided, concerted 1,2 rearrangements are forbidden.^{26, 27}

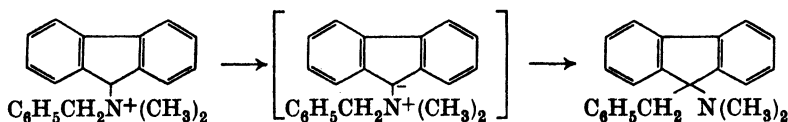
The question of mechanism was reconsidered in 1962.²⁸ This and subsequent work²⁹⁻³³ have resulted in considerable support for a dissociation-recombination ion-pair mechanism. Very recently, however, it has been suggested that the dissociation-recombination pathway involves a radical-pair intermediate.^{34, 35a} The latter proposal promises to promote renewed interest in the rearrangement.



Scope

The original examples of the Stevens rearrangement were observed in compounds which contained a carbonyl group in a position to favor initial ylide formation.¹¹⁻¹⁴ The importance of the ylide formation in controlling the course of the rearrangement is well established. It has been experimentally demonstrated that phenacyl > propargyl > allyl > benzyl > alkyl as the migration terminus in the rearrangements, reflecting the decreasing stability of the potential ylide carbanions.

For example, 9-fluorenylbenzyltrimethylammonium bromide apparently leads only to the product of benzyl migration via the stable fluorenyl



²⁵ M. J. S. Dewar, *Ann. Rept. Prog. Chem.* (Chem. Soc. London), **48**, 127 (1951).

²⁶ J. E. Baldwin and R. E. Hackler, *J. Amer. Chem. Soc.*, **91**, 3646 (1969).

²⁷ R. B. Woodward and R. Hoffmann, *Ang. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

²⁸ E. F. Jenny and J. Druetz, *Ang. Chem., Int. Ed. Engl.*, **1**, 155 (1962).

²⁰ G. Grethe, H. L. Lee and M. R. Uskoković, *Tetrahedron Lett.*, **1969**, 1937.

³⁰ A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 3046 (1968).

³¹ A. E. Jacobson and R. T. Parfitt, *J. Org. Chem.*, **32**, 1894 (1967).

³² E. F. Jenny and A. Melzer, *Tetrahedron Lett.*, **1966**, 3507.

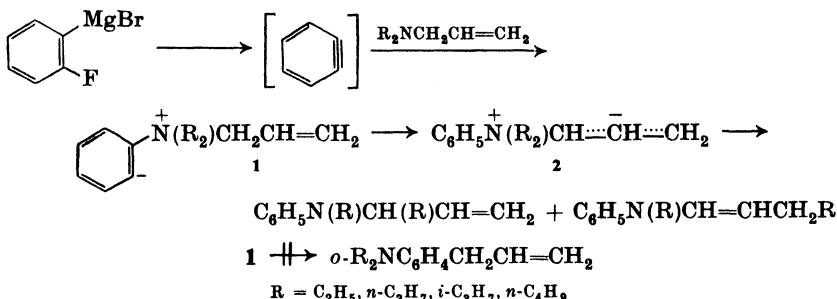
⁸³ E. F. Jenny and K. Schenker, *Ang. Chem., Int. Ed. Engl.*, **4**, 441 (1965).

⁸⁴ U. Schöllkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, **1969**, 3415; U. Schöllkopf and U. Ludwig, *Chem. Ber.*, **101**, 2224 (1968); and personal communication.

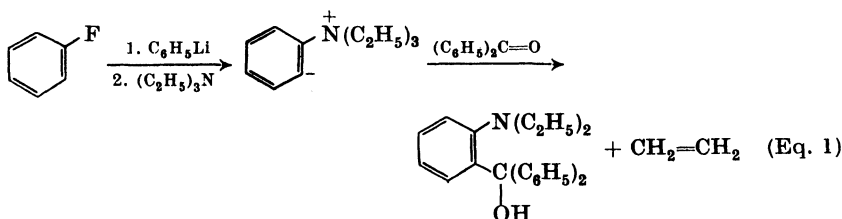
²⁸ A. R. Lepley, *J. Amer. Chem. Soc.*, **91**, 1237 (1969); A. R. Lepley, *Chem. Commun.*, **1969**, 1460; and personal communication.

^{36a} G. F. Hennion and M. J. Shoemaker, *J. Amer. Chem. Soc.*, **92**, 1769 (1970).

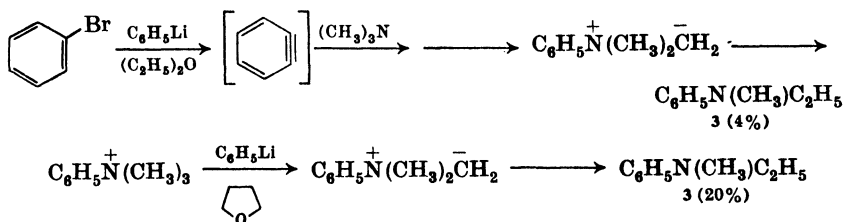
A direct reaction of the quaternary ammonium salt with a suitable base usually provides the requisite ylide precursor *in situ* for the rearrangement. Tertiary amines, when allowed to react with benzyne precursors, lead to Stevens rearrangement products by a process that presumably involves ylides.⁴⁴⁻⁴⁷ The rearrangement products obtained when a series of allyl-amines was allowed to react with 2-fluorophenylmagnesium bromide presumably arose through the allylammonium ylide **2** which comes from the less stable betaine **1** through a rapid proton transfer.⁴⁴ In these



reactions no evidence for rearrangement of the betaine **1** was found, although a similar betaine has been trapped in the reaction of Equation 1.⁴⁷



In what appears to be the only comparison of the benzyne-amine and the more general salt-base method of forming the ylide, the latter procedure



⁴⁴ H. Hellmann and G. M. Scheytt, *Ann.*, **642**, 22 (1961).

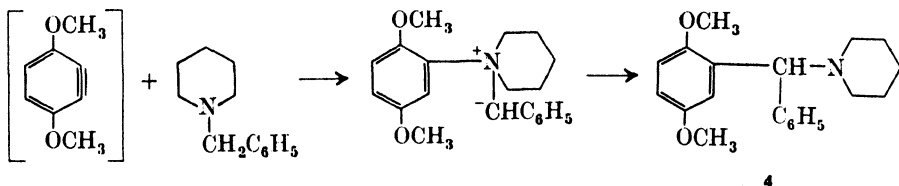
⁴⁵ H. Hellmann and W. Unseld, *Ann.*, **631**, 82 (1960).

⁴⁶ G. Wittig and E. Benz, *Chem. Ber.*, **92**, 1999 (1959).

⁴⁷ G. Wittig and W. Merkle, *Ber.*, **76**, 109 (1943).

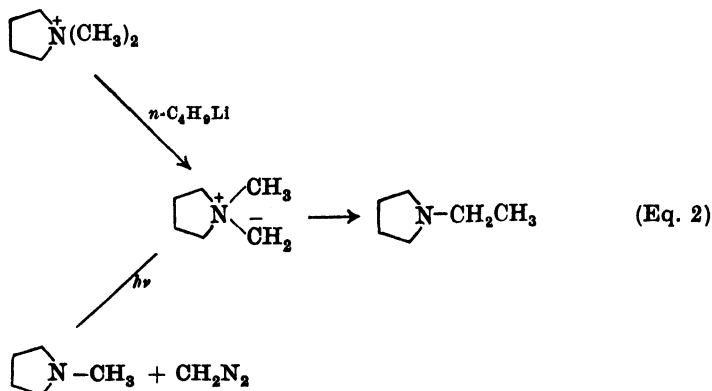
gave a better yield.⁴⁶⁻⁴⁸ However, the reaction conditions were not totally comparable and a comparison of the methods based on these two reactions may not be valid.

Of interest in these benzyne-amine promoted rearrangements is the observation of products which can be attributed to migration of an aryl



group,^{49-50a} although product 4 might arise from reaction of the benzyne with metalated N-benzylpiperidine. Again the mechanism of the benzyne-amine reaction is uncertain since related benzylpiperidinium salts undergo typical Stevens or Sommelet-Hauser rearrangements when treated with base.^{51, 52} Possibly the same ylides form in the salt-base and the benzyne-amine reactions, but are of different reactivities. This appears to occur in the generation of carbenes from different sources.⁵³

Another related source of the ylide precursor is the reaction of a tertiary amine with a carbene precursor.⁵⁴⁻⁵⁶ In one example (Eq. 2) it was



⁴⁶ F. Weygand, A. Schroll, and H. Daniel, *Chem. Ber.*, **97**, 857 (1964).

⁴⁸ G. Ehrhart and G. Seidl, *Chem. Ber.*, **97**, 1994 (1964).

⁵⁰ H. Heaney and T. J. Ward, *Chem. Commun.*, **1969**, 810.

^{50a} W. E. Truce and D. L. Heuring, *Chem. Commun.*, **1969**, 1499.

⁵¹ L. P. A. Fery and L. Van Hove, *Bull. Soc. Chim. Belges*, **68**, 65 (1959).

⁵² A. A. Aroyan, *Arm. Khim. Zh.*, **20**, 638 (1967) [*C.A.*, **68**, 86919 (1968)].

⁵³ J. Hine, *Divalent Carbon*, pp. 8-36, Ronald Press, New York, 1964.

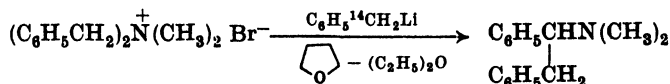
⁵⁴ W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, **1952**, 4675.

⁵⁵ V. Franzen and H. Kuntze, *Ann.*, **627**, 15 (1959).

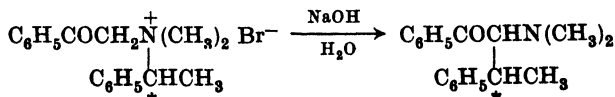
⁵⁶ M. Saunders and R. W. Murray, *Tetrahedron*, **11**, 1 (1960).

found that the salt-base⁵⁷ and carbene-amine⁵⁵ reactions give the same rearrangement products. Again the carbene pathway is not clear from these results, since the side products indicate that methylene insertion on N-methylpyrrolidine may lead to all the observed products.

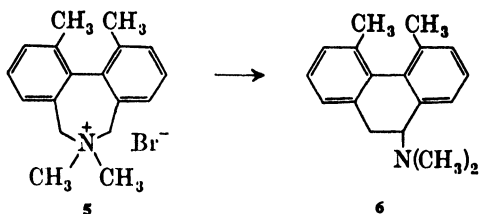
The intramolecularity of the rearrangement was initially demonstrated by Stevens¹¹ and supported by subsequent workers.²⁰⁻²² In a particularly sensitive test it was found that dibenzylidimethylammonium bromide rearranges with no incorporation of ¹⁴C when labeled benzyl lithium is used as the base.²⁰



The high stereospecificity is pertinent to the synthetic utility and mechanistic considerations of the Stevens rearrangement.^{17-19, 23} Rearrangement of phenacyl- α -phenylethyldimethylammonium bromide proceeds with greater than 95% retention of configuration.^{17, 18, 58}



Consistent with the high stereospecificity is the observation that biphenyl chirality is transferred to a developing asymmetric carbon atom during the rearrangement.⁵⁹⁻⁶² For example, the optically active heterocycle **5** leads to an optically active diastereomer of the dihydrophenanthrene **6**.⁶² One enantiomer of **5** leads to one diastereomer of **6** and the other enantiomer of **5** to the enantiomeric diastereomer of **6**. Interestingly, different



diastereomers of **6** were obtained when one enantiomer of **5** was treated with phenyllithium in diethyl ether or with sodium amide in ammonia.⁶²

⁵⁷ G. Wittig and T. F. Burger, *Ann.*, **632**, 85 (1960).

⁵⁸ U. Schöllkopf, personal communication.

⁵⁹ J. H. Brewster and R. S. Jones, Jr., *J. Org. Chem.*, **34**, 354 (1969).

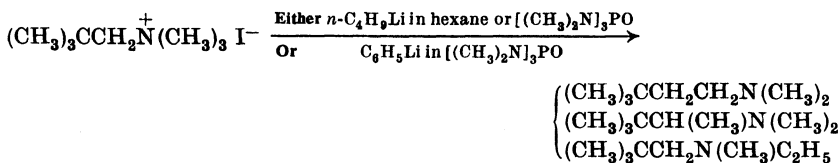
⁶⁰ H. Joshua, R. Gans, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4884 (1968); K. Mislow and H. Joshua, *ibid.*, **87**, 666 (1965).

⁶¹ R. K. Hill and T. Chan, *J. Amer. Chem. Soc.*, **88**, 866 (1966).

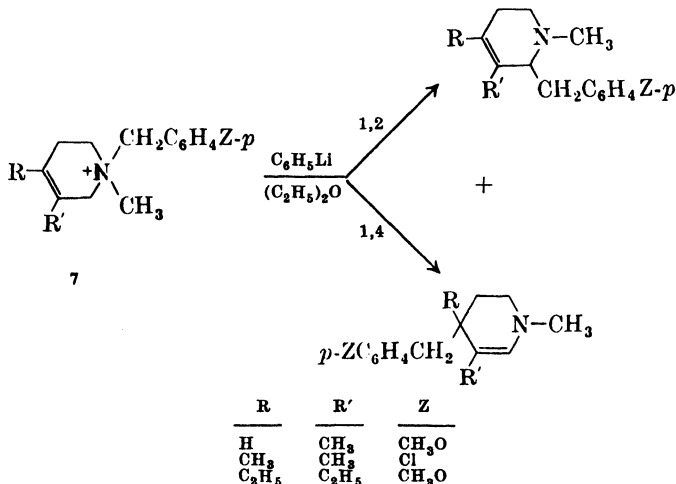
⁶² G. Wittig and H. Zimmermann, *Chem. Ber.*, **86**, 629 (1953).

This result can be attributed to mutarotation of the biphenyl chirality after rearrangement rather than to different stereospecificity in the two solvents.⁶⁰

Simple tetraalkyl quaternary ammonium salts (with the exception of tetramethylammonium)^{63, 64} have generally not been investigated, perhaps because of the strong base required for ylide formation. An interesting example is neopentylammonium iodide, which has been found to give all the possible rearrangement products.⁶⁵ An unusual aspect of this rearrangement is the observation of the N-ethyl product.



The Stevens rearrangement has been used to prepare amines of biological interest from heterocyclic quaternary ammonium salts.^{31, 66-69} The tetrahydropyridinium salts **7** undergo both 1,2 and 1,4 rearrangements.^{31, 66}



⁶³ H. Daniel and J. Paetsch, *Chem. Ber.*, **101**, 1445 (1968).

⁶⁴ W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967).

⁶⁵ S. H. Pine, B. A. Catto, and F. G. Yamagishi, unpublished results.

⁶⁶ A. E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966).

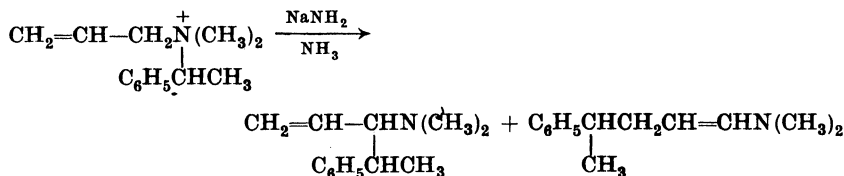
⁶⁷ J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

⁶⁸ E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

⁶⁹ M. Takeda, A. E. Jacobson, and E. L. May, *J. Org. Chem.*, **34**, 4158 (1969).

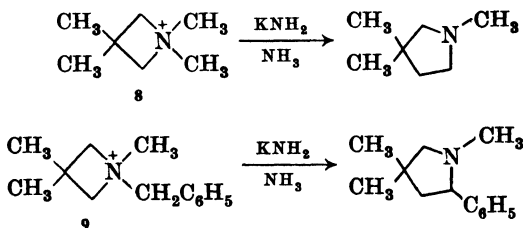
⁶⁰ R. Maeda and E. Ohsugi, *Chem. Pharm. Bull. (Tokyo)*, **16**, 897 (1968).

Many examples of concurrent 1,2 and 1,4 rearrangements in allylic systems have been reported^{28, 44, 70, 71} and provide data for an interesting discussion of the application of orbital symmetry arguments to the Stevens rearrangement.⁷² It has been suggested that the formation of products which

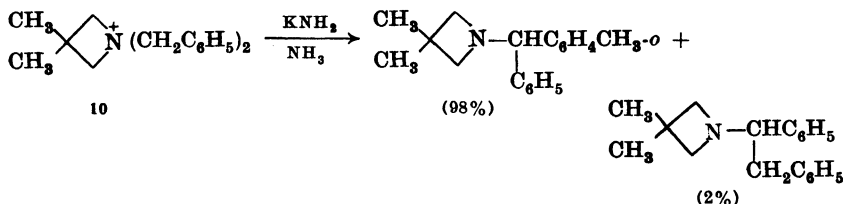


apparently violate these rules can be accounted for by invoking a thermal isomerization of the allowed rearrangement product.⁷² It will be surprising, however, if such an isomerization is found to take place at the temperature of liquid ammonia at which many of these observations have been made.⁷¹

The rearrangement of small-ring heterocyclic quaternary ammonium salts indicates that strain may influence the course of the reaction. Azetidinium salts **8** and **9** both lead to products of ring expansion.



However, the dibenzyl salt **10** provides principally Sommelet-Hauser product, with a small amount of Stevens product and no ring expansion.³⁰ The presence of the two benzyl groups in **10** may be critical in controlling the

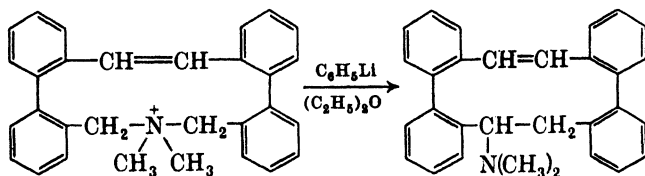
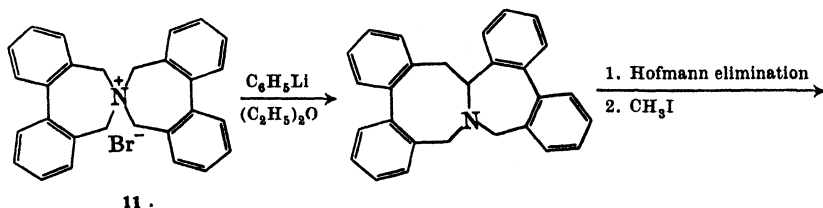


⁷⁰ H. Hellmann and G. M. Scheytt, *Ann.*, **654**, 39 (1962).

⁷¹ R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, **1967**, 1289.

⁷² R. W. Jemison and W. D. Ollis, *Chem. Commun.*, 294 (1969).

stability of the potentially competing pathways. Simple pyrrolidinium⁷³ and piperidinium^{11, 51, 52} salts, where ring strain effects are much less severe, generally do not undergo ring opening under similar conditions. An interesting ring expansion followed by ring contraction occurs in a synthetic sequence on the spiro quaternary ammonium salt **11**.⁷⁴



Competing reactions may limit the utility of the rearrangement. Competitive Sommelet-Hauser and Stevens rearrangements are discussed in a later section. Displacement of an N-alkyl group to yield a tertiary amine tends to occur with good nucleophiles and relatively weak bases, *e.g.*, alcohol-alkoxide.⁷⁵⁻⁷⁷ In compounds containing a *beta* hydrogen atom, Hofmann elimination⁴ may compete and in many cases provides the major product.^{57, 71, 78-82} The solvent-base system used appears to markedly affect the competition between elimination and rearrangement reactions. Elimination is generally favored by polar solvents with nucleophilic bases or by pyrolysis, whereas rearrangement is favored by organolithium bases in nonpolar solvents. This is illustrated by the menthyltrimethylammonium (Eq. 3)⁷⁸ and dimethylpyrrolidinium salts (Eq. 4).^{57, 82}

⁷³ L. P. A. Fery and L. Van Hove, *Bull. Soc. Chim. Belges*, **69**, 63 (1960).

⁷⁴ G. Wittig, G. Koenig, and K. Clauss, *Ann.*, **593**, 127 (1955).

⁷⁵ S. H. Pine, T. R. Phillips, and G. Bartolini, unpublished results.

⁷⁶ J. Tanaka, J. E. Dunning, and J. C. Carter, *J. Org. Chem.*, **31**, 3431 (1966).

⁷⁷ Ref. 4, pp. 350-352.

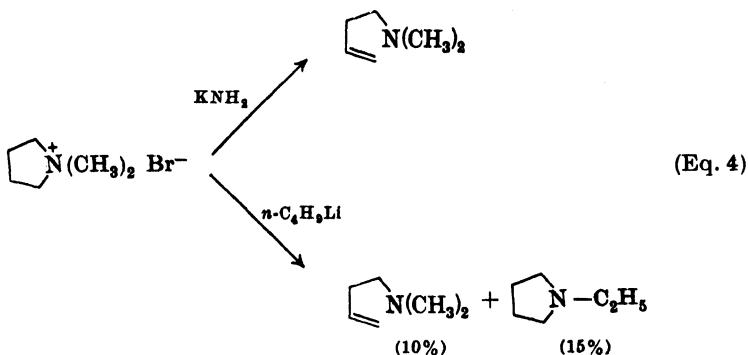
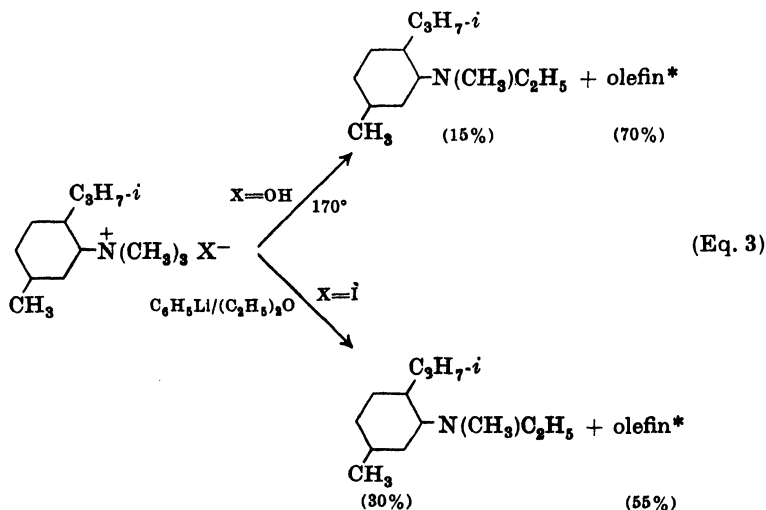
⁷⁸ M. A. Baldwin, D. V. Banthorpe, A. G. Loudon, and F. D. Waller, *J. Chem. Soc.*, **B**, 1967, 509.

⁷⁹ L. P. A. Fery and L. Van Hove, *Bull. Soc. Chim. Belges*, **69**, 79 (1960).

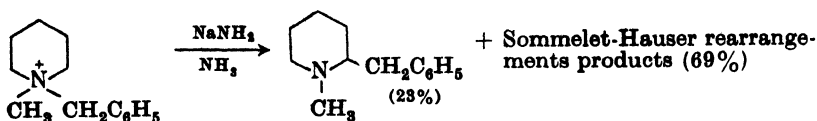
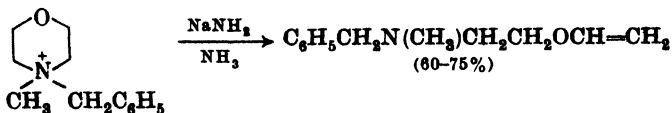
⁸⁰ C. L. Bumgardner, *J. Org. Chem.*, **27**, 1035 (1962).

⁸¹ C. L. Bumgardner, *J. Amer. Chem. Soc.*, **83**, 4420, 4423 (1961).

⁸² G. Wittig and W. Tochtermann, *Chem. Ber.*, **94**, 1692 (1961).



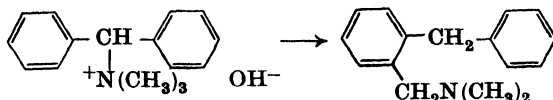
Polar and conformational effects on the competitive reactions are illustrated by a comparison of the morpholinium⁷⁹ and piperidinium⁸¹ systems.



* The "olefin" is a mixture of 2- and 3-menthene.

THE SOMMELET-HAUSER REARRANGEMENT

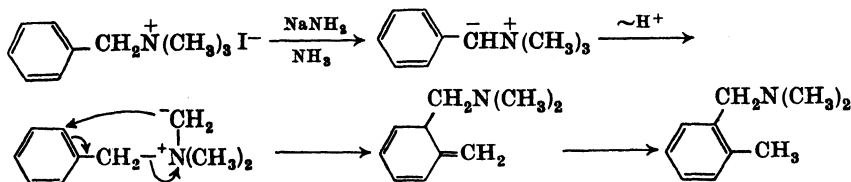
In 1937, Sommelet reported a "special kind of molecular rearrangement" after observing that the trimethylamino group of benzhydryltrimethylammonium hydroxide migrated to an *ortho* position in one of the phenyl rings.³ Although the rearrangement was originally accomplished in the sunlight, it is now known to be a base-promoted reaction where the sunlight was simply a source of heat.⁴² This brief report appears to be the



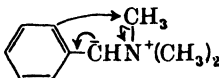
extent of the contribution of Sommelet to the reaction now bearing his name. It remained for Hauser and coworkers to investigate the rearrangement extensively and to demonstrate its generality in benzylammonium systems.

Mechanistic Considerations

Kantor and Hauser, in a broad initial study, found that benzyltrimethylammonium iodide rapidly gives a nearly quantitative yield of 2,N,N-trimethylbenzylamine when allowed to react with sodium amide in liquid ammonia.² They proposed a mechanism involving formation of the more stable benzyl carbanion ylide followed by isomerization to the methyl ylide, which then undergoes an allylic nucleophilic attack at the *ortho* position of the benzene ring. The exomethylene intermediate aromatizes to give the product

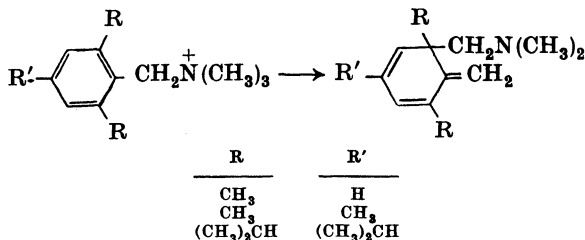


In this example of the Sommelet-Hauser rearrangement an alternative mechanism involving methyl transfer to the *ortho* position was also considered but shown, by use of ¹⁴C-labeling⁸³ and by comparison with analogous rearrangements in other systems,² not to be involved.

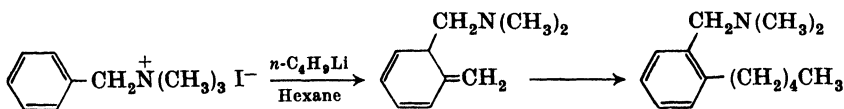


⁸³ F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **26**, 2979 (1961).

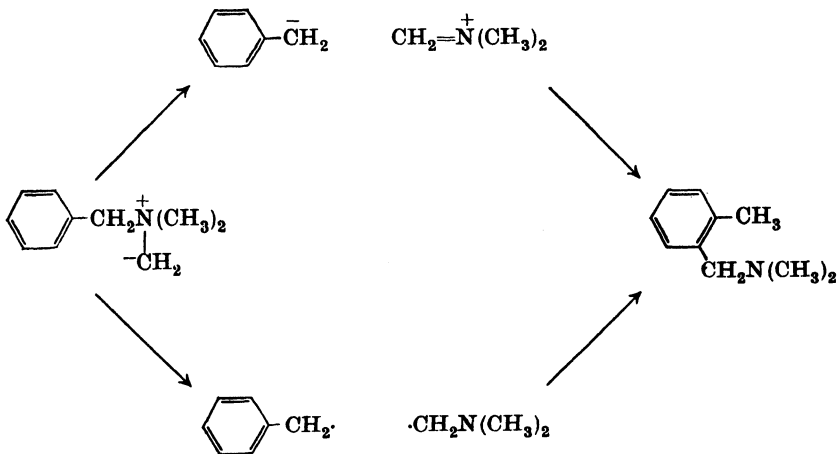
Evidence supporting the exomethylene intermediate was obtained by carrying out the rearrangement with 2,6-disubstituted⁸⁴ and 2,4,6-trisubstituted benzylammonium salts.^{85, 86} The exomethylene intermediates from these compounds cannot rearomatize to the rearrangement product and can, therefore, be isolated.



The exomethylene intermediate in the parent system has since been trapped by the formation of *N,N*-dimethyl-2-*n*-pentylbenzylamine when the rearrangement of benzyltrimethylammonium iodide was carried out with *n*-butyllithium as the base.⁸⁷



In view of the evidence supporting a dissociation-recombination mechanism for the Stevens rearrangement, a similar mechanism is attractive for



⁸⁴ C. R. Hauser and D. N. Van Eenam, *J. Org. Chem.*, **23**, 865 (1958).

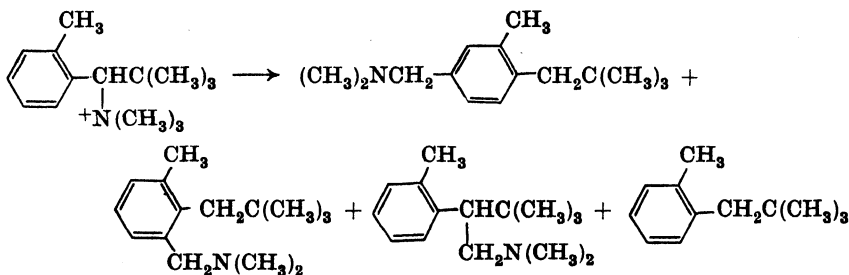
⁸⁵ D. N. Van Eenam and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 5520 (1957).

⁸⁶ C. R. Hauser and D. N. Van Eenam, *J. Amer. Chem. Soc.*, **79**, 5512 (1957).

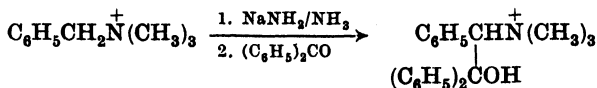
⁸⁷ S. H. Pine and B. L. Sanchez, *Tetrahedron Lett.*, **1969**, 1319.

the Sommelet-Hauser rearrangement.^{75,88-90} In this case the ion-pair intermediate to be expected involves a relatively stable benzyl carbanion.⁸⁸⁻⁹⁰ It is worth noting, however, that a radical pair is also a reasonable intermediate here.

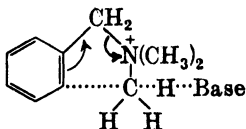
As expected if a dissociated intermediate is involved, a small amount of *para* rearrangement of the dimethylaminomethyl group is found in the rearrangement of benzyltrimethylammonium salts.⁹¹ With the more hindered α -phenylneopentylammonium salts various base-solvent systems provide up to 10% of the *para* rearrangement product.^{75, 90} More notable, an *ortho*-substituted salt may yield more of the *para* product than of the usual *ortho* product.⁷⁵ In addition, the hydrocarbons expected from reaction of the intermediate with solvent are observed along with products of the Stevens rearrangement.



The importance of initial ylide formation in the Sommelet-Hauser rearrangement has been explored by many workers.^{41-43, 92} The benzyl ylide from benzyltrimethylammonium salt was trapped under typical



Sommelet-Hauser reaction conditions using benzophenone,⁹² although no evidence for the methyl ylide could be found. The latter fact along with the observed base dependence led to the suggestion that the



⁸⁸ C. L. Bumgardner, *J. Amer. Chem. Soc.*, **85**, 73 (1963).

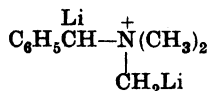
⁸⁹ Ref. 6, p. 229.

⁹⁰ S. H. Pine, *Tetrahedron Lett.*, **1967**, 3393.

⁹¹ S. H. Pine and B. L. Sanchez, unpublished results.

⁹² W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1105 (1964).

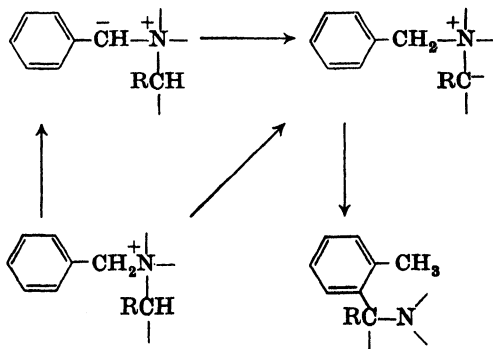
Sommelet-Hauser reaction may involve a concerted mechanism rather than initial ylide formation.⁹³ At the other extreme is the suggestion that a dilithio precursor is involved.⁴⁰



There have been no investigations of the stereochemistry or intramolecularity of the Sommelet-Hauser rearrangement. It has generally been assumed that the results would be comparable to those for the Stevens rearrangement.

Scope

In general, products obtained from the Sommelet-Hauser rearrangement suggest that formation of the carbanion of the *reacting ylide* is rate-determining.^{88, 92, 94} This sequence is applicable whether the reacting ylide is formed through an initial benzylic ylide or directly from the original



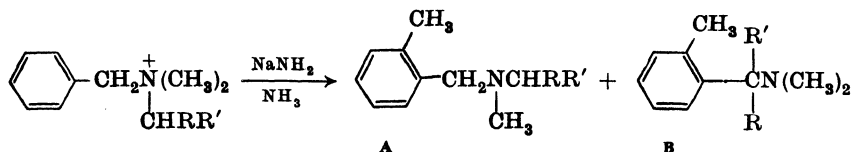
salt, as determined by the relative acidities of the hydrogen atoms involved. Table I records the results of a series of Sommelet-Hauser rearrangements in which two possible products may occur. In all cases, the major product originates from the more stable of the two possible *reacting ylide* carbanions.

Rearrangement of the unsymmetrical benzyl-*p*-methoxybenzylidimethylammonium bromide provides a further example of the importance of ylide formation in directing the course of the rearrangement. The more favorable ylide (based on expected carbanion stability) leads to the

⁹³ A. R. Lepley and R. H. Becker, *J. Org. Chem.*, **30**, 3888 (1965).

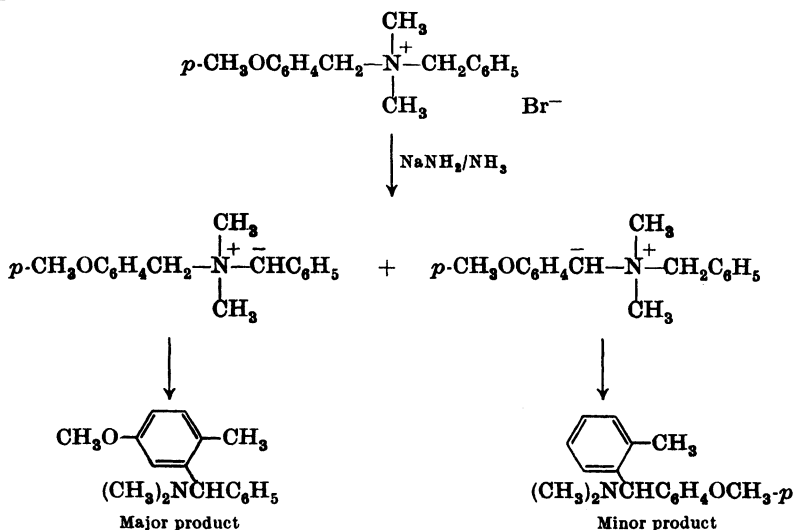
⁹⁴ K. P. Klein, R. L. Vaulx, and C. R. Hauser, *J. Amer. Chem. Soc.*, **88**, 5802 (1966).

TABLE I. COMPETITIVE SOMMELET-HAUSER REACTIONS



R	R'	Per Cent Yield		Ratio A:B	Ref.
		A	B		
CH ₃	CH ₃	70	12	5.8	95
CH ₃	H	64	12	5.3	95
C ₂ H ₅	H	42	10	4.2	95
n-C ₃ H ₇	H	47	12	3.9	95
C ₆ H ₅ CH ₂ CH ₂ CH ₂	H	26	9	3.9	88
(CH ₃) ₂ CH	H	38	8	4.7	95
Δ	H	16	64	0.25	88
CH ₂ =CH	H	—	6	<1	88

major product even though rearrangement to the less electrophilic ring is required.⁹⁵

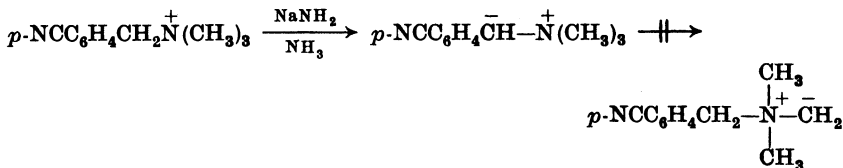


Rearrangement is inhibited when formation of the required ylide precursor is unfavorable. Thus the *p*-cyanobenzylammonium salt gives no rearrangement product when treated with sodium amide; only

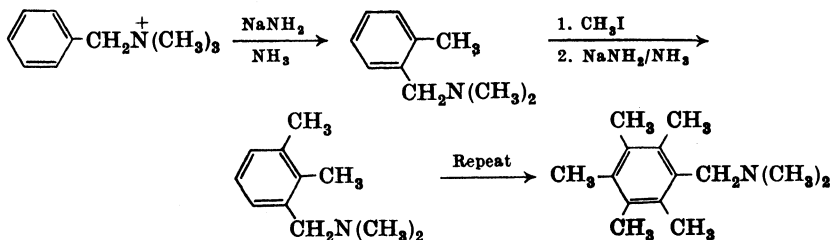
⁹⁵ F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 1542 (1962).

⁹⁶ W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **26**, 371 (1961).

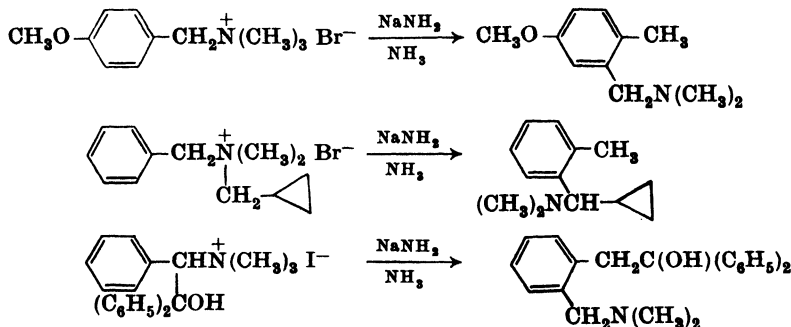
starting material is recovered.^{97, 98} This result suggests that the benzyl carbanion ylide is so stabilized by the cyano group that the methyl ylide required for rearrangement does not form.



The applicability of the Sommelet-Hauser rearrangement to most benzyl quaternary ammonium salts often provides a useful synthetic sequence to benzylamines. In addition to the vicinal polymethylbenzylamines available from the parent compound,² many substituted benzyl-



amines have been obtained from ring-substituted,^{52, 97, 99-102} nitrogen-substituted,^{36, 88, 95} and benzyl-substituted^{95, 98, 103} quaternary salts. However, if the substituent prevents formation of the requisite ylide, rearrangement will not occur.^{97, 98} Halogen substituents on the phenyl ring also



⁹⁷ W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

⁹⁸ W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1108 (1964).

⁹⁹ R. L. Vaulx, G. C. Jones, and C. R. Hauser, *J. Org. Chem.*, **27**, 4385 (1962).

¹⁰⁰ W. Q. Beard, Jr., D. N. Van Eenam, and C. R. Hauser, *J. Org. Chem.*, **26**, 2310 (1961).

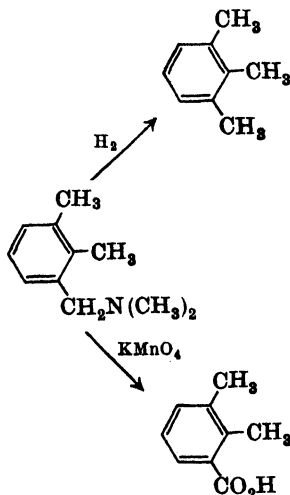
¹⁰¹ C. R. Hauser, W. Q. Beard, Jr., and F. N. Jones, *J. Org. Chem.*, **26**, 4790 (1961).

¹⁰² C. R. Hauser and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **76**, 1264 (1954).

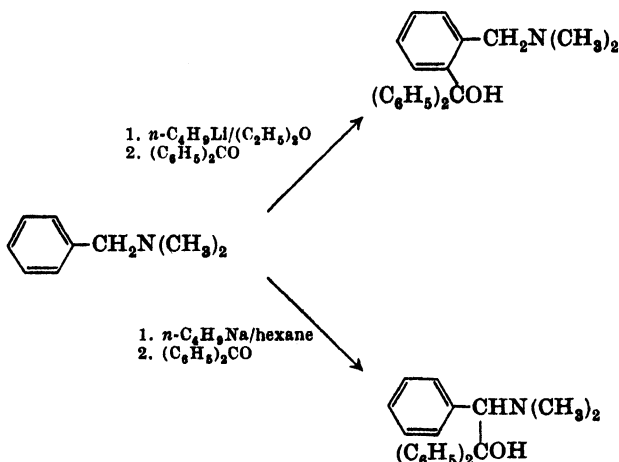
¹⁰³ W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1394 (1964).

appear to markedly decrease the yield of rearrangement product, apparently by favoring side reactions.^{96, 97}

The reductive cleavage (debenzylation)^{2, 104} or oxidation² of the rearrangement product may provide the respective substituted aromatic compound or carboxylic acid.



Specific metalation at the *ortho*-^{105–107} or α -position^{108–109} of the benzylamine products followed by typical organometallic reactions further extends the utility of the rearrangement.



¹⁰⁴ W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 263 (1953).

¹⁰⁵ K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **32**, 1479 (1967).

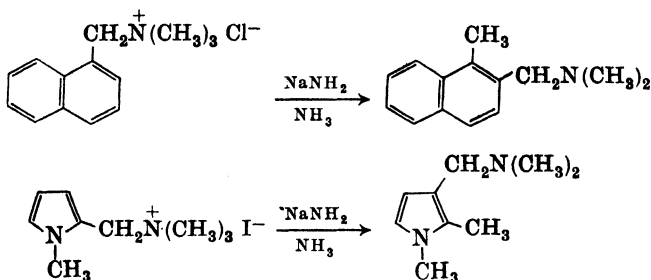
¹⁰⁶ F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).

¹⁰⁷ F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

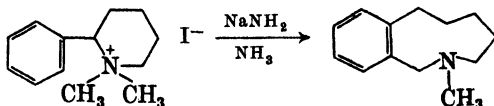
¹⁰⁸ W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **28**, 3465 (1963).

¹⁰⁹ W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

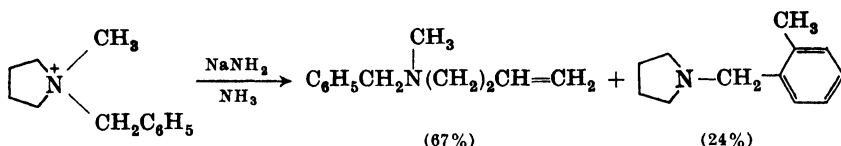
The Sommelet-Hauser rearrangement also occurs in the naphthalene system¹¹⁰ and many aromatic heterocyclic compounds.¹¹¹



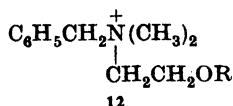
In some cases, ring expansion has been observed during the rearrangement.^{112, 113}



The major competing reactions are the Stevens rearrangement and elimination.^{4, 95, 102, 103, 114-118} Elimination becomes significant when a *beta* hydrogen atom is present¹¹⁶ but may not furnish the major product at the



usual low temperature of the reaction.^{95, 118} The close balance between rearrangement and elimination is illustrated by the benzylammonium salts 12. When $\text{R} = \text{H}$, reaction with sodium amide in liquid ammonia gave principally rearrangement, while with $\text{R} = \text{CH}_3$ only elimination



¹¹⁰ C. R. Hauser, D. N. Van Eenam, and P. L. Bayless, *J. Org. Chem.*, **23**, 354 (1958).

¹¹¹ R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, **1968**, 2134.

¹¹² G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962).

¹¹³ D. Lednicer and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 4449 (1957).

¹¹⁴ L. Wilputte-Steinert, L. P. A. Fery, and J. Nasielski, *Bull. Soc. Chim. Belges*, **78**, 77 (1969):

¹¹⁵ C. L. Bumgardner, *J. Amer. Chem. Soc.*, **88**, 5515 (1966).

¹¹⁶ L. P. A. Fery and L. Wilputte-Steinert, *Bull. Soc. Chim. Belges*, **78**, 154 (1964).

¹¹⁷ H. Daniel and F. Weygand, *Ann.*, **671**, 111 (1964).

¹¹⁸ F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 4020 (1962).

was observed.¹¹⁹ Formation of the alkoxide anion from the hydroxyl compound inhibits base attack at the adjacent *beta* hydrogen atom, whereas no such anion is formed from the ether and elimination is preferred.

COMPETITIVE STEVENS AND SOMMELET-HAUSER REARRANGEMENTS

When structurally feasible, the Stevens and Sommelet-Hauser rearrangements of quaternary ammonium salts may occur simultaneously, thus limiting their synthetic utility. However, the dependence of these competing rearrangements on conditions often permits selective reaction. The nature of the reaction medium appears to play a major role in directing the rearrangements. Sodium amide in liquid ammonia tends to lead principally to the Sommelet-Hauser product,² whereas alkyllithiums in ether or hydrocarbon solvents increase the Stevens product.^{40, 120} Generally, polar solvents favor the Sommelet-Hauser rearrangement, as illustrated by the essentially exclusive formation of 2,N,N-trimethylbenzylamine from benzyltrimethylammonium salts in liquid ammonia at -33° ,² in hexamethylphosphoramide at 25° ,⁹¹ and in dimethyl sulfoxide at 60° .¹²¹ Particularly noteworthy is the wide temperature range involved in these examples (see discussion of the influence of temperature below). In contrast, the same reaction carried out with *n*-butyllithium in ether-hexane provides almost 40% of Stevens rearrangement products, although the Sommelet-Hauser product still predominates.⁴⁰

Solubility may be a factor in the solvent effects observed. Trimethylbenzylammonium halides are essentially insoluble in ether or hydrocarbons, whereas the *p*-*t*-butylphenoxide salt is soluble in ether.³⁹ As shown in Table II, a marked difference in product ratio accompanies the change in solubility. The small changes that occur when the anion is iodide or chloride may also be related to solubility differences.

The change in the basic species may be reflected in these results. It is known that different results are often obtained with different bases in the same solvent system.^{93, 122} The change in solubility of the salt may lead to changes in basicity of the basic species and possible alteration of the solvent character.¹²³

The benzyltrimethylammonium system favors Sommelet-Hauser rearrangement in most cases,^{39, 40, 93, 120} and may not be a good test for solvent effects. The α -phenylneopentyl salts are more sensitive to solvent.

¹¹⁹ G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 806 (1962).

¹²⁰ A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).

¹²¹ K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **31**, 4276 (1966).

¹²² S. H. Pine, unpublished results.

¹²³ R. D. Singh, P. P. Rastogi, and R. Gopal, *Can. J. Chem.*, **46**, 3525 (1968).

The results of competitive rearrangements suggest that the preference for Sommelet-Hauser over Stevens rearrangement is in the order $\text{NH}_3 > (\text{CH}_3)_2\text{SO} \geq [(\text{CH}_3)_2\text{N}]_3\text{PO} > \text{hexane}$.⁷⁵ This is the order of decreasing solvent acidity.¹²⁴ The solvent may function as a proton transfer agent in the Sommelet-Hauser rearrangement pathway.¹²¹

TABLE II. THE IMPORTANCE OF SOLUBILITY IN COMPETITIVE STEVENS AND SOMMELET-HAUSER REARRANGEMENTS

$$\text{C}_6\text{H}_5\text{CH}_2\text{N}^+(\text{CH}_3)_3 \text{X}^- \rightarrow \text{A} + \text{B}$$

$$\text{A: } o\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_2 \quad \text{B: } \text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$$

Solvent	X ⁻	Salt Solubility	A:B	Ref.
n-Pentane	Cl	Insoluble	5.2	93
n-Pentane	I	Insoluble	4.0	93
Diethyl ether	I	Insoluble	1.7	40
Diethyl ether	p-(CH ₃) ₃ CC ₆ H ₄ O	Soluble	75	39
[(CH ₃) ₂ N] ₃ PO	I	Soluble	99	91
NH ₃	I	Soluble	>100	2
(CH ₃) ₂ SO	I	Soluble	>100	121

Temperature influences the competitive rearrangements. Increased temperature favors the Stevens rearrangement, although most of the comparisons have involved a change in solvent also.^{40, 125, 126} However, a recent comparison of the competitive rearrangements of dibenzyltrimethylammonium bromide in dimethyl sulfoxide over a broad temperature range supports this trend.¹²⁷

The competing rearrangements may occur through mechanistically different pathways⁹³ or from a common intermediate which partitions between the various products.^{127a} When the same ylide leads to both rearrangements, this ylide is the common intermediate. However, when different ylides are precursors of the competing rearrangements, ylide stability does not appear to govern the direction of rearrangement. The parent benzyltrimethylammonium salt illustrates this situation, for the major product, A, comes from the less stable (more reactive) ylide. Note, however, that the Sommelet-Hauser pathway involves the more stable ion-pair intermediate (the same would be true for a radical-pair intermediate), and this may be the controlling factor. The solvent trend

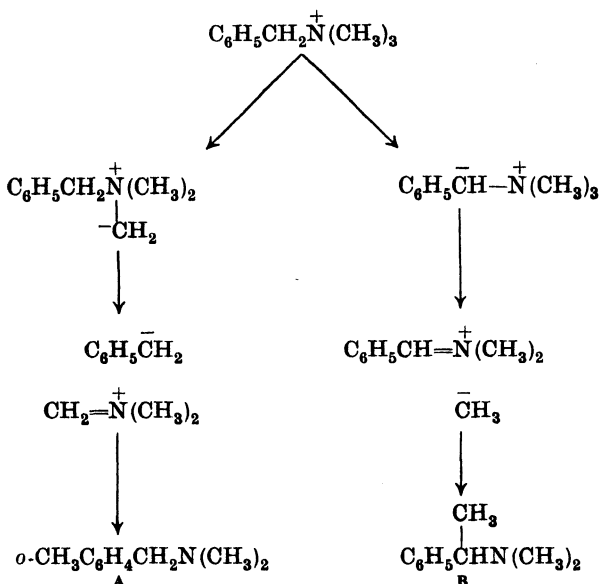
¹²⁴ H. Normant, *Ang. Chem., Int. Ed. Engl.*, **6**, 1046 (1967); Ref. 6, pp. 14, 43.

¹²⁵ G. Wittig and H. Streib, *Ann.*, **584**, 1 (1953).

¹²⁶ Ref. 5, pp. 386-391.

¹²⁷ C. L. Bumgardner, personal communication.

^{127a} J. E. Baldwin, J. E. Brown, and R. W. Cordell, *J. Chem. Soc.*, **D**, 1970, 31.



may support a more dissociated intermediate in the Sommelet-Hauser rearrangement, a possibility which has not been experimentally tested.

EXPERIMENTAL CONSIDERATIONS

The major requirement for carrying out the Stevens or Sommelet-Hauser rearrangement is a sufficiently strong base to form the requisite ylide. Although sodium hydroxide or alkoxide may be effective with phenacyl or other activated salts, stronger bases such as sodium amide or alkyllithiums are generally required. However, the stronger bases often lead to further reaction of the initial products, including elimination and rearrangement. A lower reaction temperature may minimize these side reactions, but has the disadvantage of favoring the Sommelet-Hauser over the Stevens rearrangement.

Because most quaternary ammonium salts are insoluble in nonpolar organic solvents, reactions using organolithium bases are generally run in a heterogeneous manner and tend to favor the Stevens rearrangement. The solvents liquid ammonia, dimethyl sulfoxide, and hexamethylphosphoramide generally dissolve the salts, but tend to favor the Sommelet-Hauser rearrangement. However, in the latter two solvents, raising the temperature may decrease this preference. Alcohols generally give a homogeneous reaction but usually lead to dealkylation rather than rearrangement. *Caution should be observed with simple tetraalkylammonium salts in*

sodium amide-ammonia because explosions have occurred even at low temperatures.⁶⁴

Most rearrangements are rapid and 1–4 hours is sufficient time for reaction. Potential problems with hygroscopic salts or air-sensitive bases are avoided by working in closed systems under nitrogen.

The amine products are generally recovered by extraction with dilute acid and purified by distillation or other means. The tendency of some amines to react rapidly with carbon dioxide in the air may necessitate working in closed systems throughout the procedure. Gas chromatography has been particularly useful for separating the mixtures of isomeric amines.

EXPERIMENTAL PROCEDURES

2,N,N-Trimethylbenzylamine and/or α ,N,N-Trimethylbenzylamine. The four procedures that follow are for the rearrangement of benzyltrimethylammonium salts and are also applicable to other related salts.

(a) *With Sodium Amide-Ammonia.* The preparation of benzyltrimethylammonium iodide in 94–99% yield from N,N-dimethylbenzylamine and methyl iodide and its rearrangement to 2,N,N-trimethylbenzylamine in 90–95% yield by means of sodium amide in liquid ammonia are described in *Organic Syntheses*.¹²⁸ The procedure is generally useful for rearrangements with sodium amide-liquid ammonia.

(b) *With Sodium Methylsulfinylcarbanion-Dimethyl Sulfoxide.*¹²¹ A solution of 6.95 g (0.025 mol) of benzyltrimethylammonium iodide in 50 ml of dimethyl sulfoxide was added during 1 minute to a stirred solution of 0.03 mol of sodium methylsulfinylcarbanion in 100 ml of dimethyl sulfoxide at 60–65°. A light-red color produced initially changed to yellow within 2 minutes. The reaction mixture was stirred for 1 hour and was poured into 200 ml of ice water. The resulting mixture was extracted three times with methylene chloride. The combined methylene chloride extracts were washed with cold water and extracted three times with 4 N hydrochloric acid. The acid extracts were combined and made basic with potassium hydroxide. The resulting mixture was extracted three times with diethyl ether, and the ether solution was dried over magnesium sulfate. The solvent was removed and the residual oil was distilled to give 3.1 g (82%) of 2,N,N-trimethylbenzylamine, bp 80–82° (14 mm). The picrate melted at 112–113°. A gas chromatogram of the product showed less than 1% of a high boiling contaminant.

¹²⁸ W. R. Brasen and C. R. Hauser, *Org. Syn. Coll. Vol.*, **4**, 585 (1963).

The methylene chloride that had been extracted with acid was dried over magnesium sulfate and concentrated to yield less than 0.1 g of unidentified neutral material.

(c) *With *n*-Butyllithium in Hexamethylphosphoramide-Hexane.*⁹¹ To a solution of 0.28 g (0.001 mol) of benzyltrimethylammonium iodide in 5 ml of hexamethylphosphoramide under nitrogen was added 1.2 ml of 1.7 *N* (0.002 mol) *n*-butyllithium in hexane. After 24 hours at room temperature, water was carefully added, the organic phase was extracted with pentane, and the pentane was washed with additional water. Extraction of the pentane with 3 *N* hydrochloric acid followed by regeneration of the basic material with sodium hydroxide gave 0.12 g (80%) of 2,*N,N*-trimethylbenzylamine containing less than 1% of other rearrangement products as analyzed by gas chromatography.

(d) *With *n*-Butyllithium in Diethyl Ether-Hexane.*⁴⁰ To a stirred mixture of 13.85 g (0.05 mol) of benzyltrimethylammonium iodide in 200 ml of anhydrous ether under nitrogen at 25–30° was added 39 ml (0.06 mol) of *n*-butyllithium (approximately 1.6 *M*) in hexane. After 24 hours the reaction mixture was quenched with cold water and the ether and aqueous layers were separated. The ether layer was extracted three times with 4 *N* hydrochloric acid. The acid extracts were combined and made strongly basic with potassium hydroxide (cooled and stirred), and the resulting mixture was extracted three times with ether. The combined ether extract was dried over anhydrous magnesium sulfate, and the solvent was removed to give a mixture of crude basic products in 69% yield. Gas chromatographic analysis showed that the mixture contained 10–15% of high-boiling materials. The residual 54–59% was composed of 2,*N,N*-trimethylbenzylamine (62%), α ,*N,N*-trimethylbenzylamine (39%), and β -phenylethylamine (2%).

The ether layer remaining from the acid extraction was dried over anhydrous magnesium sulfate and the solvent was removed to afford 0.05–0.25 g (1–3%) of neutral material consisting almost entirely of *n*-pentylbenzene. The original aqueous layer was treated with ethanolic picric acid to recover any unreacted quaternary iodide as its picrate which, after recrystallization from 95% ethanol, had mp 166–167°.

2,*N,N*-Trimethylbenzhydrylamine.² To a solution of 0.22 mol of sodium amide in 300 ml of liquid ammonia was added 26.2 g (0.1 mol) of dibenzyltrimethylammonium chloride over 15–20 minutes. The reaction mixture had a light-orange color during the addition of the salt, but became gray when all the salt had been added. After 3 hours the excess sodium amide was destroyed by careful addition of ammonium

chloride. The ammonia was allowed to evaporate and the residue was shaken with water and ether until it dissolved. Evaporation of the dried ether solution gave an oil that solidified to give 21.3 g (95%) of 2,N,N-trimethylbenzhydrylamine, mp 43–46°. Three recrystallizations from ethanol-water or petroleum ether (cooled to -78°) raised the melting point to 48–49°. The picrate, recrystallized from 95% ethanol, melted at 177–178°.

N,N-Dimethyl-1,2-diphenylethylamine.⁴⁰ To a stirred mixture of 15.35 g (0.05 mol) of dibenzyltrimethylammonium bromide in 300 ml of anhydrous diethyl ether under nitrogen at 68° was added 0.06 mol of *n*-butyllithium in hexane. After 24 hours the reaction mixture was quenched with cold water and the ether layer was separated and extracted three times with 4 *N* hydrochloric acid. The acid extracts were combined and made strongly basic with potassium hydroxide (cooled and stirred), and the resulting mixture was extracted three times with ether. The combined ether extract was dried over anhydrous magnesium sulfate and the solvent removed. N,N-Dimethyl-1,2-diphenylethylamine, 6.1 g (54%) was isolated by distillation [reported bp 119–123° (0.5 mm)],¹²⁹ picrate, mp 156–157°, in addition to benzyldimethylamine (14%). The neutral fraction gave *n*-pentylbenzene (16%) and stilbene (5%).

2-Benzyl-N,N-dimethylbenzylamine and N,N-Dimethyl-2,2-diphenylethylamine.¹³⁰ Benzhydryltrimethylammonium iodide (8.85 g, 0.025 mol) was added to a stirred suspension of 0.05 mol of sodium amide in 300 ml of liquid ammonia. After 3 hours the red suspension was neutralized with 1.65 g (0.03 mol) of ammonium chloride, and the ammonia was replaced by an equal volume of diethyl ether. The ether was decanted from the solid residue, which was washed twice with ether. The ether solutions were combined and dried over magnesium sulfate, and the solvent was removed. The residue was distilled to give 4.80 g (85%) of a mixture of 2-benzyl-N,N-dimethylbenzylamine and N,N-dimethyl-2,2-diphenylethylamine, bp 126–128° (1.5 mm), in the ratio 80–85:15–20 as determined by gas chromatography.

N,N-Dimethyl-1,2,2-triphenylethylamine.³⁶ A solution of 19.2 g (0.05 mol) of N,N-dimethyl-N-benzyl-1,1-diphenylmethylammonium bromide in 100 ml of water was shaken with 7.7 g (0.055 mol) of silver oxide for 36 hours. The suspension was filtered, 40 g (1.0 mol) of sodium hydroxide was added to the filtrate, and the mixture was heated on a steam bath for 1 hour. The cooled mixture was extracted with diethyl

¹²⁹ A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **32**, 1706 (1967).

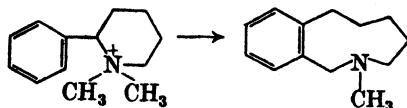
¹³⁰ K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **31**, 4275 (1966).

ether and the ether solution was extracted with 6 *N* hydrochloric acid. The acid extract was made basic, and the resulting solid was collected and recrystallized twice from methanol to give 5.2 g (35%) of *N,N*-dimethyl-1,2,2-triphenylethylamine, mp 127.5–128°.

1,2-Dimethyl-3-(dimethylaminomethyl)pyrrole.¹¹¹ To a solution of 0.24 mol of sodium amide in 250 ml of liquid ammonia was added 26.7 g (0.1 mol) of 1-methyl-2-(dimethylaminomethyl)pyrrole methiodide during 10 minutes. The reaction mixture was refluxed for 30 minutes, the ammonia was allowed to evaporate, and 250 ml of ether was added. Water (25 ml) was carefully added and the ether layer was separated. The aqueous phase was extracted with ether. The ether solution was extracted with 6 *N* hydrochloric acid. Regeneration of the basic material followed by distillation furnished 11.0 g (79%) of 1,2-dimethyl-3-(dimethylaminomethyl)pyrrole, bp 74–76° (3.5 mm).

β -Ferrocenylethyldimethylamine.¹³¹ *N,N*-Dimethylaminomethylferrocene methiodide¹³² (38.5 g, 0.1 mol) was added to a well-stirred solution of 0.2 mol of potassium amide in 500 ml of liquid ammonia during 1 hour. After an additional 3 hours excess ammonium chloride was carefully added to the brown reaction mixture and the ammonia replaced by diethyl ether. The residue was removed by filtration and carefully washed with additional ether. The ether was evaporated from the combined filtrates to give a clear amber oil which was distilled to give 10.5 g (41%) of β -ferrocenylethyldimethylamine, bp 101–103° (0.3 mm). On redistillation it boiled at 103–104° (0.35 mm); n_D^{25} 1.5805.

2,3,4,5,6,7-Hexahydro-2-methyl-1H-2-benzazonine.¹¹³ 1,1-Dimethyl-2-phenylpiperidinium iodide (74.1 g, 0.234 mol) was added to a solution of 0.46 mol of sodium amide in 900 ml of liquid ammonia during 10 minutes. The light orange-tan suspension was stirred for an additional hour and then neutralized with 23 g of ammonium chloride. The residue which remained after the ammonia had evaporated was



washed thoroughly with about 1 liter of diethyl ether. The ether was washed with water and dried over anhydrous sodium sulfate. The light-yellow oil that remained after the ether was removed afforded 38.5 g

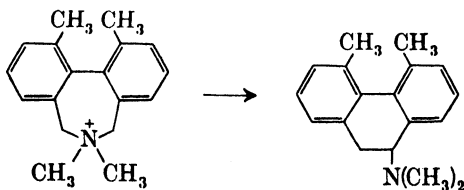
¹³¹ C. R. Hauser, J. K. Lindsay, and D. Lednicer, *J. Org. Chem.*, **23**, 358 (1958).

¹³² D. Lednicer and C. R. Hauser, *Org. Syn.*, **40**, 31 (1960).

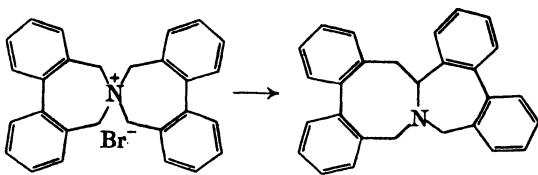
(83%) of the benzazonine, bp 104–106° (4 mm). The analytical sample, n_D^{25} 1.5380, distilled at 95.5° (3 mm), picrate mp 169–170°.

9-Dimethylamino-4,5-dimethyl-9,10-dihydrophenanthrene.⁶²

To a suspension of 0.45 g (1.35 mmol) of 6,7-dihydro-1,6,6,11-tetramethyl-5H-dibenz[c,e]azepinium bromide in 5 ml of absolute ether under nitrogen was added 1.5 ml of a 1.3 *N* solution (1.93 mmol) of phenyllithium in ether. The reaction mixture was shaken for 8 days, water was carefully added, and the organic phase was separated. Distillation gave 0.29 g (85%) of 9-dimethylamino-4,5-dimethyl-9,10-dihydrophenanthrene, bp 116.5–117.5° (0.01 mm).



3,4,5,6,9,10,11,12-Tetrabenzo-1-azabicyclo[6.5.0]3,5,9,11-tridecatetraene.⁷⁴ A suspension of 42 g (0.092 mol) of 6,6'-(7H,7'H)-spirobis[5H]-dibenz[c,e]azepinium bromide in 250 ml of 80% methanol was converted to the hydroxide by adding 15 g (0.065 mol) of silver oxide and shaking for 7 hours with three short heating periods. Filtration, evaporation, and drying under vacuum left a residue which was rearranged by heating at 160–170°. The product was recovered by distillation [bp 260–264° (0.1 mm)] to give 32 g of crude product which solidified.



Recrystallization from *n*-butanol gave 27 g (79%) of the azabicyclo-tridecatetraene, mp 174–177°. A further recrystallization from ethanol gave product with mp 176–177°.

TABULAR SURVEY

The tables list the base-promoted rearrangements of quaternary ammonium salts reported through March 1970. Compounds are divided

among the tables according to the groups attached to the ammonium nitrogen atom as follows:

Table III, alkyl, β -aralkyl, or aryl

Table IV, benzyl

Table V, arylmethyl, where aryl has two or more fused aromatic rings

Table VI, arylmethyl, where aryl is heterocyclic or ferrocenyl

Table VII, allylic

Table VIII, acetylenic

Table IX, phenacyl and related

Table X, cyclic salts in which the ammonium nitrogen atom is a ring member

If a quaternary salt contains groups from two or more of the above classes, it will be found in the table of whichever class comes latest. Thus, if a salt has two alkyl groups (Table III), a benzyl group (Table IV), and an allyl group (Table VII), it will be found in Table VII.

Within each table, compounds are arranged in the order of increasing number of carbon atoms. Compounds with the same number of carbon atoms are arranged in order of increasing complexity.

When more than one base-solvent system has been reported, separate listings are used unless the products and yields are similar. In cases where an ylide has been formed by other than the usual basic techniques, *ylide* is listed as the base. If no solvent was used, this column is blank. In addition to the usual chemical symbols, the following solvent abbreviations are used: THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; HMPA, hexamethylphosphoramide; diglyme, $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

Nonrearrangement products, i.e., elimination or substitution products, are often also formed; they are not included in the tables.

Yields are reported whenever available. If there is more than one reference, the yield reflects what I judge to be the best example of the rearrangement. In such cases the yield corresponds to the first reference listed.