

CHAPTER 1

THE SYNTHESIS OF SUBSTITUTED FERROCENES AND OTHER π -CYCLOPENTADIENYL-TRANSITION METAL COMPOUNDS

DONALD E. BUBLITZ

Western Division Research Laboratories, The Dow Chemical Company

KENNETH L. RINEHART, JR.,

University of Illinois

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INTRODUCTION

The discovery of dicyclopentadienyliron (ferrocene) in 1951^{1, 2} has led to the development of an entirely new area in the field of organometallic chemistry, that of the π -metallohydrocarbons. Representative compounds are the π -metalloarenes like dibenzenechromium, the π -metallopseudoarenes like ferrocene, and the π -metalloolefin complexes like butadieneiron tricarbonyl.

Numerous reviews³⁻⁴³ of this fascinating new branch of organometallic

¹ T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

² S. A. Miller, J. A. Tebbboth, and J. F. Tremaine, *J. Chem. Soc.*, 632 (1952).

³ S. Swaminathan and S. Ranganathan, *Current Sci. (India)*, **25**, 6 (1956).

⁴ Shiro Senoh, *Kagaku No Ryoiki*, **7**, 167 (1953) [*C.A.*, **48**, 13639 (1954)].

⁵ P. L. Pauson, in H. Zeiss, *Organometallic Chemistry*, pp. 346-379, Reinhold, New York, 1960.

⁶ P. L. Pauson, in D. Ginsburg, *Non-Benzenoid Aromatic Compounds*, pp. 107-140, Interscience, New York, 1959.

⁷ M. Rausch, M. Vogel, and H. Rosenberg, *J. Chem. Ed.*, **34**, 268 (1957).

⁸ K. Plesske, *Angew. Chem.*, **74**, 301, 347 (1962); *Angew. Chem. (Intern. Ed.)*, **1**, 312, 394 (1964).

⁹ A. N. Nesmeyanov, *Proc. Roy. Soc. (London), Ser. A.*, **246**, 495 (1958).

¹⁰ A. N. Nesmeyanov and E. G. Perevalova, *Usp. Khim.*, **27**, 3 (1958) [*C.A.*, **52**, 14579 (1958)].

¹¹ A. N. Nesmeyanov, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **7**, 249 (1962) [*C.A.*, **58**, 4596 (1963)].

¹² M. Dub, *Organometallic Compounds Literature Survey 1937-1958*, Vol. 1, Springer-Verlag, 1961.

¹³ A. N. Nesmeyanov and E. G. Perevalova, *Khim. Nauka i Promy.*, **3**, 146 (1958) [*C.A.*, **52**, 20108 (1958)].

¹⁴ P. L. Pauson, *Quart. Rev. (London)*, **9**, 391 (1955).

¹⁵ E. O. Fischer, *Angew. Chem.*, **67**, 475 (1955).

¹⁶ E. O. Fischer and H. P. Fritz, *Advan. Inorg. Chem. Radiochem.*, **1**, 55 (1959).

¹⁷ M. D. Rausch, *J. Chem. Ed.*, **37**, 568 (1960).

¹⁸ K. Schlögl, *Oesterr. Chemiker-Z.*, **59**, 93 (1958) [*C.A.*, **52**, 18358 (1958)].

¹⁹ M. E. Dyatkina, *Usp. Khim.*, **27**, 57 (1958) [*C.A.*, **52**, 14579 (1958)].

²⁰ H. Zeiss, in H. Zeiss, *Organometallic Chemistry*, pp. 380-425, Reinhold, New York, 1960.

²¹ E. O. Fischer and H. P. Fritz, *Angew. Chem.*, **73**, 353 (1961).

²² G. Wilkinson and F. A. Cotton, *Progr. Inorg. Chem.*, **1**, 1 (1959).

²³ P. L. Pauson, *Endeavour*, 175 (1962).

²⁴ M. L. H. Green, *Angew. Chem.*, **72**, 719 (1960).

²⁵ D. Braun, *Angew. Chem.*, **73**, 197 (1961).

²⁶ M. D. Rausch, *Can. J. Chem.*, **41**, 1289 (1963).

²⁷ M. D. Rausch, *Advan. Chem. Ser.*, **37**, 56 (1963).

²⁸ W. F. Little, *Survey of Progress in Chemistry*, Vol. 1, Academic, New York, 1963.

²⁹ J. M. Birmingham, *Chem. Eng. Progress*, **58**, 74 (1962).

³⁰ M. A. Bennett, *Chem. Rev.*, **62**, 611 (1962).

chemistry have appeared since that year. Some cover mainly the organic chemistry of ferrocene;^{5-13, 26-28} others cover general preparative methods, physical properties, some organic chemistry of ferrocene and related metal cyclopentadienyls;^{14-19, 29, 35, 40} still others deal largely with metal arene and metal olefin complexes (refs. 20-23, 30-34, 37, 41), with hydride complexes of transition metals,²⁴ with macromolecular organometallic compounds,²⁵ or with infrared and Raman spectral studies.³⁶ The rapid progress in π -metallohydrocarbon chemistry has in large measure been responsible for the founding of a new review series³⁸ devoted exclusively to organo-metallic chemistry; and a book has recently appeared dealing largely with the chemistry of ferrocene.³⁹

In view of this already overwhelming body of π -metallohydrocarbon literature, we have chosen arbitrarily to limit our treatment in three dimensions: to include only compounds containing cyclopentadienyl rings, of these to include only those which have been shown to undergo aromatic substitution reactions, and within this group to discuss only synthetic aspects of their chemistry. In effect, our choice very nearly restricts the discussion to syntheses of substituted ferrocenes.

Although this chapter is concerned with the synthetic aspects of aromatic cyclopentadienyl compounds, a few brief comments on bonding and geometry in ferrocene are appropriate.⁴⁴⁻⁵⁰ The bonding picture generally accepted is that which ascribes stability of the π -metallohydrocarbons to overlap of one or more d orbitals of the metal atom with the π -electron cloud of the hydrocarbon ligand. Detailed reviews of descriptions of the

³¹ R. Pettit and G. F. Emerson, *Advan. Organometal. Chem.*, **1**, 1 (1964).

³² R. Pettit, G. F. Emerson, and J. Mahler, *J. Chem. Ed.*, **40**, 175 (1963).

³³ H. D. Kaesz, *J. Chem. Ed.*, **40**, 159 (1963).

³⁴ E. O. Fischer and H. Werner, *Angew. Chem. (Intern. Ed.)*, **2**, 80 (1963).

³⁵ G. E. Coates, *Organometallic Compounds*, p. 286, Wiley, New York, 1960.

³⁶ H. P. Fritz, *Advan. Organometal. Chem.*, **1**, 239 (1964).

³⁷ R. G. Guy and B. L. Shaw, *Advan. Inorg. Chem. Radiochem.*, **4**, 77 (1962).

³⁸ *Advan. Organometal. Chem.*, F. G. A. Stone and R. West, eds., Academic, 1964.

³⁹ M. Rosenblum, *Chemistry of the Iron Group Metallocenes: Ferrocene, Ruthenocene, and Osmocene*, Wiley, 1965.

⁴⁰ J. Birmingham, *Advan. Organometal. Chem.*, **2**, 365 (1964).

⁴¹ M. L. H. Green and P. L. I. Nagy, *Advan. Organometal. Chem.*, **2**, 325 (1964).

⁴² A. N. Nesmeyanov and E. G. Perevalova, *Ann. N.Y. Acad. Sci.*, **125**, 67 (1965).

⁴³ A. N. Nesmeyanov, *Bull. Soc. Chim. France*, 1229 (1965).

⁴⁴ J. D. Dunitz and L. E. Orgel, *Nature*, **171**, 121 (1953); *J. Chem. Phys.*, **23**, 954 (1955).

⁴⁵ W. Moffitt, *J. Am. Chem. Soc.*, **76**, 3386 (1954).

⁴⁶ E. M. Shustorovich and M. E. Dyatkina, *Dokl. Akad. Nauk SSSR*, **128**, 1234 (1959); **133**, 141 (1960) [*C.A.*, **54**, 23845 (1960)].

⁴⁷ E. O. Fischer and W. Pfab, *Z. Naturforsch.*, **7b**, 377 (1952).

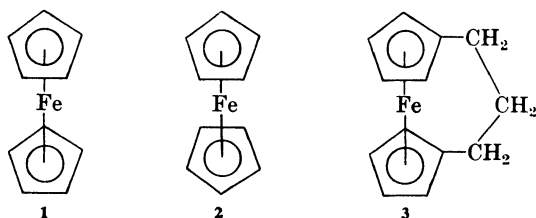
⁴⁸ E. O. Fischer and H. Leipfinger, *Z. Naturforsch.*, **10b**, 353 (1955).

⁴⁹ E. O. Fischer, *Rec. Trav. Chim.*, **75**, 629 (1956).

⁵⁰ J. D. Dunitz, L. E. Orgel, and A. Rich, *Acta Cryst.*, **9**, 373 (1956).

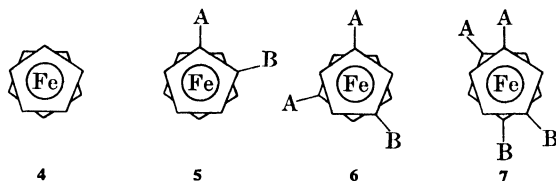
electronic structure of ferrocene and other π -metallohydrocarbons are available.^{22, 39}

All the electronic descriptions take into account the remarkable geometry of these compounds established by x-ray and electron diffraction studies.^{39, 44, 47, 51} Ferrocene, for example, was shown early to have a "sandwich" or "Doppelkegel" structure, in which the two cyclopentadienyl rings lie parallel to one another and the iron atom is buried in the π -electron cloud between them. Two conformations are possible for this "sandwich"—prismatic (1) and antiprismatic (2). In crystals, ferrocene



itself exists in the antiprismatic or staggered form (2), with the carbon atoms of one ring between those of the other. However, in solution the rings are free to rotate (except where tied together by a bridge as in 3), since the barrier to rotation of the rings of ferrocene is negligible.⁵² This means that the stereochemistry of ferrocene in the solid state is determined largely by crystal lattice forces; in agreement with this postulate, related compounds have been determined to be in various conformations:³⁹ ruthenocene and osmocene in the eclipsed conformation, diindenyliron and di-*p*-chlorophenylcyclopentadienyliron in the skew conformation.

Moreover, the number of isomers of a substituted ferrocene corresponds precisely to the number of non-equivalent positions predicted on the basis of freely rotating rings. It is, in fact, perhaps simplest to regard ferrocene as being like an ethane in which the two central carbon atoms have five substituents instead of three. One can then draw ferrocene by looking down the central bond, as in 4. It is apparent that, with freedom of ring rotation, only one heteroannularly disubstituted ferrocene (with



⁵¹ E. A. Seibold and L. E. Sutton, *J. Chem. Phys.*, **23**, 1967 (1955).

⁵² Y. T. Struchkov, *J. Gen. Chem.*, **27**, 2093 (1957).

substituents on different rings) is possible, but that ferrocenes with at least two different substituents on the same ring (homoannularly disubstituted) like **5** or **6** can exist in optically active forms (as has been demonstrated),⁵³⁻⁶⁰ and that ferrocenes with at least two different substituents on both rings (like **7**) can exist as geometrical isomers (as has also been demonstrated),^{61, 62} better described as *meso* and *racemic* than as *cis* and *trans*.

Although one can name substituted ferrocenes as derivatives of dicyclopentadienyliron, it is more convenient to name them as derivatives of ferrocene; this is the system used throughout this chapter. The rings are numbered separately, the less substituted ring being indicated by primed numbers (1', 2', etc.). In bridged ferrocenes the positions bearing the bridge are assigned the numbers 1 and 1'. For continuity of representation (important with bridged ferrocenes) we employ the prismatic symbol **1** throughout, recognizing that, in most compounds, ring rotation is possible. An example of this numbering system is found in 1,1'-trimethyleneferrocene (**3**).

Except for their structures, probably the most striking feature of the π -metallohydrocarbons is the ability of many of them to undergo aromatic substitution. Early investigations^{63, 64} indicated that ferrocene was a new type of aromatic system which readily underwent Friedel-Crafts acylation, and observations of its ability to undergo reactions typical of an aromatic system were extended to include alkylation, arylation, metalation, and sulfonation. In ferrocene the iron atom can be regarded as formally in the Fe^{II} state and, as such, to be oxidizable. For this reason, attempts to nitrate or halogenate ferrocene directly (with nitric acid or bromine) led only to oxidation of the iron nucleus to the Fe^{III} state, in which the molecule bears a net positive charge and is resistant to further electrophilic attack. The product of this oxidation, called the ferricenium ion (**8**), is water-soluble and is blue-green, whereas ferrocene itself is soluble in organic solvents but not water and is orange. The oxidation of ferrocene to ferricenium ion is a reversible process, and

⁵³ L. Westman and K. L. Rinehart, Jr., *Acta Chem. Scand.*, **16**, 1199 (1962).

⁵⁴ J. B. Thomson, *Tetrahedron Letters*, No. 6, 26 (1959).

⁵⁵ K. Schlögl and M. Fried, *Monatsh. Chem.*, **95**, 558 (1964).

⁵⁶ K. Schlögl, M. Fried, and H. Falk, *Monatsh. Chem.*, **95**, 576 (1964).

⁵⁷ K. Schlögl and M. Fried, *Tetrahedron Letters*, 1473 (1963).

⁵⁸ K. Schlögl and H. Falk, *Angew. Chem.*, **76**, 570 (1964).

⁵⁹ H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 1081 (1965).

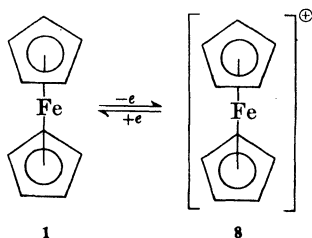
⁶⁰ H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 1065 (1965).

⁶¹ R. E. Benson and R. V. Lindsey, *J. Am. Chem. Soc.*, **79**, 5471 (1957).

⁶² K. L. Rinehart, Jr., and K. L. Motz, *Chem. Ind. (London)*, 1150 (1957).

⁶³ R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

⁶⁴ G. Wilkinson, M. Rosenblum, M. C. Whiting, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).



numerous studies on the controlled oxidation of ferrocene and its derivatives have been reported.⁶⁵⁻⁷³

Although many other cyclopentadienyl compounds like ferrocene have been discovered and, by their very existence, may be somewhat aromatic in nature, most, such as nickelocene and cobaltocene, are not capable of undergoing typical aromatic substitution reactions because they are oxidized or undergo addition reactions more readily.

The compounds discussed in this review have all been shown to undergo aromatic substitution reactions which have led to numerous derivatives of most of the parent structures. The compounds treated include ferrocene, ruthenocene, osmocene, cyclopentadienylmanganese tricarbonyl, cyclopentadienylrhenium tricarbonyl, cyclopentadienyltechnetium tricarbonyl, cyclopentadienylvanadium tetracarbonyl, and cyclopentadienylchromium nitrosyl dicarbonyl, listed in approximately descending order according to the degree to which they have been studied.

FERROCENE

Synthesis of Ferrocene and Substituted Ferrocenes from Cyclopentadienes

Numerous synthetic procedures for the preparation of ferrocene itself have appeared since the compound was first identified; they are

⁶⁵ G. L. K. Hoh, W. E. McEwen, and J. Kleinberg, *J. Am. Chem. Soc.*, **83**, 3949 (1961).

⁶⁶ J. G. Mason and M. Rosenblum, *J. Am. Chem. Soc.*, **82**, 4206 (1960).

⁶⁷ S. P. Gubin and E. G. Perevalova, *Dokl. Akad. Nauk SSSR*, **143**, 1351 (1962) [*C.A.*, **57**, 9575 (1962)].

⁶⁸ T. Kuwana, D. E. Bublitz, and G. Hoh, *J. Am. Chem. Soc.*, **82**, 5811 (1960).

⁶⁹ J. Komenda and J. Tirouflet, *Compt. Rend.*, **254**, 3093 (1962).

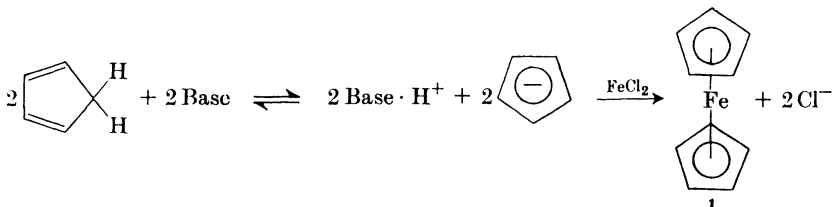
⁷⁰ J. Komenda, *Chem. Zvesti*, **18**, 378 (1964) [*C.A.*, **61**, 11622 (1964)].

⁷¹ E. G. Perevalova, S. P. Gubin, S. A. Smirnova, and A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR*, **155**, 857 (1964) [*C.A.*, **61**, 1509 (1964)].

⁷² A. N. Nesmeyanov, E. G. Perevalova, L. P. Yur'eva, and S. P. Gubin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 909 (1965) [*C.A.*, **63**, 5507 (1965)].

⁷³ D. M. Knight and R. C. Schlitt, *Anal. Chem.*, **37**, 470 (1965).

summarized in Table I. Most of them involve the treatment of cyclopentadiene with a base to give the resonance-stabilized cyclopentadienyl anion,



which then reacts with an anhydrous iron salt to give ferrocene. Bases employed range in strength from the weak base diethylamine⁷⁴ (which is added simultaneously with ferrous chloride so that the small amount of cyclopentadienyl anion formed is removed by immediate reaction with ferrous iron) to metallic sodium⁷⁵ and Grignard reagents.⁷⁶ For the laboratory preparation of ferrocene itself the diethylamine procedure is one of the best.^{74, 77, 78} Another useful procedure involves the reaction of cyclopentadiene with metallic sodium in tetrahydrofuran or 1,2-dimethoxyethane and subsequent treatment with ferrous chloride.⁷⁵ Ferric chloride is reduced to the ferrous state by the stronger bases and so may also be used, though yields are necessarily reduced.

On a commercial scale, routes proceeding directly from cyclopentadiene and iron oxides⁷⁹ or iron carbonyls⁸⁰ would probably be preferred, and ferrocene is presently available from a number of commercial sources.

For the preparation of substituted ferrocenes two basically different approaches involving "direct" or "indirect" routes can be employed. The great majority of the substituted ferrocenes reported have been prepared by the "indirect" route in which the preformed ferrocene molecule serves as a starting point. Substituents are then introduced and the products are subsequently converted to the desired material. A few of the more important examples of these indirect syntheses are discussed on pp. 13-29, and others are found under the individual classes of compounds on pp. 29-63.

The remainder of this section is devoted to "direct" syntheses of substituted ferrocenes, those in which the compound is prepared from an appropriately substituted cyclopentadiene and an iron compound in

⁷⁴ G. Wilkinson, *Org. Syn.*, **36**, 34 (1956).

⁷⁵ G. Wilkinson, *Org. Syn.*, **36**, 31 (1956).

⁷⁶ E. B. Sokolova, M. P. Shebanova, and V. A. Zhichkina, *Zh. Obshch. Khim.*, **30**, 2040 (1960) [*C.A.*, **55**, 6457 (1961)].

⁷⁷ R. L. Pruett and E. L. Morehouse, *Advan. Chem. Ser.*, **23**, 368 (1958).

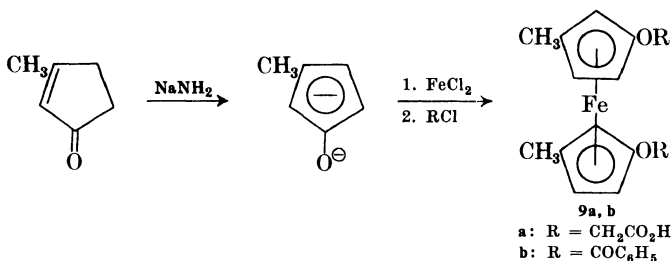
⁷⁸ K. Jones and M. F. Lappert, *J. Organometal. Chem.*, **3**, 295 (1965).

⁷⁹ E. I. du Pont de Nemours and Co., Brit. pat. 764,058 [*C.A.*, **52**, 5480 (1958)].

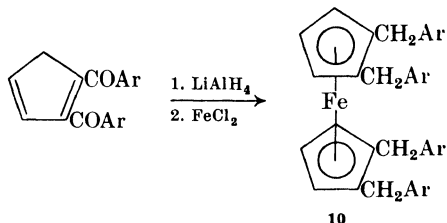
⁸⁰ A. Tartter, Ger. pat. 1,101,418 [*C.A.*, **56**, 10193 (1962)].

syntheses similar to those used for the preparation of ferrocene itself. Only the stronger bases—Grignard or organolithium reagents, metallic sodium—appear to give good yields of ferrocenes from substituted cyclopentadienes. Substituted ferrocenes prepared by direct synthesis are shown in Table II. Simple alkyl, aryl, and silyl cyclopentadienes have been most frequently employed as ferrocene precursors, but even highly substituted ferrocenes like *sym*-octaphenylferrocene have been prepared by this route.

Direct synthesis has been less frequently employed for the preparation of more functionally substituted compounds, but the symmetrical diacetyl, dicarbomethoxy, and bis(phenylazo) derivatives have been prepared from the corresponding cyclopentadienes. A dihydroxyferrocene has also been prepared from the enolate of 3-methyl-2-cyclopentenone and has been isolated as its oxyacetic acid (**9a**) and benzoate (**9b**) derivatives.^{61,82} Both of the derivatives are capable of existing as *racemic* and *meso* isomers; the *meso* forms are shown.



Functional groups are sometimes reduced in the formation of ferrocenes. For example, tetrabenzylferrocenes (**10**) are synthesized when 1,2-diaroylcyclopentadienes are treated with lithium aluminum hydride followed by ferrous chloride.⁸¹

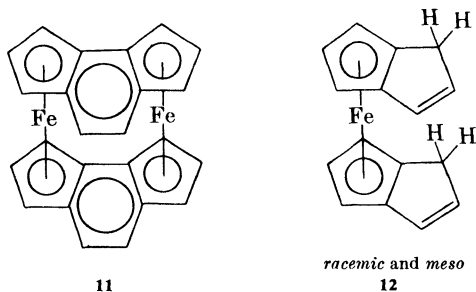


Fused-ring compounds (listed in Table II-C) have been prepared from precursor indenenes, which may be regarded as substituted cyclopentadienes and, as such, give benzoferrocenes, though in low yields. Attempts to prepare di- and tetra-benzoferrocenes from fluorenes have been

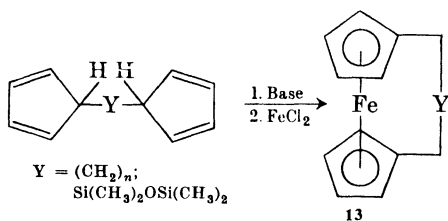
⁸¹ W. F. Little and R. C. Koestler, *J. Org. Chem.*, **26**, 3245 (1961).

⁸² R. E. Benson, U.S. pat. 2,849,470 [*C.A.*, **53**, 406 (1959)].

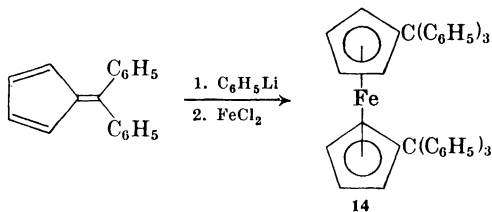
unsuccessful, but the synthesis of bis(*as*-indacenyl)iron (**11**) from the *as*-indacenyl dianion has been accomplished.⁸³ By contrast, reaction of the pentalene dianion yielded the diolefin **12** rather than a binuclear ferrocene.⁸⁴



A few ferrocene derivatives of formula **13**, containing bridges from one ring to another (listed in Table II-D), have been synthesized from precursors containing two cyclopentadiene rings linked by alkane or siloxane chains.



Fulvenes, which are readily prepared from aldehydes or ketones and cyclopentadienes,⁸⁵ are sources of a variety of ferrocenes (see Table III). Both organolithium reagents and lithium aluminum hydride add to fulvenes to give alkylcyclopentadienyl anions, which in turn react with ferrous chloride to give dialkyl ferrocenes. For example, treatment of 6,6-diphenylfulvene with phenyllithium followed by ferrous chloride gave 1,1'-ditritylferrocene (**14**),⁸⁶ while treatment of azulene with lithium



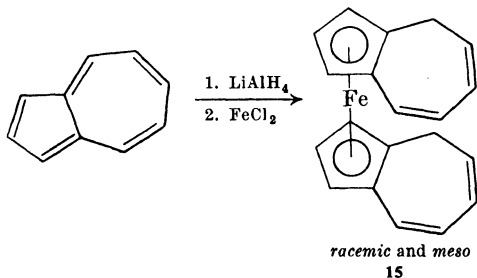
⁸³ T. J. Katz and J. Shulman, *J. Am. Chem. Soc.*, **86**, 3169 (1964).

⁸⁴ T. J. Katz and M. Rosenberger, *J. Am. Chem. Soc.*, **85**, 2030 (1963).

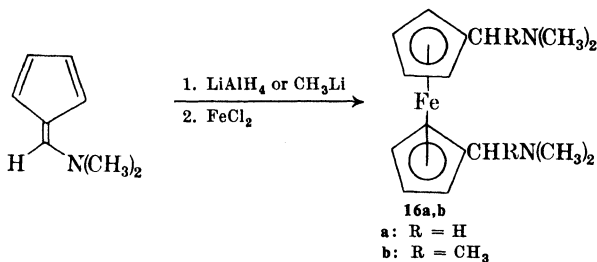
⁸⁵ J. H. Day, *Chem. Rev.*, **53**, 167 (1953).

⁸⁶ R. C. Koestler and W. F. Little, *Chem. Ind. (London)*, 1589 (1958).

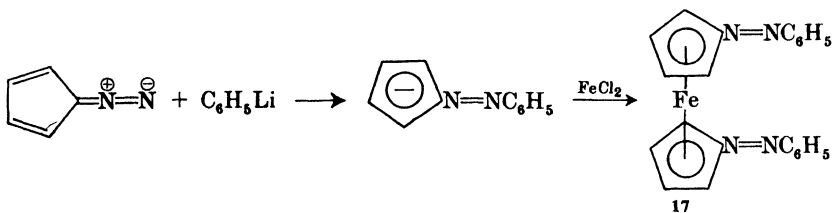
aluminum hydride, then ferrous chloride, gave the fused-ring compound (15) in 17% yield.^{87, 88} The syntheses of 1,1'-bis(dimethylaminomethyl)-



ferrocene and 1,1'-bis-(α -dimethylaminoethyl)ferrocene (16a and 16b) have been accomplished in the same way.⁹⁰



In a reaction related to the fulvene reactions discussed above, treatment of diazocyclopentadiene with phenyllithium, then with ferrous chloride, gave 1,1'-bis(phenylazo)ferrocene (17) (see Table II).



A second reaction of fulvenes occurs with strong bases which are not nucleophiles. Treatment of 6,6-dimethylfulvene with sodium amide gives a cyclopentadienyl anion which, when treated with ferrous chloride, gives 1,1'-diisopropenylferrocene (18).^{87, 88} In yet a third reaction some

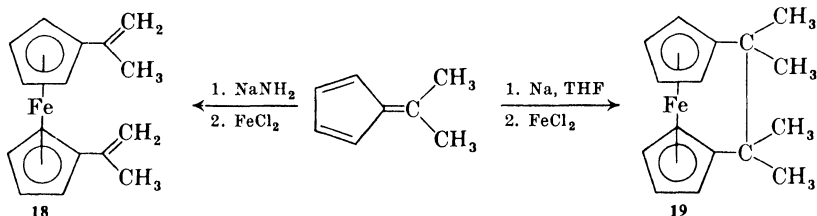
⁸⁷ G. R. Knox and P. L. Pauson, *Proc. Chem. Soc.*, 289 (1958).

⁸⁸ G. R. Knox and P. L. Pauson, *J. Chem. Soc.*, 4610 (1961).

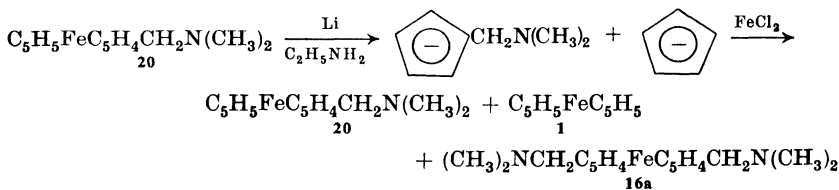
⁸⁹ K. L. Rinehart, Jr., A. K. Frerichs, P. A. Kittle, L. F. Westman, D. H. Gustafson, R. L. Pruett, and J. E. McMahon, *J. Am. Chem. Soc.* **82**, 4111 (1960).

⁹⁰ G. R. Knox, J. D. Munro, P. L. Pauson, G. H. Smith, and W. E. Watts, *J. Chem. Soc.*, 4619 (1961).

fulvenes react with sodium in tetrahydrofuran to give 1,2-dicyclopentadienylethanes which, when treated with ferrous chloride, give bridged ferrocenes (**19**),⁸⁹ although the reaction to give 1,1'-dialkenylferrocenes (like **18**) may also occur with this reagent.



Unsymmetrically substituted ferrocenes usually are prepared by substitution on ferrocene ("indirect" synthesis), but some have been prepared in a direct manner by reaction of equimolar amounts of a substituted cyclopentadienyl reagent and an unsubstituted cyclopentadienyl reagent with an iron source (see Table IV). The yields are low or unspecified, and indirect methods are far superior except for the preparation of phenylazoferrocene and benzoferrocene. An extension of the process employing a mixture of cyclopentadienes has provided a unique synthesis of 1,1'-bis(dimethylaminomethyl)ferrocene (**16a**) which cannot be prepared by substitution on ferrocene. This involves cleavage of dimethylaminomethylferrocene (**20**) with lithium in ethylamine, followed by treatment of the resulting cyclopentadienyl anions with ferrous chloride to give ferrocene (14%), dimethylaminomethylferrocene (36%), and 1,1'-bis(dimethylaminomethyl)ferrocene (15%).^{91, 92}



Useful Intermediates in the Synthesis of Substituted Ferrocenes

In the indirect synthesis of substituted ferrocenes a few key intermediates have proved especially useful. In general, these are acylated, dimethylaminomethylated, or metalated ferrocenes, easily prepared from ferrocene but sufficiently versatile and reactive to be convertible to many

⁹¹ J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 4604 (1961).

⁹² P. L. Pauson, G. R. Knox, J. D. Munro, and J. M. Osgerby, *Angew. Chem.*, **72**, 37 (1960).

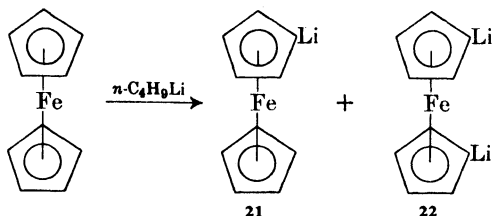
other derivatives. In this section the preparation of some of these useful intermediates is discussed in detail.

These intermediates have proved to be more useful for the synthesis of monosubstituted ferrocene derivatives than for disubstituted ferrocenes. Thus, while monoacyl ferrocenes have been used for the preparation of a host of substituted ferrocenes, comparatively little use has been made of diacyl ferrocenes in such conversions. Similarly, chloromercuriferrocene has been shown to be very useful for preparing iodoferrocene, diferrocenylmercury, etc., but little has been done with 1,1'-bis(chloromercuri)-ferrocene.

The lack of widespread use of disubstituted intermediates may be due in part to the fact that many symmetrically disubstituted ferrocenes are conveniently prepared from substituted cyclopentadienes and a base or by the route involving fulvene compounds (see pp. 11-13 and Tables II and III).

Alkali Metal Derivatives

Lithioferrocenes. *Monolithioferrocene.* Ferrocene is metalated by *n*-butyllithium to give a mixture of mono- and di-lithiated products (**21** and **22**). Attempts to circumvent the formation of the mixtures of lithiation products have been made by various authors with some success.⁹³⁻⁹⁵ Utilization of a mixed solvent system (ether-tetrahydrofuran) with varying ratios of *n*-butyllithium to ferrocene produced mono- and di-lithiated materials in varying ratios,⁹⁴ and use of 1.04 molar equivalents of *n*-butyllithium in the solvent system hexane-ether was reported to give only the monolithio product.⁹⁶



Other workers have reported the preparation of pure ferrocenyllithium by methods utilizing substituted ferrocenes as the starting material. Diferrocenylmercury (**23a**) and 2.8 molar equivalents of *n*-butyllithium

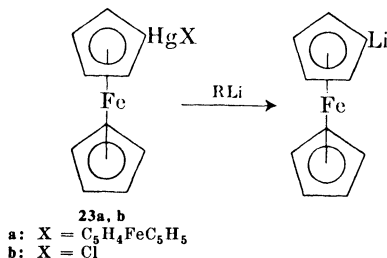
⁹³ R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

⁹⁴ D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. Ind. (London)*, 1388 (1957).

⁹⁵ D. Seyferth and J. F. Helling, *Chem. Ind. (London)*, 1568 (1961).

⁹⁶ S. I. Goldberg, L. H. Keith, and T. S. Prokopov, *J. Org. Chem.*, **28**, 850 (1963).

gave pure monolithioferrocene in 80% yield,⁹⁷ while monochloromercuriferrocene (**23b**) and ethyllithium gave only monolithioferrocene in 64–96% yield.^{95, 98, 99} The yields in both cases were based on carbonation to the acid.⁹⁸ In both of these reactions, however, one must reckon with the presence of excess alkyl- or aryl-lithium reagent as a contaminant.



Lithiation of 1,1'-dimethylferrocene leads to a mixture of 2- and 3-lithiated isomers which are converted to the corresponding acids by carbonation.⁵³ While this metalation leads to a mixture of isomers, lithiation of diphenylferrocenylcarbinol¹⁰⁰ or dimethylaminomethylferrocene^{101, 102} has been reported to give, after carbonation, the corresponding 2-substituted ferrocenoic acids as the sole products, presumably the result of coordination of the metal with the carbinol or amine.

Although the lithio derivatives of ferrocene are never isolated, they have been extremely useful intermediates in the preparation of many ferrocene derivatives (see Table V).

Dilithioferrocene. 1,1'-Dilithioferrocene (**22**) free of monolithioferrocene has been prepared only by treatment of 1,1'-bis(chloromercuri)-ferrocene with ethyllithium,⁹⁸ never by direct lithiation of ferrocene. Studies of the direct lithiation products show that, even with a 25-fold molar excess of butyllithium over ferrocene, 23% of the monolithiated product is obtained.⁹⁴ Nevertheless, dilithioferrocene is an important intermediate in the preparation of many 1,1'-disubstituted ferrocene derivatives (Table V).

Sodioferrocenes. Mono- and di-sodio derivatives of ferrocene, which

⁹⁷ M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).

⁹⁸ D. Seyferth, H. P. Hoffman, R. Burton, and J. F. Helling, *Inorg. Chem.*, **1**, 227 (1962).

⁹⁹ H. Rosenberg and R. U. Schenk, 145th National A.C.S. Meeting, New York, September 9–13, 1963; *cf. Abstracts*, p. 76Q.

¹⁰⁰ R. A. Benkeser, W. P. Fitzgerald, and M. S. Melzer, *J. Org. Chem.*, **26**, 2569 (1961).

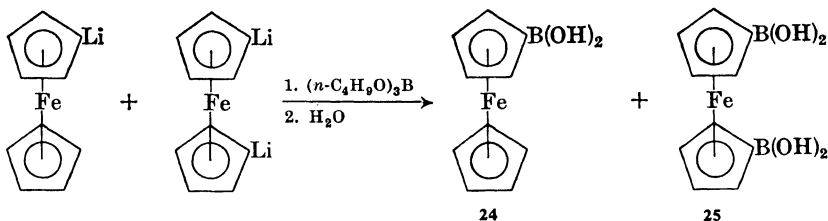
¹⁰¹ D. W. Slocum, B. W. Rockett, and C. R. Hauser, *Chem. Ind. (London)*, 1831 (1964).

¹⁰² D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 1241 (1965).

have been studied less than the lithio derivatives, are formed by exchange reactions involving phenylsodium^{103, 105} or amylsodium.^{98, 106, 107} When the product of the exchange reaction is treated with carbon dioxide,⁹⁸ trialkylchlorosilanes,^{98, 103} or triphenylbromogermane,⁹⁸ mixtures of the corresponding mono- and 1,1'-di-substituted products are obtained. In early work, when the reaction product was carbonated, the sole product identified was ferrocene-1,1'-dicarboxylic acid,¹⁰⁴ but it has subsequently been shown that the monocarboxylic acid is also formed.⁹⁸

Ferroceneboronic Acids

Ferroceneboronic Acid. One derivative prepared from lithioferrocene worthy of special note is ferroceneboronic acid (**24**), which is an important intermediate in the preparation of chloro-, bromo-, amino-, and, particularly, hydroxy-ferrocenes. Treatment of a mixture of lithiated ferrocenes with tri-*n*-butyl borate, followed by hydrolysis, leads to a mixture of ferroceneboronic acid and 1,1'-ferrocenediboronic acid (**25**),^{108, 110} separable either by fractional acidification of a mixed salt solution to give first the less soluble dibasic acid then ferroceneboronic acid,^{108, 109} or by selective extraction¹¹⁰ of the more soluble ferroceneboronic acid by diethyl ether. The latter method of separation is clearly



less tedious and seems preferable. Replacement of the boronic acid group by a variety of others has been reported for both ferroceneboronic

¹⁰³ S. I. Goldberg, D. W. Mayo, M. Vogel, H. Rosenberg, and M. Rausch, *J. Org. Chem.*, **24**, 824 (1959).

¹⁰⁴ A. N. Nesmeyanov, E. G. Perevalova, and Z. A. Beinoravichute, *Dokl. Akad. Nauk SSSR*, **112**, 439 (1957) [*C.A.*, **51**, 13855 (1957)].

¹⁰⁵ M. Okawara, Y. Takemoto, H. Kitaoka, E. Haruki, and I. Imoto, *Kogyo Kagaku Zasshi*, **65**, 685 (1962) [*C.A.*, **58**, 577 (1963)].

¹⁰⁶ P. J. Graham, U.S. pat. 2,835,686 [*C.A.*, **52**, 16366 (1958)].

¹⁰⁷ R. A. Benkeser, Y. Nagai, and J. Hooz, *J. Am. Chem. Soc.*, **86**, 3742 (1964).

¹⁰⁸ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **126**, 1004 (1959) [*C.A.*, **54**, 6673 (1960)].

¹⁰⁹ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Chem. Ber.*, **93**, 2717 (1960).

¹¹⁰ H. Schechter and J. F. Helling, *J. Org. Chem.*, **26**, 1034 (1961).

acid^{108, 109, 111-113} and substituted ferroceneboronic acids,¹¹⁴⁻¹¹⁶ (Table VI-A, B) and is illustrated for ferroceneboronic acid in Fig. 1.

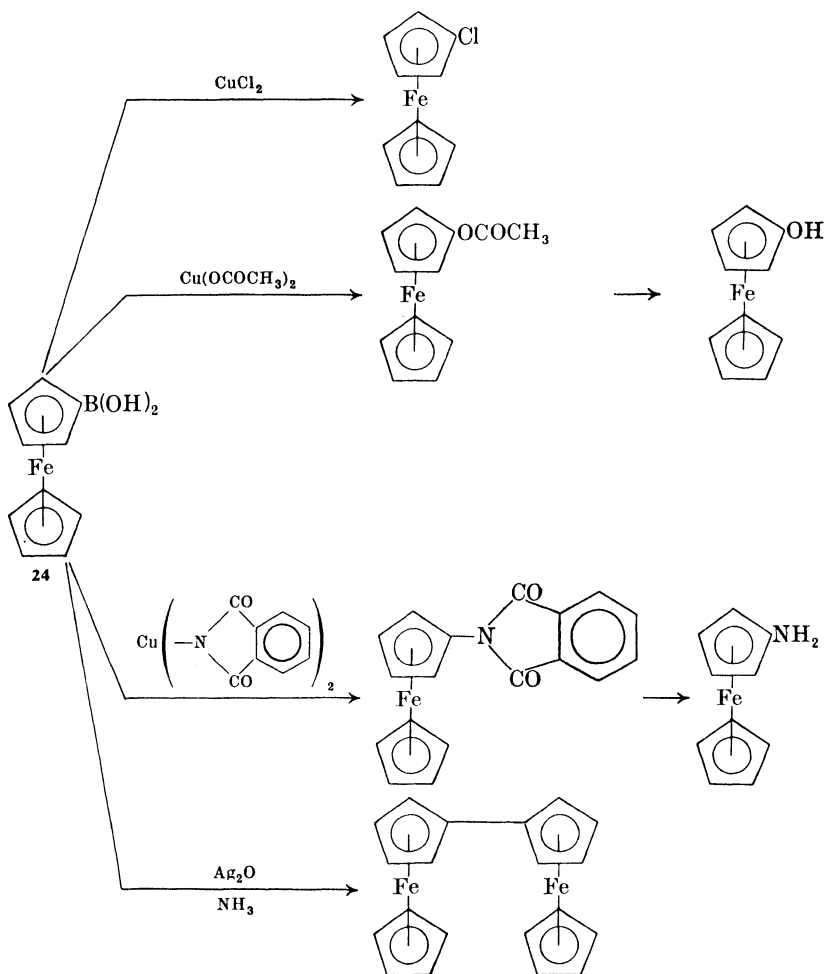


FIG. 1. Some replacement reactions of ferroceneboronic acid.

¹¹¹ A. N. Nesmeyanov, V. A. Sazonova, A. V. Gerasimenko, and V. G. Medvedeva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2073 (1962) [*C.A.*, **58**, 9133 (1963)].

¹¹² A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **129**, 1060 (1959) [*C.A.*, **53**, 16111 (1959)].

¹¹³ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Tetrahedron Letters*, No. 17, 13 (1959).

¹¹⁴ A. N. Nesmeyanov, V. A. Sazonova, V. N. Drozd, and L. A. Nikonova, *Dokl. Akad. Nauk SSSR*, **131**, 1088 (1960) [*C.A.*, **54**, 21025 (1960)].

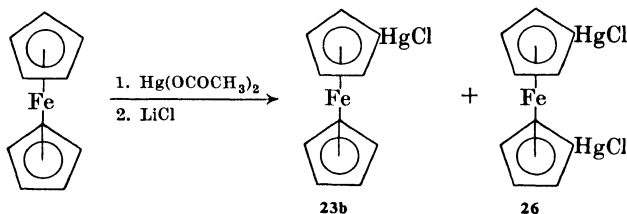
¹¹⁵ A. N. Nesmeyanov, V. A. Sazonova, V. N. Drozd, and L. A. Nikonova, *Dokl. Akad. Nauk SSSR*, **133**, 126 (1960) [*C.A.*, **54**, 24616 (1960)].

¹¹⁶ A. N. Nesmeyanov, V. A. Sazonova, and V. I. Romanenko, *Dokl. Akad. Nauk SSSR*, **157**, 922 (1964) [*C.A.*, **61**, 13343 (1964)].

1,1'-Ferrocenediboronic Acid. 1,1'-Ferrocenediboronic acid (**25**), prepared in addition to the corresponding monoacid by treatment of the mixed lithioferrocenes with tri-*n*-butyl borate,^{109, 110} has served as an intermediate for numerous disubstituted ferrocenes (Table VI-C).

Mercurated Ferrocenes

Monomercurated Ferrocenes. When ferrocene is treated with mercuric acetate in ether-methanol or ether-ethanol, a mixture of acetoxymercuri- and 1,1'-bis(acetoxymercuri)-ferrocene is formed.^{106, 117, 118} The ratio of the mercuriation products can be varied somewhat,¹¹⁸ but one cannot be prepared to the exclusion of the other. Although the mixed acetoxymercuri products have been isolated,¹⁰⁶ the usual procedure involves conversion of the products to the corresponding chloromercuri compounds (**23b** and **26**) by treatment with potassium chloride^{117, 118} or lithium chloride.¹¹⁸⁻¹²⁰ The chloromercuri derivatives are readily



separable because of the solubility of the mono-substituted product (**23b**) in hot 1-butanol¹¹⁷⁻¹¹⁹ or methylene chloride.¹²⁰ The most detailed directions also appear to give the best yield and offer an alternative procedure using sodium acetate and mercuric chloride.¹¹⁹ Other methods, involving displacement of a functional group of a substituted ferrocene, are also available for the preparation of chloromercuriferrocene, but they appear to offer no advantage. These are presented in Table VII together with direct substitution results.

p-Nitrophenylferrocene forms a dimercuration product of undesignated structure;¹²¹ this is the only reported mercuriation of a substituted ferrocene.

¹¹⁷ A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **97**, 459 (1954) [*C.A.*, **49**, 9633 (1955)].

¹¹⁸ M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 900 (1957).

¹¹⁹ M. D. Rausch, L. C. Klemann, A. Siegel, R. F. Kovar, and J. H. Maldines, Submitted to *Organometal. Syn.*

¹²⁰ R. W. Fish and M. Rosenblum, *J. Org. Chem.*, **30**, 1253 (1965).

¹²¹ A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, N. A. Simukova, and O. V. Starovskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 638 (1957) [*C.A.*, **51**, 15422 (1957)].

Chloromercuriferrocene (**23b**) has been converted to many other ferrocene derivatives as illustrated in Fig. 2. A more complete list of conversions is found in Table VIII-A.

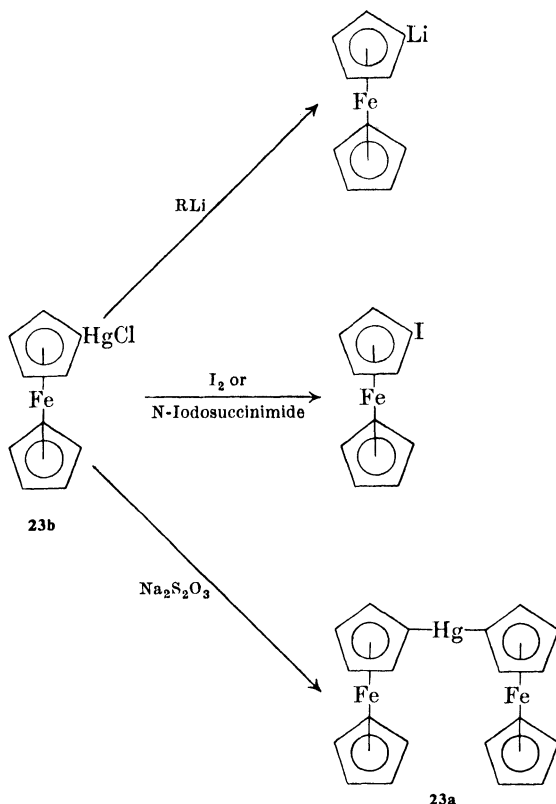


FIG. 2. Some reactions of chloromercuriferrocene.

Diferrocenylmercury (**23a**), prepared by reduction of chloromercuriferrocene,^{117, 118} has been shown to undergo displacement reactions like those of chloromercuriferrocene. Thus heating in the presence of silver^{97, 122} or palladium black¹²³ gives biferrocenyl, while reaction with *n*-butyllithium provides another route to pure monolithioferrocene.^{97, 98} These and other displacements are listed in Table VIII-B and are illustrated in Fig. 3.

¹²² M. D. Rausch, *J. Am. Chem. Soc.*, **82**, 2080 (1960).

¹²³ O. A. Nesmeyanova and E. G. Perevalova, *Dokl. Akad. Nauk SSSR*, **126**, 1007 (1959) [*C.A.*, **54**, 1478 (1960)].

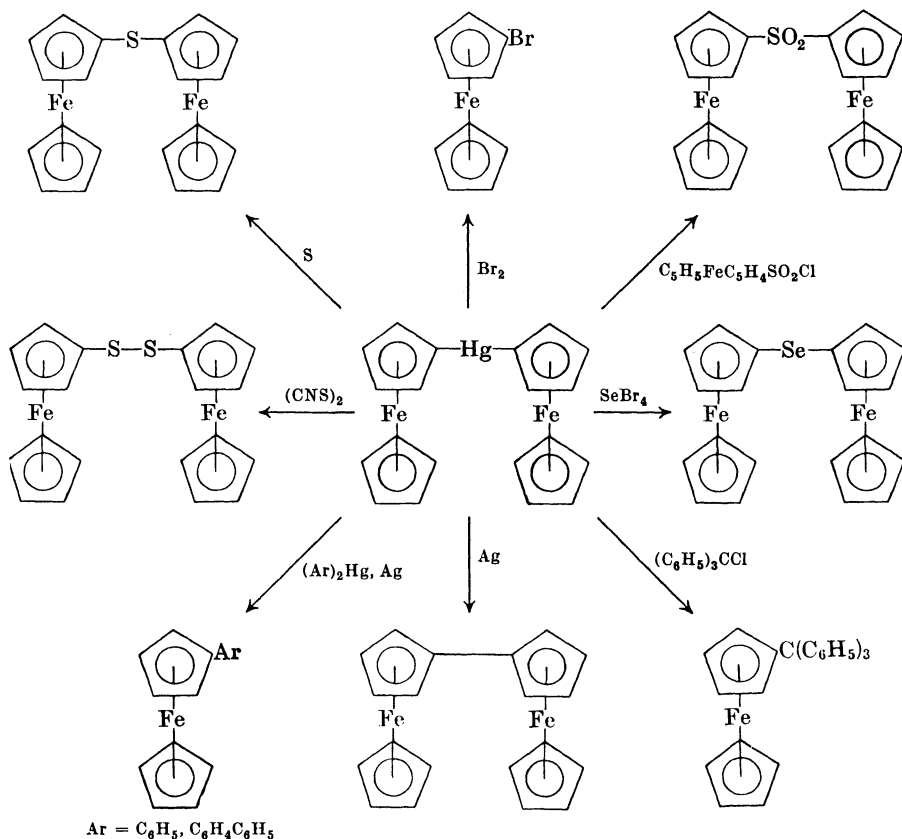


FIG. 3. Replacement reactions of diferrocenylmercury.

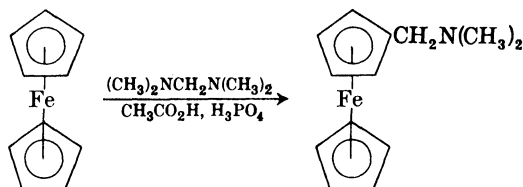
Dimercurated Ferrocenes. As described above, mercuration of ferrocene by mercuric acetate followed by treatment with potassium chloride or lithium chloride gives both mono- and di-substituted products,¹¹⁷⁻¹¹⁹ which are readily separable because of the solubility of the monosubstituted product in hot 1-butanol¹¹⁷⁻¹¹⁹ or methylene chloride.¹²⁰ Reactions of 1,1'-bis(chloromercuri)ferrocene, listed in Table VIII-C, generally parallel those of chloromercuriferrocene. Of special interest is the reaction of 1,1'-bis(chloromercuri)ferrocene with sodium iodide in ethanol to give polyferrocenylmercury.¹²⁴ Heating this polyferrocenylmercury compound with silver at 300° gives biferrocenyl and polyferrocenyl.

Dimercuration of *p*-nitrophenylferrocene has been reported but the product was of undesigned structure.¹²¹

¹²⁴ M. D. Rausch, *J. Org. Chem.*, **28**, 3337 (1963).

N,N-Dialkylaminomethyl Ferrocenes (Table IX)

Aminomethylation of ferrocene to N,N-dimethylaminomethylferrocene can be effected by reaction with formaldehyde and dimethylamine in acetic acid or by using N,N,N',N'-tetramethyldiaminomethane as the aminomethylating agent.¹²⁵ The yield is improved by using phosphoric acid in addition to acetic acid.¹²⁶ A standard preparation using added phosphoric acid gives yields of 68–81 % of the amine as its methiodide.¹²⁷ The phosphoric acid modification has been used successfully for the aminomethylation of phenylferrocene¹²⁸ and methylferrocene.¹²⁹



The most valuable reaction of dimethylaminomethylferrocene is that with methyl iodide to give (ferrocenylmethyl)trimethylammonium iodide (27),¹³⁰ which undergoes $\text{S}_{\text{N}}2$ displacement of trimethylamine by many nucleophiles—alkoxide and cyanide anions, Grignard reagents, amines, and a variety of carbanionic reagents (Table X). The quaternary methiodide treated with sodium cyclopentadienide and then with ferrous chloride gives 1,1'-bis(ferrocenylmethyl)ferrocene (28).¹³¹

Rearrangement of (ferrocenylmethyl)trimethylammonium iodide can also occur, however, and treatment with potassium amide in liquid ammonia has been shown to give β -(dimethylamino)ethylferrocene (29).¹³²

Recently a large number of ferrocenylmethylamine quaternary ammonium salts containing different N-alkyl substituents has been prepared. Subsequent reactions of these quaternary salts have been

¹²⁵ J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

¹²⁶ J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 656 (1958).

¹²⁷ D. Lednicer and C. R. Hauser, *Org. Syn.*, **40**, 31 (1960).

¹²⁸ A. N. Nesmeyanov, E. G. Perevalova, S. P. Gubin, T. V. Nikitina, A. A. Ponomarenko, and L. S. Shilovtseva, *Dokl. Akad. Nauk SSSR*, **139**, 888 (1961) [*C.A.*, **56**, 1477 (1962)].

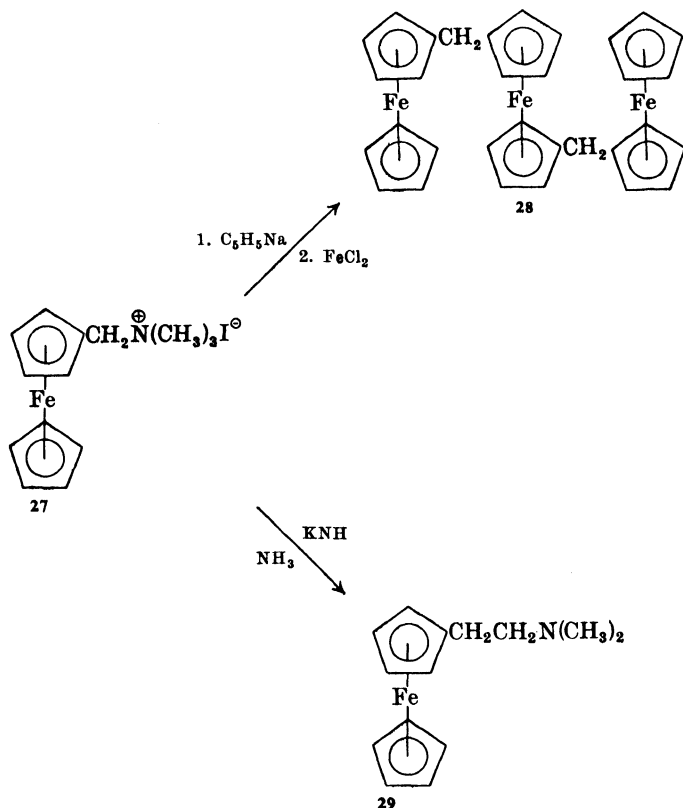
¹²⁹ A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and Yu. A. Ustynyuk, *Dokl. Akad. Nauk SSSR*, **124**, 331 (1959) [*C.A.*, **53**, 11332 (1959)].

¹³⁰ C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1956).

¹³¹ P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 3880 (1962).

¹³² C. R. Hauser, J. K. Lindsay, and D. Lednicer, *J. Org. Chem.*, **23**, 358 (1958).

reported to parallel in most cases those of the simpler ferrocenylmethyl-trimethylammonium compound.¹³³⁻¹³⁸



Methylferrocene has been shown to give 19% of a disubstituted aminomethylation product of undesigned structure in addition to the monosubstituted material.¹²⁹ This appears to be the only reported case of disubstitution in the aminomethylation reaction. Bis-(aminomethylation)

¹³³ E. G. Perevalova, Yu. A. Ustynyuk, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1045 (1963) [*C.A.*, **59**, 7557 (1963)].

¹³⁴ E. G. Perevalova, Yu. A. Ustynyuk, L. A. Ustynyuk, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977 (1963) [*C.A.*, **60**, 6865 (1964)].

¹³⁵ Yu. A. Ustynyuk and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 62 (1964) [*C.A.*, **60**, 9310 (1964)].

¹³⁶ E. G. Perevalova and Yu. A. Ustynyuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1776 (1963) [*C.A.*, **60**, 5549 (1964)].

¹³⁷ E. G. Perevalova, Yu. A. Ustynyuk, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1036 (1963) [*C.A.*, **59**, 7557 (1963)].

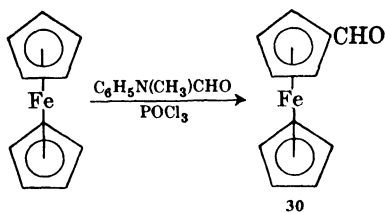
¹³⁸ A. N. Nesmeyanov, E. G. Perevalova, L. I. Leonteva and Yu. A. Ustynyuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1696 (1965) [*C.A.*, **63**, 18146 (1965)].

of ferrocene itself does not occur under the normal reaction conditions.

As discussed on pp. 12–13, 1,1'-bis(dimethylaminoalkyl)ferrocenes have been prepared by the direct route—through cleavage of the monosubstituted material by lithium in ethylamine followed by recombination of the cyclopentadienes in the presence of ferrous chloride^{91, 92} and by treatment of 6-dimethylaminofulvene with either lithium aluminum hydride or methylolithium, followed by ferrous chloride. However, conversion of bis(dimethylaminoalkyl)ferrocenes to quaternary salts for replacement reactions of the salts have not been reported.

Ferrocenecarboxaldehyde

Ferrocenecarboxaldehyde (**30**) has been prepared in one step from ferrocene by two methods. The first consists of treatment of ferrocene with phosphorus oxychloride and N-methylformanilide^{139–146} or dimethylformamide;¹³⁹ reported yields of aldehyde are as high as 80%.¹⁴⁰ The second method consists of the reaction of ferrocene and 1,1-dichloromethyl ethyl ether in the presence of aluminum chloride; the aldehyde was formed in about 50% yield.¹³¹ The former reaction has been more frequently used and is better suited for general preparative purposes. Synthesis of the aldehyde has also been accomplished commercially by the Sommelet reaction of ferrocenylmethyltrimethylammonium iodide.¹⁴⁷ Preparative routes to ferrocenecarboxaldehyde are listed in Table XI.



¹³⁹ P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

¹⁴⁰ M. Rosenblum, A. K. Banerjee, N. Danieli, R. W. Fish, and V. Schlatter, *J. Am. Chem. Soc.*, **85**, 316 (1963).

¹⁴¹ G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, **650** (1958).

¹⁴² K. Schlögl, *Monatsh. Chem.*, **88**, 601 (1957).

¹⁴³ M. Rosenblum, *Chem. Ind. (London)*, 72 (1957).

¹⁴⁴ P. J. Graham, U.S. pat. 2,849,469 [*C.A.*, **53**, 4298 (1959)].

¹⁴⁵ P. J. Graham, U.S. pat. 2,988,564 [*C.A.*, **56**, 12948 (1962)].

¹⁴⁶ C. Jutz, *Tetrahedron Letters*, No. 21, 1 (1959).

¹⁴⁷ P. Pratter, Research Organic Chemical Co., Sun Valley, California, personal communication.

The formylation of certain ferrocene derivatives by means of N-methylformanilide and phosphorus oxychloride has been accomplished.^{55, 148-152}

The two reports of the diformylation of ferrocene by N-methylformanilide in the presence of phosphorus oxychloride which have appeared describe crude material only.^{144, 145} 1,1'-Ferrocenedicarboxaldehyde has been prepared by manganese dioxide oxidation of 1,1'-bis(α -hydroxymethyl)ferrocene.⁹¹

Ferrocenecarboxaldehyde undergoes the usual reactions of an aromatic aldehyde and has been utilized for the synthesis of many substituted ferrocenes. Especially useful are its condensations with active methylene compounds (refs. 91, 126, 139-142, 149, 150, 153-162). Reactions of the aldehyde are illustrated in Fig. 4 (p. 25), and useful products derived from it are listed in Table XII. Similar reactions have been reported for the dialdehyde⁹¹ and for substituted ferrocenecarboxaldehydes.^{149, 150, 161}

Acyl Ferrocenes and Related Compounds

Acyl ferrocenes are prepared by Friedel-Crafts acylation employing acid halides or anhydrides in the presence of the usual catalysts, e.g., aluminum chloride, boron trifluoride, or phosphoric acid. They were the first substituted ferrocenes prepared and are among the most useful intermediates in the preparation of other ferrocene derivatives. However, the vastly greater reactivity of ferrocenes toward electrophilic aromatic substitution, as compared with the corresponding benzenoid derivatives, poses the problem of control of multisubstitution in acylation. This is particularly manifest in a tendency toward heteroannular disubstitution, since the second ring, unacylated, is only partially deactivated by the acyl group on the substituted ring. Usually the amount of disubstitution can be controlled by the proper choice of catalyst and ratio of reagents.

¹⁴⁸ K. Schlögl and H. Seiler, *Tetrahedron Letters*, No. 7, 4 (1960).

¹⁴⁹ K. Schlögl and M. Peterlik, *Monatsh. Chem.*, **93**, 1328 (1962).

¹⁵⁰ K. Schlögl, M. Peterlik, and H. Seiler, *Monatsh. Chem.*, **93**, 1309 (1962).

¹⁵¹ G. Tainturier and J. Tirouflet, *Compt. Rend.*, **258**, 5666 (1964).

¹⁵² G. Tainturier and J. Tirouflet, *Bull. Soc. Chim. France*, 2739 (1964).

¹⁵³ J. Tirouflet and J. Boichard, *Compt. Rend.*, **250**, 1861 (1960).

¹⁵⁴ C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 906 (1957).

¹⁵⁵ G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *Chem. Ind. (London)*, 209 (1957).

¹⁵⁶ B. Loev and M. Flores, *J. Org. Chem.*, **26**, 3595 (1961).

¹⁵⁷ I. K. Barben, *J. Chem. Soc.*, 1827 (1961).

¹⁵⁸ J. Boichard and J. Tirouflet, *Compt. Rend.*, **251**, 1394 (1960).

¹⁵⁹ K. Sonogashira and N. Hagihara, *J. Chem. Soc. Japan*, **66**, 1090 (1963) [*C.A.* **62**, 7794 (1965)].

¹⁶⁰ H. Egger and K. Schlögl, *J. Organometal. Chem.*, **2**, 398 (1964).

¹⁶¹ K. Schlögl and M. Peterlik, *Tetrahedron Letters*, 573 (1962).

¹⁶² P. daRe and E. Sainesi, *Experientia*, **21**, 648 (1965).

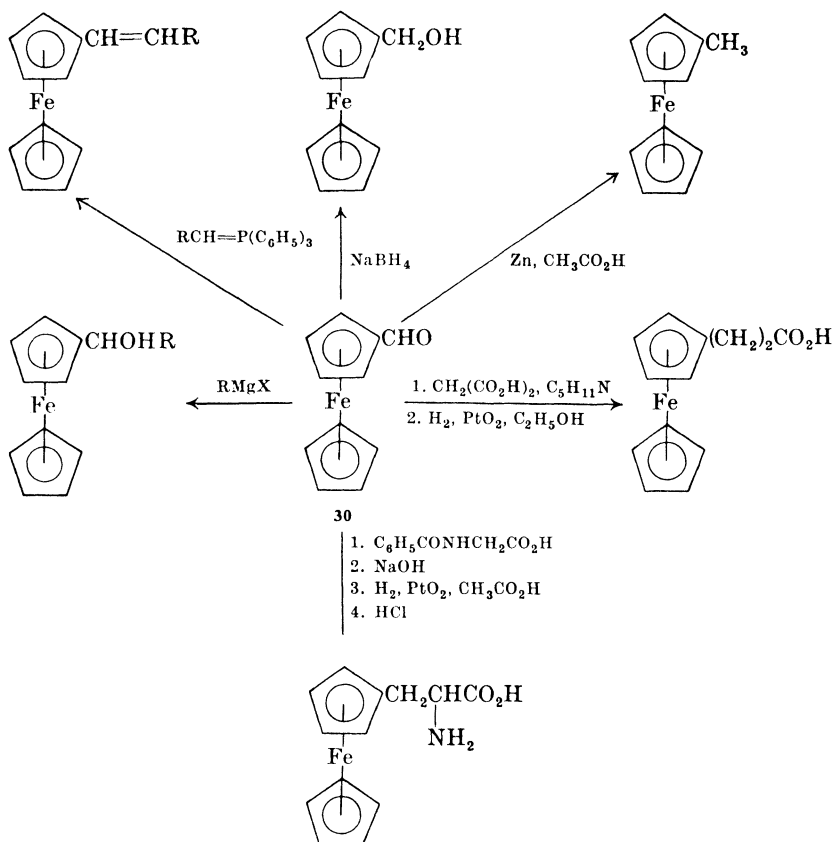


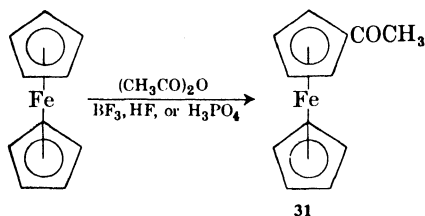
Fig. 4. Useful synthetic reactions of ferrocenecarboxaldehyde.

Monoacylated Ferrocenes. Monoacylation of ferrocenes can be accomplished readily by three procedures: with an acid anhydride-boron trifluoride complex in methylene chloride;¹⁶³ with an acid anhydride in liquid hydrogen fluoride;¹⁶⁴ and with the acid anhydride as solvent in the presence of phosphoric acid.¹³⁹ The simplest reaction, the last of the three, has found application in the commercial synthesis of acetylferrocene (**31**) (p. 26).¹⁴⁷ The amount of anhydride required obviously eliminates the last method when the anhydride is expensive, and all three methods are limited by the availability of the desired acid anhydride. The boron trifluoride procedure has been used by various workers for the acylation of substituted ferrocenes and appears to be quite practical.

¹⁶³ C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 482 (1957).

¹⁶⁴ V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3009 (1955).

However, other workers have found the reaction products to be pure diacylated materials¹⁶⁵ or mixtures of mono- and di-acylated products.¹⁶⁶ To obtain only the monosubstituted material, only 1 molar equivalent of acetic anhydride must be used.¹⁶⁷ A method of lesser importance involves the addition of Grignard reagents to cyanoferrocene,¹⁶⁸ though this method may assume greater importance in light of the ease with which cyanoferrocene can be prepared (see p. 40).^{169, 170}



Acylation of ferrocene by means of an acid chloride and aluminum chloride leads to significant amounts of disubstitution unless considerable care is taken to control the amount of aluminum chloride present. Ferrocene can form a cationic complex with aluminum chloride and hydrogen chloride that is not acylated under the usual reaction conditions.¹⁷¹ Any aluminum chloride over a stoichiometric amount will form a non-reactive complex with ferrocene and the hydrogen chloride liberated in the acylation reaction; this removal of ferrocene from the reaction is responsible for the formation of diacyl products.

Monoacyl ferrocenes that have been prepared by these methods are listed in Table XIII.

Diacylated Ferrocenes. Heteroannular Diacyl Ferrocenes. Although several procedures are available for the preparation of monoacyl ferrocenes, only two have been used for the diacylation of ferrocene. The first method involves the acid anhydride, aluminum chloride, and ferrocene. In general a molar ratio of 2:1 of acylating agent over ferrocene is sufficient, but observation of some monoacylation has been reported. The second method involves acylation by an excess of acid chloride-aluminum chloride; this procedure is used for the commercial synthesis of

¹⁶⁵ G. R. Buell, personal communication.

¹⁶⁶ K. L. Rinehart Jr., D. E. Bublitz, and D. H. Gustafson *J. Am. Chem. Soc.*, **85**, 970 (1963).

¹⁶⁷ D. E. Bublitz and K. L. Rinehart Jr. unpublished observations.

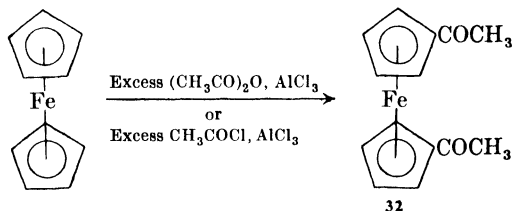
¹⁶⁸ A. N. Nesmeyanov, E. G. Perevalova, L. P. Yur'eva, and L. I. Denisovich, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2241 (1962) [*C.A.*, **58**, 12597 (1963)]

¹⁶⁹ E. G. Perevalova, L. P. Yur'eva, Yu. I. Baukov, *Dokl. Akad. Nauk SSSR*, **135**, 1402 (1960) [*C.A.*, **55**, 12378 (1961)].

¹⁷⁰ A. N. Nesmeyanov, E. G. Perevalova, and L. P. Juryeva, *Chem. Ber.*, **93**, 2729 (1960).

¹⁷¹ M. Rosenblum, J. O. Santer, and W. G. Howells, *J. Am. Chem. Soc.*, **85**, 1450 (1963).

1,1'-diacetylferrocene (**32**).¹⁴⁷ Diacyl and diaryl ferrocenes prepared by these procedures are presented in Table XIV.



Homoannular Diacyl Ferrocenes. During the diacetylation of ferrocene a small amount of 1,2-diacetylferrocene (1–2%) is formed in addition to the predominant 1,1'-diacetyl product.^{172, 173}

No other simple 1,2-diacetylferrocene has been reported from acylation—a reflection of the directive effect of the acyl group.

Diacyl groupings which are part of a second, fused carbocycle are known, however, and are discussed on pp. 49, 51.

Acylation of Substituted Ferrocenes. The acylation of substituted ferrocenes has been extensively studied, especially with regard to directive effects of substituents. A detailed discussion of these effects, given elsewhere,³⁹ is outside the scope of this review. Suffice it to generalize here that acylation of ferrocenes substituted with electron-donating substituents like alkyl groups usually gives all possible isomers, the homoannular 3-acyl isomer being favored, while acylation of ferrocenes substituted with electron-withdrawing substituents like acyl groups gives almost exclusively the heteroannular 1'-acyl isomer. A singular exception is the reported isolation of a tetraacetyl ferrocene of undesignated structure from the reaction of ferrocene with acetic anhydride in the presence of trifluoroacetic acid at 200–350°.¹⁷⁴

Acylation reactions of alkyl (refs. 62, 151, 152, 166, 172, 175–184), acyl,^{141, 178} aryl,^{185–187} halo,^{188, 189} acetamido,^{189–191} carbomethoxy,^{192, 193} alkylcarbamido ($\text{C}_5\text{H}_5\text{FeC}_5\text{H}_4\text{NHCO}_2\text{R}$),¹⁸⁹ and bridged ferrocenes^{140, 166, 176} have been reported.

¹⁷² M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

¹⁷³ J. H. Richards and T. J. Curphey, *Chem. Ind. (London)*, 1456 (1956).

¹⁷⁴ W. M. Sweeney, U.S. pat. 2,852,542 [*C.A.*, **53**, 4297 (1959)].

¹⁷⁵ A. N. Nesmeyanov, E. G. Perevalova, Z. A. Beinoravichute, and I. G. Malygina, *Dokl. Akad. Nauk SSSR*, **120**, 1263 (1958) [*C.A.*, **53**, 1293 (1959)].

¹⁷⁶ E. A. Hill and J. H. Richards, *J. Am. Chem. Soc.*, **83**, 4216 (1961).

¹⁷⁷ J. P. Monin, G. Tainturier, R. Dabard, and J. Tirouflet, *Bull. Soc. Chim. France*, 667 (1963).

¹⁷⁸ A. N. Nesmeyanov and N. A. Volkenau, *Dokl. Akad. Nauk. SSSR*, **111**, 605 (1956) [*C.A.*, **51**, 9599 (1957)].

¹⁷⁹ L. A. Day, Brit. pat. 864,198 [*C.A.*, **55**, 17647 (1961)].

¹⁸⁰ S. Birtwell, Brit. pat. 861,834 [*C.A.*, **55**, 16565 (1961)].

The diacetylation of dimethylferrocene has been described.^{62, 175} In one study four of the six possible isomeric heteroannular diacetyl-1,1'-dimethylferrocenes were characterized.⁶²

Compared to the large number of heteroannular diacyl- and diaroylferrocenes in which both groups are identical, there are relatively few in which these groups are different. Those reported are presented in Table XIV-B.

Transformations of Acyl Ferrocenes. The carbonyl groups of acyl ferrocenes and substituted acyl ferrocenes, like those of ferrocene-carboxaldehydes, undergo the same reactions as benzenoid compounds of similar structures. Both mono- and di-acyl ferrocenes are thus quite useful as synthetic intermediates en route to other ferrocenes.

Acyl ferrocenes are particularly important in the synthesis of alkyl ferrocenes (see Table XVI), of alcohols,^{140, 154, 195-209} and of alkenyl ferrocenes (see Table XVIII) from the alcohols. They also undergo the

¹⁸¹ T. Leigh, Brit. pat. 819,108 [C.A., **54**, 7732 (1960)].

¹⁸² K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

¹⁸³ Y. Nagai, J. Hooz, and R. A. Benkeser, *Bull. Chem. Soc. Japan*, **37**, 53 (1964).

¹⁸⁴ J. Tirouflet, G. Tainturier, and R. Dabard, *Bull. Soc. Chim. France*, 2403 (1963).

¹⁸⁵ M. Rosenblum and W. G. Howells, *J. Am. Chem. Soc.*, **84**, 1167 (1962).

¹⁸⁶ M. Rosenblum, *J. Am. Chem. Soc.*, **81**, 4530 (1959).

¹⁸⁷ D. E. Bublitz, W. E. McEwen, and J. Kleinberg, *J. Am. Chem. Soc.*, **84**, 1845 (1962).

¹⁸⁸ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **137**, 102 (1961) [C.A., **55**, 21081 (1961)].

¹⁸⁹ D. W. Hall and J. H. Richards, *J. Org. Chem.*, **28**, 1549 (1963).

¹⁹⁰ R. E. Bozak and K. L. Rinehart, Jr., unpublished results.

¹⁹¹ A. N. Nesmeyanov, V. N. Drozd, and V. A. Sazonova, *Izv. Akad. Nauk SSSR, Ser., Khim.*, 1205 (1965) [C.A., **63**, 13313 (1965)].

¹⁹² N. A. Nesmeyanov and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **115**, 518 (1957) [C.A., **52**, 5393 (1958)].

¹⁹³ E. G. Perevalova, M. D. Reshetova, K. I. Grandberg, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1901 (1964) [C.A., **62**, 2792 (1965)].

¹⁹⁴ M. Furdik, S. Toma, M. Dzurilla, and J. Suchy, *Chem. Zvesti*, **18**, 607 (1964) [C.A., **61**, 14710 (1964)].

¹⁹⁵ K. Schlögl and H. Egger, *Monatsh. Chem.*, **94**, 376 (1963).

¹⁹⁶ J. W. Huffman and D. J. Rabb, *J. Org. Chem.*, **26**, 3588 (1961).

¹⁹⁷ R. Dabard and B. Gautheron, *Compt. Rend.*, **254**, 2014 (1962).

¹⁹⁸ N. Sugiyama, H. Suzuki, Y. Shioura, and T. Teitei, *Bull. Chem. Soc. Japan*, **35**, 767 (1962).

¹⁹⁹ A. N. Nesmeyanov, N. S. Kochetkova, V. D. Vil'chevskaya, U. N. Sheinker, L. B. Senyavina, and M. I. Struchkova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1990 (1962) [C.A., **58**, 9133 (1963)].

²⁰⁰ N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, **79**, 2742 (1957).

²⁰¹ K. Schlögl and H. Pelousek, *Ann.*, **651**, 1 (1962).

²⁰² K. Schlögl and A. Mohar, *Monatsh. Chem.*, **92**, 219 (1961).

²⁰³ C. R. Hauser, R. L. Pruett, and T. A. Mashburn, Jr., *J. Org. Chem.*, **26**, 1800 (1961).

²⁰⁴ F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

²⁰⁵ K. L. Rinehart, Jr., R. J. Curby, Jr., D. H. Gustafson, K. G. Harbison, R. E. Bozak, and D. E. Bublitz, *J. Am. Chem. Soc.*, **84**, 3263 (1962).

²⁰⁶ M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 903 (1957).

²⁰⁷ R. Riemschneider and D. Helm, *Chem. Ber.*, **89**, 155 (1956).

²⁰⁸ D. S. Trifan and R. Bacskai, *Tetrahedron Letters*, No. 13, 1 (1960).

²⁰⁹ W. F. Little and R. E. Eienthal, *J. Org. Chem.*, **26**, 3609 (1961).

usual ketone condensation (refs. 131, 142, 153, 163, 166, 205, 210–220) and alkylation²¹² reactions, and react with Grignard reagents,^{55, 65, 207, 221–224} other organometallic reagents,^{131, 168, 202, 223} and Wittig reagents.²²⁵ Several of these reactions are illustrated in Fig. 5 (p. 30) for acetylferrocene, and a number of useful compounds obtained from acyl ferrocenes are listed in Table XV.

The behavior of the diacyl ferrocenes generally parallels that of the monoacyl derivatives. Many have been reduced to the corresponding carbinols^{226–228} and to the corresponding alkyl ferrocenes (Table XVI), and a number have been shown to undergo the usual ketone condensation reactions,^{212, 214, 216, 229–231} addition of Grignard reagents,^{207, 221} the Willgerodt reaction,²¹¹ and formation of enol acetates.²³³ Substituted acyl ferrocenes behave similarly provided that the other substituents are unreactive under the reaction conditions.

Syntheses of Substituted Ferrocenes

Alkyl Ferrocenes

Two general methods are available for the synthesis of mono- or multi-alkyl ferrocenes. The better one involves the use of appropriate acyl

²¹⁰ M. D. Rausch and L. E. Coleman, *J. Org. Chem.*, **23**, 107 (1958).

²¹¹ K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957).

²¹² C. R. Hauser and T. A. Mashburn, Jr., *J. Org. Chem.*, **26**, 1795 (1961).

²¹³ M. Furdik, P. Elecko, S. Toma, and J. Suchy, *Chem. Zvesti*, **15**, 501 (1960) [*C.A.*, **55** 16508 (1961)].

²¹⁴ M. Furdik, S. Toma, and J. Suchy, *Chem. Zvesti*, **16**, 449 (1962) [*C.A.*, **58**, 11398 (1963)].

²¹⁵ C. J. Pederson and V. Weinmayr, U.S. pat. 2,875,223 [*C.A.*, **53**, 16149 (1959)].

²¹⁶ C. E. Cain, T. A. Mashburn, Jr., and C. R. Hauser, *J. Org. Chem.*, **26**, 1030 (1961).

²¹⁷ V. Weinmayr, *Naturwiss.*, **45**, 311 (1958).

²¹⁸ L. Wolf and H. Hennig, *Z. Chem.*, **3**, 469 (1963).

²¹⁹ B. Gautheron and R. Dabard, *Bull. Soc. Chim. France*, 2009 (1963).

²²⁰ J. Boichard, J. P. Monin, and J. Tiroufflet, *Bull. Soc. Chim. France*, 851 (1963).

²²¹ R. Riemschneider and D. Helm, *Ann.*, **646**, 10 (1961).

²²² Haun-Li Wu, E. B. Sokolova, L. A. Leites and A. D. Petrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 887 (1962) [*C.A.*, **57**, 12532 (1962)].

²²³ Haun-Li Wu, E. B. Sokolova, I. I. Chlenov, and A. D. Petrov, *Dokl. Akad. Nauk SSSR*, **137**, 111 (1961) [*C.A.*, **55**, 19885 (1961)].

²²⁴ J. Boichard and J. Tiroufflet, *Compt. Rend.*, **253**, 1337 (1961).

²²⁵ P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).

²²⁶ T. A. Mashburn, Jr., and C. R. Hauser, *J. Org. Chem.*, **26**, 1671 (1961).

²²⁷ E. C. Winslow and E. W. Brewster, *J. Org. Chem.*, **26**, 2982 (1961).

²²⁸ K. Yamakawa, H. Ochi, and K. Arakawa, *Chem. Pharm. Bull. (Tokyo)*, **11**, 905 (1963) [*C.A.*, **59**, 8787 (1963)].

²²⁹ T. A. Mashburn, Jr., C. E. Cain, and C. R. Hauser, *J. Org. Chem.*, **25**, 1982 (1960).

²³⁰ M. Furdik, S. Toma, and J. Suchy, *Chem. Zvesti*, **15**, 547 (1961) [*C.A.*, **56**, 7355 (1962)].

²³¹ C. R. Hauser and C. E. Cain, *J. Org. Chem.*, **23**, 1142 (1958).

²³² C. E. Cain, T. A. Mashburn, Jr., and C. R. Hauser, *J. Org. Chem.*, **26**, 1030 (1961).

²³³ R. L. Pruett, U.S. pat. 2,947,769 [*C.A.*, **55**, 565 (1961)].

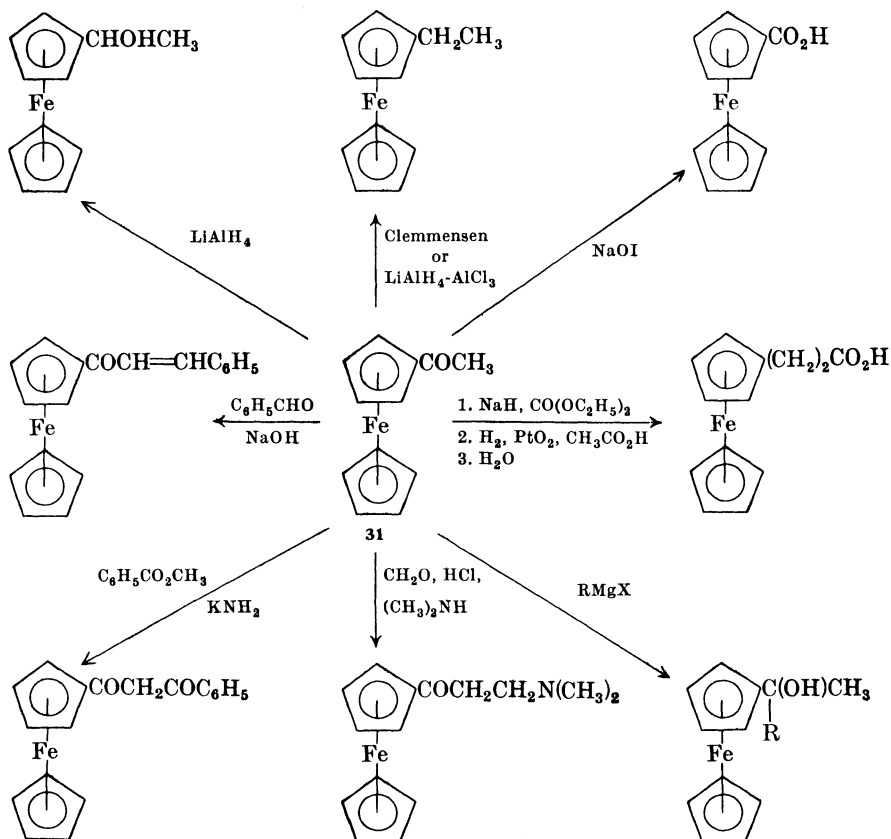


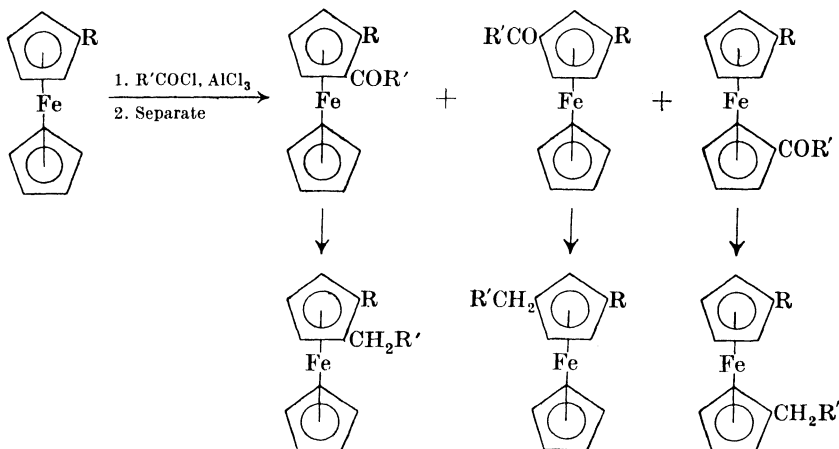
FIG. 5. Useful synthetic reactions of acetylferrocene.

ferrocenes (see pp. 24–29), which may be reduced by Clemmensen reduction, lithium aluminum hydride-aluminum chloride treatment, or catalytic hydrogenation to the corresponding alkyl ferrocenes. Other alkyl ferrocenes are obtained from acyl ferrocenes by the addition of Grignard reagents, followed by reduction of the carbinol product. By these procedures monoalkyl ferrocenes may be obtained from the monoacyl compounds and multi-alkyl ferrocenes from acylation of alkyl or acyl ferrocenes and reduction of the products. Alkyl ferrocenes prepared from acyl ferrocenes and also from alkylation (see below) are listed in Tables XVI and XVII.

Most dialkyl ferrocenes can be prepared by acylation of a monoalkyl or monoacyl ferrocene followed by chromatographic separation of the isomers and reduction to the product sought. The groups may be the same or different and, although the method can be tedious and cumbersome, it is

the preferred route to pure isomers. Acylation of acyl ferrocenes or the diacylation of ferrocene leads almost entirely to 1,1'-disubstitution products, while acylation of alkyl ferrocenes usually gives all three isomeric products; thus the route involving acylation of alkyl ferrocenes is favored for homoannular isomers.

The second general method for the preparation of mono- or multi-alkyl ferrocenes is direct alkylation of ferrocene with an appropriate Friedel-Crafts agent. Separation of the monosubstituted product from the higher-substituted materials concurrently formed is accomplished by distillation at reduced pressure or by preparative vapor phase chromatography.^{167, 234}



Although direct alkylation is intrinsically desirable, the separation of products involved is bothersome and the yield of a single product is never good. In addition to the mixture of mono- and multi-substitution products, mixtures of di- and higher-substituted materials are obtained and the separation of mixtures of dialkylated ferrocenes by the usual physical methods is difficult. Thus unresolved mixtures of di-, tri-, and poly-ethylferrocenes,²³⁵⁻²³⁷ di- and poly-isopropylferrocenes,^{235, 236} dimethylferrocenes,²³⁴ and tri- and tetra-(*t*-butyl)ferrocenes,^{236, 238} have been reported, together with isomeric tri- and tetra-ethylferrocenes.²³⁹

²³⁴ R. A. Benkeser and J. L. Bach, *J. Am. Chem. Soc.*, **86**, 890 (1964).

²³⁵ A. N. Nesmeyanov and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **114**, 800 (1957) [*C.A.*, **52**, 3794 (1958)].

²³⁶ A. N. Nesmeyanov and N. S. Kochetkova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 242 (1958) [*C.A.*, **52**, 12852 (1958)].

²³⁷ A. N. Nesmeyanov and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **109**, 543 (1956) [*C.A.*, **51**, 5057 (1957)].

²³⁸ T. Leigh, Brit. pat. 828,965 [*C.A.*, **54**, 15402 (1960)].

²³⁹ D. E. Bublit, *Can. J. Chem.*, **42**, 2381 (1964).

Because of the difficulty of separating mixtures of multi-alkyl ferrocenes, the acylation route is better; formation of mono- or di-substituted ferrocenes can be easily controlled and their reduction to the corresponding alkyl compounds proceeds in high yield. These products can in turn be further acylated and reduced if necessary. Even nonaethyl- and decaethyl-ferrocene^{149, 161} have been prepared by repeated alternate acetylation and reduction. This technique is the one currently employed commercially for the synthesis of alkyl ferrocenes.¹⁴⁷

A third method is the most convenient for preparation of many symmetrical 1,1'-dialkylated and certain tetraalkylated ferrocenes; this, the direct method, proceeds from an appropriately substituted cyclopentadiene and an iron source and has been covered earlier (see Tables II and III). Benzylferrocene is apparently the only monoalkyl ferrocene which has been prepared by the direct route.²⁴⁰

Acylation and metalation of dialkyl ferrocenes have been investigated.^{53, 175, 177, 182, 241} Oxidation of dialkyl ferrocenes with manganese dioxide gives mono- and di-acyl products (aldehydes and ketones) plus some acid.²⁴²

A few alkyl ferrocenes have been prepared by reaction of (ferrocenylmethyl)trimethylammonium iodide with various Grignard reagents.²⁴³ This reaction was mentioned on p. 21 (see also Table X).

Methylferrocene (**33**) has been obtained by reduction of the aldehyde and by reduction of a number of compounds like (ferrocenylmethyl)trimethylammonium iodide for which analogous starting materials are unavailable for other alkyl ferrocenes. These preparations are listed, with those of other alkyl ferrocenes, in Table XVI.

The formation of methylferrocene by reduction of ferrocenoic acid (**34**) or its methyl ester with lithium aluminum hydride,²⁴⁴ has been attributed to the presence of the aluminum halide used in the preparation of the hydride.¹⁶⁷ When commercial lithium aluminum hydride is used, reduction stops at ferrocenylmethanol and proceeds no further, even with excess reagent.¹⁶⁷ When lithium aluminum hydride-aluminum chloride is the reducing agent, the product is methylferrocene.^{167, 234}

An unusual route involving dimerization of an appropriately substituted ferrocene in strong acid or reaction of ferrocene and an appropriate aldehyde in acid medium is available for the preparation of symmetrical

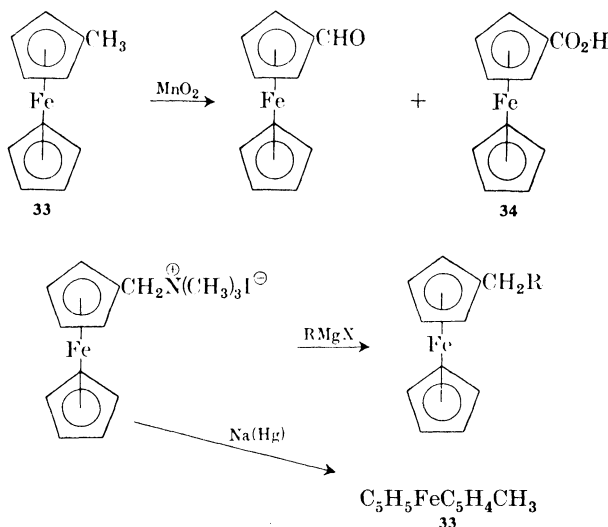
²⁴⁰ B. F. Hallam and P. L. Pauson, *J. Chem. Soc.*, 3030 (1956).

²⁴¹ J. Tirouflet, J. Monin, G. Tainturier, and R. Dabard, *Compt. Rend.*, **256**, 433 (1963).

²⁴² K. L. Rinehart, Jr., A. F. Ellis, C. J. Michejda, and P. A. Kittle, *J. Am. Chem. Soc.*, **82**, 4112 (1960).

²⁴³ A. N. Nesmeyanov, E. G. Perevalova, and L. S. Shilovtseva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1982 (1961) [*C.A.*, **56**, 10185 (1962)].

²⁴⁴ A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and Z. A. Beinoravichute, *Dokl. Akad. Nauk SSSR*, **121**, 117 (1958) [*C.A.*, **53**, 323 (1959)].



diferrocenylethanes (**40**). Thus, when ferrocene is treated with formaldehyde or benzaldehyde^{164, 245–248} in the presence of hydrogen fluoride or sulfuric acid, the product is 1,2-diferrocenylethane (**40**, $R_1 = R_2 = \text{H}$) or 1,2-diferrocenyl-1,2-diphenylethane (**40**, $R_1 = \text{H}$, $R_2 = \text{C}_6\text{H}_5$), respectively. Similarly, dimerization of ferrocenylcarbinol (**35**)²⁴⁹ or isopropenylferrocene (**37**)²⁵⁰ in sulfuric acid leads to 1,2-diferrocenylethane or to 2,3-diferrocenyl-2,3-dimethylbutane (**40**, $R_1 = R_2 = \text{CH}_3$), respectively. 1,2-Diferrocenyl-1,2-diphenylethane is similarly formed in either the acid-catalyzed decomposition of ferrocenylphenylcarbinyazide (**36**)²⁵¹ or solvolyses involving carbonium ion centers adjacent to the ferrocene nucleus.^{252–254} (See pp. 34 and 39.)

The postulated mechanism²⁴⁹ for this group of reactions involves the radical ion **38b**. Generation of the intermediate cation **38a** is extremely

²⁴⁵ K. L. Rinehart, Jr., C. J. Michejda, and P. A. Kittle, *J. Am. Chem. Soc.*, **81**, 3162 (1959).

²⁴⁶ A. N. Nesmeyanov and I. I. Kritskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 352 (1962) [*C.A.*, **57**, 11230 (1962)].

²⁴⁷ A. N. Nesmeyanov and I. I. Kritskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 253 (1956) [*C.A.*, **50**, 13886 (1956)].

²⁴⁸ V. Weinmayr, U.S. pat. 2,694,721 [*C.A.*, **49**, 15955 (1955)].

²⁴⁹ K. L. Rinehart, Jr., C. J. Michejda, and P. A. Kittle, *Angew. Chem.*, **72**, 38 (1960).

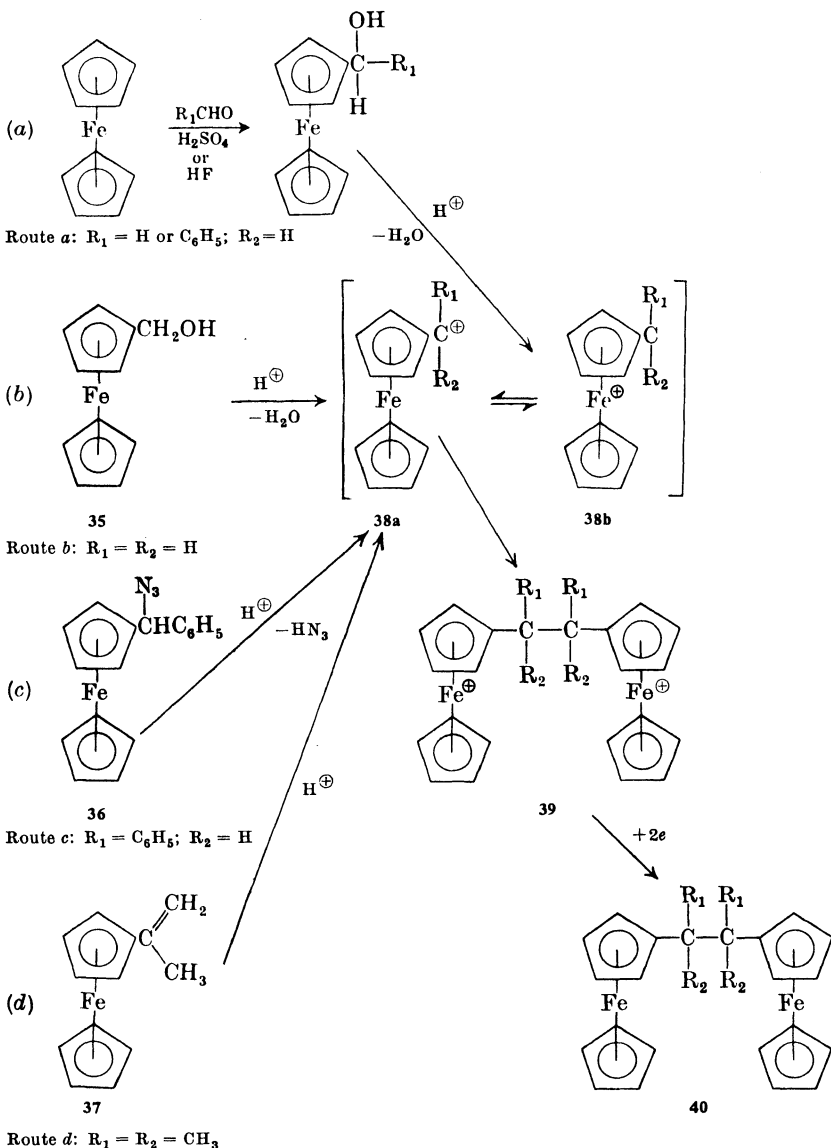
²⁵⁰ K. L. Rinehart, Jr., P. A. Kittle, and A. F. Ellis, *J. Am. Chem. Soc.*, **82**, 2082 (1960).

²⁵¹ A. Berger, W. E. McEwen, and J. Kleinberg, *J. Am. Chem. Soc.*, **83**, 2274 (1961).

²⁵² A. N. Nesmeyanov, and I. I. Kritskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2160 (1964) [*C.A.*, **62**, 10458 (1965)].

²⁵³ A. N. Nesmeyanov, V. A. Sazonova, V. N. Drozd, and N. A. Rodionova, *Dokl. Akad. Nauk SSSR*, **160**, 355 (1965) [*C.A.*, **62**, 14725 (1965)].

²⁵⁴ A. N. Nesmeyanov, V. A. Sazonova, V. N. Drozd, N. A. Rodionova, and G. I. Zudkova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2061 (1965) [*C.A.*, **62**, 14725 (1965)].



facile, and even weak acids like acetic and hydrazoic acids have been shown to protonate vinylferrocene.^{255,256}

Following the reaction, the dipositive cation **39** is reduced and the uncharged compound is isolated. Conclusive proof for the existence of

²⁵⁵ G. R. Buell, W. E. McEwen, and J. Kleinberg, *J. Am. Chem. Soc.*, **84**, 40 (1962).

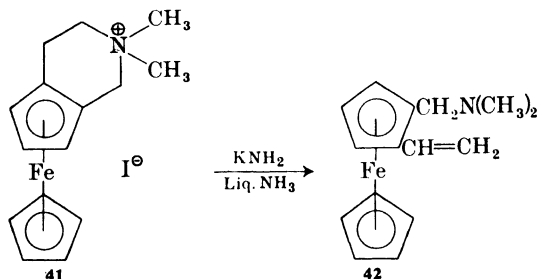
²⁵⁶ G. R. Buell, W. E. McEwen, and J. Kleinberg, *Tetrahedron Letters*, No. 5, 16 (1959).

the radical ion has not yet been reported, and an alternative reaction pathway has recently been proposed.²⁵⁷

A number of ferrocenes substituted by various hydrocarbon groups have been isolated in optically active form. The syntheses involved resolution of racemic amines and alcohols followed by removal of the functional groups.⁵⁶

Alkenyl Ferrocenes

Of the many ferrocenyl substituted olefins in which the ferrocene nucleus is attached to one of the ethylenic carbon atoms, none has been prepared by substitution on ferrocene itself. Most alkenyl ferrocenes can be prepared from one of the key intermediates discussed earlier, in a normal synthetic route to the desired compound (Table XVIII). The most common route involves dehydration over alumina of an α -hydroxyalkyl ferrocene (refs. 65, 195, 202, 204, 222, 259), but other elimination reactions,^{132, 198, 260} reactions of acyl compounds with phosphorus ylides^{91, 225, 261} and condensation reactions of ferrocenecarboxaldehyde^{154, 158} also have been used. The reaction of acyl ferrocenes with phosphorus oxychloride in dimethylformamide produces 1-chloro-1-ferrocenyl alkenes which are useful intermediates in the synthesis of ferrocenyl acetylenes and ferrocenyl allenes.²⁶² The syntheses of a large number of ferrocenyl polyenes by these methods together with the spectral properties of the products have recently been reported.^{159, 263-265} An elimination reaction worthy of special note, since it leads to a 1,2-disubstituted ferrocene (42), is shown in the accompanying equation.²⁶⁰ The quaternary methiodide 41 was prepared from the corresponding



²⁵⁷ M. Cais and A. Eisenstadt, *J. Org. Chem.*, **30**, 1148 (1965).

²⁵⁸ J. B. Thomson, *Chem. Ind. (London)*, 1122 (1959).

²⁵⁹ K. Schlögl and A. Mohar, *Naturwiss.*, **48**, 376 (1961).

²⁶⁰ D. Lednicer and C. R. Hauser, *J. Org. Chem.*, **24**, 43 (1959).

²⁶¹ G. Drefahl, G. Plötner, and I. Winnefeld, *Chem. Ber.*, **95**, 2788 (1962).

²⁶² K. Schlögl and W. Steyer, *Monatsh. Chem.*, **96**, 1520 (1965).

²⁶³ K. Schlögl and H. Egger, *Ann. Chem.*, **676**, 76 (1964).

²⁶⁴ K. Schlögl and H. Egger, *Ann. Chem.*, **676**, 88 (1964).

²⁶⁵ A. Nakamura, P. J. Kim, and N. Hagihara, *J. Organometal. Chem.*, **3**, 355 (1965).

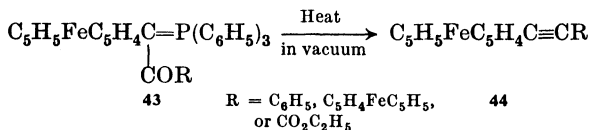
heterocyclic product derived from β -ferrocenylethylamine, formic acid, and formaldehyde.

Synthesis of certain dialkenyl ferrocenes has been accomplished by direct synthesis of the appropriately substituted iron compound (see p. 13 and Table III). The only other 1,1'-dialkenyl ferrocenes which have been reported were prepared by dehydration of the corresponding diols. They are found in the latter portion of Table XVIII.

Ferrocenyl Acetylenes

Ferrocenyl acetylenes are prepared by standard routes. Ferrocenyl-acetylene itself has been prepared by dehydrohalogenation of 1,2-dibromoethylferrocene,²⁶⁶ of β -chlorovinylferrocene, and of β,β -dichloroethylferrocene with sodium amide in liquid ammonia,¹⁹⁵ in yields of 29%, 56%, and 30%, respectively. Ferrocenylacetylene is best prepared by the dehydrohalogenation of the reaction product obtained when acetylferrocene is treated with phosphorus oxychloride in dimethylformamide (75% overall).²⁶²

The disubstituted acetylenes **44** have been prepared in excellent yields (85–93%) from the corresponding phosphorus ylides (**43**) as shown.^{225, 267}



Phenylferrocenylacetylene is also formed (in 53% yield) from bromoferrocene and potassium phenylacetylide.²⁶⁸ Dehydrohalogenation of 1-chloro-1-ferrocenyl alkenes, obtained from the respective acyl ferrocene and phosphorus oxychloride in dimethylformamide, provides a versatile route to ferrocenyl acetylenes and certain ferrocenyl alkenes.²⁶² Numerous acetylenes have been prepared, however, in which the ferrocene group is not directly attached to an acetylenic carbon atom.^{202, 225, 269} The compounds were prepared by typical reactions upon one of the ferrocene intermediates described earlier.

Dimerization of ferrocenylacetylene with cupric acetate in methanolic pyridine gave 1,4-diferrocenyl-1,3-butadiyne in 90% yield.¹⁹⁵ Treatment of a mixture of ferrocenylacetylene and phenylacetylene under identical

²⁶⁶ R. A. Benkeser and W. P. Fitzgerald, Jr., *J. Org. Chem.*, **26**, 4179 (1961).

²⁶⁷ H. Egger and K. Schlögl, *Monatsh. Chem.*, **95**, 1750 (1964).

²⁶⁸ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Doklady Akad. Nauk SSSR*, **154**, 158 (1964) [*C.A.*, **60**, 9309 (1964)].

²⁶⁹ K. Schlögl and A. Mohar, *Monatsh. Chem.*, **93**, 861 (1962).

conditions gave a 54% yield of 1-ferrocenyl-4-phenyl-1,3-butadiyne.¹⁹⁵ Other reactions involving ferrocenyl acetylenes have been reported.²⁶⁷

The synthesis of 1,1'-diethynylferrocene has been accomplished by dehydrohalogenation of 1,1'-bis-(α -chlorovinyl)ferrocene with sodium amide in liquid ammonia.²⁶²

Aryl Ferrocenes, Including Biferrocenyl and Terferrocenyl

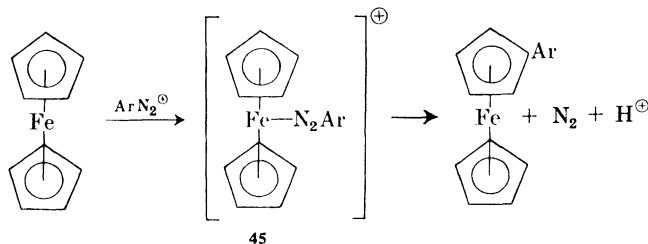
Arylation of ferrocene was first accomplished by its reaction with aryl diazonium compounds, *p*-nitrophenylferrocene being obtained in 64% yield by this method.¹¹⁷ Although this reaction is the most common method for obtaining aryl ferrocenes and is discussed below in detail, three other routes are known.

The direct synthesis of phenylferrocene from phenylcyclopentadiene and cyclopentadiene in the presence of ferrous chloride and a base²⁷⁰ has been discussed above (see Table IV).

The second method involves the demercuration of a mixture of a diaryl mercury compound and diferrocenylmercury in the presence of metallic silver.⁹⁷ This method is complicated by the need of both diferrocenylmercury and a diaryl mercury compound.

Lastly, a novel method has been reported for the preparation of pure monoaryl ferrocenes from bromoferrocene and potassium tetraarylboron compounds in the presence of cupric bromide.²⁶⁸ The inaccessibility of tetraarylboron salts, however, severely limits the scope.

The principal route to aryl ferrocenes, arylation by means of a diazonium salt, has been shown to lead to di- and even higher-substitution products.^{117, 271} Mechanistic studies of the arylation of ferrocene have been reported,^{171, 186, 272, 273} and initial formation of a ferrocene diazonium complex (45) seems likely. Yields in the range 40–60% have been



²⁷⁰ P. L. Pauson, *J. Am. Chem. Soc.*, **76**, 2187 (1954).

²⁷¹ V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3012 (1955).

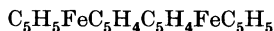
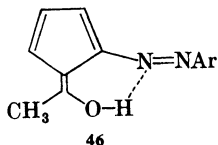
²⁷² M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *J. Am. Chem. Soc.*, **84**, 2726 (1962).

²⁷³ A. L. J. Beckwith and R. J. Leydon, *J. Am. Chem. Soc.*, **86**, 952 (1964).

realized for the monoarylated compound,²⁷⁴⁻²⁷⁶ but the yields of diarylated materials are usually below 40%. Some tri- and tetra-arylated ferrocenes of undesigned structures have been reported.^{271, 274} In general the arylations are carried out in water^{271, 272, 274, 277-279} or acetic acid.^{66, 186, 272, 275} When the arylation is carried out in the presence of a halogenated solvent such as methylene chloride or chloroform, moderate amounts of products are formed which are derived from radical attack upon the solvent. Thus, when ferrocene is treated with 2-methylbenzenediazonium chloride in chloroform, a 25% yield of ferrocenoic acid is realized.²⁸⁰

Arylations of methylferrocene,²⁷⁶ ethylferrocene,²⁷⁶ *p*-tolylferrocene,²⁷⁶ and *p*-anisylferrocene¹⁷¹ have been reported. These reactions give mixtures in which the 1,1'-disubstituted products predominate. The known diarylated compounds containing different aryl groups are the isomeric products obtained from *p*-anisylferrocene and *p*-nitrobenzenediazonium chloride.¹⁷¹ Compounds prepared by arylation and demercuration are listed in Table XIX.

The usual product of the reaction of ferrocene with aryldiazonium salts is the corresponding aryl ferrocene, and no azo coupling is observed. However, the reaction between 1,1'-diacetylferrocene and any of several aromatic diazonium salts leads to products free of iron shown to have the structure **46**.^{121, 281, 282}



47

4,4'-Diferrocenylbiphenyl and the corresponding 3,3'-isomer are formed in 15% and 58% yields, respectively, when 4- and 3-ferrocenylbromobenzene are treated with magnesium in diglyme at 100° and then allowed to react with carbon dioxide.²⁸³

²⁷⁴ A. N. Nesmeyanov, E. G. Perevalova, and R. V. Golovnya, *Dokl. Akad. Nauk SSSR*, **99**, 539 (1954) [*C.A.*, **49**, 15918 (1955)].

²⁷⁵ G. D. Broadhead and P. L. Pauson, *J. Chem. Soc.*, 367 (1955).

²⁷⁶ E. G. Perevalova, N. A. Simukova, T. V. Nikitina, P. D. Reshetov, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 77 (1961) [*C.A.*, **55**, 17645 (1961)].

²⁷⁷ S. I. Goldberg, *J. Org. Chem.*, **25**, 482 (1960).

²⁷⁸ A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and L. S. Shilovtseva, *Dokl. Akad. Nauk SSSR*, **102**, 535 (1955) [*C.A.*, **50**, 4925 (1956)].

²⁷⁹ W. F. Little and A. K. Clark, *J. Org. Chem.*, **25**, 1979 (1960).

²⁸⁰ W. F. Little, K. N. Lynn, and R. Williams, *J. Am. Chem. Soc.*, **85**, 3055 (1963).

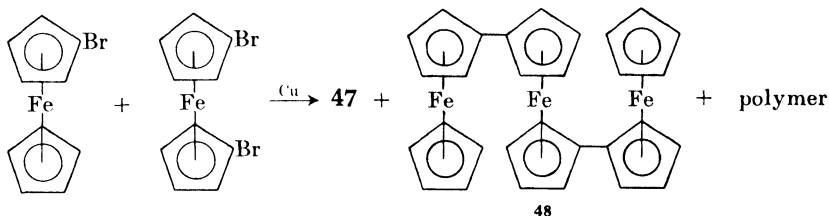
²⁸¹ A. N. Nesmeyanov, E. G. Perevalova, N. A. Simukova, Yu. N. Sheinker, M. D. Reshetova, *Dokl. Akad. Nauk SSSR*, **133**, 851 (1960) [*C.A.*, **54**, 24790 (1960)].

²⁸² R. E. Bozak, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **84**, 1589 (1962).

²⁸³ W. F. Little, A. K. Clark, G. S. Benner, and C. Noe, *J. Org. Chem.*, **29**, 713 (1964).

Biferrocenyl (47) has not been obtained by the diazotization of aminoferrocene, but it has been prepared by other routes. It was observed first as a by-product in the preparation of tri-(*n*-hexyl)silylferrocene,²⁸⁴ and its structure was established later.^{122, 285}

Better coupling reactions which have been used for the synthesis of biferrocenyl are presented in Table XX. These reactions include demercuration of diferrocenylmercury (Fig. 3),^{97, 122, 123} Ullmann coupling of haloferrocenes,^{122, 285-288} coupling of ferroceneboronic acid by ammoniacal silver oxide (Fig. 1),^{108, 109} and coupling of lithioferrocene by cobalt bromide.^{289, 290} 1,1'-Terferrocenyl (1,1'-diferrocenylferrocene, 48) has been prepared in 14% yield, together with polyferrocenylene, by reaction of a mixture of bromo- and 1,1'-dibromo-ferrocene with copper powder.²⁹¹ It has also been prepared by the direct route from ferrocenylcyclopentadiene.²⁹²



Acetylation of biferrocenyl has recently been studied and the three possible monoacetyl biferrocenyls have been isolated.²⁹³⁻²⁹⁵ Ullmann coupling was used as a route to both mono- and di-acetyl biferrocenyls of known structure.²⁹⁶

²⁸⁴ S. I. Goldberg and D. W. Mayo, *Chem. Ind. (London)*, 671 (1959).

²⁸⁵ S. I. Goldberg, D. W. Mayo and J. A. Alford, *J. Org. Chem.*, **28**, 1708 (1963).

²⁸⁶ E. G. Perevalova and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **132**, 1093 (1960) [*C.A.*, **54**, 21027 (1960)].

²⁸⁷ M. D. Rausch, U.S. pat. 3,010,981 [*C.A.*, **56**, 8750 (1962)].

²⁸⁸ M. D. Rausch, *J. Org. Chem.*, **26**, 1802 (1961).

²⁸⁹ K. Hata, I. Motoyama, and H. Watanabe, *Bull. Chem. Soc. Japan*, **37**, 1719 (1964).

²⁹⁰ I. J. Spilners and J. P. Pellegrini, Jr., *J. Org. Chem.*, **30**, 3800 (1965).

²⁹¹ A. N. Nesmeyanov, V. N. Drozd, V. A. Sazonova, V. I. Romanenko, A. K. Prokofev, and L. A. Nikonova, *Izv. Akad. Nauk, SSSR, Otd. Khim. Nauk*, 667 (1963) [*C.A.*, **59**, 7556 (1963)].

²⁹² K. L. Rinehart, Jr., D. G. Ries, C. H. Park, and P. A. Kittle, National Am. Chem. Soc. Meeting, Denver, January, 1964, Abstracts, p. 23C.

²⁹³ K. Yamakawa, N. Ishibashi, and K. Arakawa, *Chem. Pharm. Bull. (Japan)*, **12**, 119 (1964).

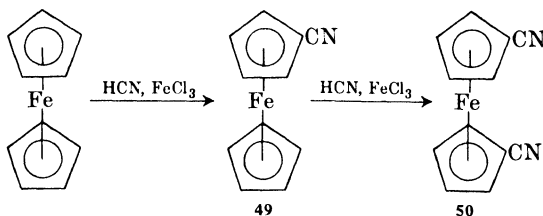
²⁹⁴ S. I. Goldberg and J. S. Crowell, *J. Org. Chem.*, **29**, 996 (1964).

²⁹⁵ M. D. Rausch, *J. Org. Chem.*, **29**, 1257 (1964).

²⁹⁶ S. I. Goldberg and R. L. Matteson, *J. Org. Chem.*, **29**, 323 (1964).

Cyano Ferrocenes

Cyanoferrocene (ferrocenonitrile, **49**) was reported by three groups of workers^{139, 141, 155} who utilized various reagents to dehydrate ferrocene-carboxaldoxime. Subsequent methods of synthesis have involved reaction of halo ferrocenes with cuprous cyanide^{109, 297} or direct cyanation of ferrocenium chloride by hydrogen cyanide in the presence of ferric chloride.^{169, 170} Syntheses of cyanoferrocene and substituted cyano ferrocenes are presented in Table XXI.



The direct cyanation of substituted ferrocenes has been little investigated.^{169, 170} A mechanism has been suggested¹⁷¹ and the simplicity of the reaction makes it appealing. Electronic effects greatly influence the position of substitution; thus alkyl groups give homoannular and heteroannular substitution products while halo and cyano groups only give heteroannular products.^{169, 170, 298, 299}

Acetylation of cyanoferrocene gives exclusively 1'-acetylcyanoferrrocene¹⁸⁹ because of the ring-deactivating effect of the cyano group. When cyanoferrocene is allowed to react with Grignard reagents or organolithium compounds, the corresponding ketones are obtained.¹⁶⁸

1,1'-Dicyanoferrrocene (**50**) has been obtained by dehydration of 1,1'-dicarboxamidoferrrocene,³⁰⁰ and better by dehydration of 1,1'-ferrocenedicarboxaldoxime.⁹¹ Cyanation of cyanoferrocene or ferrocene in tetrahydrofuran-liquid hydrogen cyanide containing ferric chloride has been shown to produce 1,1'-dicyanoferrrocene in 23–27% or 68% yield, respectively.^{169, 170, 301}

²⁹⁷ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **130**, 1030 (1960) [*C.A.*, **54**, 12089 (1960)].

²⁹⁸ A. N. Nesmeyanov, E. G. Perevalova, and K. I. Grandberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1903 (1964) [*C.A.*, **62**, 2793 (1965)].

²⁹⁹ A. N. Nesmeyanov, E. G. Perevalova, L. P. Yur'eva, and L. N. Kakurina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1897 (1964) [*C.A.*, **62**, 2793 (1965)].

³⁰⁰ N. A. Nesmeyanov and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **120**, 1267 (1958) [*C.A.*, **53**, 1292 (1959)].

³⁰¹ N. A. Nesmeyanov, E. G. Perevalova, L. P. Yuryeva, and K. I. Grandberg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1772 (1962) [*C.A.*, **58**, 7971 (1963)].

Ferrocenecarboxylic Acids and Their Derivatives

Ferrocenoic acid (ferrocenecarboxylic acid, **34**) has been prepared in numerous ways (see Table XXII). The majority of the methods involve one of the key intermediate ferrocenes mentioned earlier, and the most common preparations of ferrocenoic acid or substituted ferrocenoic acids involve carbonation of lithio ferrocenes^{53, 93-95, 117, 302} or oxidation of acetyl ferrocenes with a variety of reagents.^{142, 164, 182, 192, 303-305} Commercial production of ferrocenoic acid is accomplished by oxidation of acetylferrocene.¹⁴⁷

As noted on p. 14, lithiation of ferrocene gives a mixture of the corresponding acids upon carbonation. Separation of the mixed acids is generally accomplished by extraction with ether, in which only the monobasic acid is soluble.⁹⁴ Methods of effecting monolithiation have also been discussed earlier.

Three derivatives of ferrocenoic acid have been prepared by substitution on ferrocene—ferrocenecarboxamides,^{306, 307} alkyl and aryl thiolferrocenoates,³⁰⁸ and ferrocenonitrile (see preceding section). One method for the preparation of ferrocenecarboxamides involves the reaction of ferrocene or certain of its alkyl derivatives with either N,N-diphenylcarbonyl chloride or carbonyl chloride itself in the presence of aluminum chloride.^{55, 307} The second method involves the reaction of ferrocene with an isocyanate in the presence of aluminum chloride.³⁰⁶ Amides prepared by these reactions are found in Table XXIV. Substitution reactions on ferrocene have not led to ferrocene diamides, in accord with the view that the carbonyl chloride-aluminum chloride complex is a weak acylating reagent.³⁰⁷ The amides formed in the reaction involving isocyanates were found to be resistant to hydrolysis by acid or base, with the exception of the ethyl compound, which was hydrolyzed by acid.³⁰⁶ In contrast the N,N-diphenylamide **51** formed in the diphenylcarbonyl chloride route is hydrolyzed by base, the overall yield of acid being 46%.³⁰⁷

Treatment of ferrocene with an alkyl or aryl chlorothiolformate and aluminum chloride produces the corresponding alkyl or aryl thiolferrocenoate **52**.³⁰⁸ Hydrolysis of methyl thiolferrocenoate provides

³⁰² J. Tirouflet, E. Laviron, R. Dabard, and J. Komenda, *Bull. Soc. Chim. France*, **857** (1963).

³⁰³ V. Weinmayr, U.S. pat. 2,683,157 [*C.A.*, **49**, 10364 (1955)].

³⁰⁴ L. Wolf and M. Beer, *Naturwiss.*, **44**, 442 (1957).

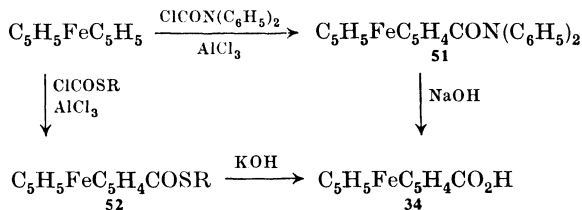
³⁰⁵ A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **45** (1962) [*C.A.*, **57**, 865 (1962)].

³⁰⁶ M. Rausch, P. Shaw, D. Mayo, and A. M. Lovelace, *J. Org. Chem.*, **23**, 505 (1958).

³⁰⁷ W. F. Little and R. Eisenthal, *J. Am. Chem. Soc.*, **82**, 1577 (1960).

³⁰⁸ D. E. Bublitz and G. H. Harris, *J. Organometal. Chem.*, **4**, 404 (1965).

ferrocenoic acid in yields up to 80%, and replacement of the methylthio group by hydrazine and amines has also been reported.³⁰⁸



Two methods for the preparation of ferrocenoic acid via acid derivatives give especially good yields. They are by way of cyanoferrrocene^{169, 170} followed by hydrolysis³⁰⁹ (69% overall) and via methyl thiolferrocenoate³⁰⁸ followed by hydrolysis (70% overall). Methods of preparation of ferrocene mono- and di-carboxylic acid are presented in Table XXII, and substituted ferrocenoic acids are listed in Table XXIII.

Ferrocenoic acid has been converted to the usual acid derivatives (refs. 91, 93, 117, 142, 164, 189, 204, 304–307, 313–318). When heated to 250–350° in an atmosphere of nitrogen, it gives the ferrous salt of ferrocenoic acid in 75% yield.³¹⁹

Of the three possible isomeric ferrocene dicarboxylic acids only the 1,1' and 1,2 diacids are known. The 1,2 isomer was obtained by hypochlorite oxidation of 1,2-diacetylferrocene, and its conversion to a cyclic anhydride was utilized in the proof of structure of 1,2-diacetylferrocene.¹⁷³

The 1,1' isomer has been obtained in various ways, most of which utilize the key intermediates (see Table XXIII). The preparation of pure ferrocene-1,1'-dicarboxylic acid by hypohalite oxidation of 1,1'-diacetylferrocene^{63, 228, 320} is the commercial method.¹⁴⁷ The most common method, carbonation of a dimetalated ferrocene, simultaneously produces monocarboxylated material which must be removed by solvent extraction. Even molar ratios of 25:1 of *n*-butyllithium to ferrocene still

³⁰⁹ A. N. Nesmeyanov, E. G. Perevalova, L. P. Yur'eva, and K. I. Grandberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1377 (1963) [*C.A.*, **59**, 15310 (1963)].

³¹⁰ G. R. Knox and P. L. Pauson, *J. Chem. Soc.*, 692 (1958).

³¹¹ A. N. Nesmeyanov and B. N. Strunin, *Dokl. Akad. Nauk SSSR*, **137**, 106 (1961) [*C.A.*, **55**, 19885 (1961)].

³¹² D. E. Bublitz and K. L. Rinehart, Jr., *Tetrahedron Letters*, 827 (1964).

³¹³ H. L. Lau and H. Hart, *J. Org. Chem.*, **24**, 280 (1959).

³¹⁴ N. Baggett, A. B. Foster, A. H. Haines, and M. Stacey, *J. Chem. Soc.*, 3528 (1960).

³¹⁵ E. M. Acton and R. M. Silverstein, *J. Org. Chem.*, **24**, 1487 (1959).

³¹⁶ A. C. Haven, Jr., U.S. pat. 2,816,904 [*C.A.*, **52**, 5479 (1958)].

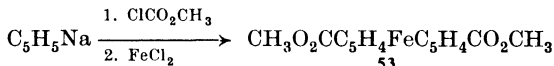
³¹⁷ A. C. Haven, Jr., U.S. pat. 3,035,074 [*C.A.*, **57**, 13806 (1962)].

³¹⁸ K. Schlögl and H. Seiler, *Naturwiss.*, **45**, 337 (1958).

³¹⁹ R. L. Schaaf, *J. Org. Chem.*, **27**, 107 (1962).

³²⁰ F. W. Knobloch and W. H. Rauscher, *J. Polymer Sci.*, **54**, 651 (1961).

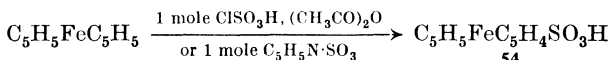
produce 23% of monobasic acid.⁹⁴ Hydrolysis of the dinitrile may offer an attractive, still little investigated, alternative. Another route to the dibasic acid is from 1,1'-dicarbomethoxyferrocene (**53**) which is prepared directly in 28% yield from cyclopentadienylsodium and methyl chloroformate in the presence of ferrous chloride.⁹¹



Ferrocene-1,1'-dicarboxylic acid forms the usual derivatives of a dibasic acid (refs. 63, 93, 105, 117, 192, 228, 277, 300, 320). However, reports of the preparation of the 1,1'-dialdehyde from the corresponding acid chloride seem dubious,²⁷⁷ and attempts to form the intramolecular, bridged anhydride with dicyclohexylcarbodiimide have been unsuccessful.²²⁸ The dimethyl ester **53** can be reduced by lithium aluminum hydride to 1,1'-bis(hydroxymethyl)ferrocene¹⁰⁴ or to 1,1'-dimethylferrocene by lithium aluminum hydride-aluminum chloride.^{167, 234}

Ferrocenesulfonic Acids and Their Derivatives

Ferrocenesulfonic acid (**54**) is obtained by two equally useful methods involving treatment of ferrocene either with an equimolar amount of chlorosulfonic acid in acetic anhydride (66% yield)³¹⁰ or with an equimolar amount of the dioxane-sulfur trioxide complex in ethylene dichloride (62% yield).³²¹ In both methods the sulfonic acid is isolated as the



dihydrate. A less important route, from the standpoint of yield, is the reaction of ferrocene with 0.25 molar equivalent of 100% sulfuric acid in acetic anhydride. The sulfonic acid was isolated as the ammonium salt in 25% yield.¹⁶⁴

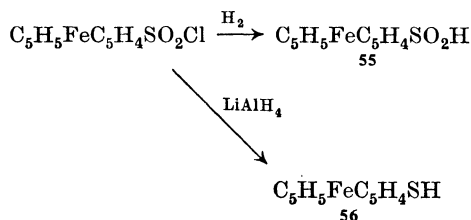
Ferrocene-1,1'-disulfonic acid has been obtained as the free acid from the reaction of ferrocene, either with 2.0 molar equivalents of chlorosulfonic acid in acetic anhydride,³¹⁰ or with 3.0 molar equivalents of the dioxane-sulfur trioxide complex,³²¹ or with 1.5 molar equivalents of 100% sulfuric acid in acetic anhydride.¹⁶⁴ The disulfonic acid has also been reported as a product from treatment of acetyl- or 1,1'-diacetyl-ferrocene with the sulfur trioxide complex, with apparent replacement of the acetyl groups.³¹¹ It is noteworthy that in the sulfonation reactions no mixtures of mono- and di-substitution products have been reported under the conditions employed.

³²¹ A. N. Nesmeyanov, E. G. Perevalova, and S. S. Churanov, *Dokl. Akad. Nauk SSSR*, **114**, 335 (1957) [*C.A.* **52**, 368 (1958)].

Sulfonation reactions have been carried out on acetylferrocene,³¹¹ phenylferrocene,¹²⁸ 1,1'-dicarbomethoxyferrocene,³¹¹ ferrocenoic acid,³²² and methyl ferrocenoate.³²² From the monosubstituted ferrocenes named, the product formed has the 1,1' orientation, as would be anticipated from the deactivating influence of the substituent on the ring in which it is present.

Ferrocenesulfonic acids undergo the functional group modifications characteristic of aryl sulfonic acids.^{311, 321-324} The lead salt of the disulfonic acid on treatment with phosphorus oxychloride gives the disulfonyl chloride.³²³

Hydrogenation of ferrocenesulfonyl chloride leads to ferrocenesulfonic acid (**55**);^{310, 321, 324} reduction by lithium aluminum hydride gives ferrocenethiol (**56**).^{310, 323} Both are convertible to a large number of derivatives. Ferrocenyl disulfide, diferrocenyl sulfone, and ferrocenyl phenyl sulfone, as mentioned earlier (see Table VIII-B), have been prepared from diferrocenylmercury.^{325, 326}



Bridged Ferrocenes

Ferrocene is theoretically capable of conversion to compounds having three possible types of cyclized structures, **57**, **58**, and **59**. Of the three types shown, only **57** and **59** have been synthesized. Compounds of the type **59** are called bridged ferrocenes and are discussed here. They are also included in a recent book on bridged aromatic compounds.³²⁷ Structures of type **57** are discussed in the following section on ferroöcarbocyclic compounds.

³²² A. N. Nesmeyanov and O. A. Reutov *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 926 (1959) [*C.A.*, **54**, 469 (1960)].

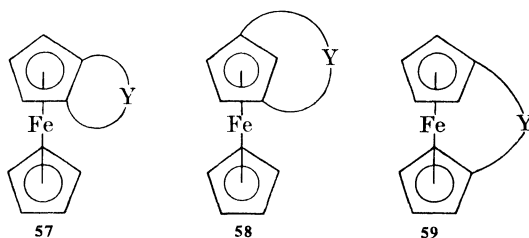
³²³ A. N. Nesmeyanov, E. G. Perevalova, S. S. Churanov, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **119**, 949 (1958) [*C.A.*, **52**, 17225 (1958)].

³²⁴ E. G. Perevalova, O. A. Nesmeyanova, and I. G. Luk'yanova, *Dokl. Akad. Nauk SSSR* **132**, 853 (1960) [*C.A.*, **54**, 21025 (1960)].

³²⁵ A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 47 (1962) [*C.A.*, **57**, 12532 (1962)].

³²⁶ A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **119**, 288 (1958) [*C.A.*, **52**, 14579 (1958)].

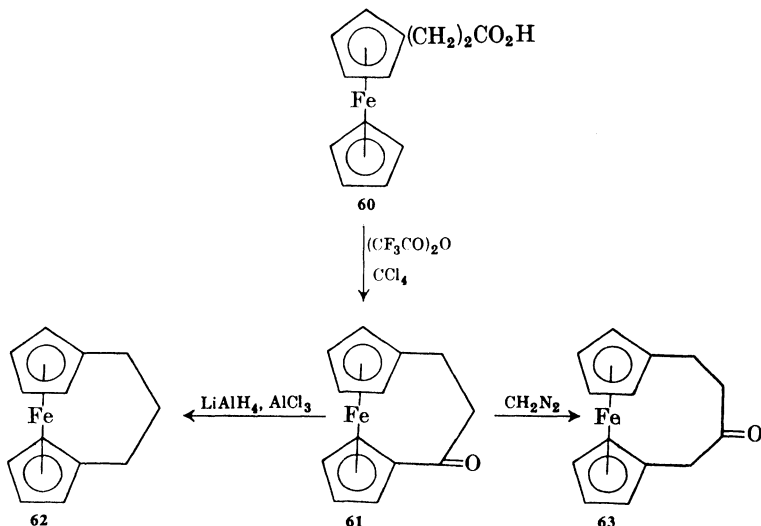
³²⁷ B. H. Smith, *Bridged Aromatic Compounds*, Academic, New York, 1964.



β -Ferrocenylpropionic acid (**60**), an important precursor of bridged ferrocenes, is available by any of four synthetic routes. Two of these are of equal utility and have been noted earlier, that via ethyl ferrocenoylacetate (68% overall yield of the propionic acid from acetylferrocene)^{163, 205, 211} in Fig. 5 and that via the Doebner condensation of ferrocenecarboxaldehyde with malonic acid¹⁴² in Fig. 4.

A third method, of lesser importance, involves the hydrolysis and decarboxylation of ferrocenylmethylmalonic ester³²⁸ prepared from *N,N*-dimethylaminomethylferrocene methiodide. β -Ferrocenylpropionic acid is obtained in 56% yield from the methiodide. The fourth method of preparation is the Willgerodt reaction of propionylferrocene (4% yield).²¹¹

The first published synthesis of a bridged ferrocene, 1,1'-(α -ketotrimethylene)ferrocene (**61**), utilized the cyclization of β -ferrocenylpropionic acid with polyphosphoric acid.³²⁹ The synthesis has been improved by the use of trifluoroacetic anhydride in carbon tetrachloride.^{140, 176, 205}



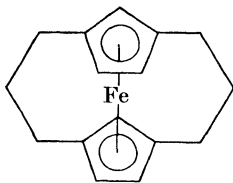
³²⁸ C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 1246 (1957).

³²⁹ K. L. Rinehart, Jr., and R. J. Curby, Jr., *J. Am. Chem. Soc.*, **79**, 3290 (1957).

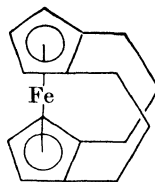
1,1'-(α -Ketotrimethylene)ferrocene (**61**) has been shown to undergo a number of the reactions of other acyl ferrocenes—conversion to the alcohol,^{140, 205} the enol acetate,¹⁴⁰ and the olefin.³³⁰ Reduction to 1,1'-trimethyleneferrocene (**62**) is accomplished by lithium aluminum hydride-aluminum chloride,^{150, 205, 331} by catalytic hydrogenation,^{176, 332} by the Wolff-Kishner¹⁴⁰ and by the Clemmensen¹⁴⁰ procedures in yields of 99%, 70–90%, 70%, and 90%, respectively. The trimethyleneferrocene **62** has also been prepared in a direct fashion from 1,3-dicyclopentadienylpropane (see Table II).^{333, 334} Structural and conformational studies of certain monobridged ferrocenes have been reported.^{335–337}

Treatment of **61** with diazomethane gives a mixture of two insertion products, mostly 1,1'-(β -ketotetramethylene)ferrocene (**63**).¹⁴⁰ Wolff-Kishner reduction of the latter gives a 75% yield of 1,1'-tetramethyleneferrocene.¹⁴⁰

1,1'-Trimethyleneferrocene (**62**) undergoes acetylation to a mixture of the 2- and 3-acetyl derivatives,^{140, 166, 176} whereas formylation apparently gives only the 3-formyl derivative.^{148, 150} Both 3-formyl- and 3-acetyl-1,1'-trimethyleneferrocene have been converted via the corresponding propionic acid to 1,1',3,3'-bis(trimethylene)ferrocene (**64**).^{148, 150, 166} Similarly, 2-acetyl-1,1'-trimethyleneferrocene gives 1,1',2,2'-bis(trimethylene)ferrocene (**65**).¹⁶⁶ Synthesis of the bis bridged compound **64** has also been accomplished by stepwise closure of ferrocene-1,1'-dipropionic acid followed by reduction.^{148, 166}



64



65

Repetition of these sequences gives the tris(trimethylene)ferrocenes **66** and **67**.^{149, 161, 166} The reported synthesis of a tetrabridged ferrocene by a similar series of reactions¹⁴⁹ has been disproved.³¹² Considerable amounts of homoannular cyclized products (of the general type **57**) are obtained in

³³⁰ M. N. Applebaum, R. W. Fish, and M. Rosenblum, *J. Org. Chem.*, **29**, 2452 (1964).

³³¹ K. Schlögl, A. Mohar, and M. Peterlik, *Monatsh. Chem.*, **92**, 921 (1961).

³³² K. Schlögl and H. Seiler, *Monatsh. Chem.*, **91**, 79 (1960).

³³³ A. Lüttringhaus and W. Kullick, *Makromol. Chem.*, **44–46**, 669 (1961).

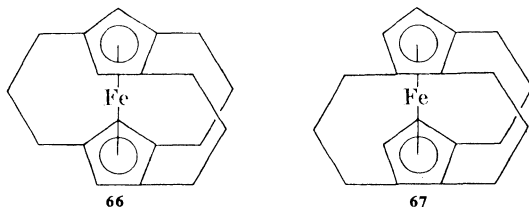
³³⁴ A. Lüttringhaus and W. Kullick, *Angew. Chem.*, **70**, 438 (1958).

³³⁵ M. Rosenblum, A. K. Banerjee, N. Danieli, and L. K. Herrick, *Tetrahedron Letters*, **423** (1962).

³³⁶ N. D. Jones, R. E. Marsh, and J. H. Richards, *Acta Cryst.*, **19**, 330 (1965).

³³⁷ M. B. Lange and K. N. Trueblood, *Acta Cryst.*, **19**, 373 (1965).

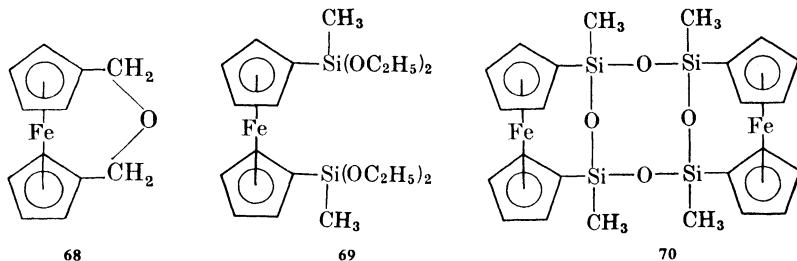
these sequences; their formation, attributed to steric hindrance in the cyclization step,^{140, 166} is discussed below.



Treatment of α,α -dimethyl- β -ferrocenylpropionic acid with trifluoroacetic anhydride gave a mixture of 1,1'- and 1,2-(α -keto- β,β -dimethyltrimethylene)ferrocene.¹⁴⁰ Reduction of the former gave 1,1'-(β,β -dimethyltrimethylene)ferrocene.

Acyloin condensations of ferrocene-1,1'-dialiphatic acid esters have given a series of bridged ferrocenes in which the bridges contain from four to nine carbon atoms,³³² and a Dieckmann condensation of dimethyl ferrocene-1,1'-diacetate gave 1,1'-(β -ketotrimethylene)ferrocene.³³⁸

The first bridged ferrocene reported containing an oxygen atom in the bridge was the intramolecular ether (68) of 1,1'-bis(hydroxymethyl)ferrocene, formed when the diol was treated with *p*-toluenesulfonic acid;⁸⁹ other chemists later demonstrated that 1,1'-bis(α -hydroxyethyl)ferrocene forms a similar compound.²²⁶⁻²²⁸



Bridged ferrocenes containing both silicon and oxygen in the bridge have been prepared principally from 1,1'-bis(methyldiethoxysilyl)ferrocene (69).³³⁹ Treatment of 69 with acid in aqueous dioxane gave 1,3-(1,1'-ferrocenylene)-1,3-dimethyl-1,3-diethoxydisiloxane in 77% yield, while treatment with acid in aqueous ethanol gave 1,3-(1,1'-ferrocenylene)-1,3-dimethyl-1,3-dihydroxydisiloxane in 21% yield.³³⁹ Treatment of 69 with acidic aqueous dioxane at 80° gave the cyclic tetrasiloxane 70 in yields of 11-24%. Treatment of 1,1'-bis(dimethylethoxysilyl)ferrocene

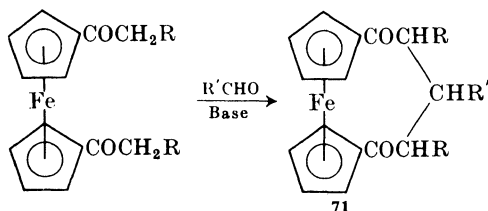
³³⁸ W. Mock and J. H. Richards, *J. Org. Chem.*, **27**, 4050 (1962).

³³⁹ R. L. Schaaf, P. T. Kan, and C. J. Lenk, *J. Org. Chem.*, **26**, 1790 (1961).

with acid in aqueous dioxane gave a 90% yield of 1,3-(1,1'-ferrocenylene)-tetramethyldisiloxane, for which a direct synthesis has also been reported (see Table II).³³⁹

Monobridged ferrocenes prepared by the same routes are presented in Table XXV. Those prepared in a direct manner from a substituted cyclopentadiene and an iron source are found in the latter portions of Tables II and III and are discussed on pp. 11, 13.

Numerous bridged ferrocenes of the type **71** prepared by the reaction of 1,1'-diacylferrocenes with various aldehydes are summarized in Table XXVI. ^{214. 340-343}



Ferroçocarbocyclic Compounds

Treatment of γ -ferrocenylbutyric acid with polyphosphoric acid^{196. 205. 329. 344} or, better, trifluoroacetic anhydride^{176. 205. 329} leads to 2,3-ferroçocyclohexenone, [1,2-(α -ketotetramethylene)ferrocene (**72a**)], in yields of 15–86%. The synthesis of γ -ferrocenylbutyric acid is readily accomplished by reaction of ferrocene with succinic anhydride^{196. 211} in the presence of aluminum chloride to give, in 87–91% yield, β -ferrocenoylpropionic acid which is then reduced. When the methyl ester acid chloride was used in place of succinic anhydride the corresponding ester was obtained in 32% yield.³⁴⁴ The keto acid can be reduced by various methods to the desired γ -ferrocenylbutyric acid in 71–98% yield.^{196. 205. 211. 344} 1,2-(α -Ketotetramethylene)ferrocene (**72a**) has been reduced to **72b** by the Clemmensen reduction³⁴⁵ or lithium aluminum hydride-aluminum chloride,¹⁶⁷ and to the corresponding alcohol by lithium aluminum hydride.^{176. 208} Dehydration of the alcohol with alumina gave

³⁴⁰ M. Furdik, S. Toma, and J. Suchy, *Chem. Zvesti*, **15**, 789 (1961).

³⁴¹ M. Furdik, S. Toma, J. Suchy, and P. Elecko, *Chem. Zvesti*, **15**, 45 (1961) [*C.A.*, **55**, 18692 (1961)].

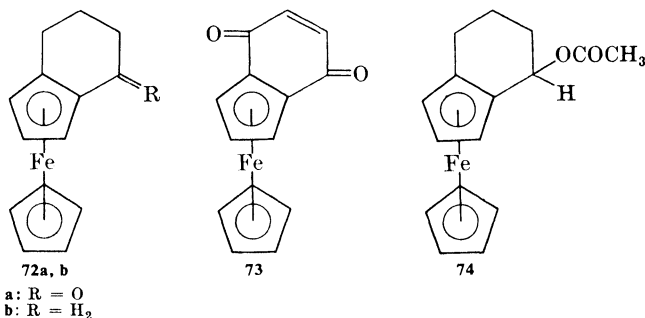
³⁴² M. Furdik and S. Toma, *Acta Fac. Rerum Nat. Univ. Comenianae, Chimia*, **7**, 545 (1963) [*C.A.*, **61**, 10706 (1964)].

³⁴³ M. Furdik, M. Dzurilla, S. Toma, and J. Suchy, *Acta Fac. Rerum Nat. Univ. Comenianae, Chimia*, **8**, 569 (1964) [*C.A.*, **61**, 12033 (1964)].

³⁴⁴ A. N. Nesmeyanov, N. A. Vol'kenau, and V. D. Vil'chevskaya, *Dokl. Akad. Nauk SSSR*, **118**, 512 (1958) [*C.A.*, **52**, 11019 (1958)].

³⁴⁵ A. N. Nesmeyanov, L. A. Kazitsyna, B. V. Lokshin, V. D. Vil'chevskaya, *Dokl. Akad. Nauk SSSR*, **125**, 1037 (1959) [*C.A.*, **53**, 21857 (1959)].

1,2-ferroço-1,3-cyclohexadiene.⁵⁷ Addition of Grignard reagents or hydrazoic acid to **72a** proceeds normally,^{56, 57, 224} and the ketone, a racemic mixture, has been resolved via the (–)menthylhydrazide.⁵⁴ The absolute configuration of **72a** has also been established.^{58, 346} Oxidation of the ketone by manganese dioxide gives the novel ferroçobenzoquinone (**73**).²⁴²



The epimeric acetates, **74**, have been extremely useful in studies of the stereochemical course of the solvolysis of groups on carbon atoms adjacent to the ferrocene nucleus.^{208, 347}

Cyclization of α -phenyl- and β -phenyl- γ -ferrocenylbutyric acid in the presence of polyphosphoric acid leads to mixtures of *exo*- and *endo*-1,2-(α -keto- β -phenyltetramethylene)ferrocene and *exo*- and *endo*-1,2-(α -keto- γ -phenyltetramethylene)ferrocene, respectively.^{348, 349} The absolute configurations of these products have recently been reported.⁶⁰ Cyclization reactions have also been studied for γ -(2,1'-diethylferrocenyl)- and γ -(3,1'-diethylferrocenyl)-butyric acid.^{184, 350} Similar treatment of δ -ferrocenylvaleric acid with either polyphosphoric acid or trifluoroacetic anhydride gives 2,3-ferroçocycloheptenone in 14–28% yield.^{205, 329}

While cyclization of β -ferrocenylpropionic acid reportedly gives only 1,1'-(α -ketotrimethylene)ferrocene (**61**), cyclization of other ferrocenylpropionic acids with trifluoroacetic anhydride leads to homocyclic ketones, **75**, **76**, **77**, **78**, in addition to the corresponding bridged ketones.^{140, 166} It is thus evident that steric factors begin to play an important part in determining the course of the reaction when substituents are present either in the propionic side chain, as in the precursor to **78**, or adjacent to the position of potential electrophilic attack, as in the precursors to **75**, **76**, and **77**. Similarly, when the two carbon atoms adjacent to the

³⁴⁶ H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 266 (1965).

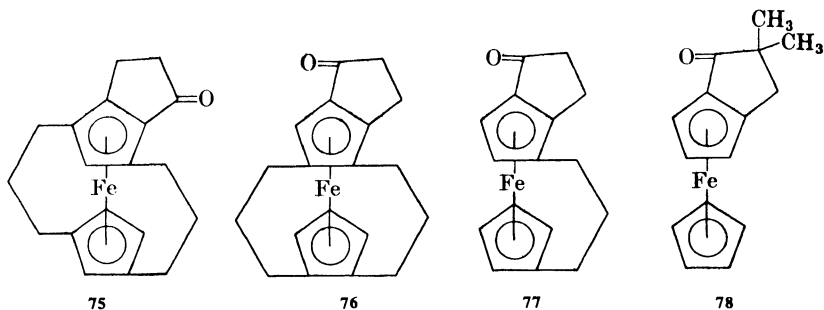
³⁴⁷ J. H. Richards, *Proc. Paint Res. Inst.*, 1433 (1964).

³⁴⁸ R. Dabard and B. Gautherson, *Bull. Soc. Chim. France*, 667 (1963).

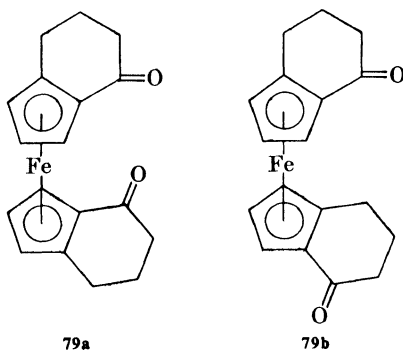
³⁴⁹ J. Tirouffet, R. Dabard, and B. Gautheron, *Compt. Rend.*, **256**, 1315 (1959).

³⁵⁰ R. Dabard, G. Tainturier, and J. Tirouffet, *Bull. Soc. Chim. France*, 2009 (1963).

ferrocene nucleus are constrained in a plane as in *o*-ferrocenylbenzoic acid, only the homoannular product of cyclization (**80**) appears to be formed (see below).^{186, 187}



Treatment of ferrocene-1,1'-dibutyric acid with polyphosphoric acid gave a 46% yield of 1,2,1',2'-bis(α -ketotetramethylene)ferrocene as a mixture of diastereoisomers.³⁵¹ The separation of these isomers into a racemic pair (**79a**) and a meso compound (**79b**) has been accomplished by two groups.^{177, 205, 241} The absolute configurations of these compounds have been investigated.³⁴⁸ Reduction of the mixed isomers leads to bis(tetrahydroindenyl)iron.³⁵¹



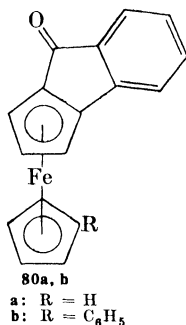
The acid chlorides of *o*-ferrocenylbenzoic acid¹⁸⁷ and 1',2-diphenylferrocenoic acid¹⁸⁶ react with aluminum chloride to give 2,3-ferrocindenones **80a** and **80b**, respectively. The former compound, **80a**, has served as a starting material for studies of benzopentalenylcyclopentadienyliron.³⁵²⁻³⁵⁴

³⁵¹ A. N. Nesmeyanov, N. A. Vol'kenau, and V. D. Vil'chevskaya, *Dokl. Akad. Nauk SSSR*, **111**, 362 (1956) [*C.A.*, **51**, 9600 (1957)].

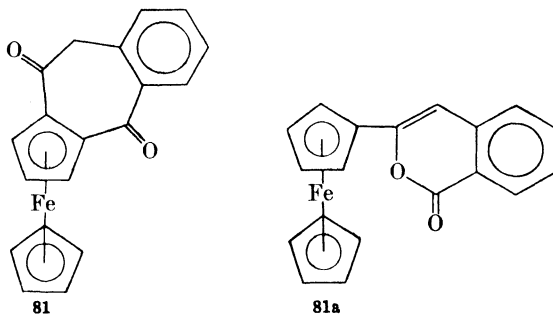
³⁵² M. Cais, R. Raveh, and A. Modiano, *Israel J. Chem.*, **1**, 228 (1963).

³⁵³ M. Cais, A. Modiano, N. Tirosh, and A. Eisenstadt, *Proc. Internat. Conf. Coord. Chem. 8th Conf.*, Vienna September 7, 1964, p. 229.

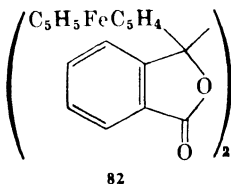
³⁵⁴ M. Cais, A. Modiano, and A. Raveh, *J. Am. Chem. Soc.*, **87**, 5607 (1965).



Cyclization of *o*-carboxyphenylacetylferrocene in polyphosphoric acid has been reported to yield the cyclic ketone **81**,^{224, 355} however, later investigation revealed it to be the ferrocenylisocoumarin **81a**.³⁵⁵



When *o*-ferrocenoylbenzoic acid^{344, 356} or its methyl ester³⁴⁴ was treated with sulfuric acid, the product was reported to be 2,3-ferroçonaphthoquinone; however, further investigation has shown the product to have the structure **82**.³⁵⁷



Some mono- and di-ferroçocarbocyclic compounds have been prepared by routes not involving substitution reactions on ferrocene. Thus

³⁵⁵ J. Boichard, *Compt. Rend.* **253**, 2702 (1961).

³⁵⁶ W. B. Hardy and E. Klingsberg, U.S. Pat. 2,900,401 [*C.A.*, **54**, 569 (1960)].

³⁵⁷ A. N. Nesmeyanov, V. D. Vil'chevskaya, and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **138**, 390 (1961) [*C.A.*, **55**, 21080 (1961)].

benzoferrrocene was prepared directly from the sodium salts of cyclopentadiene and indene by treatment with ferrous chloride (see Table IV).^{358, 359} When bis(indenyl)iron is treated with sodium cyclopentadienide, ligand exchange occurs, giving benzoferrrocene (4%) and ferrrocene (34%).³⁵⁹ This reaction is said to account for the lack of formation of bis(indenyl)iron during the preparation of benzoferrrocene as mentioned above. Catalytic reduction of benzoferrrocene leads to 1,2-tetramethylene-ferrrocene.^{358, 359}

The reaction of azulene with lithium aluminum hydride followed by addition of ferrous chloride gave the fused-ring compound **15** in 17% yield.⁸⁸ Bis(indenyl)iron and substituted bis(indenyl)iron compounds prepared from indenenes are included in Table II. Catalytic reduction of bis(indenyl)iron produces bis(tetrahydroindenyl)iron [1,2;1',2'-bis(tetramethylene)ferrrocene],³⁶⁰ similar reduction of **15** gives 1,2;1',2'-bis(pentamethylene)ferrrocene.⁸⁸

Ferroçocarbo-cyclic compounds are listed in Table XXVII.

Ferrocenyl Heterocycles and Ferroço Heterocyclic Compounds

The first reported ferroço heterocyclic compound, in which the cyclopentadienyl and heterocyclic rings are fused, was N-methyltetrahydropyridoferrrocene (**83**), prepared from β -ferrrocenylethylamine, formaldehyde, and formic acid.^{260, 361} Similarly, Bischler-Napieralski ring closure of N-acetyl- or N-formyl- β -ferrrocenylethylamine gives the corresponding dihydropyridoferrrocenes (e.g., **84**),^{362, 363} which are reduced by lithium aluminum hydride to the corresponding tetrahydropyridoferrrocenes.^{362, 363}

Numerous heterocyclic compounds containing the ferrrocene nucleus have been reported; this discussion is limited to those which contain a ferrocenyl substituent bonded directly to the heterocyclic ring. Reaction of ferrocenyllithium with pyridine or quinoline produces the 2-ferrrocenyl substituted compound (e.g., **85**) in yields of 24–32% and 3%, respectively.^{364, 365} The three isomeric (methylferrrocenyl)pyridines formed by reaction of methylferrrocenyllithium and pyridine are also known.³⁶⁵ Catalytic reduction of 2-ferrrocenylpyridine leads to 2-ferrrocenylpiperidine

³⁵⁸ R. B. King and M. B. Bisnette, *Angew. Chem.*, **75**, 642 (1963).

³⁵⁹ R. B. King and M. B. Bisnette, *Inorg. Chem.*, **3**, 796 (1964).

³⁶⁰ E. O. Fischer and D. Seus, *Z. Naturforsch.*, **9b**, 386 (1954).

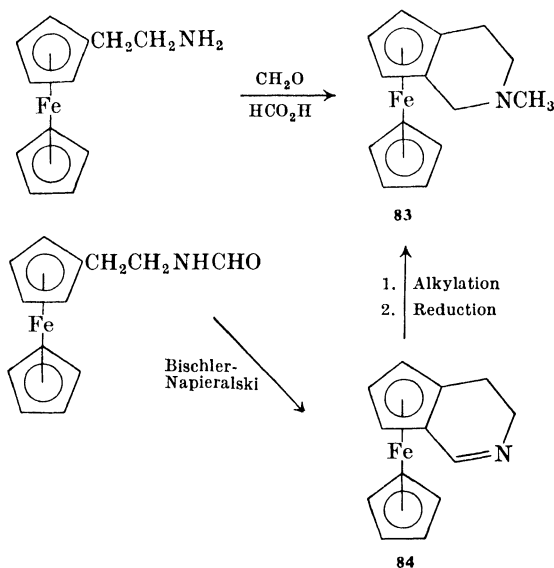
³⁶¹ J. M. Osgerby and P. L. Pauson, *Chem. Ind. (London)*, 196 (1958).

³⁶² J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 4600 (1961).

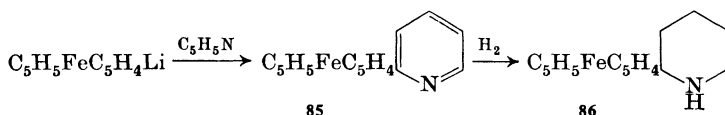
³⁶³ J. M. Osgerby and P. L. Pauson, *Chem. Ind. (London)*, 1144 (1958).

³⁶⁴ A. N. Nesmeyanov, V. A. Sazonova, and A. V. Gerasimenko, *Dokl. Akad. Nauk SSSR* **147**, 634 (1962) [*C.A.*, **58**, 9133 (1963)].

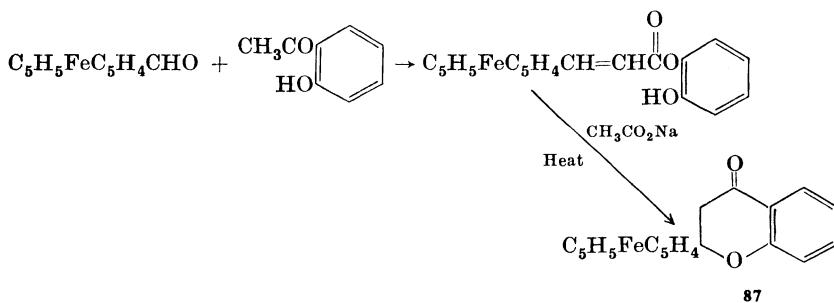
³⁶⁵ K. Schlögl and M. Fried, *Monatsh. Chem.*, **94**, 537 (1963).



(**86**) in 59% yield.³⁶⁵ Diazotization of 3-aminopyridine followed by reaction with ferrocene gives 3-ferrocenylpyridine in 27% yield.³⁶⁵

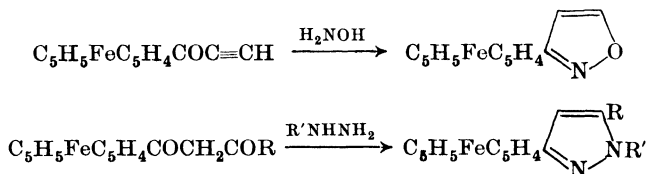


Reaction of 1,2-diferrocenylethane with hydrazine produces 3,6-diferrocenyl-4,5-dihydropyridazine.³⁶⁶ The formation of 2-ferrocenylchromanone (**87**) proceeds as shown. 3-Ferrocenylisocoumarin (**81a**) is also known.³⁵⁵ The resolution of certain optically active ferrozo heterocyclic compounds has recently been reported.⁵⁶



³⁶⁶ N. Sugiyama and T. Teitei, *Bull. Chem. Soc. Japan*, **35**, 1423 (1962).

A larger number of five-membered heterocyclic compounds bearing a ferrocenyl substituent has been reported. Representative syntheses of this family are shown in the accompanying equations.

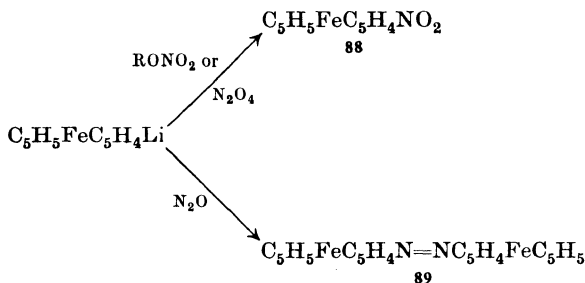


Ferrocenyl and ferroço heterocyclic compounds and their methods of synthesis are listed in Table XXVIII.

No compounds are known which contain heterocyclic rings fused to both ferrocene rings. The known disubstituted compounds (listed at the end of Table XXVIII) are all ferrocenyl substituted heterocyclic structures, prepared either by reaction with dilithioferrocene or by addition of hydrazine to bis-(β -diketone) derivatives of ferrocene.

Nitro and Azo Ferrocenes

Nitroferrocene (**88**) has never been obtained by electrophilic nitration of ferrocene. The ease with which ferrocene undergoes oxidation to ferricenium salts precludes the use of the nitrating agents common in benzene chemistry, since these are also strongly oxidizing. The synthesis of nitroferrocene has been achieved, however, by two routes: the reaction of lithioferrocene in diethyl ether at -70° with dinitrogen tetroxide³⁶⁷ or *n*-propyl nitrate.³⁶⁸ Reduction of nitroferrocene by chemical^{367, 368} or electrolytic³⁶⁹ processes gives aminoferrocene.



³⁶⁷ J. F. Helling and H. Shechter, *Chem. Ind. (London)*, 1157 (1959).

³⁶⁸ H. Grubert and K. L. Rinehart, Jr., *Tetrahedron Letters*, No. 12, 16 (1959).

³⁶⁹ A. M. Hartley and R. E. Visco, *Anal. Chem.*, **35**, 1871 (1963).

When lithioferrocene is treated with nitrous oxide, azoferrocene (**89**) can be isolated in 25–30% yield.^{370, 371} Air oxidation of aminoferrocene in the presence of cuprous bromide provides azoferrocene in yields up to 99%.¹¹⁶ Treatment of azoferrocene with sulfuric or hydrochloric acid gave aminoferrocene in yields of 10–44%,³⁷¹ and its reduction by catalytic hydrogenation³⁷⁰ or zinc in sodium hydroxide³⁷¹ gave aminoferrocene in yields of 23–76%. Attempts to reduce azoferrocene to hydrazoferrocene have been unsuccessful. The synthesis of phenylazoferrocene has been achieved directly from phenylazocyclopentadiene and cyclopentadiene in the presence of an iron salt and a base, as mentioned in Table IV. It is also formed, in addition to phenylazoxyferrocene, from aminoferrocene and azobenzene.³⁷² Catalytic reduction of phenylazoferrocene by hydrogen in methanol gives phenylhydrazoferrocene, while reduction in acetic acid gives aminoferrocene.³⁷³

Dinitroferrocene has not been reported, but syntheses of two bis-(arylaazo) ferrocenes have been reported utilizing the appropriately substituted azocyclopentadienes and an iron source (see Table II). 1,1'-Bis(phenylazo)ferrocene is reduced catalytically to either bis(phenylhydrazo)ferrocene³⁷³ or 1,1'-diaminoferrocene.^{373, 374}

Halo Ferrocenes

Although the ease with which the iron atom in ferrocene is oxidized from Fe(II) to Fe(III) precludes the formation of halo ferrocenes by halogenation of ferrocene, these compounds have been synthesized by displacement reactions on either ferrocenylmercuric chloride or ferroceneboronic acid. The reaction of halogens with diferrocenylmercury (Fig. 2) or ferrocenylmercuric chloride (Fig. 3)^{110, 114, 286, 375, 376} is of value only for the preparation of iodoferrocene; bromoferrocene has been made by this route, but the yields are low.³⁷⁵ The reaction of N-halosuccinimides with ferrocenylmercuric chloride (Fig. 2) is useful for synthesis of both bromo- and iodo-ferrocene.¹²⁰ The second method, the reaction of ferroceneboronic acid with cuprous halides (Fig. 1),^{108, 109, 114} is useful for the preparation of chloro- and bromo-ferrocene.

³⁷⁰ A. N. Nesmeyanov, E. G. Perevalova, and T. V. Nikitina, *Tetrahedron Letters*, No. 1, 1 (1960).

³⁷¹ A. N. Nesmeyanov, E. G. Perevalova, and T. V. Nikitina, *Dokl. Akad. Nauk SSSR*, **138**, 1118 (1961) [*C.A.*, **55**, 24707 (1961)].

³⁷² A. N. Nesmeyanov, T. V. Nikitina, and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 197 (1964) [*C.A.*, **60**, 9310 (1964)].

³⁷³ G. R. Knox, *Proc. Chem. Soc.*, 56 (1959).

³⁷⁴ G. R. Knox and P. L. Pauson, *J. Chem. Soc.*, 4615 (1961).

³⁷⁵ A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **100**, 1099 (1955) [*C.A.*, **50**, 2558 (1956)].

³⁷⁶ M. D. Rausch, *J. Org. Chem.*, **26**, 3579 (1961).

Halo ferrocenes undergo the usual reactions characteristic of an aryl halide. Cyanation of chloroferrocene has been shown to occur exclusively in the unsubstituted ring.^{169, 170} Chloroferrocene and bromoferrocene have been acetylated with acetyl chloride and aluminum chloride.^{188, 189} Both chloro- and bromo-ferrocene have been converted to acetoxysterrocene with cupric acetate,^{109, 112, 188, 297} to the nitrile with cuprous cyanide,²⁹⁷ and to diferrocenyl by the Ullmann reaction.²⁹⁶ Bromoferrocene reacts with a number of sodium and potassium tetraarylboron compounds to form the corresponding aryl ferrocenes.²⁶⁸ It has also been converted to N-ferrocenylphthalimide,^{188, 297} to ferrocenyl azide,³⁷⁷ and to a variety of sulfones³⁷⁹ and amines.¹¹⁶ Substituted bromoferrocenes have been shown to react similarly.^{115, 305} Iodoferrrocene has been converted to diferrocenyl^{122, 286-288} and to various ferrocenyl aryl ethers and sulfides.^{288, 380} Both bromo- and iodo-ferrocene form Grignard reagents.¹¹⁰ Recent studies of the reaction between chloroferrocene and certain organolithium compounds have demonstrated the possible existence of a ferrocene intermediate.³⁸¹

The dihalo ferrocenes in which both halogens are identical are prepared from bis(chloromercuri)ferrocene or ferrocenylen-1,1'-diboric acid, while mixed halides are prepared from bis(haloferrocenyl)mercury or haloferrocenylmercuric chlorides. 1'-Iodochloroferrocene under Ullmann conditions gave an 88% yield of bis-(1'-chloroferrocenyl).²⁹¹ Similar treatment of a mixture of bromo- and dibromo-ferrocene gives 1,1'-diferrocenylferrocene (1,1'-terferrocenyl, **48**).²⁹¹

Syntheses of mono- and di-halo ferrocenes are listed in Table XXIX.

Aminoferrrocene

The most common synthesis of aminoferrrocene (**90**) is the hydrogenolysis of an N-ferrocenylurethane.^{204, 315, 317, 318} It may also be prepared by reaction of ferrocenyllithium with either O-benzylhydroxylamine²⁷⁸ or methoxyamine (see equations on p. 57).³¹⁵

Aminoferrrocene is also obtained by the reduction of phenylazoferrrocene (35-100%),³⁷²⁻³⁷⁴ nitroferrocene,³⁶⁷⁻³⁶⁹ azoferrrocene (23-76%),^{370, 371} ferrocenylazide (72%),³⁷⁷ and phenylazoxyferrocene (65%).³⁷² Reaction of

³⁷⁷ A. N. Nesmeyanov, V. N. Drozd, and V. A. Sazonova, *Dokl. Akad. Nauk SSSR*, **150**, 321 (1963) [*C.A.*, **59**, 5196 (1963)].

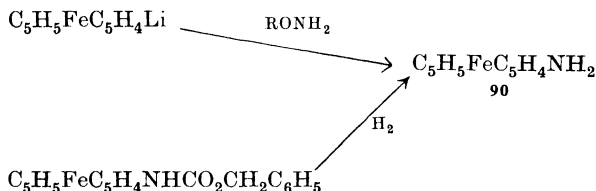
³⁷⁸ A. N. Nesmeyanov, V. N. Drozd, and V. A. Sazonova, *Dokl. Akad. Nauk SSSR*, **150**, 102 (1963) [*C.A.*, **59**, 7558 (1963)].

³⁷⁹ V. N. Drozd, V. A. Sazonova, and A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR*, **159**, 591 (1964) [*C.A.*, **62**, 7794 (1965)].

³⁸⁰ M. D. Rausch, U.S. pat. 3,604,026 [*C.A.*, **58**, 10241 (1963)].

³⁸¹ J. W. Huffman, L. H. Keith, and R. L. Asbury, *J. Org. Chem.*, **30**, 1600 (1965).

³⁸² S. I. Goldberg and L. H. Keith, *J. Chem. Eng. Data*, **9**, 250 (1964).



bromoferrocene with the copper salt of phthalimide leads to N-ferrocenylphthalimide which, upon cleavage by hydrazine, affords aminoferrocene in 82% yield.^{109, 297}

N-Acylferrocenylamines are, in low yield, the products of the Schmidt reaction of acyl ferrocenes.³⁸³

Aminoferrocene is reported to decompose on standing but is stable as its N-acetyl derivative.^{204, 278} N-Ethylation of **90** to the mono- and di-ethylated derivatives has been accomplished using ethyl fluoride in the presence of boron trifluoride etherate.³⁸⁴ Reactions of **90** with isocyanates,³¹⁸ chloroformates,^{189, 374} phosgene,^{315, 318} acid chlorides,^{204, 220, 278, 315} and aldehydes^{158, 220} have been reported. In addition Diels-Alder adducts of N-ferrocenylmaleimide have been investigated.³⁸⁵ The lack of a report of a diazonium salt is noteworthy.

The preparation of 1,1'-diaminoferrocene in 62% yield has been reported from reduction of ferrocenylene-1,1'-diazide³⁷⁷ and from catalytic hydrogenation of 1,1'-bis(phenylazo)ferrocene.^{373, 374} The material was reported to be unstable on standing and was not characterized except as its reaction products with methyl-, ethyl-, and phenyl-chlorocarbonate which produced stable carbamate derivatives.

Hydroxyferrocene and Its Derivatives

Hydroxyferrocene was first obtained from treatment of ferroceneboronic acid with cupric acetate, followed by alkaline hydrolysis of acetoxyferrocene (Fig. 1) to give hydroxyferrocene in 88% yield.^{112, 113} The yield was only 60% when acetoxyferrocene was treated with phenylmagnesium bromide.¹¹² Cupric propionate has been used in place of cupric acetate, but with no apparent advantage.¹¹² Hydroxyferrocene has also been obtained in 30% yield by treatment of benzenediazaminoferrocene with sulfuric acid.³⁷⁸ When benzenediazaminoferrocene was treated with hydrochloric acid followed by sodium 2-naphtholate, a 28% yield of ferrocenyl 2-naphthyl ether resulted.³⁷⁸ Hydroxyferrocene, liberated

³⁸³ M. Cais and N. Narkis, *J. Organometal. Chem.*, **3**, 188 (1965).

³⁸⁴ A. N. Nesmeyanov, V. A. Sazonova, and V. I. Romanenko, *Dokl. Akad. Nauk SSSR*, **152**, 1358 (1963) [*C.A.*, **60**, 1793 (1964)].

³⁸⁵ M. Furdik, S. Toma, and J. Suchy, *Chem. Zvesti*, **17**, 21 (1963) [*C.A.*, **59**, 10116 (1963)].

³⁸⁶ M. R. Barusch and E. G. Lindstrom, U.S. pat. 2,834,796 [*C.A.*, **52**, 16366 (1958)].

from basic solutions by carbon dioxide, is unstable in air and decomposes on standing over periods of several days but is stable under nitrogen. Esters and ethers of hydroxyferrocene appear to be stable.

Acetoxyferrocene in alkali with dimethyl sulfate or chloroacetic acid gave the methyl ether (90%) or ferrocenyloxyacetic acid (82%).^{109, 115} Reaction of hydroxyferrocene with allyl bromide in acetone in the presence of potassium carbonate gave an 84% yield of the allyl ether.¹¹⁵ The allyl ether does not rearrange under the usual conditions for the Claisen rearrangement.

Substituted halo ferrocenes react with cupric acetate to give the corresponding substituted acetoxy ferrocenes. Thus 1'-acetoxyferrocene-carboxylic acid and its methyl ester³⁰⁵ and also 1'-acetoxy-1-ethyl- and 1'-acetoxy-1-acetyl-ferrocene have been obtained from their respective bromo-substituted precursors.¹⁸⁸ In a double reaction, 1'-bromoferroceneboronic acid gives 1,1'-diacetoxyferrocene.¹⁰⁹ Other derivatives of 1,1'-dihydroxyferrocene reported are the dimethyl derivatives **9a** and **9b**, obtained by the reaction sequence on p. 10.^{61, 82} The dibenzoate was hydrolyzed to the extremely air-sensitive dihydroxydimethylferrocene.

1,1'-Dihydroxyferrocene is also very sensitive to air oxidation.^{109, 115} The compound was prepared by treatment of ferrocene-1,1'-diboronic acid or 1'-bromoferroceneboronic acid with cupric acetate to give 1,1'-diacetoxyferrocene (in yields of 40–83%) which was hydrolyzed to the free dihydroxy compound. Although the latter was unstable, it could be converted to the more stable dibenzoate, bis(benzene sulfonate), or bis(oxyacetic acid).

Ferrocenes Substituted with Phosphorus-, Sulfur-, Selenium-, Silicon-, Germanium-, or Arsenic-Containing Groups

The preparation and chemical properties of many types of substituted ferrocenes have been treated in earlier sections. While most of these ferrocenes contain only carbon atoms bonded directly to the ferrocene nucleus, a significant number of substituents containing heteroatoms bonded to ferrocene have been noted. They include the oxygen-, nitrogen- and halogen-containing substituents of the immediately preceding sections, the lithio, sodio, mercuri, and boronic acid derivatives useful as synthetic intermediates, and the ferrocenyl Grignard reagents (pp. 14–20, 56). This section describes substituted ferrocenes in which still other heteroatoms are bonded directly to a ferrocene ring.

Ferrocenylphosphorus Compounds. Of ferrocenes containing heteroatoms bonded to the nucleus, only compounds having a ferrocene-phosphorus bond or ferrocene-arsenic bond (see p. 60) have been prepared

by substitution on ferrocene itself. The reaction of ferrocene with phenyldichlorophosphine or diphenylchlorophosphine in the presence of aluminum chloride leads to the formation of diferrocenylphenylphosphine and ferrocenyldiphenylphosphine, respectively.³⁸⁷ Treatment of ferrocene with phosphorus trichloride in the presence of aluminum chloride gives triferrocenylphosphine oxide and diferrocenylphosphinic acid as the major products.³⁸⁸ When ferrocene is treated with *N,N*-diethylphosphoramidous dichloride $[(C_2H_5)_2NPCl_2]$ and aluminum chloride, triferrocenylphosphine and its oxide are obtained. Variation of the amounts of reactants leads to other phosphorus derivatives of ferrocene.³⁸⁹ No derivatives have been reported in which two phosphorus atoms are bonded to the ferrocene molecule.

Ferrocenylsulfur Compounds. Compounds containing ferrocene bonded directly to a sulfur atom in lower oxidation states are obtained by three methods. The first is the reduction of ferrocenesulfonyl chloride (p. 44) to mercaptoferrocene and its subsequent reaction to give other products. The second is the reaction between a halo ferrocene (p. 56) and the sodium salt of an aryl thiol to produce aryl ferrocenyl sulfides. The third method (Fig. 3, p. 20) involves the reaction between diferrocenylmercury and various sulfur-containing reagents. References to these preparative methods are found in the appropriate sections above.

Ferrocenylselenium Compounds. Diferrocenyl selenide, the only selenium-containing ferrocene, is prepared from diferrocenylmercury (Fig. 3) and selenium tetrabromide in chloroform.³²⁶

Ferrocenylsilicon Compounds. Many derivatives of ferrocene have been prepared in which a silicon atom is bonded to the ferrocene ring. Some of them have already been mentioned (pp. 11, 47).

The preparation of triphenylsilylferrocene from ferrocenyllithium and triphenylchlorosilane⁹³ has been described. The reaction can be extended to include trimethylchlorosilane¹¹⁸ and tri-(*n*-hexyl)chlorosilane,^{103, 285} and to the use of sodioferrocene.⁹⁸

The ferrocene-silicon bond is rather weak, and silicon substituents may often be removed by acidic hydrolysis.³⁹⁰ Dimethylphenylsilylferrocene has been prepared by acidic hydrolysis of lithium (1'-phenyldimethylsilyl-1-ferrocenyl)dimethylsilanolate (**91**).³⁹¹

Treatment of 1,3-(1,1'-ferrocenylene)tetramethyldisiloxane with sodium

³⁸⁷ G. P. Sollott, H. E. Mertwoy, S. Portnoy, and J. L. Snead, *J. Org. Chem.*, **28**, 1090 (1963).

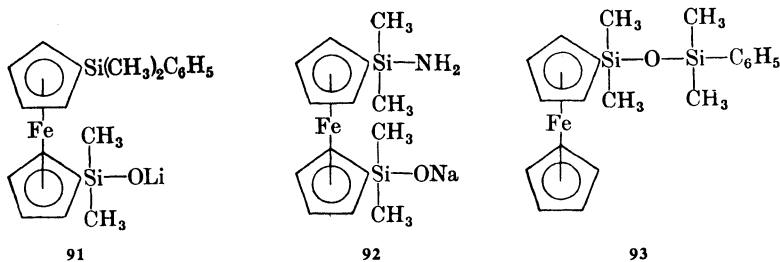
³⁸⁸ G. P. Sollott and E. Howard, Jr., *J. Org. Chem.*, **27**, 4034 (1962).

³⁸⁹ G. P. Sollott and W. R. Peterson, Jr., *J. Organometal. Chem.*, **4**, 491 (1965).

³⁹⁰ G. Marr and D. E. Webster, *J. Organometal. Chem.*, **2**, 99 (1964).

³⁹¹ P. T. Kan, C. T. Lenk, and R. L. Schaaf, *J. Org. Chem.*, **26**, 4038 (1961).

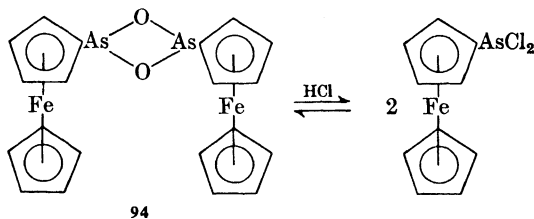
amide gives the intermediate **92** which, upon reaction with dimethylphenylchlorosilane followed by hydrolysis, gives 1-ferrocenyl-3-phenyltetramethyldisiloxane (**93**).³⁹¹ When trimethylsilylferrocene is treated with alcoholic acid, ferrocene results.³⁹⁰



Numerous disubstituted ferrocenes have been prepared in which the substituent is silicon. However, the majority of these compounds were prepared directly from the appropriately substituted cyclopentadiene and ferrous chloride and are found in Table II-A. The other derivatives that have been reported were made by the reaction of the appropriately substituted silyl chloride with either 1,1'-disodio- or 1,1'-dilithio-ferrocene.

Ferrocenylgermanium Compounds. Triphenylgermylferrocene, the only monosubstituted ferrocenylgermanium compound reported, was prepared from sodioferrocene or 1,1'-ferrocenylenedimagnesium bromide by reaction with triphenylbromogermane.⁹⁸ 1,1'-Bis(triphenylgermyl)ferrocene has been prepared by three routes. One of these, utilizing triphenylgermylcyclopentadiene and ferrous chloride,⁹⁸ is listed in Table II. Another method, treatment of a mixture of mono- and di-sodioferrocene with triphenylgermanium bromide, gives the material in 13% yield.⁹⁸ The last method, the reaction between 1,1'-ferrocenylenedimagnesium bromide and triphenylbromogermane, produces the material in unstated yield.⁹⁸

Ferrocenylarsenic Compounds. Treatment of ferrocene with arsenic(III) chloride in the presence of aluminum chloride gives arsenosferrocene (**94**) in 22% yield.³⁹² Treatment of this material with hydrochloric acid converts it to ferrocenyldichloroarsine (95%) in a reversible



³⁹² G. P. Sollott and W. R. Peterson, Jr., *J. Org. Chem.*, **30**, 389 (1965).

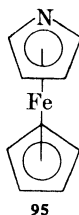
reaction. The conversion of these products to other derivatives is the only route reported for the preparation of other ferrocenylarsenic compounds.

The metalated ferrocenes discussed in this section are shown in Table XXX.

Azaferrocene (π -Cyclopentadienyl- π -pyrrolyliron)

Azaferrocene (**95**) has been prepared by two methods. The more useful of the two involves the reaction of potassiumpyrrole with cyclopentadienyliron dicarbonyl iodide³⁹³ in benzene solution to provide the desired compound in 22% yield.³⁹⁴ This method has also been applied successfully to 2,4- and 2,5-dimethylpyrrole to give the dimethyl derivatives in 20% and 32% yield, respectively.

The second method of preparation involves the reaction of a mixture of sodiumpyrrole and cyclopentadienylsodium with ferrous chloride.³⁵⁹ The yield is only 0.85% and no substituted pyrroles have been shown to react.



Ferrocene-Containing Polymers

Numerous polymers have been prepared in which a ferrocene is the repeating unit. They can be grouped into three general structural categories: (a) polymethylene- and polyalkyl-ferrocenylenes; (b) polyferrocenyleneamides; (c) ferrocenylene-containing polyurethanes and polyureas.

When ferrocene is allowed to react with an aldehyde in the presence of a catalyst such as sulfuric acid or zinc chloride, polymers of the type **96** are formed.³⁹⁶⁻³⁹⁹ The same products are obtained when the correspondingly

³⁹³ R. B. King and F. G. A. Stone, *Inorg. Syn.*, **8**, 110 (1963).

³⁹⁴ K. K. Joshi, P. L. Pauson, A. R. Qazi, and W. H. Stubbs, *J. Organometal. Chem.*, **1**, 471 (1964).

³⁹⁵ Imperial Chemical Industries Ltd., Fr. pat. 79,755 (Addn. to 1,305,312) [*C.A.*, **59**, 11567 (1963)].

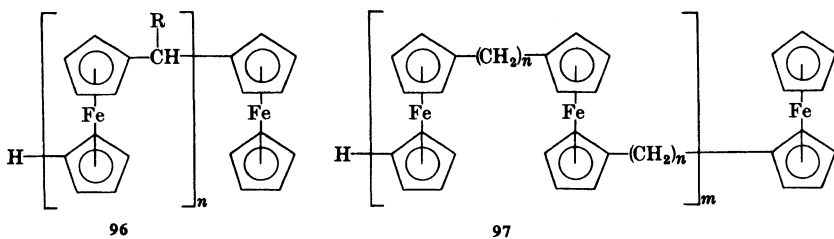
³⁹⁶ H. Valot, *Compt. Rend.*, **258**, 5870 (1964).

³⁹⁷ E. W. Neuse, *Nature*, **204**, 179 (1964).

³⁹⁸ E. W. Neuse, K. Koda, and E. Carter, *Macromol. Chem.*, **84**, 213 (1965).

³⁹⁹ E. W. Neuse and K. Koda, *J. Organometal. Chem.*, **4**, 475 (1965).

substituted ferrocenylcarbinols are polymerized.⁴⁰⁰⁻⁴⁰² Infrared analysis shows that the polymer contains all three possible substitution arrangements (1,2; 1,3; and 1,1').⁴⁰⁰ Polyferrocenylenemethylenes of type **97** have been obtained in unstated yields by treatment of the corresponding α,ω -bis(cyclopentadienyl)alkanes with a base and ferrous chloride.³³⁴ Treatment of *N,N*-dimethylaminomethylferrocene with zinc chloride has produced polymers of type **96** ($R = H$).⁴⁰³⁻⁴⁰⁵



($R = H, CH_3, C_6H_5, 2-C_4H_9O$)

Polyferrocenylalkylenes have been obtained by treating alkyl-substituted ferrocenes with di-*t*-butyl peroxide.⁴⁰⁶⁻⁴⁰⁹ When ferrocene itself is heated with di-*t*-butyl peroxide in the presence of haloaromatic compounds such as *p*-dichlorobenzene or 1-bromonaphthalene, polymers are formed which incorporate the haloaryl moiety as well.^{407, 408} When the polymerization of ferrocene is carried out in acetone, four isopropylidene groups are incorporated per ferrocene molecule.⁴⁰⁸

Homopolymerization of acetylferrocene with zinc chloride at 200° gives polyferrocenylacetylene,⁴⁰⁸ and when 1,1'-diacetylferrocene is treated with zinc chloride at 180° the resulting polymer is crosslinked by 1,1'-ferrocenylene groups.⁴⁰⁸ *trans*-Cinnamoylferrocene does not form a homopolymer in the presence of azoisobutyronitrile or benzoyl peroxide, but it can be copolymerized with a variety of monomers.⁴¹⁰ In contrast

⁴⁰⁰ E. W. Neuse and D. S. Trifan, *J. Am. Chem. Soc.*, **85**, 1952 (1963).

⁴⁰¹ A. Wende and H. J. Lorkowski, *Plaste Kautschuk*, **18**, 32 (1963) [*C.A.*, **59**, 4050 (1963)].

⁴⁰² E. W. Neuse and E. Quo, *Bull. Chem. Soc. Japan*, **38**, 931 (1965).

⁴⁰³ E. W. Neuse and E. Quo, *Nature*, **205**, 494 (1965).

⁴⁰⁴ E. W. Neuse and E. Quo, *J. Polymer Sci.*, **3A**, 1499 (1965).

⁴⁰⁵ E. W. Neuse, E. Quo, and W. G. Howells, *J. Am. Chem. Soc.*, **30**, 4071 (1965).

⁴⁰⁶ A. N. Nesmeyanov, V. V. Korshak, V. V. Voevodski, N. S. Kochetkova, S. L. Sosin, R. B. Materikova, T. N. Bolotnikova, V. M. Chibrikov, and N. M. Bazhin, *Dokl. Akad. Nauk SSSR*, **137**, 1370 (1961) [*C.A.*, **55**, 21081 (1961)].

⁴⁰⁷ Ya. M. Paushkin, T. P. Vishnyakova, I. I. Patalakh, T. A. Sokolinskaya, and F. F. Machus, *Dokl. Akad. Nauk SSSR*, **149**, 856 (1963) [*C.A.*, **59**, 4049 (1963)].

⁴⁰⁸ I. M. Paushkin, L. S. Polak, T. P. Vishnyakova, I. I. Patalakh, F. F. Machus, and T. A. Sokolinskaya, *J. Polymer Sci.*, **1C**, 1481 (1963).

⁴⁰⁹ S. L. Sosin, V. V. Korshak, and V. P. Alekseeva, *Dokl. Akad. Nauk SSSR*, **149**, 327 (1963) [*C.A.*, **59**, 4049 (1963)].

⁴¹⁰ L. E. Coleman, Jr., and M. D. Rausch, *J. Polymer Sci.*, **28**, 207 (1958).

to cinnamoylferrocene, vinylferrocene has been shown to form a homopolymer as well as copolymers with other monomers.²⁰⁴ Crosslinking of these polymers has been accomplished by carrying out the reaction in the presence of formaldehyde.²⁰⁴

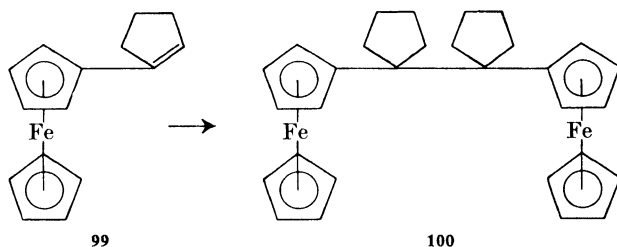
The product obtained from diazotized poly-(*p*-aminostyrene) and ferrocenium ion is poly-(*p*-ferrocenylmethylstyrene), in which the iron atom is in the +3 oxidation state.⁴¹¹ It has been proposed for use as an oxidation-reduction resin.

The polyferrocenylene amides have been prepared by standard methods from diphenylferrocene-1,1'-dicarboxylate,⁴¹² or 1,1'-bis(chlorocarbonyl)-ferrocene^{105, 320} and a variety of amines.

Polyurethanes containing ferrocenylene groups have been prepared from various 1,1'-di-(α -hydroxyalkyl)ferrocenes and diisocyanates or ferrocene-1,1'-diisocyanate and a variety of diols.¹⁰⁵ Reaction of ferrocene diisocyanate with diamines leads to the formation of polyureas.¹⁰⁵ Silicon-containing ferrocene polymers have also been reported.^{413, 414}

Ligand Exchange Reactions

An early investigation of the reaction of ferrocene, 1,2-dichloroethane, and aluminum chloride yielded a product (originally described as "pentaethanodiferrocene")⁴¹⁵ which, later investigations demonstrated, could be obtained from ferrocene and aluminum chloride in the absence of 1,2-dichloroethane.⁴¹⁶⁻⁴¹⁸ Several products are formed; one was recently assigned the structure **100**^{418, 419} and it was suggested that the material was formed from **99**. The precursor **99** has been observed previously



⁴¹¹ B. Sansoni and O. Sigmund, *Angew. Chem.*, **73**, 299 (1961).

⁴¹² L. Plummer and C. S. Marvel, *J. Polymer Sci.*, **2A**, 2559 (1964).

⁴¹³ E. V. Wilkus and W. H. Rauscher, *J. Org. Chem.*, **30**, 2889 (1965).

⁴¹⁴ G. Greber and M. L. Hallensleben, *Makromol. Chem.*, **83**, 148 (1965).

⁴¹⁵ A. N. Nesmeyanov and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **126**, 307 (1959) [*C.A.* **53**, 21856 (1959)].

⁴¹⁶ S. I. Goldberg *J. Am. Chem. Soc.*, **84**, 3022 (1962).

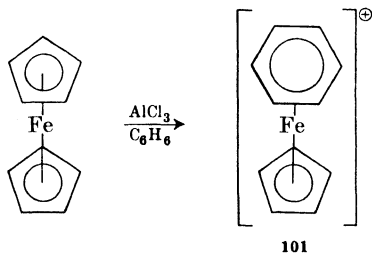
⁴¹⁷ S. G. Cottis and H. Rosenberg, *Chem. Ind. (London)*, 860 (1963).

⁴¹⁸ S. G. Cottis and H. Rosenberg, *J. Polymer Sci.*, **2B**, 295 (1964).

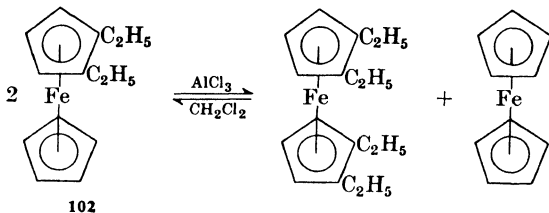
⁴¹⁹ A. N. Nesmeyanov, N. S. Kochetkova, P. V. Petrovskii, and E. I. Fedin, *Dokl. Akad. Nauk SSSR*, **152**, 875 (1963) [*C.A.*, **60**, 6367 (1964)].

in the reaction between ferrocene and hydrogen fluoride at 100°. ¹⁶⁴ Although these reactions are not true ligand exchanges, they demonstrate the ability of Lewis acids to transform ferrocene to substituted derivatives.

True ligand exchange reactions of ferrocene have been observed more recently in the presence of basic and Lewis acid catalysts. ^{239, 359, 420-422} In addition, thermal exchange has been reported. ⁴²³ When ferrocene is heated in benzene solution in the presence of aluminum chloride, the cyclopentadienyliron(II)benzene cation (**101**) is formed. It may be isolated as the tetraphenylborate salt. ⁴²⁰⁻⁴²² When acetyl- and ethylferrocene are used, the major products are acetylcyclopentadienyliron(II)benzene and cyclopentadienyliron(II)benzene cations, respectively. Other benzenoid compounds such as tetralin and mesitylene give similar compounds.



When the reaction is carried out in a solvent incapable of forming a stable complex like **101**, the reaction follows a different course. Thus, when ethylferrocene is treated with aluminum chloride in methylene chloride, analysis of the reaction mixture indicates the presence of ferrocene, ethylferrocene, and 1,1'-diethylferrocene. ²³⁹ This reaction has been shown to be an equilibrium, and proof of ring migration as opposed to alkyl group migration has been presented since no product with a 1,3 orientation was observed to have been formed when 1,2-diethylferrocene (**102**) was rearranged.



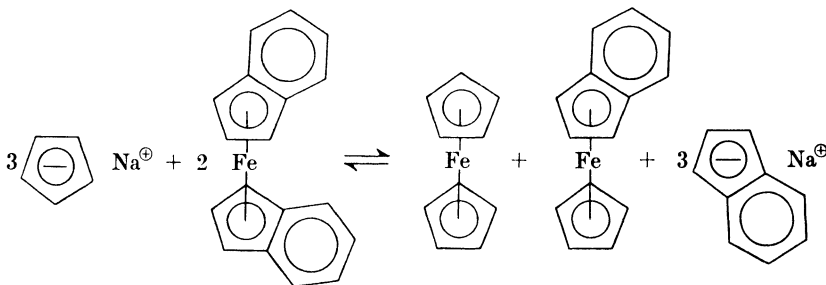
⁴²⁰ A. N. Nesmeyanov, N. A. Vol'kenau, and I. N. Bolesova, *Dokl. Akad. Nauk SSSR*, **149**, 615 (1963) [*C.A.*, **59**, 6438 (1963)].

⁴²¹ A. N. Nesmeyanov, N. A. Vol'kenau, and I. N. Bolesova, *Tetrahedron Letters*, 1725 (1963).

⁴²² A. N. Nesmeyanov, N. A. Vol'kenau, and L. S. Shilovtseva, *Dokl. Akad. Nauk SSSR*, **160**, 1327 (1965) [*C.A.*, **62**, 14722 (1965)].

⁴²³ H. P. Fritz and L. Schaefer, *Z. Naturforsch.*, **19b**, 169 (1964).

Base-catalyzed ring migration occurs when *bis*(indenyl)iron is treated with cyclopentadienylsodium in tetrahydrofuran; the products formed are ferrocene and benzoferrocene.³⁵⁹ The equilibrium has been shown to be to the right in boiling tetrahydrofuran; as noted above (p. 52), this

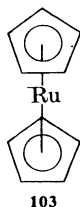


accounts for the lack of formation of *bis*(indenyl)iron in the preparation of benzoferrocene.

When ferrocene and hexachlorocyclopentadiene are heated together at 120°, a product of the empirical formula $C_5H_5Cl_2Fe$ is formed.⁴²³ Its structure has not been conclusively proved, but it is known to be dimeric, ligand exchange of chloride for cyclopentadiene having occurred. Thus in this case the order of stability is the opposite of that observed for ferrocene versus dicyclopentadienyldiiron tetracarbonyl. The latter compound gives ferrocene and iron carbonyl on heating.

RUTHENOCENE

Ruthenocene (dicyclopentadienylruthenium, **103**) was first prepared, in 20% yield, by the reaction of cyclopentadienylmagnesium bromide with ruthenium(III) acetylacetonate.⁴²⁴ Later its synthesis from anhydrous ruthenium(III) chloride and cyclopentadienylsodium in 1,2-dimethoxyethane was reported.^{425, 426} When a mixture of anhydrous ruthenium(III) chloride and metallic ruthenium was employed in the reaction with



⁴²⁴ G. Wilkinson, *J. Am. Chem. Soc.*, **74**, 6146 (1952).

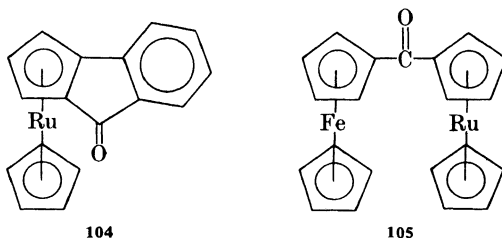
⁴²⁵ E. O. Fischer, M. D. Rausch, and H. Grubert, *Chem. Ind. (London)*, 765 (1958).

⁴²⁶ E. O. Fischer and H. Grubert, *Chem. Ber.*, **92**, 2302 (1959).

cyclopentadienylsodium,⁴²⁷ yields of 56–69% based on the total ruthenium available were realized. Labeled ruthenocene (¹⁰⁶Ru) has been prepared in a carrier-free state in unspecified yields.⁴²⁸

Ruthenocene is somewhat more stable thermally than ferrocene and undergoes electrophilic substitution less readily. Acylation gives both mono- and di-substitution products under conditions where ferrocene gives disubstitution.^{425, 429} A homoannular dibenzoylruthenocene, obtained in unspecified amounts, has been assigned the 1,2 structure on the basis of nuclear magnetic resonance studies.^{187, 430, 431}

A number of substituents other than acetyl have also been introduced. Ruthenocenecarboxaldehyde has been obtained both by formylation using N-methylformanilide and phosphorus oxychloride (9%)¹⁸⁷ and by acid-catalyzed decomposition of phenylruthenocenylcarbonyl azide (7%). The acid-catalyzed decomposition of the azide gave, in addition to the aldehyde, 5% of 2,3-ruthenocindene (**104**) along with the other usual products of the reaction.¹⁸⁷



Reaction of ruthenocene with phenyl isocyanate in the presence of aluminum chloride gave N-phenylruthenocenecarboxamide in 20% yield,⁴²⁹ metalation with *n*-butyllithium followed by carbonation gave a mixture of the mono- and di-carboxylic acids,⁴²⁹ mercuric acetate in acetic acid gave the mono- and di-mercurated products.⁴²⁹ Acylation of ruthenocene with ferrocenoyl chloride in the presence of aluminum chloride yielded ferrocenyl ruthenocenyl ketone (**105**).

Like ferrocenes, substituted ruthenocenes undergo the usual reactions characteristic of their organic substituents. For example, vinylruthenocene can be prepared in 47% over-all yield by the reduction of acetyl-ruthenocene to the corresponding alcohol followed by dehydration with alumina.²⁵⁵ Similarly, acetyl- and benzoyl-ruthenocene give ethyl- and

⁴²⁷ D. E. Bublitz, W. E. McEwen, and J. Kleinberg, *Org. Syntheses*, **41**, 96 (1961).

⁴²⁸ H. Götte and M. Wenzel, W. German pat. 1,049,860 and 1,059,452 [*C.A.*, **55**, 2685, 6495 (1961)].

⁴²⁹ M. D. Rausch, E. O. Fischer, and H. Grubert, *J. Am. Chem. Soc.*, **82**, 76 (1960).

⁴³⁰ D. E. Bublitz, J. Kleinberg, and W. E. McEwen, *Chem. Ind. (London)*, 936 (1960).

⁴³¹ M. D. Rausch and V. Mark, *J. Org. Chem.*, **28**, 3225 (1963).

benzyl-ruthenocene upon reduction with lithium aluminum hydride-aluminum chloride.⁴³² Ruthenocene compounds which have been prepared by substitution reactions on ruthenocene are presented in Table XXXI.

Bis(indenyl)ruthenium has been prepared in 12% yield from indenyl-sodium and a mixture of ruthenium(III) chloride and ruthenium metal,⁴³⁴ and in unstated yield from indenylmagnesium bromide and ruthenium(III) acetylacetonate.⁴³³ Studies of its magnetic and physical properties have also been reported.⁴³⁴⁻⁴³⁷ Catalytic reduction to bis(tetrahydroindenyl)-ruthenium proceeds in nearly quantitative yield.⁴³⁴

OSMOCENE

The preferred synthesis of osmocene (dicyclopentadienylsodium) involves treatment of cyclopentadienylsodium with osmium(IV) chloride in 1,2-dimethoxyethane to obtain the desired material in 22-23% yield.^{425, 426} The same reaction in tetrahydrofuran gave the product in 10% yield.⁴³⁸ The reaction of cyclopentadienyl Grignard reagent with osmium chloride, apparently in a mixture of oxidation states, gave osmocene in poor yield.^{14, 439}

Osmocene has been shown to undergo Friedel-Crafts acylation to give acetyl- and benzoyl-osmocene.^{425, 429, 438, 440} Whereas ferrocene and ruthenocene give disubstitution or mixtures of mono- and di-substitution products, osmocene gives only a monoacylated product, even under the forcing conditions of high temperature and use of a large excess of acylating reagent.⁴²⁹ A recently reported exception is 1,1'-diacetylosmocene, which has been obtained under vigorous conditions; however, the yield was only 0.1%.⁴³¹ Other comparisons in this metal series have also been reported.^{187, 255, 390} Metalation with *n*-butyllithium followed by carbonation led to a mixture of the mono- and di-carboxylic acids of osmocene.⁴²⁹ Reaction of osmocenyllithium with trimethylchlorosilane gave trimethylsilylosmocene in unstated yield.³⁹⁰

Substituted osmocenes, like the other metallocenes, undergo reactions characteristic of the substituents. Thus acetylosmocene can be converted

⁴³² V. Mark and M. D. Rausch, *Inorg. Chem.*, **3**, 1067 (1964).

⁴³³ M. Dub, *Organometallic Compounds Literature Survey 1937-1958*, Vol. 1, 193, Springer-Verlag (1961).

⁴³⁴ J. H. Osiecki, C. J. Hoffman, and D. P. Hollis, *J. Organometal. Chem.*, **3**, 107 (1965).

⁴³⁵ E. O. Fischer, *Rec. Trav. Chim.*, **75**, 629 (1956).

⁴³⁶ E. O. Fischer and H. Leipfinger, *Z. Naturforsch.*, **10b**, 353 (1955).

⁴³⁷ E. O. Fischer and U. Piesbergen, *Z. Naturforsch.*, **11b**, 758 (1956).

⁴³⁸ E. A. Hill and J. H. Richards, *J. Am. Chem. Soc.*, **83**, 3840 (1961).

⁴³⁹ Ascertained at an earlier date by D. E. Bublitz in a personal communication from E. R. Lippincott.

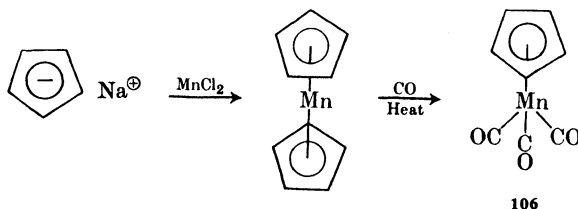
⁴⁴⁰ R. Riemschneider, *Monatsh. Chem.*, **90**, 658 (1959).

to vinylsocene by reduction followed by dehydration of the resulting carbinol with alumina²⁵⁵ or to ethylsocene by reduction with lithium aluminum hydride-aluminum chloride.⁴³² Although benzoylsocene can be converted to osmocenyphenylcarbonylazide, treatment of this azide with concentrated sulfuric acid gives benzoylsocene as the only isolable organometallic compound.¹⁸⁷ Osmocene compounds prepared by substitution on osmocene are presented in Table XXXI.

CYCLOPENTADIENYLMANGANESE TRICARBONYL

Synthesis of the Parent Compound

Cyclopentadienylmanganese tricarbonyl (**106**) is, in some respects, simpler than ferrocene since it contains only one cyclopentadienyl ring. It can be prepared by the reaction of bis(cyclopentadienyl)manganese with carbon monoxide under various conditions of elevated temperature and pressure⁴⁴¹⁻⁴⁴⁶ in yields up to 80%.⁴⁴³ The bis(cyclopentadienyl)manganese may be previously prepared or generated *in situ*, the latter approach being preferred. Cyclopentadienylmanganese tricarbonyl has also been prepared by reaction of dicyclopentadiene with manganese



pentacarbonyl,⁴⁴⁷ by reaction of cyclopentadienylsodium with manganese pentacarbonyl bromide,⁴⁴⁸ and by reaction of bis(cyclopentadienyl)manganese with iron pentacarbonyl.⁴⁴⁹

Direct Synthesis of Cyclopentadienylmanganese Tricarbonyl Derivatives

Several substituted cyclopentadienylmanganese tricarbonyl derivatives have been prepared directly from the appropriately substituted

⁴⁴¹ T. S. Piper, F. A. Cotton, and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **1**, 165 (1955).

⁴⁴² J. E. Brown and H. Shapiro, U.S. pat. 2,818,417 [*C.A.*, **52**, 8535 (1958)].

⁴⁴³ E. O. Fischer and K. Plesske, *Chem. Ber.*, **91**, 2719 (1958).

⁴⁴⁴ D. C. Freeman, Jr., Brit. pat. 858,442 [*C.A.*, **56**, 3514 (1962)].

⁴⁴⁵ E. O. Fischer and R. Jira, *Z. Naturforsch.*, **9b**, 618 (1954).

⁴⁴⁶ H. Shapiro, U.S. pat. 2,916,504 [*C.A.*, **54**, 15402 (1960)].

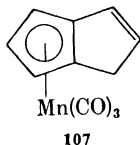
⁴⁴⁷ Ethyl Corp., Brit. pat. 782,738 [*C.A.*, **52**, 3851 (1958)].

⁴⁴⁸ J. Kozikowski, U.S. pat. 3,015,668 [*C.A.*, **57**, 866 (1962)].

⁴⁴⁹ J. Kozikowski and M. L. Larson, U.S. pat. 2,870,180 [*C.A.*, **53**, 11407 (1959)].

bis(cyclopentadienyl)manganese compounds. Others have been obtained from the substituted cyclopentadiene and a mixture of manganese(II) chloride and carbon monoxide or a complex manganese carbonyl.^{446, 448}

A unique synthesis of π -dihydropentalenylmanganese tricarbonyl (**107**) resulted from the tetramerization of acetylene in the presence of dimanganese decacarbonyl at elevated temperature and pressure; the yield was 40%.^{450, 451} Methylcyclopentadienylmanganese tricarbonyl was suggested as a possible intermediate in the formation of **107** for, when



the former was heated at elevated temperatures with acetylene at 600 p.s.i., the dihydropentalene resulted in 27% yield. The dihydropentalene derivative was also formed from cyclooctatetraene and dimanganese decacarbonyl in unspecified yields.

The compounds which have been prepared via the direct synthetic route are listed in Table XXXII.

Routes to Substituted Cyclopentadienylmanganese Tricarbonyl Derivatives via Substitution Reactions

Metalation

Cyclopentadienylmanganese tricarbonyl and its methyl homolog both reacted with mercuric acetate in the presence of alcoholic calcium chloride⁴⁵² to give the monochloromercurated derivative in 37% yield. In absolute ethanol, in addition to the monosubstituted compounds, bischloromercurated derivatives of undesigned structures were obtained in 14% and 18% yields, respectively.⁴⁵² The chloromercurated derivative of cyclopentadienylmanganese tricarbonyl has also been obtained by treatment of the sulfinic acid with mercuric chloride in ethanol; the yield was 80%.⁴⁵³ Chloromercuricyclopentadienylmanganese tricarbonyl reacted with sodium thiosulfate in aqueous acetone to give bis(cyclopentadienylmanganese tricarbonyl)mercury in 78% yield⁴⁵² and gave the same compound with *n*-butyllithium.⁴⁵³ Chloromercuricyclopentadienylmanganese tricarbonyl^{452, 453} has also been used for the preparation of

⁴⁵⁰ T. H. Coffield, K. J. Ihrman, and W. Burns, *J. Am. Chem. Soc.*, **82**, 4209 (1960).

⁴⁵¹ T. H. Coffield, K. J. Ihrman, and W. Burns, *J. Am. Chem. Soc.*, **82**, 1251 (1960).

⁴⁵² A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1683 (1962) [*C.A.*, **58**, 4590 (1963)].

⁴⁵³ M. Cais and J. Kozikowski, *J. Am. Chem. Soc.*, **82**, 5667 (1960).

iodocyclopentadienylmanganese tricarbonyl (96% yield) by treatment with iodine in refluxing carbon tetrachloride.⁴⁵²

Acylation

Cyclopentadienylmanganese tricarbonyl undergoes the usual Friedel-Crafts type reactions with acid chlorides and anhydrides.^{443, 454} Acetyl-cyclopentadienylmanganese tricarbonyl^{443, 454-456} and benzoylcyclopentadienylmanganese tricarbonyl^{443, 455-457} have been obtained and undergo the usual reactions characteristic of the functional groups present. Their ability to undergo pinacol formation is noteworthy.^{458, 459} Acylation by methyl chlorothioformate gives the corresponding methyl thiolester of the metallocene.³⁰⁸

Treatment of cyclopentadienylmanganese tricarbonyl with succinic or glutaric anhydride in the presence of aluminum chloride gave the β -metallocenoylpropionic acid^{443, 460} and the γ -metallocenoylbutyric acid.⁴⁶⁰ Clemmensen reduction of these acids provided the metallocenylbutyric and -valeric acids which were cyclized with polyphosphoric acid to the cyclic ketones **108** and **109** in 70% and 85% yields.⁴⁶⁰ The absolute configuration of the cyclic ketone **108** has recently been determined.⁴⁶¹

The aldehyde of cyclopentadienylmanganese tricarbonyl, prepared in 81% yield by lithium aluminum tri-(*t*-butoxy)hydride reduction of the corresponding acid chloride, has been converted to the β -metallocenylpropionic acid via the corresponding acrylic acid. When the propionic acid was treated with polyphosphoric acid, the homocyclic ketone **110** was obtained in 65% yield.^{450, 462} Reduction followed by dehydration led to the dihydropentalenyl derivative **107**.⁴⁶²

The carboxylic acid chloride of cyclopentadienylmanganese tricarbonyl reacted with cyclopentadienylmanganese tricarbonyl in the presence of aluminum chloride to give the dimetallocenyl ketone **111** in 28% yield,⁴⁶³ and with ferrocene to give the mixed dimetallocenyl ketone **112** in unstated yield.⁴⁶³ The latter material was further acylated by the carboxylic

⁴⁵⁴ F. A. Cotton and J. B. Leto, *Chem. Ind. (London)*, 1368 (1958).

⁴⁵⁵ A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1780 (1961) [*C.A.*, **56**, 8733 (1962)].

⁴⁵⁶ E. O. Fischer and K. Plesske, *Brit. pat.* 864,834 [*C.A.*, **55**, 22338 (1961)].

⁴⁵⁷ J. Kozikowski, R. E. Maginn, and M. S. Klove, *J. Am. Chem. Soc.*, **81**, 2995 (1959).

⁴⁵⁸ E. Cuingnet and M. Adalberon, *Compt. Rend.*, **257**, 461 (1963).

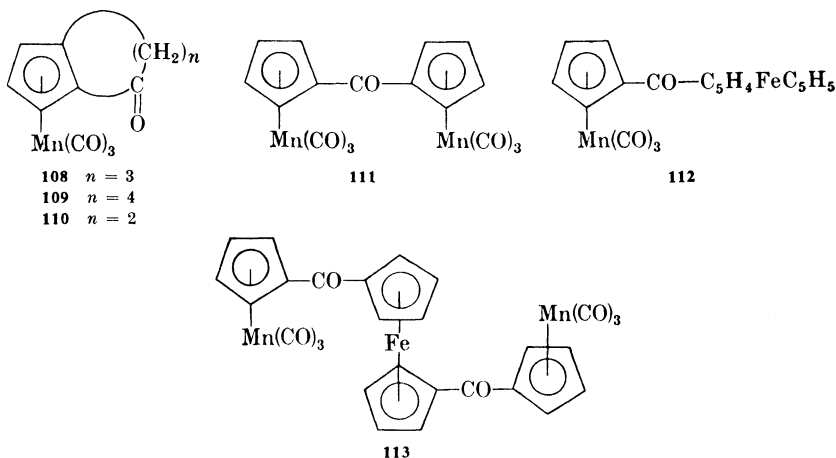
⁴⁵⁹ E. Cuingnet and M. Tarterat-Adalberon, *Bull. Soc. Chim. France*, 3721 (1965).

⁴⁶⁰ M. Cais and A. Modiano, *Chem. Ind. (London)*, 202 (1960).

⁴⁶¹ S. G. Cottis, H. Falk, and K. Schlögl, *Tetrahedron Letters*, 2857 (1965).

⁴⁶² M. Cais, A. Modiano, N. Tirosh, A. Eisenstadt, and A. Rubinstein, *Intern. Union Pure Appl. Chem., Abstr. A*, 166 (1963) (London).

⁴⁶³ M. Cais and M. Feldkimmel, *Tetrahedron Letters*, 440 (1961).



acid chloride of cyclopentadienylmanganese tricarbonyl to give the dimetalloceonoyl ferrocene **113** in 82% yield.⁴⁶³

Methylcyclopentadienylmanganese tricarbonyl reacts similarly with acetyl chloride,^{464, 465} benzoyl chloride,^{457, 459, 464, 465} *p*-chlorobenzoyl chloride,⁴⁶⁶ succinyl chloride,⁴⁶⁶ and phthalyl chloride,⁴⁶⁶ except that a mixture of isomers is obtained in each case. Some of these mixture have been separated and positional assignments for certain isomers have been made.⁴⁶⁷⁻⁴⁷⁰

Alkylation

Alkylation of cyclopentadienylmanganese tricarbonyl has been studied, but not so thoroughly as alkylation of ferrocene. Ethyl bromide and aluminum chloride gave a 63% yield of ethylcyclopentadienylmanganese tricarbonyl,⁴⁵⁵ while cyclohexyl chloride gave a mixture of mono- and disubstituted products⁴⁵⁷ and isobutylene a mixture of mono-, di, and tri-*t*-butylated products. When *t*-butyl chloride was used as the alkylating agent, a 69% yield of *t*-butylcyclopentadienylmanganese tricarbonyl was obtained.⁴⁷¹ Repeated acetylation and reduction to the corresponding ethyl compound have led to pentäethylcyclopentadienylmanganese

⁴⁶⁴ R. Riemschneider and H. G. Kassahn, *Z. Naturforsch.*, **14b**, 348 (1959).

⁴⁶⁵ J. Kozikowski, U.S. pat. 2,916,503 [*C.A.*, **54**, 5693 (1960)].

⁴⁶⁶ R. Riemschneider and H. G. Kassahn, *Chem. Ber.*, **92**, 3208 (1959).

⁴⁶⁷ R. Riemschneider, K. Petzoldt, and W. Herrmann, *Z. Naturforsch.*, **16b**, 279 (1961).

⁴⁶⁸ R. Riemschneider and W. Herrmann, *Ann. Chem.*, **648**, 68 (1961).

⁴⁶⁹ R. Riemschneider and K. Petzoldt, *Z. Naturforsch.*, **15b**, 627 (1960).

⁴⁷⁰ E. Cuingnet and M. Adalberon, *Compt. Rend.*, **258**, 3053 (1964).

⁴⁷¹ K. N. Anisimov and N. E. Kolobova, *Izv. Akad. Nauk SSSR, Otd. Khim.* 721 (1962) [*C.A.*, **57**, 15135 (1962)].

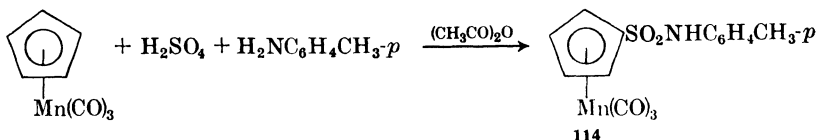
tricarbonyl.⁴⁷² Chloromethylation of the parent compound **106** has been effected by means of hydrogen chloride, zinc chloride, and formaldehyde⁴⁷³ or bis(chloromethyl) ether.⁴⁷⁴ The chloromethylcyclopentadienylmanganese tricarbonyl thus obtained is a versatile intermediate to many other derivatives.⁴⁷⁵

Alkylation reactions of methylcyclopentadienylmanganese tricarbonyl have also been reported.⁴⁶⁵

Miscellaneous Reactions

Although formylcyclopentadienylmanganese tricarbonyl has been prepared, as mentioned above, via the acid chloride, its synthesis has not been effected by substitution. However, formylation of the methyl homolog was accomplished by means of hydrogen cyanide, hydrogen chloride, and aluminum chloride.⁴⁷⁶

Sulfonation with sulfuric acid (100%) in the presence of acetic anhydride and *p*-toluidine at 100° gave a 93% yield of the corresponding cyclopentadienylmanganese tricarbonyl sulfotoluidide **114**, from which a host of other sulfonic esters and amides have been prepared.⁴⁵³



Aminocyclopentadienylmanganese tricarbonyl has been synthesized by two routes, Curtius degradation of the acylazide^{383, 477} and the Schmidt reaction applied to the acetyl or benzoyl derivative of the parent metallocene.^{383, 478, 479} The best yield (64%) is obtained by the Curtius method.

A series of halo derivatives has recently been synthesized from aminocyclopentadienylmanganese tricarbonyl via the diazonium salt intermediate⁴⁸⁰ which, in contrast to that of ferrocene, is stable.

⁴⁷² A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and I. B. Zlotina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1326 (1964) [*C.A.*, **61**, 12024 (1964)].

⁴⁷³ A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2233 (1963) [*C.A.*, **60**, 9303 (1964)].

⁴⁷⁴ A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Dokl. Akad. Nauk SSSR*, **157**, 622 (1964) [*C.A.*, **61**, 9519 (1964)].

⁴⁷⁵ A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Dokl. Akad. Nauk SSSR*, **162**, 112 (1965) [*C.A.*, **63**, 5666 (1965)].

⁴⁷⁶ R. Riemschneider and K. Petzoldt, *Z. Naturforsch.*, **17b**, 785 (1962).

⁴⁷⁷ E. Cuingnet and M. Adalberon, *Compt. Rend.*, **257**, 181 (1963).

⁴⁷⁸ E. Cuingnet and M. Adalberon, *Compt. Rend.*, **258**, 5884 (1964).

⁴⁷⁹ E. Cuingnet and M. Tarterat-Adalberon, *Bull. Soc. Chim. France*, 3734 (1964).

⁴⁸⁰ M. Cais and N. Narkis, *J. Organometal. Chem.*, **3**, 269 (1965).

Ethynylcyclopentadienylmanganese tricarbonyl has been prepared by the dehydrohalogenation of α -chlorovinylcyclopentadienylmanganese tricarbonyl.²⁶² Presumably other acylcyclopentadienylmanganese tricarbonyl derivatives may serve as precursors for the latter compounds and subsequently be converted to other ethynyl derivatives.

Derivatives of cyclopentadienylmanganese tricarbonyl prepared via substitution reactions are listed in Table XXXIII.

The ability of the cyclopentadienylmanganese tricarbonyl nucleus to stabilize an α -carbonium ion was found to be less than that of ferrocene.⁴⁸¹ Deuterium exchange reactions for the protons of cyclopentadienylmanganese tricarbonyl have been investigated, the rate being comparable to that of benzene.⁴⁸²

Azacyclopentadienylmanganese Tricarbonyl (π -Pyrrolylmanganese Tricarbonyl)

Azacyclopentadienylmanganese tricarbonyl has been prepared in unstated yield by reaction of pyrrole with dimanganese decacarbonyl in 1,2-dimethoxyethane at 130°, ⁴⁹⁴ and in 66% yield by the reaction between the potassium salt of pyrrole and dimanganese decacarbonyl in ligroin.³⁹⁴ The latter reaction has also been successfully applied to mono-, di-, and tetra-methyl pyrroles.

Substitution reactions of azacyclopentadienylmanganese tricarbonyl have not been reported.

Ligand Exchange Reactions

Numerous photochemical substitution reactions have been reported for cyclopentadienylmanganese tricarbonyl and its homologs that involve not the cyclopentadienyl ring but the carbonyl ligands.⁴⁸³⁻⁴⁹² Under appropriate conditions the reaction of cyclopentadienylmanganese

⁴⁸¹ W. E. McEwen, J. A. Manning, and J. Kleinberg, *Tetrahedron Letters*, 2195 (1964).

⁴⁸² A. N. Nesmeyanov, D. N. Kursanov, V. N. Setkina, N. V. Kislyakova, N. S. Kochetkova, and R. B. Materikova, *Dokl. Akad. Nauk SSSR*, **143**, 351 (1962) [*C.A.*, **57**, 5938 (1963)].

⁴⁸³ W. Strohmeier and K. Gerlach, *Z. Naturforsch.*, **15b**, 675 (1960).

⁴⁸⁴ W. Strohmeier and D. Von Hobe, *Z. Naturforsch.*, **16b**, 402 (1961).

⁴⁸⁵ W. Strohmeier and C. Barbeau, *Z. Naturforsch.*, **17b**, 848 (1962).

⁴⁸⁶ W. Strohmeier, H. Laporte, and D. von Hobe, *Chem. Ber.*, **95**, 455 (1962).

⁴⁸⁷ G. E. Schroll, U.S. pat. 3,054,740 [*C.A.*, **58**, 5723 (1963)].

⁴⁸⁸ R. S. Nyholm, S. S. Sandhu, and M. H. B. Stiddard, *J. Chem. Soc.*, 5916 (1963).

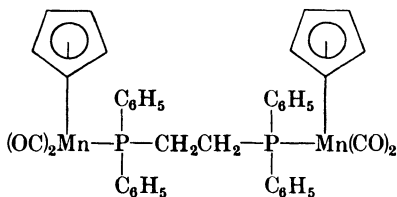
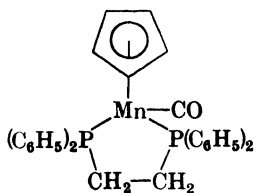
⁴⁸⁹ W. Strohmeier, J. F. Guttenberger, and H. Hellman, *Z. Naturforsch.*, **19b**, 353 (1964).

⁴⁹⁰ W. Strohmeier and J. F. Guttenberger, *Chem. Ber.*, **96**, 2112 (1963).

⁴⁹¹ W. Strohmeier and J. F. Guttenberger, *Chem. Ber.*, **97**, 1256 (1964).

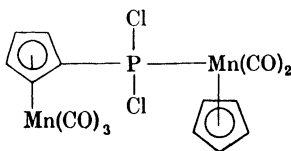
⁴⁹² W. Strohmeier and J. F. Guttenberger, *Chem. Ber.*, **97**, 1871 (1964).

tricarbonyl with 1,2-bis(diphenylphosphino)ethane can give either **115** or **116**.⁴⁸⁸ Compounds which have been prepared by a photochemically

**115****116**

induced ligand exchange reaction of cyclopentadienylmanganese tricarbonyl are presented in Table XXXIV.

When cyclopentadienylmanganese tricarbonyl is allowed to react with phosphorus trichloride in the presence of aluminum chloride, the binuclear reaction product **117** is formed.⁴⁹³

**117**

CYCLOPENTADIENYL RHENIUM TRICARBONYL

Recent studies have shown that cyclopentadienylrhodium tricarbonyl, like the related manganese compound, is aromatic. The parent compound has been prepared from both dicyclopentadiene and rhodium pentacarbonyl (50% yield)⁴⁹⁵ and from sodium cyclopentadienide and rhodium pentacarbonyl chloride (60–89% yield).^{496, 497} Cyclopentadienylthallium has also been employed in the latter reaction.⁴⁹⁶ Use of the simple rhodium(III) chloride with cyclopentadienylsodium gave only 16% of the desired compound.⁴⁹⁹ When indenylsodium and rhodium pentacarbonyl chloride were utilized, an 80% yield of indenylrhodium tricarbonyl was obtained.⁴⁹⁷

⁴⁹³ A. N. Nesmeyanov, K. N. Anisimov, and Z. P. Valueva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 763 (1964) [*C.A.*, **61**, 3132 (1964)].

⁴⁹⁴ K. K. Joshi and P. L. Pauson, *Proc. Chem. Soc.*, 326 (1962).

⁴⁹⁵ M. L. H. Green and G. Wilkinson, *J. Chem. Soc.*, 4314 (1958).

⁴⁹⁶ A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and L. I. Baryshnikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 193 (1963) [*C.A.*, **58**, 12588 (1963)].

⁴⁹⁷ E. O. Fischer and W. Fellman, *J. Organometal. Chem.*, **1**, 191 (1964).

⁴⁹⁸ A. N. Nesmeyanov, K. N. Anisimova, N. E. Kolobova, and L. I. Baryshnikov, *Dokl. Akad. Nauk SSSR*, **154**, 646 (1964) [*C.A.*, **60**, 10713 (1964)].

⁴⁹⁹ R. L. Pruett and E. L. Morehouse, *Chem. Ind. (London)*, 980 (1958).

Substitution reactions carried out on cyclopentadienylrhenium tricarbonyl include acylation, sulfonation, and metalation. The usual Friedel-Crafts conditions gave the acetyl and benzoyl derivatives in 43–67% and 41–61% yields, respectively.^{497, 498} Sulfonation in acetic anhydride-sulfuric acid provided the corresponding cyclopentadienylrhenium tricarbonyl sulfonic acid, isolated as the *p*-toluidine salt,⁵⁰⁰ while both the mono- and di-chloromercuri derivatives were obtained by treatment with alcoholic mercuric acetate followed by a source of chloride ion.⁵⁰⁰ The yields of mercuration and sulfonation reaction products were unstated. Deuterium exchange reactions for the protons of cyclopentadienylrhenium tricarbonyl have been investigated, the rate being comparable to that of the manganese analog.⁵⁰¹

CYCLOPENTADIENYLTECHNETIUM TRICARBONYL

Cyclopentadienyltechnetium tricarbonyl has been prepared in 86% yield from technetium(IV) chloride, carbon monoxide, and cyclopentadienylsodium in the presence of copper powder⁵⁰² and has been shown to be capable of undergoing substitution reactions similar to those of the related manganese and rhenium compounds. Thus benzoylcyclopentadienyltechnetium tricarbonyl is obtained in 50% yield by the usual acylation procedure.⁴⁹⁷

Further studies should reveal a parallel between the degree of reactivity of the group VIIB metal cyclopentadienyl tricarbonyls and that of the similarly related group VIII metallocenes of iron, ruthenium, and osmium.

CYCLOPENTADIENYLVANADIUM TETRACARBONYL

Cyclopentadienylvanadium tetracarbonyl (118) has been prepared, in yields up to 94%, by treatment of bis(cyclopentadienyl)vanadium with carbon monoxide under pressure.^{503, 504} A standard preparation reports over-all yields of 15–25% from cyclopentadienylsodium and vanadium(III) chloride.⁵⁰⁵ Acetylation and propionylation have been reported.^{506, 507}

⁵⁰⁰ A. N. Nesmeyanov, N. E. Kolobova, K. N. Anisimov, and L. I. Baryshnikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1135 (1964) [*C.A.*, **61**, 7034 (1964)].

⁵⁰¹ A. N. Nesmeyanov, D. N. Kursanov, V. N. Setkina, N. V. Kislyakova, N. E. Kolobova, K. N. Anisimov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 762 (1965) [*C.A.*, **63**, 3669 (1965)].

⁵⁰² C. Palm, E. O. Fischer, F. Baumgärtner, *Naturwiss.*, **49**, 279 (1962).

⁵⁰³ E. O. Fischer and W. Hafner, *Z. Naturforsch.*, **9b**, 503 (1954).

⁵⁰⁴ R. L. Pruett in W. I. Jolly, *Preparative Inorganic Reactions*, Vol. 2, p. 187, Interscience, New York, 1965.

⁵⁰⁵ R. B. King and F. G. A. Stone, *Inorg. Syn.*, **7**, 100 (1963).

⁵⁰⁶ F. Calderazzo, G. Rebaudo, and R. Ercoli, *Chim. Ind. (Milan)*, **42**, 52 (1960).

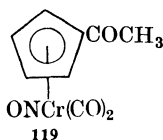
⁵⁰⁷ R. Riemschneider, O. Goehring, and M. Krüger, *Monatsh. Chem.*, **91**, 305 (1960).

The best yields (65%) of acetylcyclopentadienylvanadium tetracarbonyl were obtained using acetic anhydride-aluminum chloride in methylene chloride.⁵⁰⁸ With the exception of methylcyclopentadienyl-, 1-acetyl-*x*-methylcyclopentadienyl-, and 1-propionyl-*x*-methylcyclopentadienylvanadium tetracarbonyl,⁵⁰⁷ all prepared in unspecified yields, the derivatives mentioned above are the only ones reported for this compound.



CYCLOPENTADIENYLCHROMIUM NITROSYL DICARBONYL

Cyclopentadienylchromium nitrosyl dicarbonyl was first prepared, in 80% yield, from bis(cyclopentadienylchromium tricarbonyl) and nitric oxide at room temperature.⁵⁰⁹ Its ability to undergo electrophilic substitution was demonstrated by its acetylation under the usual conditions to give a 75% yield of acetylcyclopentadienylchromium nitrosyl dicarbonyl (119).



EXPERIMENTAL PROCEDURES

Ferrocene.^{74, 75} The detailed procedure in *Organic Syntheses* is also useful for the preparation of many 1,1'-disubstituted compounds from the correspondingly substituted cyclopentadienes. The use of sodium hydride dispersed in mineral oil obviates the necessity of dispersing the sodium or cutting it into small chips.¹⁶⁷ Sodium hydride dispersion is available from Metal Hydrides, Inc., Beverly, Massachusetts.

Mixed Lithiated Ferrocenes.⁹³ A solution of 5.0 g. (0.027 mole) of ferrocene in 75 ml. of anhydrous diethyl ether is placed in an oven-dried three-necked flask fitted with a stirrer, a dropping funnel, and a water-cooled condenser, and 0.08 mole of commercial *n*-butyllithium is added dropwise with stirring. The stirring is stopped after 1 hour, and the mixture is allowed to stand for 24 hours under an atmosphere of nitrogen.

Analysis by carbonation to the corresponding acids indicates a 35% conversion to metalated products, consisting of 70% mono- and 30%

⁵⁰⁸ E. O. Fischer and K. Plesske, *Chem. Ber.*, **93**, 1006 (1960).

⁵⁰⁹ E. O. Fischer and K. Plesske, *Chem. Ber.*, **94**, 93 (1961).

di-lithioferrocene. The mixture of mono- and di-lithioferrocene can be converted to any of a number of useful compounds.

Ferrocenyllithium.⁹⁸ A Schlenk tube containing 1.77 g. (4.2 mmoles) of chloromercuriferrocene is evacuated and filled with argon. Diethyl ether (9 ml.) and ethyllithium (9.3 mmoles, 9.2 ml. of 1.01 *M* solution) in ether are added in succession at 27°. The mixture is stirred for 45 minutes, then cooled to 0°. Analysis by carbonation to ferrocenecarboxylic acid indicates a 64% yield of monolithioferrocene.

1,1'-Dilithioferrocene.⁹⁸ To 2.76 g. (4.2 mmoles) of 1,1'-bis-(chloromercuri)ferrocene in 9 ml. of diethyl ether is added 18.1 mmoles of 0.99 *M* ethyllithium solution. The reaction mixture is stirred at room temperature for 1 hour. Analysis by carbonation indicates a 44% yield of 1,1'-dilithioferrocene, while characterization of the lithium reagent solution with trimethylchlorosilane gives 1,1'-bis(trimethylsilyl)ferrocene in 36% yield and trimethylsilylferrocene in 8% yield.

Ferroceneboronic Acid and 1,1'-Ferrocenediboronic Acid.¹¹⁰ A mixture of lithiated ferrocenes is prepared in 220 ml. of tetrahydrofuran-diethyl ether (1:1 by volume) from *n*-butyllithium (~0.27 mole) and 16.7 g. (0.09 mole) of ferrocene. The mixture is filtered through glass wool and then added dropwise in 2 hours to 72.5 g. (0.315 mole) of tri-*n*-butyl borate in 50 ml. of diethyl ether at -70°. A solid forms. The mixture is warmed during 1.5 hours to room temperature, decomposed with 100 ml. of 10% aqueous sodium hydroxide, and filtered. The ether solution is extracted nine times with 10% aqueous sodium hydroxide (total volume 400 ml.). Acidification of the basic solution with 10% sulfuric acid at 0° gives a yellow precipitate which is washed with water. Soxhlet extraction of the precipitate with diethyl ether for 4 days removes 9.02 g. (44%) of ferroceneboronic acid, which is obtained as a yellow powder after evaporation of solvent; m.p. 136-140° dec. Remaining as an insoluble yellow powder from the Soxhlet extraction is 4.42 g. (18%) of 1,1'-ferrocenediboronic acid, dec. ~200°.

The ether solution which has been washed with alkali is concentrated; filtration and vacuum sublimation of the precipitate gives 4.93 g. (29%) of crude ferrocene.

Chloromercuriferrocene.¹¹⁹ This well-documented procedure gives both mono- and di-mercurated derivatives, which are separable.

N,N-Dimethylaminomethylferrocene.¹²⁷ This derivative is one of the most useful. The procedure described in *Organic Syntheses* has also been applied to aminomethylation of alkyl ferrocenes.

Ferrocenecarboxaldehyde.¹⁴⁰ Ferrocene (11.16 g., 0.06 mole) is added in small portions over a period of 15 minutes to a vigorously stirred solution prepared from 21.6 g. (0.16 mole) of N-methylformanilide and

15.3 g. (0.10 mole) of phosphorus oxychloride. The purple viscous mixture is stirred for 1 hour at room temperature and then at 65–70° for 2 hours in a nitrogen atmosphere. The mixture is then cooled to 0°, and 50 g. of sodium acetate dissolved in 400 ml. of water is added and the solution stirred overnight. The mixture is extracted twice with 400 ml. of diethyl ether, and the ether extracts are combined and washed successively with 1 *N* HCl, water, saturated sodium bicarbonate solution, and finally water, all saturated with sodium chloride. The ether extract is concentrated to 50 ml. and shaken with a cold solution of 40 g. of sodium bisulfite in 100 ml. of water. The bisulfite addition compound is collected, washed with cold saturated aqueous sodium bisulfite then with ether, and is finally dried (yield 15.40 g.).

The bisulfite addition compound is taken up in 200 ml. of 2 *N* sodium hydroxide, and the liberated aldehyde is extracted into ether. The combined ether extract is washed with saturated sodium chloride solution, then dried over magnesium sulfate. Removal of solvent leaves 10.2 g. of dark purple crystals of the aldehyde (80%).

Acetylferrocene. *Phosphoric Acid Method.*¹³⁹ A mixture of 93 g. (0.5 mole) of ferrocene, 250 ml. of acetic anhydride, and 20 ml. of 85% phosphoric acid is heated at 100° for 10 minutes.* The reaction mixture is cooled slightly and poured onto ice. After standing overnight, the mixture is neutralized with 200 g. of sodium carbonate monohydrate in 200 ml. of water. The resulting brown pasty mass is cooled in an ice bath and filtered. The tan product is washed four times with 100-ml. portions of water and filtered. The granular product is dried in a vacuum desiccator over phosphorus pentoxide. Sublimation of the crude product at 100°/1 mm. gives 81.5 g. (71%) of an orange crystalline product, m.p. 85–86° after recrystallization from *n*-heptane.

*Hydrogen Fluoride Method.*¹⁶⁴ A mixture of 84 g. of ferrocene, 270 ml. of acetic anhydride, and 400 g. of hydrogen fluoride is stirred at 40–45° for 12 hours. Upon dilution with 3 l. of cold water to ensure complete precipitation of the product, 89 g. (86%) of acetylferrocene is obtained as an orange solid melting at 80–84°. Crystallization from isooctane gives orange needles, m.p. 85–86°.

*Boron Trifluoride Method.*¹⁶³ A stirred solution of 93.0 g. (0.5 mole) of ferrocene and 51 g.† (0.5 mole) of acetic anhydride in 800 ml. of methylene chloride, cooled in an ice bath, is saturated with gaseous boron trifluoride. (There is a copious evolution of white fumes.) The amber

* Slightly better results are obtained if the reaction mixture is carefully heated to 100° (exothermic) then quenched.¹⁶⁷

† The amount of acetic anhydride has been changed by the present authors from that in the reference. Use of the original amount gives a mixture of mono- and di-acetylferrocene.

solution soon becomes deep purple. After the reaction mixture has been stirred for 0.5 hour, it is allowed to come to room temperature during 4 hours. Excess aqueous sodium acetate is then added with stirring and cooling, and the two layers are separated. The methylene chloride layer is combined with a methylene chloride extract of the aqueous layer and is washed with water, saturated sodium bicarbonate solution, and dried over magnesium sulfate. After filtration, the solvent is removed and the residue is recrystallized from hexane to give 102 g. (90%) of orange needles of acetylferrocene, m.p. 85–86°.

1,1'-Diacetylferrocene.¹⁷² Ferrocene (30 g., 0.16 mole) dissolved in 100 ml. of dry methylene chloride is added over a period of 15 minutes to a stirred mixture of 53 g. (0.04 mole) of aluminum chloride and 32 ml. (0.45 mole) of acetyl chloride in 200 ml. of dry methylene chloride. The reaction, carried out in an atmosphere of dry nitrogen to avoid oxidation of ferrocene, proceeds readily at room temperature with immediate evolution of hydrogen chloride and the formation of an intensely violet solution.

The mixture is stirred at room temperature for 2 hours, then cooled, decomposed with ice, and filtered from aluminum hydroxide. The aluminum hydroxide is washed with chloroform until colorless. The separated aqueous phase is extracted several times with chloroform, and these extracts, combined with the main body of organic solution, are washed to neutrality. The pale blue color of the aqueous solution suggests little oxidation of ferrocene. The deep red organic solution is concentrated to about 200 ml. and dried by distilling the solvent on the steam bath. At this point 100 ml. of cyclohexane is added, and the solution is again concentrated to a volume of 200 ml. When cooled, large ruby-red rectangular plates of 1,1'-diacetylferrocene (24.4 g.), m.p. 127.5–128.5°, deposit. The second crop, after one recrystallization, weighs 7.0 g., m.p. 127.5–128.5°. The total yield is thus 31.4 g. (72%). An analytical sample of this substance melts at 130–131°.

1,1'-Di-*t*-butylferrocene.⁸⁸ Dimethylfulvene (2.12 g., 0.02 mole) in 10 ml. of diethyl ether is added to methylolithium prepared in a nitrogen atmosphere from 0.33 g. (0.05 g. atom) of lithium and 3.15 g. (0.0248 mole) of methyl iodide. The mixture is stirred for 0.5 hour, 1.625 g. (0.01 mole) of ferric chloride in 20 ml. of ether is added to the pale yellow precipitate to produce a blue mixture, and stirring is maintained for a further 2.5 hours. The ferrocenium salt mixture is poured on 100 g. of ice and 100 ml. of 12.5% titanous chloride solution, and the red-yellow ethereal solution is removed and dried over anhydrous sodium sulfate and zinc dust. Removal of the solvent in a nitrogen atmosphere affords 3.65 g. of an oil, which is chromatographed on alumina with ligroin as

solvent; the eluate is evaporated, yielding 1,1'-di-*t*-butylferrocene as a red-brown oil (2.8 g., 94%).

TABULAR SURVEY

The tables which follow are arranged in the order in which the compounds with which they deal are treated in the text, and the titles of the tables correspond rather closely to those of the paragraphs. Thus tables dealing with the preparation of ferrocenes from cyclopentadienes or fulvenes appear first. Next come tables dealing with the preparation or utilization of the key intermediates like chloromercuriferrocene, then tables summarizing ferrocenes bearing particular substituents—the acyl ferrocenes, alkenyl ferrocenes, etc. Finally are listed derivatives of other organometallic compounds like cyclopentadienylmanganese tricarbonyl.

Within individual tables there is, inevitably, some variation in order, reflecting the differing contents of the tables. For example, entries in Table I, dealing with the direct preparation of ferrocene from cyclopentadiene, are arranged in the general order of decreasing strength of the base employed, while entries in Table XI, dealing with various routes to ferrocenecarboxaldehyde, are arranged in order of the complexity of the starting material, and the entries of Table XXVIII, containing ferrocene heterocycles, are arranged primarily in order of heterocycle ring size and secondarily in order of number of heteroatoms in the ring.

For the bulk of the tables, in which a number of substituted ferrocenes are recorded together, the compounds are arranged in the order of substituents as follows: hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, and aryl groups, followed by substituents containing other functional groups but with a carbon atom bonded to the ring, followed by substituents with a heteroatom bonded to the ring. The latter substituents are arranged primarily according to group in the periodic table—alkali metals first, halogens last—and secondarily according to period in the periodic table—lithium before sodium, etc. Among alkyl groups the order of increasing total number of carbon atoms is followed primarily and the order of increasing branching secondarily. Many tables are subdivided into parts A, B, C, etc., for example, according to whether the ferrocenes are mono-, di, or multi-substituted.

Most of the tables are regarded as reasonably complete, but Tables XII and XV give only representative examples of derivatives prepared from ferrocenecarboxaldehyde and acyl ferrocenes, respectively.

In this tabular survey, as well as in the text, the literature through December 1965 has been covered.

CHAPTER 2

THE γ -ALKYLATION AND γ -ARYLATION OF DIANIONS OF β -DICARBONYL COMPOUNDS

THOMAS M. HARRIS AND CONSTANCE M. HARRIS
Vanderbilt University

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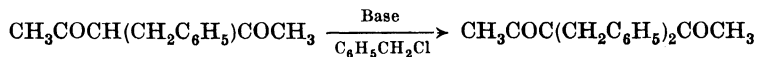
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INTRODUCTION

It is well known that β -diketones can undergo condensations at the α -methylene group with alkyl halides and certain other reagents through the intermediate formation of monoanions. For example, acetylacetone on treatment with an alkali metal or an alkali metal alkoxide or carbonate forms a monoanion which can be alkylated with alkyl halides. With benzyl chloride the α -benzyl derivative is formed.¹



These reactions are often carried out in boiling acetone, benzene, or toluene and in general proceed rather slowly. A second alkylation at the α position is frequently a side reaction.¹

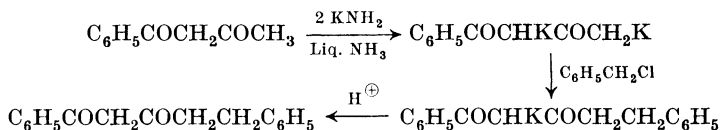


In 1958 Hauser and Harris reported that, if benzoylacetone or acetylacetone is first converted to the dipotassium salt, the salt undergoes alkylation and other carbon-carbon condensations at the terminal methyl group rather than at the methylene group.² The dipotassium salts were prepared by treatment of the diketones with 2 molecular equivalents of potassium amide in liquid ammonia. Rapid alkylation occurred when the salts were treated with 1 equivalent of benzyl chloride and, after acidification, the terminal monobenzoylation derivatives were obtained in good

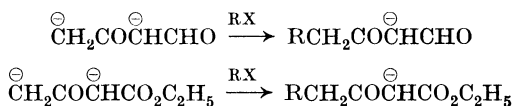
¹ G. T. Morgan and C. J. A. Taylor, *J. Chem. Soc.*, **127**, 797 (1925).

² C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

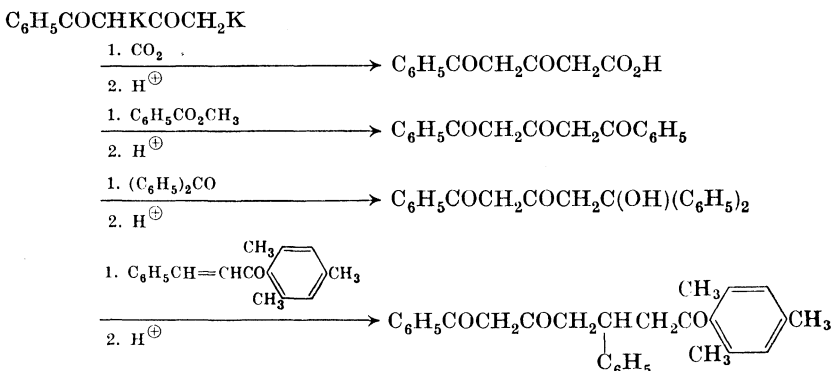
yield. Dibenzylation was not observed. In this chapter the alkylations of these and other β -diketones via their dianions will be surveyed.



β -Keto aldehydes and β -keto esters have also been converted to dianions by similar procedures; the dianions undergo alkylation reactions at the γ positions.^{3, 4} These alkylations will also be discussed.



Alkylation can be considered a typical reaction of these carbanions. The successful alkylation of a dicarbanion is an indication that acylation, carboxylation, and aldol-type condensations can also be effected. Thus the results obtained with alkylating agents are useful in predicting and understanding the reactions of the dianions of β -dicarbonyl compounds with many other electrophilic condensing agents. Reactions that have been observed include carboxylation with carbon dioxide,⁵ acylation with aromatic and aliphatic esters,^{4, 6-8} carbonyl addition reactions with aldehydes and ketones^{4, 8-10} and 1,4-additions to α,β -unsaturated compounds.^{6, 8, 10} Some of these are illustrated by the accompanying equations.



³ T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **84**, 1750 (1962).

⁴ J. F. Wolfe, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3249 (1964).

⁵ T. M. Harris and C. M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).

⁶ F. B. Kirby, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 2266 (1963).

⁷ S. D. Work and C. R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).

⁸ T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 3186 (1965).

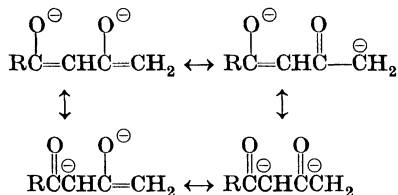
⁹ R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

¹⁰ R. J. Light, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **26**, 1344 (1961).

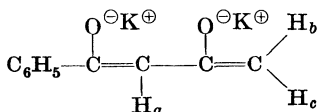
Arylations, although apparently mechanistically different from alkylations,¹¹ are included in this chapter because of their formal similarity to alkylations and because alkylation and arylation are methods for directly converting β -diketones into higher homologs without increasing their functionality.

MECHANISM

Chemical evidence indicates that the intermediates in the reaction of β -dicarbonyl compounds at the γ position are the *bis*-enolate anions resulting from proton abstraction at both the α and the γ positions. Although canonical resonance forms having one or both negative charges on oxygen are undoubtedly important contributors, the dialkali metal salts will henceforth be pictured as dicarbanions to emphasize the high reactivity at the γ carbon atom.



The nuclear magnetic resonance spectrum of the dipotassium salt of benzoylacetone provides physical evidence that the species present is an α,γ -dianion.¹² The spectrum shows, in addition to the aromatic multiplet, a singlet and two doublets. The singlet has been assigned to proton *a* and the doublets to protons *b* and *c*.¹² Protons *b* and *c* are coupled by approximately 2 cps. The facts that protons *b* and *c* have different chemical shifts and that the coupling constant is quite small¹³ support the contention that the terminal anion is more accurately represented as a planar enolate anion than as a tetrahedral carbanion.



Chemical evidence for dianion formation is that a β -diketone such as dibenzoylmethane, having only α -hydrogen atoms, has been found to react with only 1 molecular equivalent of potassium amide in liquid

¹¹ K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

¹² M. L. Miles, C. G. Moreland, D. M. von Schrititz, and C. R. Hauser, *Chem. & Ind. (London)*, 2098 (1966).

¹³ H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

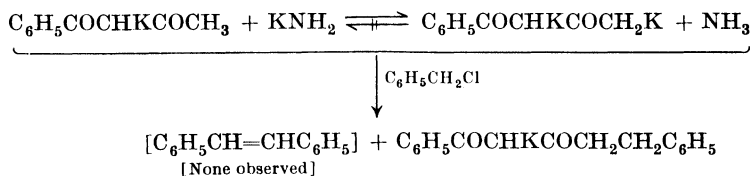
ammonia,¹⁴ whereas a β -diketone such as benzoylacetone, having both α - and γ -hydrogen atoms, reacts with 2 molecular equivalents of the base. The fact that alkylation and other condensations occur at the γ position of dicarbanions is *prima facie* evidence that this was the site of secondary ionization, since alkylations at this position are not observed when 1:1 ratios of dicarbonyl compound and base are employed. Additional evidence has been obtained from titration of disodioacetylacetone with acid. The salt was found to be dibasic and to be essentially free of ammonia.¹⁵

The possibility remains that acetylacetone, which has two terminal methyl groups as well as an α -methylene group, might form a 1,5-dicarbanion, $\text{CH}_2\overset{\ominus}\text{COCH}_2\overset{\ominus}\text{COCH}_2$, instead of a 1,3-dicarbanion,



There is no evidence to support this proposal. Some 1,5-dialkylation has been observed in the alkylation of dipotassioacetylacetone. However, this has been accounted for in another manner (p. 163).¹⁶

Evidently the γ -hydrogen atoms of singly ionized β -diketones or β -keto aldehydes are sufficiently acidic that treatment with a stoichiometric amount of alkali metal amide affords essentially complete conversion to the dicarbanions; that is, these dianions are weaker bases in ammonia than is amide ion. If the base strengths of amide ion and the dianion had been similar, significant amounts of amide ion and monoanion of the dicarbonyl compound would have remained in equilibrium with the dianion. The evidence that such a situation does not exist is that stilbene formation has usually not been observed during the alkylation



of these dianions, for example, dipotassiobenzoylacetone, with benzyl chloride.² Benzyl chloride is known to undergo displacement reactions with carbanions but exclusively self-condensation on treatment with amide ion.¹⁷ The latter reaction pathway would be able to compete with

¹⁴ T. M. Harris and C. R. Hauser, unpublished results.

¹⁵ T. M. Harris, unpublished results.

¹⁶ K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 61 (1965).

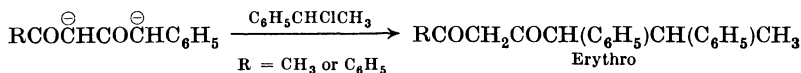
¹⁷ C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

alkylation if significant amounts of amide ion were present.* The self-condensation of benzyl chloride is characterized by a vivid, transient violet coloration of the reaction mixture which permits visual detection of this side reaction.¹⁸ The inability to obtain stilbene or to observe this violet coloration during alkylations of dianions is evidence that essentially no amide ion remains in the dianion reaction mixture.

In general, good results have been obtained with β -keto aldehydes, and there is no indication that dianion formation is not complete. However, on the basis of limited study of ethyl acetoacetate, it is possible that this β -keto ester is not completely converted to the dianion by potassium amide.⁴

Alkylation at the α position of diketones has not been observed during the dianion reactions, even when excess alkyl halide is employed. Not only is the nucleophilicity of the monocarbanion too low for observable reaction to occur under these conditions, but also apparently the nucleophilicity of the α position of the dianion is substantially less than that of the γ position. Alkylations are presumably simple displacement reactions, although the details of the mechanism have not been investigated.

Alkylation reactions appear to have a high degree of stereospecificity. The alkylations of the disodium salts of 1-phenyl-2,4-pentanedione and 1,4-diphenyl-1,3-butanedione with α -phenethyl chloride gave exclusively the corresponding erythro products.^{18a}



In the first case ($\text{R} = \text{CH}_3$), the threo isomer was demonstrated to be stable to the alkylation conditions. Therefore it can be concluded that the more stable erythro isomer was the direct product of the alkylation reaction.^{18a}

Alkylations of the dianion of 2-formyl-1-decalone occur at the 9 position to generate an additional asymmetric center (see p. 176). Considerable stereospecificity exists in these reactions also.

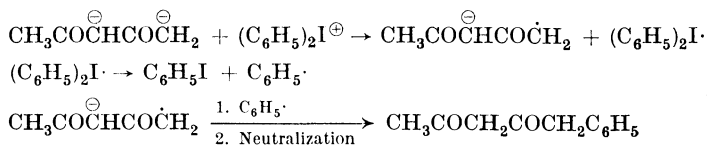
The arylation of dicarbanions with diaryliodonium salts appears to be at least partially a free-radical reaction. It has been postulated¹¹ that one electron is transferred from the dicarbanion to the iodonium ion to afford the anion radical of the diketone. The resulting diphenyliodine decomposes to iodobenzene and phenyl radical. The phenyl radical couples primarily at the γ position of the diketone anion radical. The

* The self-condensation of benzyl chloride by amide ion and the benzylation of a carbanion, that of diphenylmethane, have been shown to occur at comparable rates.¹⁸

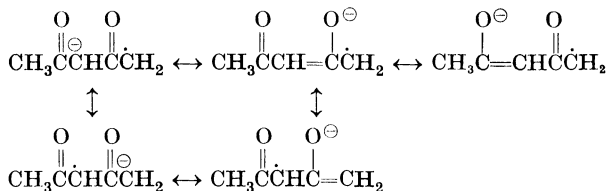
¹⁸ C. R. Hauser and P. J. Hamrick, *J. Am. Chem. Soc.*, **79**, 3142 (1957).

^{18a} D. M. von Schriltz and C. R. Hauser, unpublished results.

sequence is illustrated with acetylacetone dicarbanion and diphenyliodonium ion in the accompanying scheme.



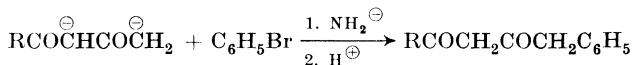
In support of this mechanism, both biphenyl and α -phenylacetylacetone have been detected in trace amounts.¹¹ The α -phenylated diketone was accounted for by resonance contributors to the intermediate anion radical in which the free electron is on the α - as well as on the γ -carbon atom. Apparently the difference in reactivity of the α and γ positions of the anion radical is less than the difference in reactivity of the two positions of the dianion.



Additional support for the free-radical mechanism of phenylation is the observation that, although dipotassioacetylacetone is inert toward iodobenzene, in the presence of diphenyliodonium chloride a significant amount of iodobenzene does react to form the γ -phenylation product. When disodioacetylacetone (2 equivalents) was treated with diphenyliodonium chloride, the yield was 92%. However, if an equivalent amount of iodobenzene was added simultaneously with the iodonium salt, a yield in excess of quantitative (109% based on iodonium salt) was obtained.¹¹

The possibility that the arylation reaction is partly direct displacement cannot be eliminated. Direct displacement has been postulated in naphthylations of other anions by 1- and 2-naphthyl methyl sulfone and 1-fluoronaphthalene.¹⁹ On the other hand, it is possible that certain alkylations such as those with benzyl chloride may proceed by a single electron transfer similar to the phenylation reaction.

Finally, several arylations have been effected with halobenzenes and excess amide ion.^{2, 11} These reactions undoubtedly involve arylation by benzyne intermediates.



¹⁹ J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.*, **78**, 6265 (1956).

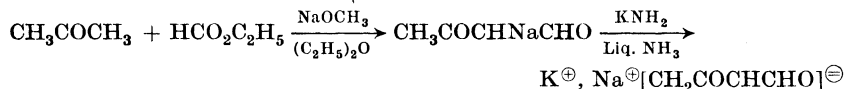
SCOPE AND LIMITATIONS

Preparation of Dianions

The dicarbanions of β -diketones are prepared by addition of the diketone to 2 equivalents of alkali amide in liquid ammonia. The amides of lithium, sodium, and potassium have been employed in this reaction. Conversion to the dianions is apparently rapid.

The solubility of the salts in liquid ammonia cannot be readily predicted. Although potassium amide is much more soluble in liquid ammonia than is sodium amide or lithium amide, disodioacetylacetone is more soluble in this medium than either the dipotassium or the dilithium salt.¹⁶ The greater solubility of the disodium salt in ammonia has also been observed with other aliphatic diketones.²⁰

The dianions of β -keto aldehydes have usually been prepared by addition of the monosodium salt of the keto aldehyde to potassium amide in liquid ammonia.^{3, 21} Such a procedure is necessary with acetoacetaldehyde and other keto aldehydes lacking substituents at the α position because these compounds readily undergo aldol condensations leading to 1,3,5-triacetylbenzenes.²² The monosodium salts of many β -keto aldehydes are conveniently prepared by acylation of the corresponding ketone with formate esters and sodium alkoxides.²² The condensations occur in high yield, and the sodium salts have been used without subsequent purification. The formation of sodioformylacetone and its conversion to the dianion are illustrated in the accompanying scheme.



With α -substituted β -keto aldehydes the procedure involving the monosodium salt is not necessary because these compounds do not readily undergo self-condensation.²² However, the monosodium salts have commonly been employed since these keto aldehydes are also prepared by formylation of the corresponding ketones and are conveniently isolated as their sodium salts.²³

Keto ester dianions have been prepared principally by means of potassium amide,^{4, 24} although sodium amide may sometimes be satisfactory.²⁵

²⁰ K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 1035 (1966).

²¹ T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963).

²² C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 87-89 (1954).

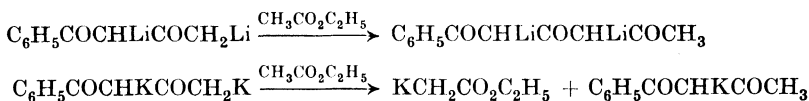
²³ S. Boatman, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 82 (1965).

²⁴ V. I. Gunar, L. F. Kudryavtseva, and S. I. Zav'yalov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1343 (1962) [*Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1431 (1962)] [*C.A.*, **58**, 2378 (1963)].

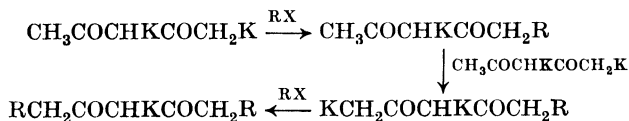
²⁵ R. L. Carney and T. M. Harris, unpublished results.

Alkylations of Acetylacetone (Table III)

The dialkali metal salts of acetylacetone show certain distinct differences in reactivity. These differences cannot be correlated with solubility in ammonia but can be correlated with the size of the alkali metal ion. The dilithium salt has more covalent character and is markedly less reactive in alkylation reactions than is the disodium or dipotassium salt. The alkylation of dilithioacetylacetone with *n*-butyl bromide is reported to be only 25% complete after twice the reaction period employed to obtain 67–73% alkylation of disodioacetylacetone.¹⁶ This lack of reactivity does not extend to all classes of reactions of dilithium salts because these salts have been found to be uniquely useful for condensations with aliphatic esters and with ketones having relatively acidic α -hydrogen atoms.^{7, 9} For example, acylation of dilithiobenzoylacetone with ethyl acetate proceeds rapidly and at a rate much greater than proton abstraction from the ester.⁷ On the other hand, disodio- and dipotassio-benzoylacetone selectively ionize the ester.⁷



Disodium and dipotassium salts of acetylacetone were initially considered to have essentially the same properties.²⁶ However, a fundamental difference in the chemistry of the two salts of acetylacetone was later detected by gas chromatographic analysis of alkylation products.^{16, 27} Alkylation of dipotassioacetylacetone was found to afford significant amounts (14–26%) of the 1,5-dialkylation product in addition to the normal terminal alkylation product.¹⁶ Although this might have occurred through a 1,5-dianion, $\overset{\ominus}{\text{CH}}_2\text{COCH}_2\overset{\ominus}{\text{COCH}}_2$, it is more likely that as monoalkylation products are formed they react with dipotassioacetylacetone to form a new dianion that subsequently undergoes further alkylation.



The amount of dialkylation is somewhat dependent on the addition rate of alkyl halide to dipotassioacetylacetone; very slow addition lengthens

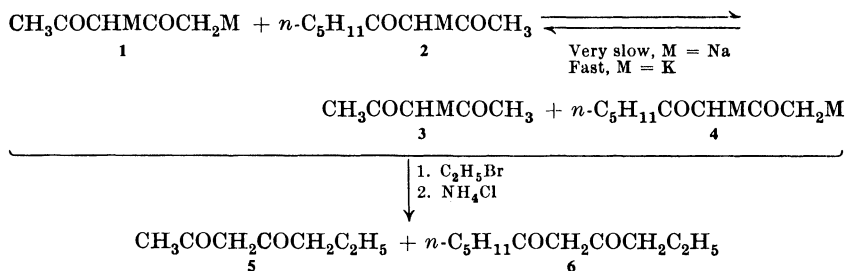
²⁶ R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960).

²⁷ K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 1946 (1963).

the time in which proton abstraction can occur and hence increases the extent of dialkylation.

On the other hand, disodioacetylacetone undergoes alkylation with alkyl halides without observable formation of dialkylation products.¹⁶ Apparently proton interchange between a monoanion and a dianion is much slower with sodium salts than with potassium salts. However, the difference in alkylation rates is much less, if any. Similarly alkylation of dithioacetylacetone, although impractical because of the low reaction rate, does not afford dialkylation products.¹⁶

The difference between the dipotassium salt of acetylacetone and the more covalent disodium salt was clearly demonstrated by treatment of mixtures of the dianion of acetylacetone (1) and the monoanion of another diketone (2) with an alkyl halide.¹⁶ The yield of terminal alkylation product arising from the initially monoionized diketone was a measure of the extent to which dianion interchange had occurred. In addition, the monoanion of acetylacetone (3) and the dianion (4) of the other diketone were employed in the reverse experiment.



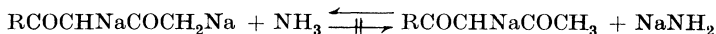
In the case of the potassium salts, when equal molar mixtures either of 1 and 2 or of 3 and 4 were stirred for 2 hours before alkylation, an approximate 4:1 mixture of alkylation products 5 and 6 was obtained.¹⁶ Even after only 6 minutes of mixing, nearly the same results were obtained, indicating that equilibration was largely complete.

With the sodium salts, dianion interchange was not observed.¹⁶ Alkylation of a mixture of sodium salts 1 and 2 afforded only 5, and alkylation of 3 and 4 afforded only 6.¹⁶ This result was obtained even after the mono- and di-sodium salts were stirred together for 2 hours.

The metallic cation effect is made more striking by the fact that rapid dianion interchange occurred with the sparingly soluble potassium salts rather than with the highly soluble sodium salts.

One additional conclusion to be drawn from this study is that the disodium salts are not significantly involved in proton transfers with ammonia to form sodium amide and the monoanion of the diketone. This

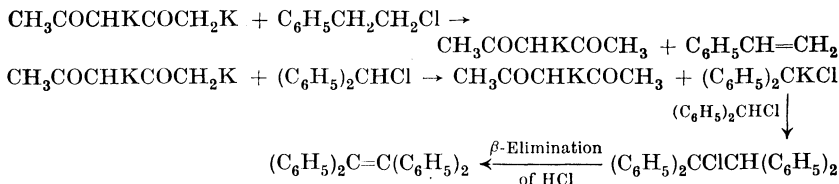
fact has been useful in interpretation of the results obtained in the alkylation of unsymmetrical diketones (see next section).



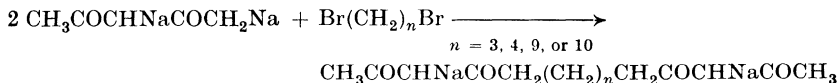
Many examples of alkylation of the disodium and dipotassium salts of acetylacetone have been reported (see Table III). The results obtained with the disodium salts are better in most cases, largely because dialkylation products are not produced.

Primary and secondary aliphatic halides have been used with almost uniform success; yields with disodioacetylacetone typically range from 55% to 80%. The alkylation of dipotassioacetylacetone with isopropyl bromide was effected in only 27% yield,²⁶ but a 66% yield was achieved in a similar alkylation of disodioacetylacetone.¹⁶ Alkylation with *sec*-butyl bromide has been accomplished in 78% yield.¹⁶

Among alkylations with simple halides, failures have been reported with *t*-butyl chloride, β -phenethyl chloride, and benzhydryl chloride.²⁶ The cause of failure with the first of these is probably the inherent lack of reactivity of tertiary alkyl halides in displacement reactions. The failures with β -phenethyl chloride and benzhydryl chloride stem from the alkaline properties of dianions; high yields of styrene and tetraphenylethylene, respectively, were obtained from the reactions.²⁶ Tetraphenylethylene can arise by self-alkylation of benzhydryl chloride by means of its anion.¹⁷



The alkylation of disodioacetylacetone with dihaloalkanes has been used to synthesize *bis*- β -diketones. Tri-, tetra-, nona-, and deca-methylene bromides have been employed successfully.²⁸

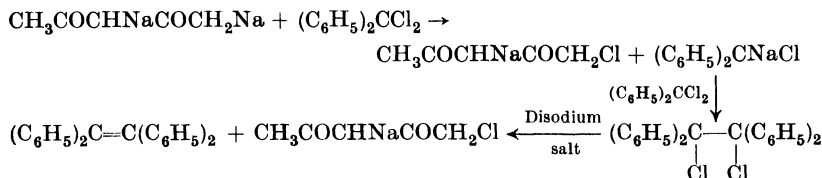


Failures in the preparation of *bis*- β -diketones have been reported with methylene chloride, ethylene chloride, and ethylene bromide.²⁸ With ethylene bromide a mixture of two unidentified products was obtained.²⁸ Attempted alkylation by *o*-, *m*-, and *p*-xylylene bromide has been reported.²⁹ The desired alkylation probably occurred, but the products

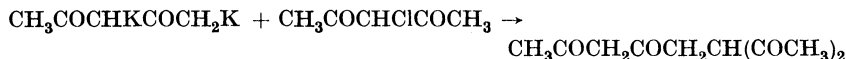
²⁸ K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

²⁹ M. M. Coombs and R. P. Houghton, *J. Chem. Soc.*, 5015 (1961).

were not characterized. The reaction of disodioacetylacetone with dichlorodiphenylmethane afforded a 70% yield of tetraphenylethylene.²⁸ The mode of formation of this hydrocarbon has been suggested to be that shown in the accompanying scheme.²⁸ However, other mechanisms involving free radicals or carbenes are also possible.

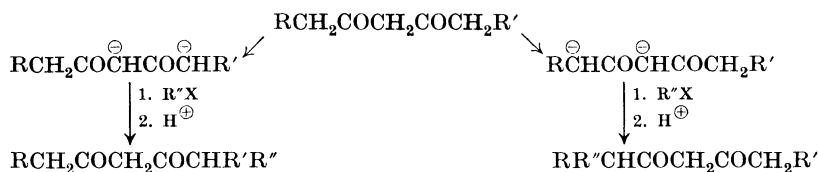


One rather unusual alkylation has been employed for preparation of a *bis*- β -diketone. The alkylation of dipotassioacetylacetone by 3-chloro-2,4-pentanedione has been reported.^{30, 30a} The yield was low.



Alkylations of Unsymmetrical β -Diketones (Table IV)

A problem of practical importance in the alkylation of the dianions of β -diketones is that many diketones are at least theoretically capable of forming two different dianions and therefore of producing two isomeric products upon alkylation. This situation arises in unsymmetrical diketones whenever both carbonyl groups are flanked by carbon atoms bearing one or more hydrogen atoms.



Results of studies of the effect of diketone structure on the formation of dianions under these circumstances appear to have considerable generality for prediction of the site of secondary ionization and subsequent alkylation in unsymmetrical systems. Because a high degree of specificity has been observed in most of the systems investigated, the alkylation of unsymmetrical diketones through dianions has usually led to only one product.

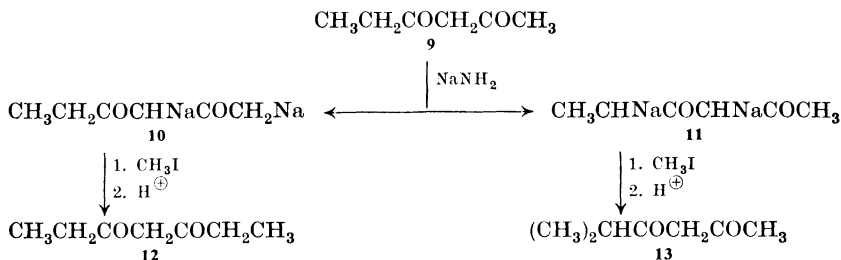
³⁰ R. J. Gritter and E. L. Patmore, *Proc. Chem. Soc.*, 328 (1962).

^{30a} E. L. Patmore, Doctoral Dissertation, University of Connecticut, 1963 (*Dissertation Abstr.*, 64-3553).

It appears well established that methyl-methylene β -diketones having one aliphatic γ substituent (**7**) undergo alkylation through dicarbanions to



form mainly or entirely the methyl alkylation product **8**. The most rigorously investigated substrate, 2,4-hexanedione (**9**), was treated with 2 equivalents of sodium amide.³¹ This might have led to dianion **10** or **11** or a mixture of the two. Treatment of the reaction mixture with methyl iodide gave an 89:11 mixture, as determined by gas chromatography, of the methyl and the methylene alkylation products **12** and **13**, respectively. Thus alkylation at the methyl group greatly predominated over that at the methylene group.



It has been concluded that the formation of the salts **10** and **11** is essentially an irreversible process (see p. 164) so that they are probably not interconvertible under the reaction conditions.³¹ Therefore the formation of the dianions and the alkylation products is under kinetic rather than thermodynamic control, and the dianion that predominates as an intermediate is not necessarily the less basic of the two.*

Additional evidence that the ratio of alkylation products reflects reasonably well the ratio of dianions formed lies in the fact that acetyl- and propionyl-type dianions do not differ greatly in their nucleophilicities and, actually, propionyl-type dianions are more reactive than the acetyl type.²⁰ Thus, even if the dianions had been interconvertible, the effect on the interpretation of the experiment would not be great, because the alkylation product **13** of the propionyl-type dianion was formed in only minor amounts from 2,4-hexanedione (**9**).

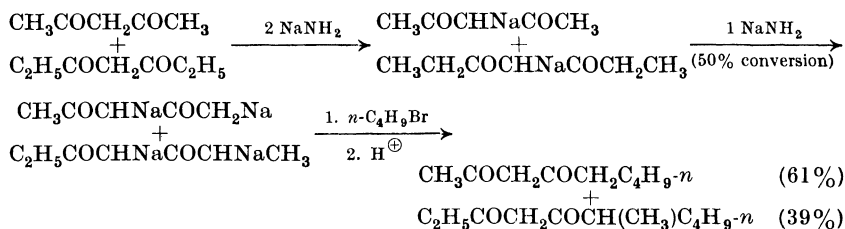
Alkylation of dipotassiopropionylacetone gave similar results.³¹ It is quite likely that the isomeric dipotassium salts of this β -diketone equilibrate with one another, particularly if the monoanion or another proton

³¹ K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 663 (1966).

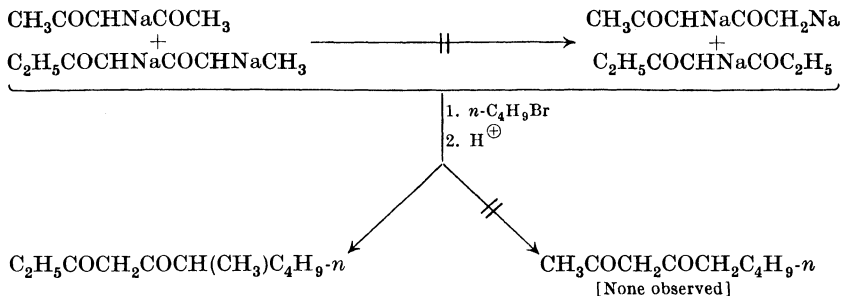
* The term basicity is used in the thermodynamic sense. The less basic anion is the more stable and would be the predominant species if the anions could be equilibrated with one another.

donor of comparable pK_a is present. Moreover, the dipotassium salt(s) is largely precipitated in the reaction medium. Thus the extent of equilibration and the relative reactivity of the two dianions probably reflect solubility factors as well as anion stability. Nevertheless alkylation at the methyl position predominates.

A study has also been made of the competitive formation of disodium salts in which the competing sites were on two different diketone molecules.³¹ A sufficient amount of sodium amide was added to an equimolar mixture of acetylacetone and dipropionylmethane to convert one-half of the mixture to dianions and the remainder to monoanions. The mixture was treated with excess *n*-butyl bromide. Analysis of the products by gas chromatography indicated that the dianion of acetylacetone had predominated over that of dipropionylmethane in a ratio of 61:39.

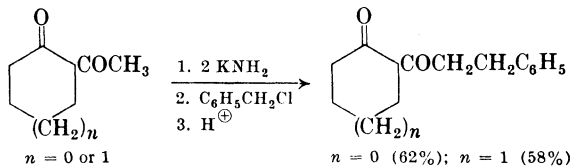


The two disodium salts were not in equilibrium with one another. When a mixture of disodiopropionylmethane and monosodioacetylacetone in liquid ammonia was stirred for 30 minutes before treatment with *n*-butyl bromide, only the alkylation product of dipropionylmethane was obtained.³¹

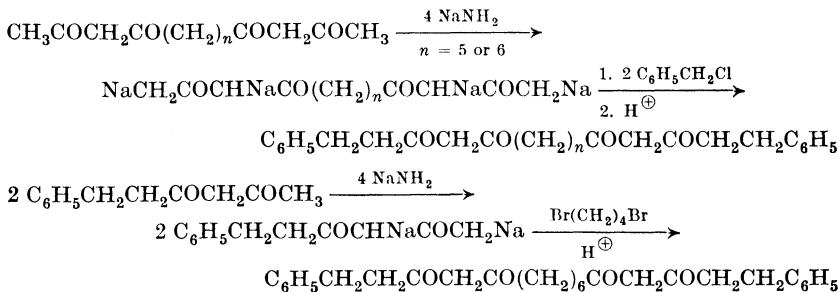


The competitive ionization of a mixture of acetylacetone and dipropionylmethane also has been conducted with potassium amide.³¹ The same preference for alkylation of acetylacetone was observed. In fact, the reaction was somewhat more selective, and an 83:17 ratio of the products was obtained.

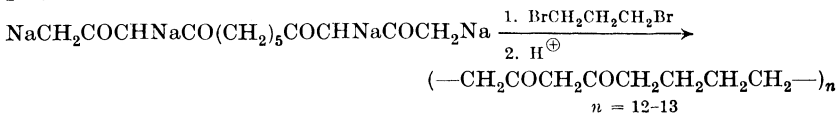
In addition to the alkylation of simple aliphatic methyl-methylene diketones two cyclic systems have been studied.³² α -Acetylcyclohexanone and α -acetylcyclopentanone both undergo alkylation by means of dipotassium salts exclusively at methyl positions.



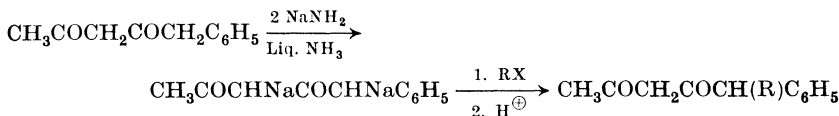
The specificity of reaction at methyl groups has been observed in the dialkylation of two *bis*- β -diketones by means of tetra-anions.³³ One of the products was also synthesized independently by a dianion alkylation with a dihalide which required alkylation to occur preferentially at a methyl position.²⁸



Treatment of one tetrasodio-*bis*- β -diketone with a dihalide afforded a polymeric β -diketone.³³



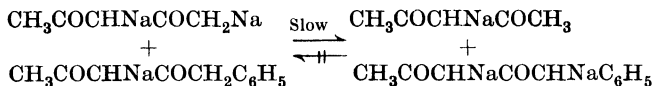
Methyl-methylene β -diketones having aryl groups at the γ position can be expected to undergo alkylation and other condensations at the γ -methylene group rather than at the methyl group. Alkylations of the disodium salt of 1-phenyl-2,4-pentanedione with four halides have all afforded the 1-alkylation products.^{18a, 31}



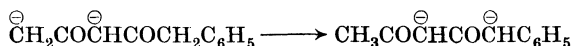
³² T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

³³ K. G. Hampton and C. R. Hauser, *J. Org. Chem.*, **30**, 2934 (1965).

It is possible that an equilibrium exists between the 1,3- and 3,5-disodium salts of 1-phenyl-2,4-pentanedione because a slow intermolecular proton transfer has been observed between the monosodium salt of this diketone and disodioacetylacetone.¹¹

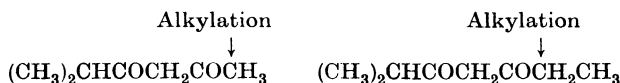


However, the reverse reaction is not observed with these diketones, indicating that the phenylacetyl-type dianion is substantially more stable, i.e., less basic, than that of acetylacetone.¹¹ As a consequence the 1,3-dianion of 1-phenyl-2,4-pentanedione can be expected to be more stable than the 3,5-dianion. This raises the question whether the 3,5-dianion might not be initially formed and then gradually converted to the 1,3-dianion.



The possibility receives some support from studies of phenylacetone; although the methylene anion of this ketone is more stable,³⁴ kinetically controlled formylation occurs at the methyl position.³⁵ However, there is at present no direct evidence bearing on this problem with 1-phenyl-2,4-pentanedione, and the slowness of proton interchange between the sodium salt of 1-phenyl-2,4-pentanedione and disodioacetylacetone indicates that initial ionization of the aryl β -diketone at the 1-methylene position is more likely than at the 5-methyl position.

A study has been made of the alkylation of the disodium salts of two other types of unsymmetrical diketones; in one, the competition was between an isobutyryl group and an acetyl group, and in the other between an isobutyryl group and a propionyl group.³¹ In both cases alkylation was observed almost exclusively at the position of less substitution, as indicated by arrows in the accompanying formulas.

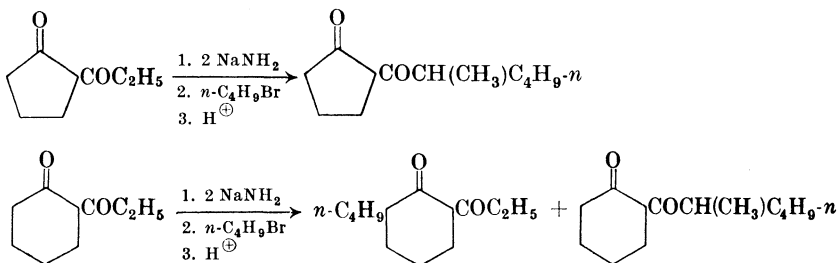


The alkylation of two diketones, 2-propionylcyclopentanone and 2-propionylcyclohexanone, in which the substituents are both methylene groups has been studied. Alkylation of 2-propionylcyclopentanone

³⁴ H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

³⁵ L.-M. Roch, *Ann. Chim. (Paris)*, [3] **6**, 105 (1961).

occurred preferentially on the propionyl group, whereas with 2-propionyl-cyclohexanone little selectivity between ring and chain alkylation was observed.^{36, 37}



The specificity of γ -alkylation and other γ -condensations of unsymmetrical β -diketones can be summarized as follows: When disodium salts are employed, the preferred site of reaction will be phenylacetyl > acetyl > propionyl > isobutyryl. The same sequence may in many cases be observed with potassium salts, but strict adherence is not assured.

It would be of considerable theoretical interest to determine the relative basicities of the various types of dianions, particularly with a closely related group of β -diketones. However, the inability of sodium mono- and di-anions to equilibrate in liquid ammonia is a complicating factor, as is the insolubility of many of the dipotassium salts in liquid ammonia.

Recent studies have shown that the kinetically preferred ionization of unsymmetrical monoketones often does not lead to the more stable anion.^{34, 35, 38-41} However, it has been suggested that the order of ease of formation of disodium salts of diketones qualitatively represents the order of acidity of the γ -hydrogen atoms.²⁰ No experimental verification of this has been made.

Alkylations of Other β -Diketones (Table V)

The other β -diketones that have been alkylated through their dianions may be considered in two groups: the benzoylacylmethanes and symmetrical diketones other than acetylacetone.

³⁶ K. G. Hampton and C. R. Hauser, unpublished results.

³⁷ D. R. Bryant and C. R. Hauser, unpublished results.

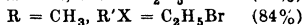
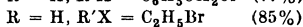
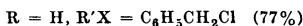
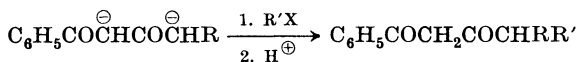
³⁸ H. O. House, *Modern Synthetic Reactions*, Chapter 7, Benjamin, New York, 1965.

³⁹ H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 4395 (1965).

⁴⁰ D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

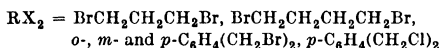
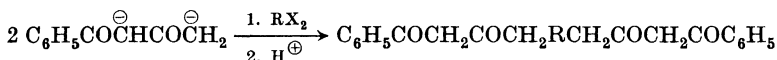
⁴¹ H. M. E. Caldwell, *J. Chem. Soc.*, 2442 (1951).

Benzoylacetone and the higher benzoylacylmethanes are incapable of alkylation through more than one dianion. Benzoylacetone has been alkylated with benzyl chloride and ethyl bromide.^{2, 20} The ethylation of

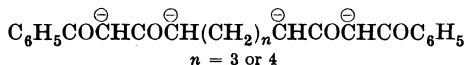


1-phenyl-1,3-pentanedione has also been effected.²⁰ The dianion of 1-phenyl-1,3-hexanedione has been prepared. Alkylation has not been reported, although an aldol condensation proceeded satisfactorily.³³

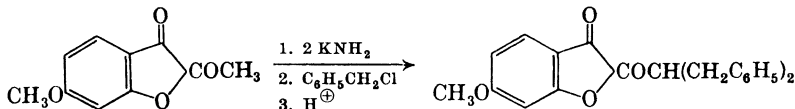
The alkylation of dianions of benzoylacetone with dihaloalkanes has been reported. The reactions give rise to *bis*- β -diketones. Dihalides that have been employed successfully include tri- and tetra-methylene bromide and the *o*-, *m*-, and *p*-xylylene halides.^{28, 29}



In addition, the two *bis*-dianions shown by the accompanying formula have been prepared and twofold condensations have been effected with them.³³ Although alkylation has not been reported, these anions would presumably yield *bis*-alkylation products.

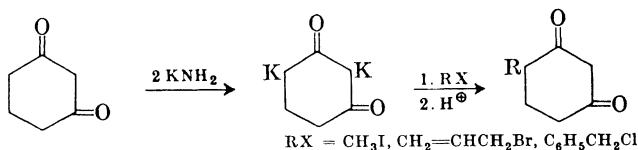


The dipotassium salt of 2-acetyl-6-methoxycoumaran-3-one has been prepared. Treatment of this dianion with a stoichiometric amount of benzyl chloride afforded the dibenzylation product in 21% yield. No monobenzylation product was detected, but much of the coumaran-3-one was recovered.⁴²

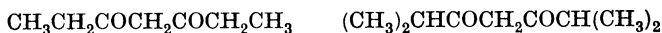


Alkylation of 1,3-cyclohexanedione with three alkyl halides has been reported. The dipotassium salt was employed and the 4-alkyl derivatives were isolated in 17–45% yield.²⁴ The disodium salt did not benzylate as smoothly as the dipotassium salt.

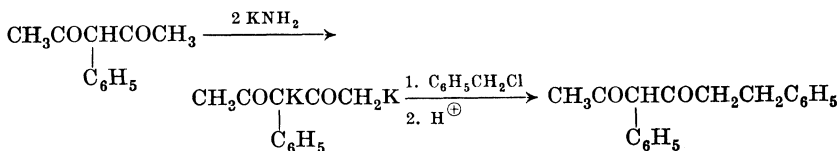
⁴² W. I. O'Sullivan and C. R. Hauser, *J. Org. Chem.*, **25**, 839 (1960).



Other symmetrical diketones that have been alkylated include di-propionylmethane and diisobutyrylmethane.^{20, 31}



Only one alkylation of the dianion of an acyclic diketone having a single substituent at the reactive methylene position has been reported, and it proceeded with difficulty.⁴³ The dipotassium salt of 3-phenyl-2,4-pentanedione is readily formed but is very insoluble in ammonia. No benzylation was observed after a 2-hour reaction period in that solvent. When the alkylation was conducted in diethyl ether, reaction took place to only a slight extent. However, in a mixture of ammonia and pyridine alkylation took place rapidly and the benzylation product was obtained in 62% yield.



Further study is necessary to determine whether substituents on the active methylene group of diketones invariably lead to difficulty in effecting subsequent condensations of the dianions.

Relative Reactivities of Diketone Dianions

In most synthetic applications the need to know the relative nucleophilicity of dianions does not arise; however, such information might be useful in situations in which two different dianions are present in a molecule or a solution and the alkylation of only one is desired. One report has appeared describing studies of the reactivity of different types of disodio- β -diketones toward alkyl halides.²⁰ In that investigation two dianions were formed in equal concentration in liquid ammonia and the mixture was treated with an alkyl halide. The amount of alkyl halide employed was equal to no more than one-half the total quantity of the dianions. The compositions of the product mixtures were determined by gas chromatography, and the nucleophilicity ratios were computed on the

⁴³ W. I. O'Sullivan and C. R. Hauser, *J. Org. Chem.*, **25**, 1110 (1960).

TABLE I. COMPETITIVE ALKYLATION OF DISODIO- β -DIKETONES WITH ALKYL HALIDES IN LIQUID AMMONIA

Disodium Salt A	Disodium Salt B	Alkyl Halide	Nucleophilicity Ratio, A/B
$\text{CH}_3\text{COCHNaCOCH}_2\text{Na}$	$\text{CH}_3\text{CH}_2\text{COCHNaCOCHNaCH}_3$	$n\text{-C}_4\text{H}_9\text{Br}$	1/6.4
"	"	$n\text{-C}_4\text{H}_9\text{Cl}$	1/5.1
"	"	$n\text{-C}_4\text{H}_9\text{I}$	1/4.3
"	"	$\text{sec-C}_4\text{H}_9\text{Br}$	1/3.8
"	"	$i\text{-C}_4\text{H}_9\text{Br}$	1/7.5
$\text{CH}_3\text{COCHNaCOCH}_2\text{Na}$	$\text{CH}_3\text{COCHNaCOCHNaC}_6\text{H}_5$	$n\text{-C}_4\text{H}_9\text{Br}$	1/0.52
$\text{CH}_3\text{CH}_2\text{COCHNaCOCHNaCH}_3$	$(\text{CH}_3)_2\text{CHCOCHNaCOCNa}(\text{CH}_3)_2$	$n\text{-C}_4\text{H}_9\text{Br}$	1/1.0
$\text{C}_6\text{H}_5\text{COCHNaCOCH}_2\text{Na}$	$\text{C}_6\text{H}_5\text{COCHNaCOCHNaCH}_3$	$\text{C}_2\text{H}_5\text{Br}$	1/2.7

assumption that only bimolecular alkylation reactions were occurring and that there were no side reactions. The results are shown in Table I.

From the results in Table I it can be concluded that, over the range of compounds studied, the nucleophilicities do not vary much more than one order of magnitude. The order of reactivity, isobutyryl \simeq propionyl $>$ acetyl $>$ phenylacetyl, is reasonably independent of both alkyl halide and diketone. If meaningful data are to be obtained, studies of this type must be limited to cases in which both dianions are soluble.

It should be noted that a relationship exists between the nucleophilicity of a dianion and its ease of formation; that is, the most readily formed is the least reactive. One exception is that an isobutyryl-type dianion, although more difficult to form than a propionyl type, is of approximately the same reactivity. It has been suggested that the isobutyryl-type dianion is more basic than the propionyl type (see p. 171).²⁰ Thus it seems probable that the reactivity of the isobutyryl dianion is reduced by steric hindrance to the approach of the alkyl halide.

Alkylations of β -Keto Aldehydes (Table VI)

A variety of β -keto aldehydes has been alkylated through dianions. They include cases in which the anion undergoing alkylation is primary, secondary, or tertiary.

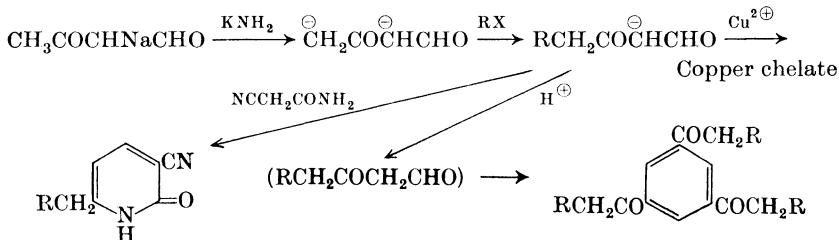
Primary anions are involved in the alkylations of acetoacetaldehyde and its α -substituted derivatives. Acetoacetaldehyde itself is unstable* and polymerizes to 1,3,5-triacetylbenzene,⁴⁵ but its monosodium derivative is stable. Treatment of monosodioacetoacetaldehyde with 1 equivalent of potassium amide affords the dianion which is relatively soluble in

* Free acetoacetaldehyde has been isolated under carefully controlled conditions and characterized.⁴⁴ β -Keto aldehydes with an α -substituent cannot undergo this self-condensation.

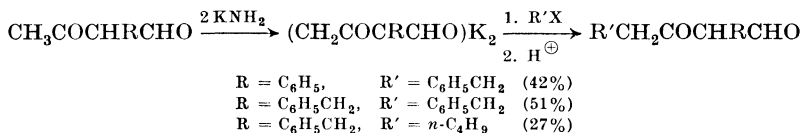
⁴⁴ D. Dahm, R. Johnson, and F. H. Rathmann, *Proc. N. Dakota Acad. Sci.*, **12**, 19 (1958) *C.A.*, **53**, 2084a (1959)].

⁴⁵ R. L. Frank and R. H. Varland, *Org. Syntheses, Coll. Vol. 3*, 829 (1955).

liquid ammonia. Alkylation at the γ position has been effected with methyl, *n*-butyl, *n*-octyl, and benzyl halides in good yields.²¹ The products are unstable and, if isolated as the keto aldehyde, condense gradually to give triacylbenzenes. The alkylated keto aldehydes have been isolated as their copper chelates by treatment with cupric acetate of the salts remaining after evaporation of the ammonia from the alkylation reaction. In addition, three of the reaction products have been treated with cyanoacetamide to give the 6-alkyl-3-cyano-2-pyridones in high yields.²¹ These reactions are illustrated in the accompanying scheme.



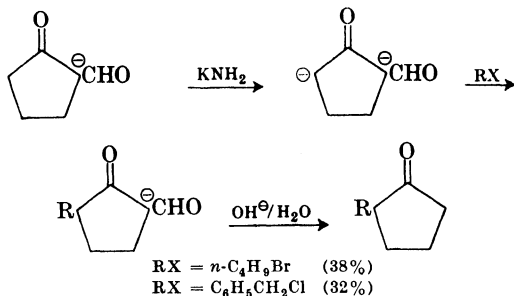
The dianions of α -phenyl- and α -benzyl-acetoacetaldehyde have been prepared.^{8, 21} The keto aldehydes having an α -substituent are sufficiently stable to permit handling. Dianion formation has been effected by treatment with 2 equivalents of potassium amide. Alkylation of the resulting dipotassium salts afforded keto aldehydes that were also sufficiently stable to be isolated.^{8, 21}



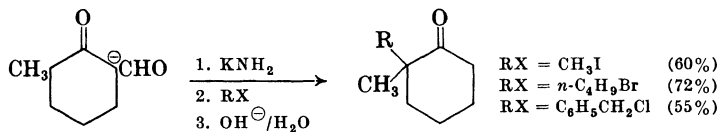
Alkylations of the formyl derivatives of several cyclic ketones have been effected. The α -formylcycloalkanones are sufficiently stable that they can be handled directly. However, most reactions have employed the monosodium salts as starting materials, and the alkylation products usually have been isolated as derivatives.

α -Formylcyclopentanone and α -formylcyclohexanone have both been converted to secondary dianions by treatment of their monosodium salts with 1 equivalent of potassium amide in liquid ammonia.²³ In addition, the dianion of α -formylcyclohexanone has been prepared from the free keto aldehyde by treatment with 2 equivalents of potassium amide.²⁴ Alkylation of these dianions has been effected with several alkyl halides.^{23, 24} Most products have been isolated as copper chelates, 3-cyano-2-pyridones, or monosubstituted cycloalkanones.^{23, 24} The over-all yields in the alkylations followed by hydrolyses ranged from 32% to

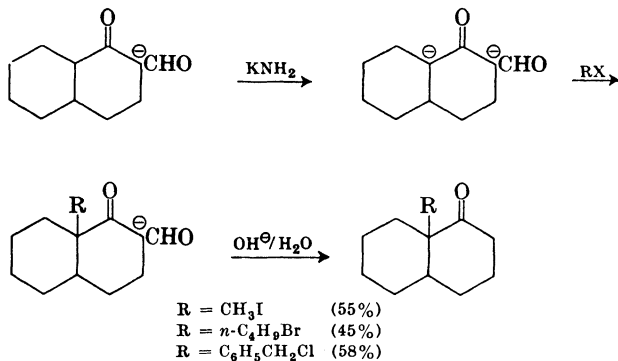
41%. The procedure for preparation of monoalkylcyclopentanones is illustrated; cyclohexanone derivatives were prepared similarly.



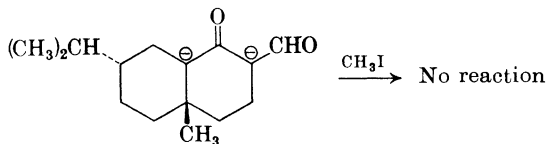
Two dianions have been studied in which alkylation took place at a tertiary site yielding a product with quarternary substitution. The alkylation products of 2-formyl-6-methylcyclohexanone were not isolated directly, although they presumably could be.²³ Instead they were converted to copper chelates, cyanopyridones, or α -alkyl- α -methylcyclohexanones. The last of these reactions is illustrated in the accompanying scheme.



2-Formyl-1-decalone has been alkylated at the 9-position.^{3, 23} The initial reaction products were hydrolyzed to the 9-alkyl-1-decalones or converted to other derivatives. The alkylation with methyl iodide afforded an approximately equal mixture of *cis*- and *trans*-9-methyl-1-decalone. Alkylation with *n*-butyl bromide yielded only 9-butyl-*cis*-1-decalone, and benzylation afforded only one stereoisomer which was presumably 9-benzyl-*cis*-1-decalone.



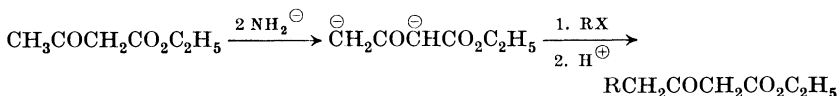
However, methylation of the dianion of a formyldecalone having *trans* alkyl groups at positions 7 and 10 failed.⁴⁶ Apparently, the alkyl substituents shielded both sides of the enolate anion from nucleophilic attack on the alkyl halide.



Alkylations of β -Keto Esters (Table VII)

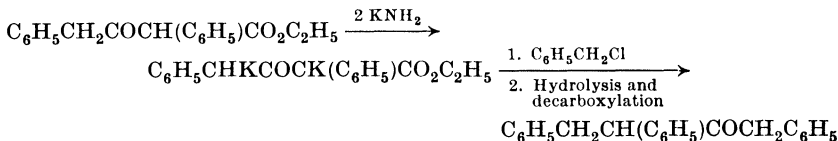
Four β -keto esters have been studied with regard to their ability to form dianions and subsequently to undergo alkylation at the γ position. Additional study is needed to define fully the optimum conditions and the limitations of these reactions.

The dipotassium salt of ethyl acetoacetate has been prepared by addition of the ester to 2 equivalents of potassium amide in liquid ammonia.⁴ Alkylation with methyl iodide and ethyl bromide gave the γ -alkylated products in yields of 37% and 29%, respectively.⁴ These yields did not change significantly when the period during which the dianion was allowed to form was varied from a few minutes to an hour. Alkylation failed with *n*-butyl bromide and benzyl chloride. However, benzylation of ethyl disodioacetoacetate has been effected in low yield.²⁵



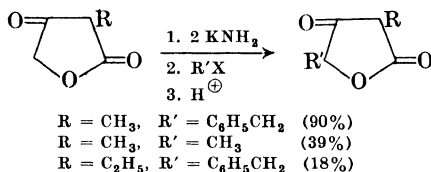
One possible explanation for the poor results obtained in these alkylations is that ethyl acetoacetate may be only partially converted to the dianion by amide ion. As a result, amide ion would be still present in the reaction mixtures to compete with dianion for the alkyl halide.

Alkylation of ethyl α,γ -diphenylacetoacetate has also been reported.⁴ The dipotassium salt with benzyl chloride gave, after decarboxylation, a 44% yield of 1,3,4-triphenyl-2-butanone. Alkylation is presumed to have occurred at the γ position, not at the α .



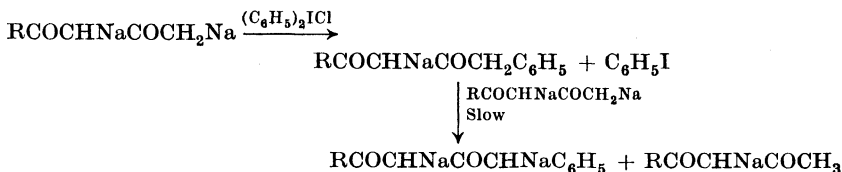
⁴⁶ J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Letters*, 4807 (1965).

Two substituted tetronic acids have been alkylated at the 5 position by means of their dipotassium salts. Three alkylations have been reported. The yields varied widely.²⁴



Arylations of β -Dicarbonyl Compounds (Table VIII)

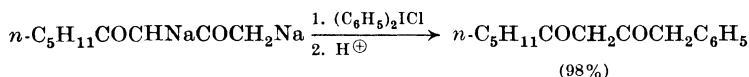
The arylation of dianions of β -dicarbonyl compounds has been investigated principally with β -diketones. The preferred method of phenylation and of most other arylations involves treatment of the disodium salt with the appropriate diaryliodonium chloride.¹¹ The reaction is mechanistically complex and appears to involve a single electron transfer (see p. 160). The stoichiometry is difficult to determine because the product-forming arylation reaction is followed by a slower proton transfer from the initial product to the disodiumdiketone leading to the eventual consumption of 2 equivalents of disodium salt. Although it has not been observed, the resulting anion could also conceivably undergo phenylation.



An additional problem in determining the proper stoichiometry of the reaction is that, under the reaction conditions, iodobenzene acts as a phenylating agent (see p. 161).¹¹ Thus between 1 and 2 equivalents of disodio- β -diketone are required for each equivalent of product produced, but possibly more than 1 equivalent of product is formed from each equivalent of diaryliodonium salt. This problem of stoichiometry leads to difficulty in the evaluation of yields. The yields reported in the next paragraph and in Table VIII are calculated on the basis of an assumed stoichiometry of 2:1 of disodio- β -diketone:diaryliodonium salt. This neglects the contribution of phenylation by iodobenzene, a contribution which can be estimated as no more than 10% of the total observed arylation.

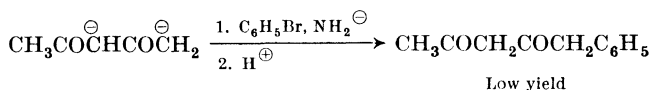
Phenylation of disodio- β -diketones by this method has been achieved in yields of 50–98%. *p*-Tolylation and *p*-chlorophenylation have been

accomplished with the corresponding 4,4'-dimethyldiphenyliodonium chloride and 4,4'-dichlorodiphenyliodonium chloride. The yields (21–44%) were somewhat less than those obtained in phenylation. With unsymmetrical aliphatic diketones of the methyl-methylene type, arylation at the methyl position was observed exclusively, as illustrated with 2,4-nonanedione.¹¹

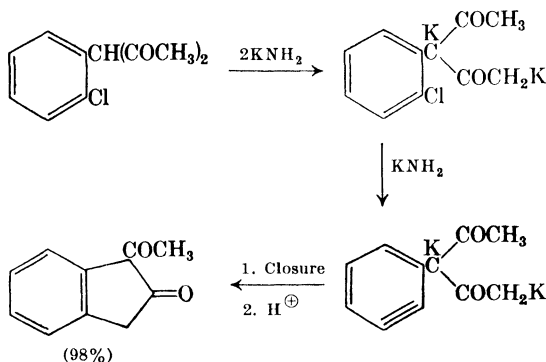


No arylations of the dianions of β -keto aldehydes or β -keto esters with diaryliodonium salts have been reported.

Phenylation of disodio- and dipotassio-acetylacetone with benzyne has been reported. Bromobenzene was added to a mixture of the dianion and amide ion in liquid ammonia. However, reactions other than phenylation of the dianion by benzyne apparently predominated inasmuch as the yields were only 13–18%.^{2, 11}

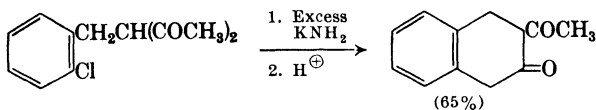


Arylations by most substituted bromobenzenes would be expected to be even poorer because mixtures of isomeric aromatic substitution products could arise. However, aryne phenylation is satisfactory when the arylation reaction is intramolecular and a ring closure is effected. One example of this is the ring closure of 3-(*o*-chlorophenyl)-2,4-pentanedione.⁴⁷

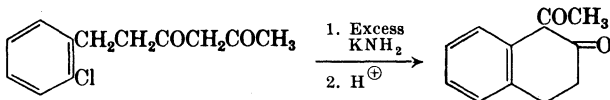


Another example of this reaction is the cyclization of 3-(*o*-chlorobenzyl)-2,4-pentanedione.⁴⁷

⁴⁷ T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **29**, 1391 (1964).

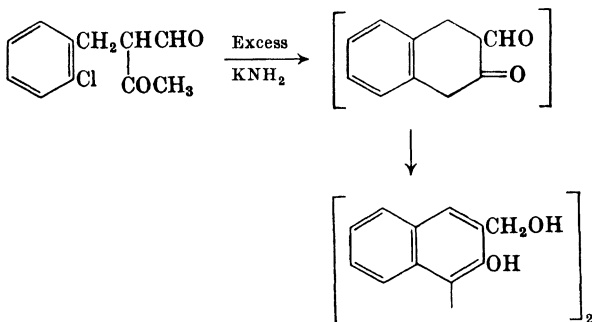


Interestingly, similar treatment of 6-(*o*-chlorophenyl)-2,4-hexanedione gave 1-acetyl-2-tetralone.⁴⁸ It is not known whether the cyclization



involved the monoanion or the dianion of the diketone. If the dianion is involved, this is an unusual situation in which steric conditions lead to preferential reaction of the normally unreactive α -methylene anion.

One cyclization involving a β -keto aldehyde has been reported. Although the initial cyclization probably proceeded normally, the resulting 3-formyl-2-tetralone underwent subsequent transformations leading to a binaphthol derivative under the conditions of the reaction and isolation.⁴⁷



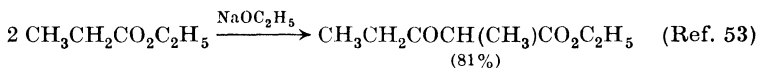
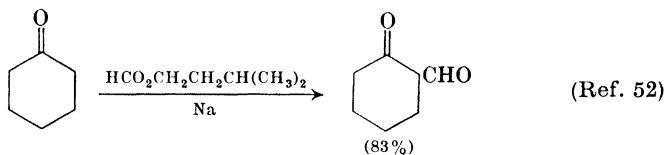
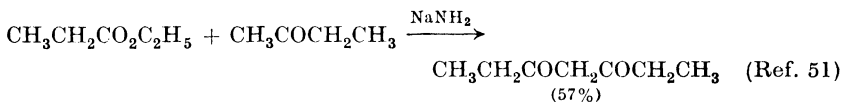
COMPARISON WITH OTHER METHODS

β -Dicarbonyl compounds have been prepared by a number of methods. Most important among these is the Claisen condensation. This, in its many modifications, has been used widely for the preparation of β -diketones, β -keto aldehydes, and β -keto esters. The scope of this reaction is summarized in two earlier volumes of *Organic Reactions*.^{49, 50} Examples are shown in the accompanying scheme.

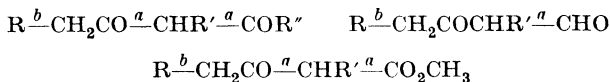
⁴⁸ J. F. Bunnett and J. A. Skorez, *J. Org. Chem.*, **27**, 3836 (1962).

⁴⁹ C. R. Hauser and B. E. Hudson, *Org. Reactions*, **1**, Chapter 9 (1942).

⁵⁰ C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, Chapter 3 (1954).



An important consideration in the comparison of the dianion alkylation reaction with the Claisen condensation and other synthetic methods is that the Claisen procedure and most other methods assemble dicarbonyl compounds by carbon-carbon condensations between a carbonyl group and the α-methylene carbon (points *a*). The dianion method, on the other hand, couples alkyl, aryl, and other groups to the γ position (points *b*) of existing dicarbonyl compounds. Thus the choice of synthetic routes is often dictated by the relative availability of starting materials. If the alkyl halide is more readily available than the corresponding alkylated acid or ketone, the dianion method will often be the preferred synthetic method.



γ-Alkylated Acetylacetones

For the preparation of β-diketones of the 1-alkylated 2,4-pentanedione type, alkylation of disodioacetylacetone is often preferable to Claisen condensations. The dianion reaction has to commend it the high yields that have been obtained and the absence of failures except with tertiary alkyl halides and certain very sensitive halides. In addition, acetylacetone and a multitude of the alkyl halides are readily available commercially.

Several basic reagents have been employed for effecting Claisen condensations. The most common is sodium, although sodium amide is probably of equal merit. The acetylation of an aliphatic methyl-methylene ketone occurs principally at the methyl group; however, self-condensation of the ester or of the ketone often competes. The product

⁵¹ J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).

⁵² H. Rupe and O. Klemm, *Helv. Chim. Acta*, **21**, 1539 (1938).

⁵³ S. M. McElvain, *J. Am. Chem. Soc.*, **51**, 3124 (1929).

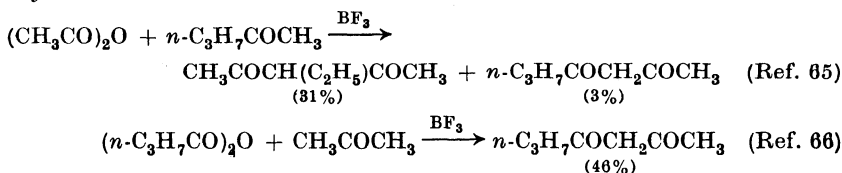
commonly is isolated by use of the copper chelate as an intermediate. A comparison of the yields obtained in the preparation of diketones of this type by the dianion method and by the base-catalyzed Claisen condensation method involving acylations of acetone with esters and of ketones with ethyl acetate is shown in Table II.

TABLE II. COMPARISON OF METHODS FOR PREPARATION OF 1-ALKYLATED 2,4-PENTANEDIONES

Diketone	Dianion Method		Ethyl Acetate, Ketone, and Na		Acetone, Ester, and Base		
	Yield (%)	Ref.	Yield (%)	Ref.	Yield (%) (Base)	Refs.	
C ₂ H ₅ COCH ₂ COCH ₃	59, 65	16	60	54	60	(NaNH ₂)	56
n-C ₃ H ₇ COCH ₂ COCH ₃	70	16	59	54	25	(Na)	59
(CH ₃) ₂ CHCH ₂ - COCH ₂ COCH ₃	66	16	64	55	—	—	—
n-C ₅ H ₁₁ COCH ₂ COCH ₃	67, 73	16	61*	56	65-80	(NaH)	60
n-C ₅ H ₁₁ COCH ₂ COCH ₃	77	26	69	57	—	—	—
n-C ₆ H ₁₃ COCH ₂ COCH ₃	66, 79	16	69	54	92	(NaH)	61, 62
CH ₂ =CHCH ₂ CH ₂ - COCH ₂ COCH ₃	65	26	Good	58	—	—	—
C ₆ H ₅ CH ₂ CH ₂ - COCH ₂ COCH ₃	73	16	—	—	35	(Na)	63

* NaNH_2 was used in this reaction.

The boron fluoride method for acylation of ketones has not been widely used for preparation of 1-alkyl-2,4-pentanediones. Acetylation of methyl-methylene type ketones occurs mainly on the methylene side to give 3-alkyl-2,4-pentanediones as shown in the accompanying scheme. There has been relatively limited experience with boron fluoride-catalyzed acylation of acetone.⁶⁴⁻⁶⁶



⁵⁴ C. Weygand and H. Baumgärtel, *Ber.*, **62**, 574 (1929).

⁵⁵ J. M. Sprague, L. J. Beckham, and H. Adkins, *J. Am. Chem. Soc.*, **56**, 2665 (1934).

⁵⁶ R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945).

⁵⁷ G. T. Morgan and E. Holmes, *J. Chem. Soc.*, **127**, 2891 (1925).

⁵⁸ G. Leser, *Bull. Soc. Chim. France*, [3] **27**, 64 (1902).

⁵⁹ G. T. Morgan, H. D. K. Drew, and C. R. Porter, *J. Chem. Soc.*, **125**, 737 (1924).

⁶⁰ F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).

⁶¹ V. L. Hansley, U.S. pat. 2,158,071 [C.A., **33**, 6342 (1939)].

⁶² V. L. Hansley, U.S. pat. 2,218,023 [C.A., **35**, 1066 (1941)].

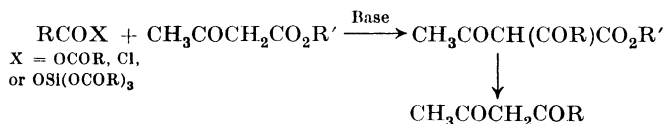
⁶³ G. T. Morgan and C. R. Porter, *J. Chem. Soc.*, **125**, 1273 (1924).

⁶⁴ C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 186 (1954).

⁶⁵ C. R. Hauser and J. T. Adams, *J. Am. Chem. Soc.*, **66**, 345 (1944).

⁶⁶ J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 284 (1945).

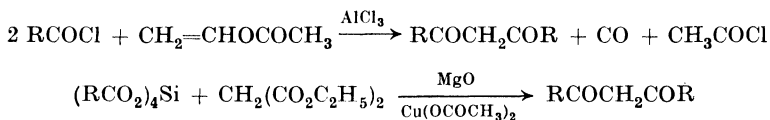
Other methods for the preparation of these diketones include acylation of ethyl or *t*-butyl acetoacetate to form diketo esters. The ester linkage is cleaved and decarboxylation is effected to give the corresponding diketone. Acylating agents include acid anhydrides, acid chlorides, and tetra-acyloxysilanes.⁶⁷⁻⁶⁹



Other Aliphatic Diacylmethanes

2,4-Pentanediones with one or more aliphatic substituents at both the 1 and the 5 position can be prepared by alkylation of the appropriate diketones through their dianions; the specificity of the alkylation of unsymmetrical diketones has been discussed on p. 166. The other major method for preparation of these compounds is by base-catalyzed Claisen condensations.⁵⁰ The Claisen procedure is often the one of choice when the appropriate esters and ketones are available, since the diketones can be prepared in one step. The dianion procedure requires the use of β -diketones as starting materials and hence often entails an additional step since relatively few β -diketones are commercially available. Nevertheless, because the yields that have been observed in the alkylation of the dianions of aliphatic diacylmethanes have been very good, this is an attractive method.

Special methods for the preparation of the symmetrical diacylmethanes include the aluminum chloride-catalyzed acylation of vinyl acetate with 2 equivalents of an acid chloride and the diacylation of diethyl malonate with tetra-acyloxysilanes.^{69, 70}



1-Phenyl-1,3-alkanediones

The γ alkylation products of benzoylacetone have been successfully prepared by the dianion method. Two examples of the advantageous

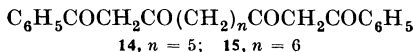
⁶⁷ W. H. Reeder and G. A. Lescisin, U.S. pat. 2,369,250 [C.A., **40**, 901 (1946)].

⁶⁸ A. Treibs and K. Hintermeier, *Chem. Ber.*, **87**, 1163 (1954).

⁶⁹ Y. K. Yur'ev and Z. V. Belyakova, *J. Gen. Chem. USSR (Eng. Trans.)*, **29**, 1432 (1959).

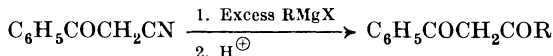
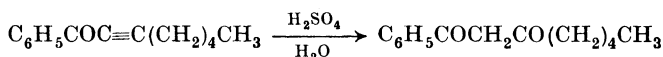
⁷⁰ A. Sieglitz and O. Horn, *Chem. Ber.*, **84**, 607 (1951).

use of the dianion procedure involve synthesis of the *bis*- β -diketones **14** and **15** in yields of 58% and 89%, respectively.²⁸



The alternative syntheses of these compounds by condensation of sodioacetophenone with pimelyl chloride and diethyl suberate have been effected in yields of 25% and 5%, respectively.⁷¹ For the preparation of most simple diketones the dianion method and the Claisen method are of equal merit, since the base- or boron fluoride-catalyzed acylation of acetophenone and the base-catalyzed acylation of ketones with methyl benzoate also usually occur in high yield.

In addition, hydration of phenyl acetylenic ketones⁷² and treatment of benzoylacetonitrile with Grignard reagents^{73, 74} have been employed in the synthesis of 1-phenyl-1,3-alkanediones. These routes are shown in the accompanying scheme.



α -Acyl Derivatives of Cyclic Ketones

α -Acetylcyclohexanone, α -acetylcyclopentanone, and presumably the α -acetyl derivatives of most other cyclic ketones undergo alkylation at the methyl position through the use of dianions (see p. 169). Higher acyl derivatives of cyclopentanone, but not of cyclohexanone, undergo condensations largely at the side chain methylene position (see p. 171).

Other methods for synthesizing diketones of this type include intermolecular Claisen condensations effected by strong bases or by boron fluoride and Dieckmann condensations.⁷⁵ Acylations of cyclopentanone under basic conditions are generally unsatisfactory because of rapid self-condensation of the cyclic ketone. (See reactions at top of p. 185.)

The acylation of enamines of cyclic ketones has been employed for the

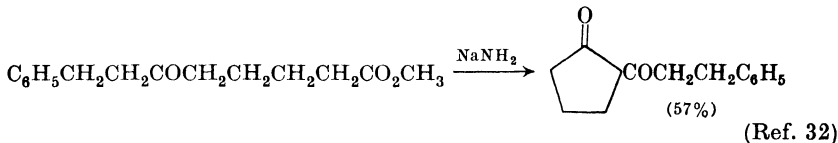
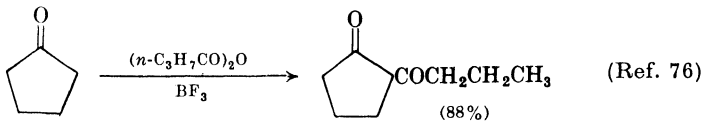
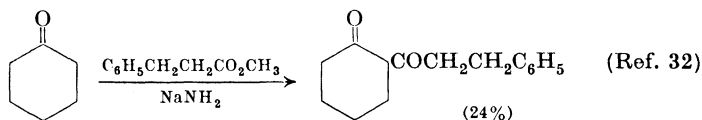
⁷¹ D. F. Martin, M. Shamma, and W. C. Fernelius, *J. Am. Chem. Soc.*, **80**, 4891 (1958).

⁷² C. Moureu and R. Delange, *Compt. Rend.*, **131**, 710 (1900).

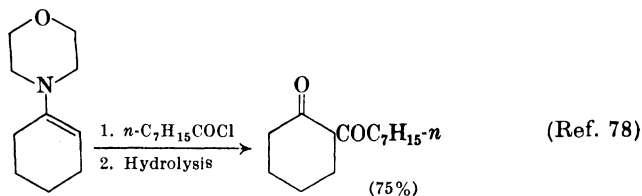
⁷³ C. E. Rehberg and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 2785 (1941).

⁷⁴ A. Mavrodin, *Bull. Soc. Chim. Romania*, **15**, 99 (1933) [*C.A.*, **28**, 3396 (1934)].

⁷⁵ J. P. Schaefer and J. J. Bloomfield, *Org. Reactions*, **15**, 1-203 (1967).

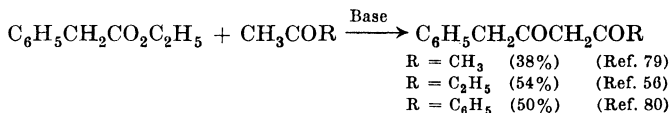


synthesis of α-acyl derivatives of cyclic ketones, although its practicality has not been established for acyclic systems.^{77, 78}



γ-Aryl Diketones

The use of diaryliodonium chlorides as arylating agents for β-diketones appears to be an excellent method for the preparation of γ-aryl diketones.¹¹ Certain of these compounds have also been prepared by the acylation of the appropriate ketone with ethyl phenylacetate in approximately 50% yield.



An attempted boron fluoride-catalyzed acylation of acetone with phenylacetic anhydride was unsuccessful.⁶⁶

⁷⁶ R. M. Manyik, F. C. Frostick, J. J. Sanderson, and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 5030 (1953).

⁷⁷ J. Szmuszkovicz, *Advan. Org. Chem.* **4**, 1-113 (1963).

⁷⁸ G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

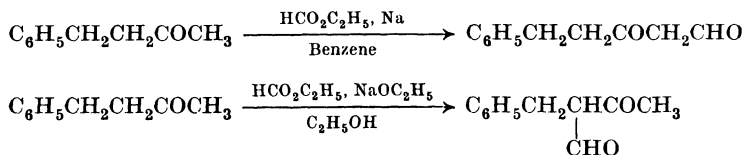
⁷⁹ G. T. Morgan and C. R. Porter, *J. Chem. Soc.*, **125**, 1271 (1924).

⁸⁰ C. Bülow and H. Grotowsky, *Ber.*, **34**, 1483 (1901).

Phenylacetone is not a suitable starting material for preparation of 1-phenyl-2,4-alkanediones since boron fluoride-catalyzed acylation occurs principally at the 1 position.⁸¹ Basic methods give a mixture of 1- and 3-acylation with a low combined yield.⁸²

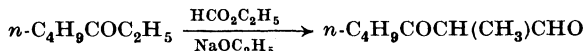
Acyclic β -Keto Aldehydes

The dianion procedure appears to be a highly effective method for preparation of acyclic β -keto aldehydes. One alternative method that has been widely used is the formylation of ketones with a formate ester and sodium or a sodium alkoxide.²² This is an excellent procedure with acetone and other symmetrical ketones. The point of formylation of unsymmetrical methyl-methylene ketones is reported to be dependent upon the acylation conditions.³⁵ In alcoholic solvents the point of formylation is predominantly the 3-methylene group, whereas in aprotic systems formylation at the 1 position usually predominates. However,



there are numerous reports that formylation in aprotic solvents does not give exclusive formation of the 1-formyl derivatives, and that significant amounts of the 3-formyl derivatives are also formed.^{21, 83-87}

For the synthesis of acyclic β -keto aldehydes with a single substituent at the α position, the dianion procedure provides a highly specific route. In the alternative procedure, formylation of an unsymmetrical ketone would in most cases be expected to occur on both sides of the carbonyl group with little specificity. Nevertheless formylation of one such ketone has been reported in which only one of the isomeric products was observed.⁸⁸



⁸¹ C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).

⁸² G. T. Morgan, H. D. K. Drew, and C. R. Porter, *Ber.*, **58**, 341 (1925).

⁸³ R. P. Mariella and E. Godar, *J. Org. Chem.*, **22**, 566 (1957).

⁸⁴ E. E. Royals and K. C. Brannock, *J. Am. Chem. Soc.*, **75**, 2050 (1953).

⁸⁵ E. E. Royals and K. C. Brannock, *J. Am. Chem. Soc.*, **76**, 1180 (1954).

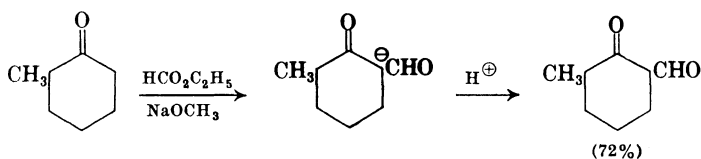
⁸⁶ R. P. Mariella and R. Stansfield, *J. Am. Chem. Soc.*, **73**, 1368 (1951).

⁸⁷ E. E. Royals and E. R. Covington, *J. Am. Chem. Soc.*, **77**, 3155 (1955).

⁸⁸ R. P. Mariella and V. Kvinge, *J. Am. Chem. Soc.*, **70**, 3126 (1948).

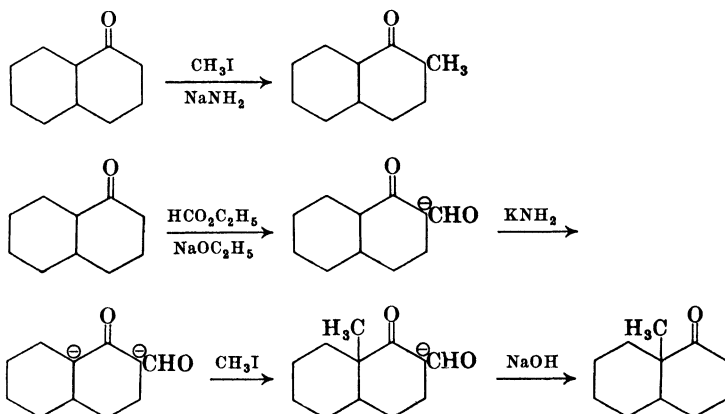
Formyl Derivatives of Alkylated Cyclic Ketones

The principal alternative to the alkylation of α -formyl derivatives of cyclic ketones through their dianions is the acylation of the corresponding alkylated cyclic ketones with formate esters. The latter reaction usually can be effected in high yield and is free of side reactions since base-catalyzed formylation is not observed at methinyl positions. For example, 2-methylcyclohexanone affords only one formylation product.⁸⁹



The shortcoming of the acylation reaction is that the α -alkylated cyclic ketones are often not readily available because direct alkylation of cyclic ketones usually affords mixtures of mono-, di-, and poly-alkylation products.^{34, 38-40}

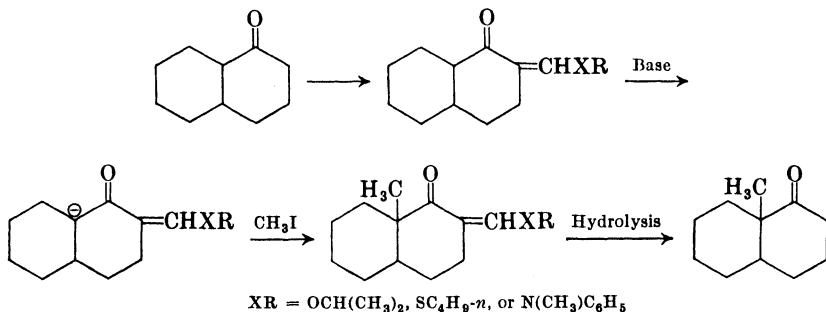
As a consequence of the difficulty associated with the direct synthesis of α -alkylated cyclic ketones, alkylation of the dianions of their formyl derivatives followed by removal of the formyl group provides a useful method for the preparation of these ketones. One example of the utility of the dianion procedure is in the preparation of 9-methyldecalone. Direct alkylation of decalone affords mainly the 2-methyl derivative.⁹⁰



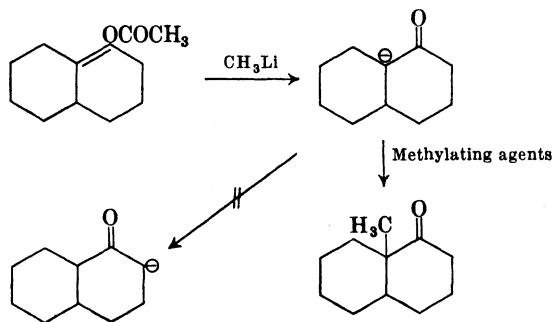
⁸⁹ W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

⁹⁰ J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 823 (1937).

Alternative procedures involve alkylating compounds in which the formyl group has been converted to an enol ether,⁸⁹ enol thioether,⁹¹ or enamine.⁹²



In addition the 9-anion of 1-decalone has been prepared by cleavage of 1-acetoxy- $\Delta^{1,9}$ -octalin with methyllithium.⁹³ Because under aprotic conditions the 9-anion is not in equilibrium with the 2-anion, exclusive 9-alkylation can be effected.



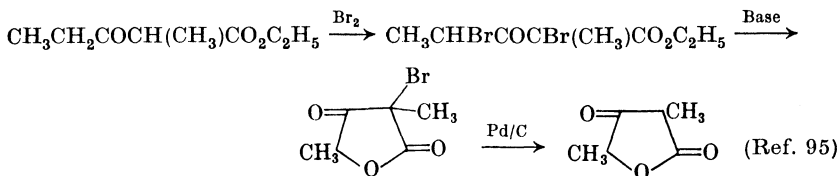
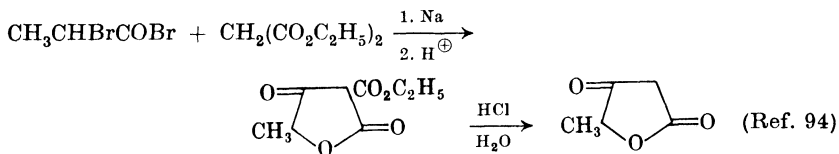
β -Keto Esters

The alkylation of dianions derived from simple β -keto esters has not yet been widely explored, and only limited success has been achieved in the alkylation of ethyl acetoacetate, the simplest member of the series.⁴ The preparation of β -keto esters by the acylation of esters was reviewed in Volume 1 of *Organic Reactions*.⁴⁹ The use of the dianion reaction for the preparation of 5-alkyltetronic acids appears to be practical.²⁴ Some alternative syntheses of these compounds are by the following routes.

⁹¹ R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

⁹² A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

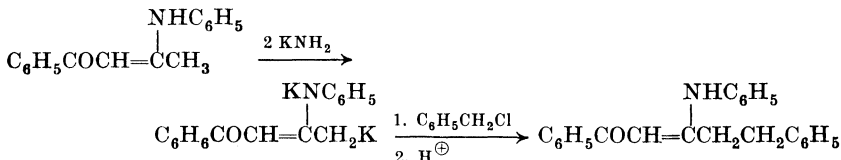
⁹³ H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).



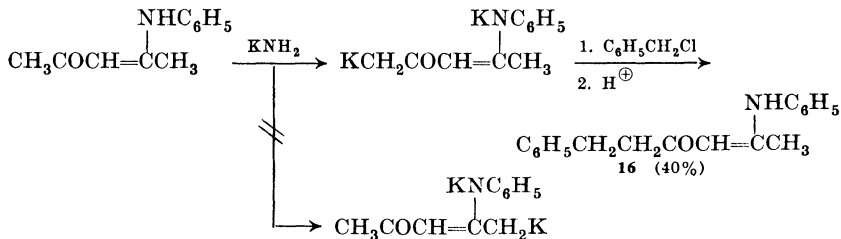
RELATED MULTIPLE ANIONS OF CARBONYL COMPOUNDS

Dianion formation from several compounds closely related to β -diketones has been investigated. Certain of these dianions have been alkylated.

The amino analogs of β -diketones have been studied briefly. The product arising from condensation of aniline and benzoylacetone at the acetyl carbonyl group was alkylated at the methyl position in 63% yield via the dipotassium salt.⁹⁶



The reaction of the anilino derivative of acetylacetone was also investigated. Secondary ionization of this compound apparently occurred at the methyl group adjacent to the carbonyl group in preference to that next to the anilino group, since treatment of the dipotassium salt with benzyl chloride gave only the corresponding benzylation product **16**.⁹⁶



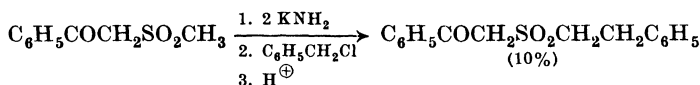
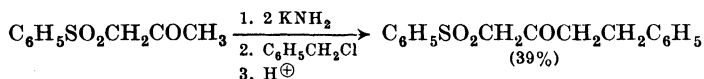
⁹⁴ E. Benary, *Ber.*, **44**, 1759 (1911).

⁹⁵ N. M. Chopra, W. Cooker, B. E. Cross, J. T. Edward, D. H. Hayes, and H. P. Hutchison, *J. Chem. Soc.*, 594 (1955).

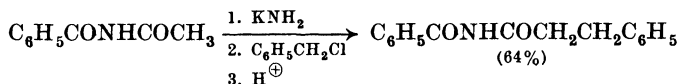
⁹⁶ S. Boatman and C. R. Hauser, *J. Org. Chem.*, **31**, 1785 (1966).

The condensation products of methylamine with acetylacetone and with benzoylacetone were not successfully converted to dianions under comparable conditions.⁹⁶ Presumably the phenyl group of the anilino compounds participated in charge delocalization of the dipotassium salts.

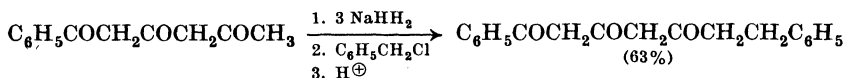
A sulfone analog of benzoylacetone, phenylsulfonylacetone, has been alkylated in fair yield at the terminal position.⁹⁷ The isomeric 2-methylsulfonylacetophenone has been alkylated similarly. The reaction failed in liquid ammonia, but a low yield was obtained in a mixture of ammonia and pyridine.⁹⁸



N-Benzoylacetamide has been benzylated at the methyl position. Other imides have been alkylated similarly.⁹⁹



Some 1,3,5-triketones are capable of conversion to trianions by treatment with 3 equivalents of alkali amide. Again, the least stabilized anion is the site of alkylation.^{100, 101}



A similar result has been obtained with dehydracetic acid. Aldol condensations occur at the acetyl position by means of piperidine catalysis.¹⁰² When dehydracetic acid is treated with 3 equivalents of sodium amide, ionization of the hydroxyl hydrogen, an acetyl hydrogen, and a 6-methyl hydrogen occur to form a tri-anion. The 6-methyl anion is most reactive, and condensations with *n*-propyl bromide, benzophenone, and methyl benzoate occur at that position.¹⁰³

⁹⁷ W. I. O'Sullivan, D. F. Tavares, and C. R. Hauser, *J. Am. Chem. Soc.*, **83**, 3453 (1961).

⁹⁸ N. M. Carroll and W. I. O'Sullivan, *J. Org. Chem.*, **30**, 2830 (1965).

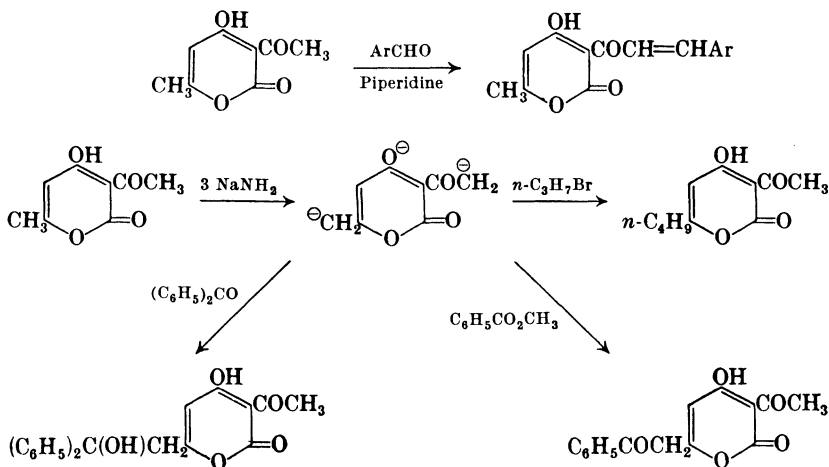
⁹⁹ S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Am. Chem. Soc.*, **86**, 872 (1964).

¹⁰⁰ K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).

¹⁰¹ T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.*, **89**, 6734 (1967).

¹⁰² R. H. Wiley, C. H. Jarboe, and H. G. Ellert, *J. Am. Chem. Soc.*, **77**, 5102 (1955).

¹⁰³ T. M. Harris and C. M. Harris, *Chem. Commun.*, 699 (1966).



EXPERIMENTAL CONDITIONS

The amides of the three common alkali metals, lithium, sodium, and potassium, have all been employed for the preparation of the dianions of diketones, but only the last two have been used with keto aldehydes and keto esters. Dilithioacetylacetone has been alkylated, but the reaction proceeds too slowly to be generally practical.¹⁶ Although sodium amide and potassium amide are of equal usefulness for the alkylation of many dicarbonyl compounds, sodium amide is preferred for alkylation of acetylacetone for reasons discussed on p. 163. In general the disodium salt of the dicarbonyl compound is preferred over the dipotassium salt whenever proton transfer to the dianion from other carbonyl compounds or from ammonia competes substantially with alkylation.

The effective stoichiometry of the alkylation reaction should be considered. The ratio of alkali amide to dicarbonyl compound must be carefully regulated. Insufficient alkali amide leads to incomplete conversion of monoanion to dianion. Excess alkali amide reacts with alkyl halide, probably as fast as or faster than does the dianion. Excess alkyl halide can be employed without causing dialkylation to occur since the monoanion is not sufficiently reactive for secondary alkylation at the α -methylene group. However, because most dianions are highly reactive, excess alkyl halide usually serves no useful purpose because the reactions are complete within a few minutes.

Moisture and carbon dioxide contamination of the reaction mixture reduces the amount of base present, thereby reducing the yield. In most reactions it is probably desirable to use about 10% excess of alkali

amide, followed by a corresponding excess of alkyl halide to minimize losses from these sources.

With few exceptions, alkylations have been conducted in liquid ammonia or liquid ammonia containing some diethyl ether or tetrahydrofuran at the normal boiling point of the solution. Diethyl ether alone has been reported to be a somewhat inferior solvent for alkylation, and low yields were obtained despite the higher reaction temperature.²⁶ The use of pyridine as a solvent has been reported to give good results with 3-phenyl-2,4-pentanedione; the dianion was too insoluble in ammonia for alkylation to proceed at a reasonable rate.⁴³

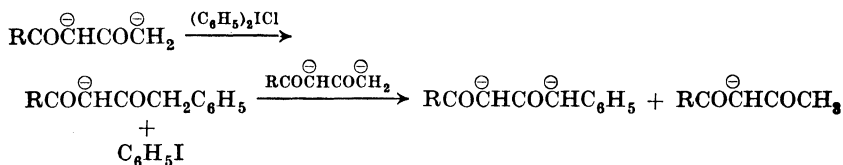
In some diketone alkylations the reaction mixtures have been neutralized with ammonium chloride before evaporation of the ammonia. In others this step has been omitted. It is not clear whether neutralization in this manner serves any definite purpose.

In the alkylation of diketones the products have usually been isolated by addition of diethyl ether and dilute hydrochloric acid to the residue that remained after evaporation of the liquid ammonia. The ethereal solution was collected and the aqueous solution re-extracted with ether to remove dissolved diketone. The combined ethereal extracts were dried and evaporated to afford in most cases relatively pure product. Further purification has been effected by distillation or recrystallization.

Initial isolation as a copper chelate has generally not been necessary. This is in contrast to the base-catalyzed Claisen condensations where preparation of the copper chelates has often been required for adequate purification of the reaction products.

In the alkylation of keto aldehydes the reaction mixtures have not been treated with ammonium chloride because it is advantageous to keep the keto aldehydes as monoanions to avoid self-condensation or reaction with ammonia. The alkylation products of α -substituted keto aldehydes have been isolated by acidification of the salts that remained after evaporation of the ammonia. When an α -substituent was not present, acidification yielded the unstable keto aldehydes which gradually underwent self-condensation to form 1,3,5-triacylbenzenes. However, in most cases the products have been converted directly to derivatives. Treatment of the residual salts with copper acetate, cyanoacetamide, or alkali afforded the copper chelates, 3-cyano-2-pyridones, or de-formylated ketones, respectively.

The optimum conditions for arylations of β -diketones with diaryliodonium salts are not so well defined as are the conditions for alkylation reactions. The molar ratio of reactants that has been employed is 4:2:1 of sodium amide, diketone, and diaryliodonium salt.¹¹ This ratio is based on the theoretical reaction sequence in the accompanying scheme.



This reaction sequence is not totally accurate in that some phenylation probably occurs by means of the iodobenzene and the second step, conversion of the phenylation product to dianion, is relatively slow. Evidence for this has been discussed on p. 161. These complications are believed to be of minor importance, and the yields in Table VIII have been calculated on the basis of this stoichiometry.

The arylated diketones have been isolated by procedures similar to those employed with alkylated diketones. It has sometimes been found useful to wash the ethereal solution of the product with sodium thiosulfate solution if the product is contaminated with iodine.

EXPERIMENTAL PROCEDURES

2,4-Nonanedione.* A suspension of sodium amide (1.1 moles) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with an air condenser, a ball-sealed mechanical stirrer, and a glass stopper. In the preparation of this reagent, commercial, anhydrous, liquid ammonia (800 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color, a few crystals of ferric nitrate hexahydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 25.3 g. (1.1 g. atoms) has been added.

After the sodium amide formation is complete, as indicated by the disappearance of the blue color, the glass plug is replaced by a pressure-compensated addition funnel containing 60.0 g. (0.60 mole) of acetylacetone in 40 ml. of anhydrous diethyl ether. The top of the addition funnel is fitted with a nitrogen inlet tube. The reaction flask is immersed at least 3 in. into a dry ice-acetone bath, and simultaneously the slow introduction of dry nitrogen through the inlet tube is begun. After the reaction mixture is thoroughly cooled (about 20 minutes), acetylacetone is added intermittently in small portions over 10 minutes. The acetylacetone should be added in spurts which fall on the surface of the reaction mixture rather than on the wall of the flask. The cooling bath is removed and,

* This procedure is adapted from that of Hampton, Harris, and Hauser¹⁰⁴ which appears in *Organic Syntheses*.¹⁰⁴

¹⁰⁴ K. G. Hampton, T. M. Harris, and C. R. Hauser, *Org. Syntheses*, **47**, 92 (1967).

after 20 minutes, the nitrogen purge is stopped and 68.5 g. (0.50 mole) of *n*-butyl bromide in 40 ml. of anhydrous diethyl ether is introduced dropwise during 10–20 minutes. The addition funnel is rinsed with a small volume of anhydrous ether, which is added to the reaction mixture.

After 30 minutes, 400 ml. of anhydrous ether is added, and the ammonia is removed by cautious heating on the steam bath. Addition of 200 g. of crushed ice causes a thick slurry to form. Next a mixture of 60 ml. of concentrated hydrochloric acid and 10 g. of crushed ice is added. The reaction mixture is stirred until all solids are dissolved, then transferred to a separatory funnel, the flask being washed with a little ether and dilute hydrochloric acid. The ether layer is separated, and the water layer, which should be acidic, is further extracted three times with 100-ml. portions of ether. The combined ethereal extracts are dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, the residue is distilled through a 12-in. Vigreux column to give initially a small forerun, b.p. 32–110°/19 mm., principally acetylacetone, and then 63.0–63.6 g. (81–82%) of 2,4-nonanedione, b.p. 100–103°/19 mm., as a colorless liquid.

The addition of acetylacetone to liquid ammonia is highly exothermic. Moreover ammonia vapor reacts with the β -diketone to produce an insoluble ammonium salt, which tends to clog the tip of the addition funnel. Cooling the reaction mixture to dry ice temperature reduces the vigor of the reaction and minimizes the clogging of the addition funnel.

Other methods have also been employed to add acetylacetone to sodium amide in liquid ammonia. They include addition of the ammonium salt of the diketone^{2, 26} and the direct addition of the diketone.⁶ The latter procedure has been employed satisfactorily when the diketone is added in a fine stream from a syringe.¹⁵ Other diketones do not offer this problem.

1,12-Diphenyl-1,3,10,12-dodecanetetrone (Alkylation with a Di-halide).²⁸ To a suspension of 0.2 mole of sodium amide in 400–700 ml. of liquid ammonia, prepared as described on p. 193, 16.2 g. (0.10 mole) of benzoylacetone is added in solid form from an Erlenmeyer flask through Gooch tubing. After 30 minutes a solution of 10.8 g. (0.05 mole) of tetramethylene bromide in 20 ml. of diethyl ether is added during 10 minutes. After 1 hour an additional 250 ml. of diethyl ether is added, and the reaction mixture is placed on a steam bath. When the liquid ammonia has evaporated, the resulting suspension is cooled to about 10° and a mixture of 100 g. of crushed ice and 60–80 ml. of cold, concentrated hydrochloric acid is added. A portion of the product crystallizes and is collected by filtration. The two layers of the filtrate are separated. The ethereal layer is combined with three ethereal extracts of the aqueous

layer and the solvent is evaporated. The residue is combined with the previously collected solid and recrystallized from a mixture of benzene and methanol to give 16.8 g. (89%) of 1,12-diphenyl-1,3,10,12-dodecanetetrone, m.p. 108–109°.

Copper Chelate of 5-Phenyl-1,3-pentanedione.²¹ Sodioacetoacetaldehyde is prepared in the following manner. In a 2-l. three-necked flask equipped with a calcium chloride drying tube, a nitrogen inlet tube, and a ball-sealed mechanical stirrer are placed 43 g. (0.8 mole) of sodium methoxide and 1 l. of anhydrous diethyl ether. The flask is purged with dry nitrogen and cooled with an ice bath. The inlet tube is replaced by a pressure-compensated addition funnel containing 49.3 g. (0.85 mole) of acetone and 74.0 g. (1.0 mole) of ethyl formate. The solution is added over 15 minutes and the funnel is then replaced by the nitrogen inlet tube. The reaction mixture is allowed to warm to room temperature and then to stand for 10 hours. The thick suspension is filtered with suction and the filter cake washed with ether. A rubber dam is secured tightly over the top of the funnel. It is pulled down onto the surface of the filter cake by the suction to protect the salt from atmospheric moisture. After most of the solvent has been removed, the salt is dried further in a vacuum oven at about 70°, powdered, and stored in a tightly capped bottle. The solid must be finely powdered to allow complete reaction in the following procedure; this is most easily accomplished if the powdering is done before the solid is completely dry. The fine powder is returned to the vacuum oven for completion of drying. Approximately 75 g. (87%) of sodioacetoacetaldehyde is obtained. It can be stored without apparent decomposition if protected from moisture.

In a 500-ml. three-necked flask equipped with a vapor-tight stirrer, an air condenser, and a glass stopper is placed 250 ml. of commercial, anhydrous, liquid ammonia. A minimum amount of potassium is added to the stirred solution to produce a permanent blue color. To the liquid is added approximately 0.05 g. of hydrated ferric chloride followed by 4.3 g. (0.11 g. atom) of potassium. The resulting dark blue solution of potassium is converted to a colorless solution of potassium amide in 10–30 minutes.

To the potassium amide solution is added cautiously 10.8 g. (0.10 mole) of sodioacetoacetaldehyde by means of a powder funnel. An olive green solution is formed. After 15 minutes, 13.9 g. (0.11 mole) of benzyl chloride is added. During the early part of the addition of benzyl chloride, the reaction develops a dark purple coloration, indicating formation of stilbene. This color disappears before more than about 15% of the halide has been added. The mix
the ammonia is evaporated as

added. The resulting suspension is shaken with 125 ml. of cold water and, after most of the suspended material has dissolved, the two layers are separated. The ether layer is extracted twice with water, and the aqueous solutions are combined and washed once with ether.

The aqueous solution, which contains the monoanion of 5-phenyl-1,3-pentanedione, is added to 200 ml. of saturated aqueous cupric acetate to which 6.6 g. (0.11 mole) of acetic acid has been added. The resulting heavy grey-blue precipitate which immediately forms is separated by extractions with chloroform (4×100 ml.). The chloroform solutions are combined and dried over magnesium sulfate. The solvent is evaporated and the residue is recrystallized from a mixture of ethanol and chloroform to give 16.5 g. (80%) of fairly pure copper chelate of 5-phenyl-1,3-pentanedione, m.p. 171–174°. Recrystallization from a mixture of chloroform and ethanol gives with good recovery dark blue plates, m.p. 176–178°.

The monoanion of 5-phenyl-1,3-pentanedione can be converted to a pyridone. Cyanoacetamide (6 g., 0.072 mole) and piperidinium acetate (0.5 g.) are added to an aqueous solution of the monoanion (derived from 0.056 mole of the dianion of acetoacetaldehyde and 7.08 g. (0.056 mole) of benzyl chloride). The solution is heated under reflux for 2 hours, cooled, and acidified with acetic acid to give 9.6 g. (73%) of 6-phenethyl-3-cyano-2(1)-pyridone, m.p. 186–190°. The melting point is raised to 204–205° by recrystallization from a mixture of acetone and ethanol.

2-*n*-Butyl-2-methylcyclohexanone (Formylation, Alkylation, and Removal of the Formyl Group).¹⁰⁵ A mixture of 123.2 g. (1.1 moles) of 2-methylcyclohexanone and 81.4 g. (1.1 moles) of ethyl formate is added dropwise (rapidly) to a stirred suspension of 54 g. (1.0 mole) of commercial, methanol-free sodium methoxide in 2 l. of anhydrous diethyl ether at 0–10°. After the addition is complete, the mixture is stirred for 15 minutes at this temperature and then for 12 hours at room temperature. Preferably the formylation is conducted under a dry nitrogen atmosphere. The thick suspension is filtered by suction, and the filter cake is washed with anhydrous ether, care being taken to protect the product from atmospheric moisture. The salt is partially dried in a vacuum oven at 70°, powdered, dried completely, and stored in a tightly capped bottle. Sodio-2-formyl-6-methylcyclohexanone, a cream-colored powder, is obtained in 80–85% yield (130–138 g.).

In a 1-l. three-necked flask equipped with a dry ice condenser and a ball-sealed mechanical stirrer is placed 700 ml. of commercial, anhydrous,

¹⁰⁵S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Syntheses* **48**, 40 (1968). This procedure is a modification of the procedure discussed in reference ²⁸

liquid ammonia. A solution of 0.18 mole of potassium amide is prepared from 7.0 g. of potassium by the method described on p. 195. To the solution is added through a powder funnel 24.9 g. (0.15 mole) of sodio-2-formyl-6-methylcyclohexanone. The escaping ammonia blows away some of the finely powdered salt if the addition is not made carefully.

After 1 hour, a solution of 27.4 g. (0.2 mole) of *n*-butyl bromide in 50 ml. of anhydrous ether is added dropwise through a pressure-compensated addition funnel. The mixture is stirred for 3 hours, the dry ice condenser is replaced with a water-cooled condenser, and the ammonia is then evaporated carefully on a steam bath as 400 ml. of anhydrous ether is added. After the ether has been heated under reflux for 5 minutes, 100 g. of ice is added cautiously, followed by 300 ml. of cold water. When the solid has dissolved, the layers are separated, and the ether layer is extracted twice with 50-ml. portions of cold water.

The combined water layers are placed in a round-bottomed flask equipped with an efficient water condenser, and 6.4 g. of sodium hydroxide is added. The mixture is warmed to about 60° and the condenser is removed briefly to allow ether vapor to escape. The condenser is replaced and the mixture is heated under reflux until an acidified aliquot no longer gives a red color with ethanolic ferric chloride. The mixture is cooled and extracted with three 200-ml. portions of ether. The combined ethereal extracts are washed with dilute hydrochloric acid and dried over anhydrous magnesium sulfate. The ether is evaporated and the residue is distilled at reduced pressure to give 17–19 g. (67–75%) of 2-*n*-butyl-2-methylcyclohexanone, b.p. 116–118°/20 mm. A higher-boiling fraction of 2-formyl-6-*n*-butyl-6-methylcyclohexanone, b.p. 201–203°/20 mm., will be obtained if sufficient time is not allowed for hydrolysis.

An alternative isolation procedure involves steam distillation of the basic aqueous solution of the alkylation product until no further organic material distills. This may be done either after or instead of boiling the basic solution. The steam distillate is extracted with ether; the ethereal solution is dried, evaporated, and the residue distilled.

1-Phenyl-2,4-pentanedione (Arylation with Diphenyliodonium Chloride).¹¹ Diphenyliodonium chloride is prepared from benzene, potassium iodate, sulfuric acid, and acetic anhydride by the method of Beringer and co-workers.¹⁰⁶ The salt is recrystallized from methanol to give colorless crystals, m.p. 225–226°.

A solution of 0.1 mole of disodioacetylacetone is prepared from 10.0 g. of acetylacetone and 0.2 mole of sodium amide in 600 ml. of liquid ammonia as described on p. 193. During 5–10 minutes 15.8 g. (0.05 mole) of diphenyliodonium chloride is added to the solution through Gooch

¹⁰⁶ F. M. Beringer, E. J. Geering, I. Kuntz, and M. Mausner, *J. Phys. Chem.*, **60**, 141 (1956).

tubing from an Erlenmeyer flask. After 1 hour, 500 ml. of diethyl ether is added to the suspension while the ammonia is carefully evaporated on the steam bath. The ether suspension is heated under reflux for 1 hour, cooled in an ice bath, and 100 g. of ice and 20 ml. of concentrated hydrochloric acid are added. The ethereal layer is separated and the aqueous layer is extracted several times with diethyl ether. If the combined ethereal solution contains iodine and appears very dark, it should be extracted with aqueous sodium thiosulfate until no further diminution of color occurs. The ethereal solution is dried with magnesium sulfate, filtered, and the ether removed. The residual liquid is distilled under reduced pressure to give 8.1 g. (92%) of 1-phenyl-2,4-pentanedione, b.p. 138–141°/13 mm. The crude reaction mixture contains traces of benzene, biphenyl, and 3-phenyl-2,4-pentanedione, as indicated by gas chromatography.

TABULAR SURVEY

Tables III through VIII list examples of alkylation and arylation of the dianions of dicarbonyl compounds which were reported before October 1966. Certain results reported after this date are also included.

In each table the entries are in order of increasing number of carbon atoms in the dianion being alkylated, and, for a given dianion, in order of increasing number of carbon atoms in the halide.

TABLE III. ALKYLATIONS OF ACETYLACETONE DIANION

Alkyl Halide	Alkali Amide	Product(s)	Yield, (%)	Refs.
CH_3I	NaNH_2 KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}_3$ $\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{COCH}_2\text{COCH}_2\text{CH}_3$	59, 65 35, 46 26, 18	16 16
CH_2Cl_2	NaNH_2	Alkylation failed	—	28
$\text{C}_2\text{H}_5\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_2\text{H}_5$	70	16
$\text{ClCH}_2\text{CH}_2\text{Cl}$	NaNH_2	Alkylation failed	—	28
$\text{BrCH}_2\text{CH}_2\text{Br}$	NaNH_2	Alkylation failed	—	28
$n\text{-C}_3\text{H}_7\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_3\text{H}_7$	77	15
$i\text{-C}_3\text{H}_7\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_3\text{H}_7$	66	16
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_3\text{H}_7$	27	26
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}=\text{CH}_2$	65	26
$\text{CH}_2=\text{CHCH}_2\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2(\text{CH}_2)_3\text{CH}_2\text{COCH}_2\text{COCH}_3$	69-78	28
$\text{Br}(\text{CH}_2)_3\text{Br}$	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2(\text{CH}_2)_3\text{CH}_2\text{COCH}_2\text{COCH}_3$	40	28
	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	—	20
$n\text{-C}_4\text{H}_9\text{Cl}$	LiNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	25	16
$n\text{-C}_4\text{H}_9\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	67-82	11, 16, 20, 31, 104
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	68	26
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$ + $n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	43, 53 16, 14	16
$n\text{-C}_4\text{H}_9\text{I}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	—	20
$i\text{-C}_4\text{H}_9\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	78	16, 20
$\text{sec-C}_4\text{H}_9\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_4\text{H}_9$	78	16, 20
$t\text{-C}_4\text{H}_9\text{Cl}$	KNH_2	Alkylation failed	—	26
$\text{Br}(\text{CH}_2)_4\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2(\text{CH}_2)_4\text{CH}_2\text{COCH}_2\text{COCH}_3$	80	28
$\text{CH}_3\text{COCHClCOCH}_3$	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}(\text{COCH}_3)_2$	Low	30, 30a

TABLE III. ALKYLATIONS OF ACETYLACETONE DIANION (Continued)

Alkyl Halide	Alkali Amide	Product(s)	Yield, (%)	Refs.
$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{Br}$	KNH_2	Alkylation failed	—	30a
$n\text{-C}_6\text{H}_{13}\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_{13}\text{-}^n$	69	101
$n\text{-C}_7\text{H}_{15}\text{Br}$	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_7\text{H}_{15}\text{-}^n$	77	26
$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	LiNH_2	Alkylation failed	—	26
	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$	69-73	16, 26
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$	60	2, 26
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5 +$ $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$	41, 39	16
		$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_8\text{H}_{17}\text{-}^n$	22, 16	
$n\text{-C}_8\text{H}_{17}\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_8\text{H}_{17}\text{-}^n$	66, 79	16
	KNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_8\text{H}_{17}\text{-}^n +$ $n\text{-C}_8\text{H}_{17}\text{CH}_2\text{COCH}_2\text{COCH}_2\text{C}_8\text{H}_{17}\text{-}^n$	31-67	26, 16
		Alkylation failed	14-42	
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{Cl}$	KNH_2	Alkylation failed	—	26
$o\text{-C}_6\text{H}_4(\text{CH}_2\text{Br})_2$	KNH_2	Alkylation failed	—	29
$m\text{-C}_6\text{H}_4(\text{CH}_2\text{Br})_2$	KNH_2	Alkylation failed	—	29
$p\text{-C}_6\text{H}_4(\text{CH}_2\text{Br})_2$	KNH_2	Alkylation failed	—	29
$\text{Br}(\text{CH}_2)_3\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2(\text{CH}_2)_3\text{CH}_2\text{COCH}_2\text{COCH}_3$	81	28
$\text{Br}(\text{CH}_2)_{10}\text{Br}$	NaNH_2	$\text{CH}_3\text{COCH}_2\text{COCH}_2(\text{CH}_2)_{10}\text{CH}_2\text{COCH}_2\text{COCH}_3$	73	28
$(\text{C}_6\text{H}_5)_2\text{CHCl}$	KNH_2	Alkylation failed	—	26
$(\text{C}_6\text{H}_5)_2\text{CCl}_2$	NaNH_2	Alkylation failed	—	28

TABLE IV. ALKYLATIONS OF THE DIANIONS OF UNSYMMETRICAL ALIPHATIC AND ALCYCLIC DIKETONES

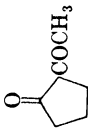

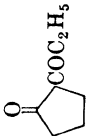


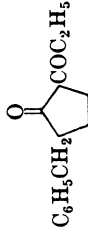
Diketone	Alkali Amide	Alkyl Halide	Product(s)	Yield (%)	Refs.
$C_2H_5COCH_2COCH_3$	$NaNH_2$	CH_3I	$C_2H_5COCH_2COCH_2CH_3 + (CH_3)_2CHCOCH_2COCH_3$	56-66	31
	KNH_2	CH_3I	$C_2H_5COCH_2COCH_2CH_3 + (CH_3)_2CHCOCH_2COCH_3$	—	31
$i-C_3H_7COCH_2COCH_3$	$NaNH_2$	CH_3I	$i-C_3H_7COCH_2COCH_2CH_3 + (CH_3)_3CCOCH_2COCH_3$	56	31
	KNH_2	$C_6H_5CH_2Cl$		62	32
$i-C_3H_7COCH_2COC_2H_5$	$NaNH_2$	CH_3I	$i-C_3H_7COCH_2COCH(CH_3)_2 + (CH_3)_3CCOCH_2COC_2H_5$	58	31
	$NaNH_2$	$n-C_4H_9Br$		60	36
	KNH_2	$C_6H_5CH_2Cl$		63	37
Principal isomer					
					

TABLE IV. ALKYLATIONS OF THE DIANIONS OF UNSYMMETRICAL ALIPHATIC AND ALCYCLIC DIKETONES (Continued)

Diketone	Alkali Amide	Alkyl Halide	Product(s)	Yield (%)	Refs.
	KNH ₂	C ₆ H ₅ CH ₂ Cl		58	32
<i>n</i> -C ₅ H ₁₁ COCH ₂ COCH ₃	NaNH ₂	C ₂ H ₅ Br	<i>n</i> -C ₅ H ₁₁ COCH ₂ COCH ₂ C ₂ H ₅	70	16
	NaNH ₂	<i>n</i> -C ₄ H ₉ Br	<i>n</i> -C ₅ H ₁₁ COCH ₂ COCH ₂ C ₄ H ₉ · <i>n</i>	68	16
	KNH ₂	C ₆ H ₅ CH ₂ Cl	<i>n</i> -C ₅ H ₁₁ COCH ₂ COCH ₂ CH ₂ C ₆ H ₅	52	26
	NaNH ₂	<i>n</i> -C ₄ H ₉ Br	+	82	36
			55:45		
	KNH ₂	C ₆ H ₅ CH ₂ Cl	+	69	37

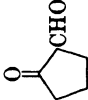
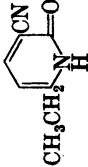

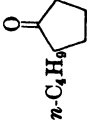

$C_6H_5CH_2COCH_2COCH_3$	$NaNH_2$	CH_3I	$C_6H_5CH(CH_3)COCH_2COCH_3$	—	31
	$NaNH_2$	$n-C_4H_9Br$	$C_6H_5CH(C_4H_9-n)COCH_2COCH_3$	77	11, 20, 31
	$NaNH_2$	$C_6H_5CH_2Cl$	$C_6H_5CH(CH_2C_6H_5)COCH_2COCH_3$	77	31
	$NaNH_2$	$C_6H_5CHClCH_3$	$C_6H_5CH(CH_3)CH(C_6H_5)COCH_2COCH_3$ (erythro)	44	18a
$C_6H_5CH_2CH_2COCH_2COCH_3$	KNH_2	$n-C_4H_9Br$	$C_6H_5CH_2CH_2COCH_2COCH_2C_4H_9-n$	67	26
	$NaNH_2$	$Br(CH_2)_4Br$	$C_6H_5CH_2CH_2COCH_2COCH_2(CH_2)_4-$ $CH_2COCH_2COCH_2CH_2C_6H_5$	38	28
$n-C_9H_{19}COCH_2COCH_3$	KNH_2	$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_2COCH_2COCH_2CH_2C_6H_5$	59	32
	KNH_2	$C_6H_5CH_2Cl$	$n-C_9H_{19}COCH_2COCH_2CH_2C_6H_5$	52	26
	KNH_2	$n-C_8H_{17}Br$	$n-C_8H_{19}COCH_2COCH_2C_8H_{17-n}$	71	26
$CH_3COCH_2CO(CH_2)_5-$ $COCH_2COCH_3$	$NaNH_2$	$Br(CH_2)_3Br$	$(CH_2)COCH_2COCH_2CH_2CH_2CH_2)_n$ ($n = 12-13$)	77	33
	$NaNH_2$	$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_2COCH_2CO(CH_2)_5-$ $COCH_2COCH_2CH_2C_6H_5$	67	33
$CH_3COCH_2CO(CH_2)_6-$ $COCH_2COCH_3$	$NaNH_2$	$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_2COCH_2CO(CH_2)_6-$ $COCH_2COCH_2CH_2C_6H_5$	62	33

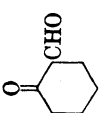

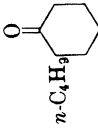
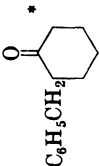
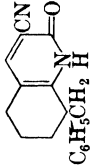
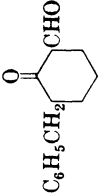
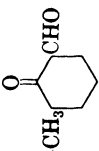
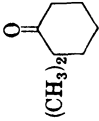
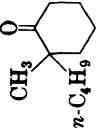
TABLE V. ALKYLATIONS OF THE DIANIONS OF DIKETONES NOT INCLUDED IN TABLES III AND IV

Diketone	Alkali Amide	Alkyl Halide	Product	Yield (%)	Refs.
	KNH_2	CH_3I		17	24
	KNH_2	$\text{CH}_2=\text{CHCH}_2\text{Br}$		21	24
	NaNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		—	24
	KNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		45	24
$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{H}_5$	NaNH_2	$n\text{-C}_4\text{H}_9\text{Cl}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{CH}(\text{C}_4\text{H}_9)_2$	—	20
	NaNH_2	$n\text{-C}_4\text{H}_9\text{Br}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{CH}(n\text{-C}_4\text{H}_9)_2$	73	20, 31
	NaNH_2	$n\text{-C}_4\text{H}_9\text{I}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{CH}(n\text{-C}_4\text{H}_9)_2$	—	20
	NaNH_2	$\text{sec-C}_4\text{H}_9\text{Br}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{CH}(\text{sec-C}_4\text{H}_9)_2$	83	20
	NaNH_2	$i\text{-C}_4\text{H}_9\text{Br}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{CH}(i\text{-C}_4\text{H}_9)_2$	78	20

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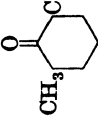
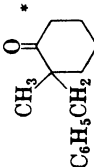
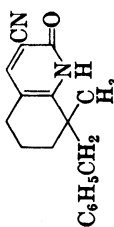
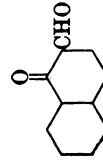
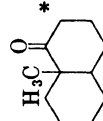
TABLE VI. ALKYLATIONS OF THE DIANIONS OF KETO ALDEHYDES

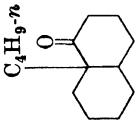
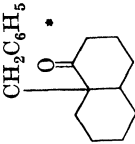
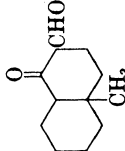
Keto Aldehyde	Dialkali Salt	Alkyl Halide	Product	Yield (%)	Refs.
					
$\text{CH}_3\text{COCH}_2\text{CHO}$	Na, K	CH_3Br	$(\text{CH}_3\text{CH}_2\text{COCHCHO})_2\text{Cu}$	66	21
	Na, K	CH_3I		61	21
	Na, K	CH_3I	$\text{C}_6\text{H}_5(\text{COCH}_2\text{CH}_3)_{1,3,5}$	27	21
	Na, K	$n\text{-C}_4\text{H}_9\text{Br}$	$(n\text{-C}_4\text{H}_9\text{CH}_2\text{COCHCHO})_2\text{Cu}$	72	21
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	$(\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCHCHO})_2\text{Cu}$	80	21
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		73	21
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	$\text{C}_6\text{H}_5(\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5)_{1,3,5}$	29	21
	Na, K	$n\text{-C}_8\text{H}_{17}\text{Br}$	$(n\text{-C}_8\text{H}_{17}\text{CH}_2\text{COCHCHO})_2\text{Cu}$	55	21
	Na, K	$n\text{-C}_4\text{H}_9\text{Br}$		38	23
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		32	23

	Na, K	CH ₃ I		36	23
	Na, K	<i>n</i> -C ₄ H ₉ Br		41	23
	Na, K	C ₆ H ₅ CH ₂ Cl		40	23
	Na, K	C ₆ H ₅ CH ₂ Cl		40	23
	K	C ₆ H ₅ CH ₂ Cl		20	24
	Na, K	CH ₃ I		60	23
	Na, K	<i>n</i> -C ₄ H ₉ Br		67-75	23, 105

* This product was also isolated as the copper chelate of the keto aldehyde.

TABLE VI. ALKYLATIONS OF THE DIANIONS OF KETO ALDEHYDES (Continued)

Keto Aldehyde	Dialkali Salt	Alkyl Halide	Product	Yield (%)	Refs.
 <chem>CC1CCCCC1=O</chem> (contd.)	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	 <chem>CC1CCCCC1=O</chem> <chem>CC1CCCCC1=O</chem>	55	23
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	 <chem>CC1CCCCC1=O</chem> <chem>CC1CCCCC1=O</chem>	80	23
$\text{CH}_3\text{COCH}(\text{C}_6\text{H}_5)\text{CHO}$ $\text{CH}_3\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)\text{CHO}$	K K K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ $n\text{-C}_4\text{H}_9\text{Br}$ $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}(\text{C}_6\text{H}_5)\text{CHO}$ $n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)\text{CHO}$ $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)\text{CHO}$	42 27 51	8 21 21
 <chem>c1ccccc1C2CCCCC2=O</chem>	Na, K	CH_3I	 <chem>C[C@H]1(C)CCCCC1=O</chem> <i>(cis:trans/46:54)</i>	55	23

				45	23
	Na, K	$n\text{-C}_4\text{H}_9\text{Br}$	(<i>cis</i>)		
				58	23
	Na, K	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	(probably <i>cis</i>)		
	—	CH_3I	Alkylation failed	—	46

* This product was also isolated as the copper chelate of the keto aldehyde.

TABLE VII. ALKYLATIONS OF THE DIANIONS OF KETO ESTERS

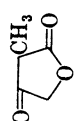
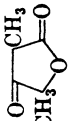

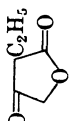

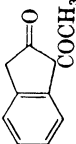
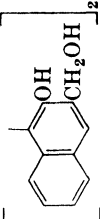

Keto Ester	Alkali Amide	Alkyl Halide	Product	Yield (%)	Ref.
$\text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$ 	NaNH_2	CH_3I	$\text{CH}_3\text{CH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$	Low	25
	KNH_2	CH_3I	$\text{CH}_3\text{CH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$	36, 37	4
	KNH_2	$\text{C}_2\text{H}_5\text{Br}$	$\text{C}_2\text{H}_5\text{CH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$	27, 29	4
	LiNH_2	$n\text{-C}_4\text{H}_9\text{Br}$	Alkylation failed	—	25
	NaNH_2	$n\text{-C}_4\text{H}_9\text{Br}$	Alkylation failed	—	4
	KNH_2	$n\text{-C}_4\text{H}_9\text{Br}$	Alkylation failed	—	25
	NaNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	$\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$	41	25
	KNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	Alkylation failed	—	4
	KNH_2	CH_3I		39	24
	KNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		90	24
	KNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		18	24
	KNH_2	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{C}_6\text{H}_5)\text{COCH}_2\text{C}_6\text{H}_5$	44	4

TABLE VIII. ARYLATIONS OF THE DIANIONS OF DICARBONYL COMPOUNDS

Dicarbonyl Compound	Alkali Amide	Arylating Agent	Product	Yield (%)	Ref.
$\text{CH}_3\text{COCH}_2\text{COCH}_3$	NaNH_2 KNH_2	$\text{C}_6\text{H}_5\text{Br}$ $\text{C}_6\text{H}_5\text{Br}$	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$ $\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	18 13	11 2
	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	92	11
	NaNH_2	$(p\text{-ClC}_6\text{H}_4)_2\text{ICl}$	$\text{CH}_3\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_4\text{Cl}$	44	11
$\text{C}_2\text{H}_5\text{COCH}_2\text{COC}_2\text{H}_5$	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$\text{C}_2\text{H}_5\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	50	11
$n\text{-C}_3\text{H}_7\text{COCH}_2\text{COCH}_3$	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$n\text{-C}_3\text{H}_7\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	98	11
$n\text{-C}_5\text{H}_{11}\text{COCH}_2\text{COCH}_3$	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$n\text{-C}_5\text{H}_{11}\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	78	11
	NaNH_2	$(p\text{-CH}_3\text{C}_6\text{H}_4)_2\text{ICl}$	$n\text{-C}_5\text{H}_{11}\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_4\text{CH}_3$	21	11
$\text{C}_6\text{H}_5\text{COCH}_2\text{COCH}_3$	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$\text{C}_6\text{H}_5\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	61	11
	NaNH_2	$(p\text{-CH}_3\text{C}_6\text{H}_4)_2\text{ICl}$	$\text{C}_6\text{H}_5\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_4\text{CH}_3$	44	11
$o\text{-ClC}_6\text{H}_4\text{CH}(\text{COCH}_3)_2$	KNH_2	—		98	47
$o\text{-ClC}_6\text{H}_4\text{CH}_2\text{CH}(\text{CHO})\text{COCH}_3$	KNH_2	—		29	47
$o\text{-ClC}_6\text{H}_4\text{CH}_2\text{CH}(\text{COCH}_3)_2$	KNH_2	—		65	47
$n\text{-C}_9\text{H}_{19}\text{COCH}_2\text{COCH}_3$	NaNH_2	$(\text{C}_6\text{H}_5)_2\text{ICl}$	$n\text{-C}_9\text{H}_{19}\text{COCH}_2\text{COCH}_2\text{C}_6\text{H}_5$	53	11

CHAPTER 3

THE RITTER REACTION

L. I. KRIMEN AND DONALD J. COTA

Abbott Laboratories

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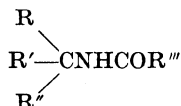
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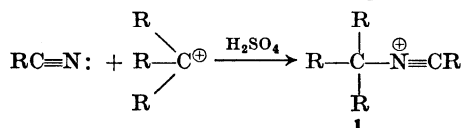
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INTRODUCTION

The formation of N-substituted amides by the addition of nitriles to alkenes in the presence of concentrated sulfuric acid, described first by Ritter in 1948,¹ is one of the newer synthetic reactions available to the organic chemist. The reaction has since been extended to the addition of nitriles to a wide variety of compounds capable of forming a carbonium ion, and it constitutes the only really useful procedure for the preparation of amides of tertiary carbinamines,

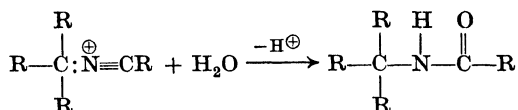


In its most general form the Ritter reaction involves the nucleophilic addition of a nitrile to a carbonium ion in the presence of sulfuric acid.

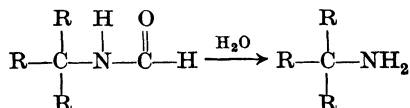


¹ J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).

Subsequent dilution with water yields the amide. When hydrogen cyanide is employed as the nitrile, the resulting N-alkylformamide can be



readily hydrolyzed to the corresponding carbinamine; thus the tertiary carbinamines are readily available.



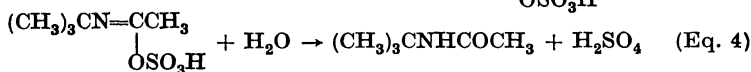
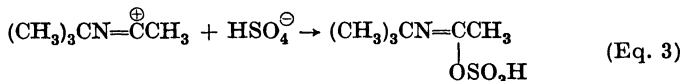
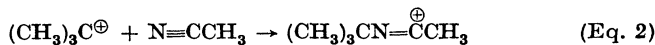
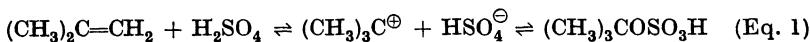
If a nucleophilic center is suitably placed in the primary adduct 1, a wide variety of heterocyclic compounds can be prepared.

Attention has been given primarily to reactions in which the carbonium ion is generated in sulfuric acid or, less commonly, in sulfonic acids, phosphoric acid, or boron trifluoride. For comparison analogous reactions which are initiated by a nitrilium ion, formed from a nitrile and a Friedel-Crafts catalyst, have been included in the discussion of related reactions.

Cursory surveys of the Ritter reaction have appeared in *Russian Chemical Reviews* where Zil'berman dealt with the formation of new nitrogen-carbon bonds² and in *Advances in Heterocyclic Chemistry* in which Johnson reviewed its utility in heterocyclic syntheses.³

MECHANISM

The mechanism suggested by Ritter and his associates in their initial papers is illustrated in the following scheme for the reaction between isobutene and acetonitrile.^{1, 4, 5}



² E. N. Zil'bermann, *Usp. Khim.*, **29**, 709 (1960) [*Russ. Chem. Rev.*, English transl., 311 (1960)].

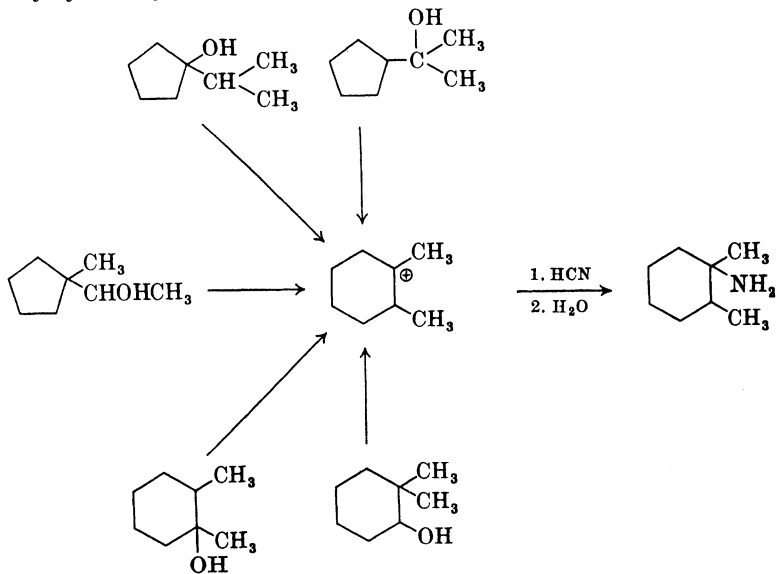
³ F. Johnson and R. Madroñero, in A. R. Katritzky and A. J. Boulton, eds., *Advances in Heterocyclic Chemistry*, Vol. 6, pp. 95-146, Academic Press, New York, 1966.

⁴ J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

⁵ J. J. Ritter, U.S. pat. 2,573,673 [*C.A.*, **46**, 9584h (1952)].

The possibility that the reaction could proceed by the addition of acetamide under acid conditions was discounted when substitution of acetamide for acetonitrile gave no reaction product.¹

Ritter's proposal that the reaction proceeds via a carbonium ion intermediate has been substantially supported by the studies of Jacquier and Christol.⁶⁻¹⁷ They described the synthesis of amines by the reaction of cycloalkanols, secondary aliphatic alcohols, cyclosubstituted alcohols, and alicyclic alcohols containing a spiro structure with potassium cyanide in sulfuric acid. In many reactions there is an intramolecular rearrangement of the Meerwein type,¹⁸ including ring expansion or contraction, leading to the amine resulting from the reaction of hydrogen cyanide with the most stable carbonium ion. For example, 1-isopropylcyclopentanol, 1-methylcyclopentylmethylcarbinol, cyclopentyl dimethylcarbinol, 1,2-dimethylcyclohexanol, and 2,2-dimethylcyclohexanol all yield 1,2-dimethylcyclohexylamine.¹⁶



⁶ H. Christol, R. Jacquier, and M. Mousseron, *Bull. Soc. Chim. France*, 1027 (1957).

⁷ H. Christol and A. Laurent, *Bull. Soc. Chim. France*, 920 (1958).

⁸ H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. France*, 2313 (1961).

⁹ H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. France*, 2319 (1961).

¹⁰ H. Christol, A. Laurent, and G. Solladie, *Bull. Soc. Chim. France*, 877 (1963).

¹¹ H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 1299 (1966).

¹² H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 1307 (1966).

¹³ H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 3193 (1966).

¹⁴ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 556 (1954).

¹⁵ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 596 (1957).

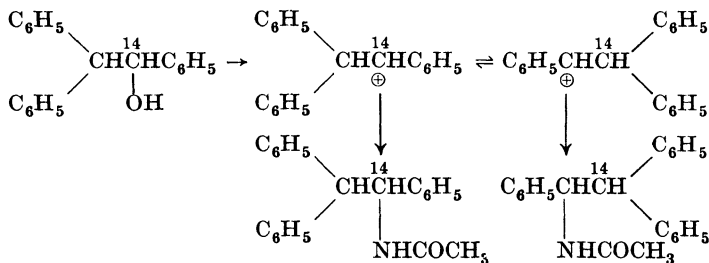
¹⁶ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 600 (1957).

¹⁷ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 917 (1953).

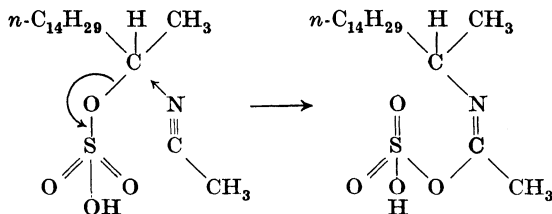
¹⁸ H. Meerwein, *Ann.*, **417**, 255 (1918).

Further support for a carbonium ion mechanism was furnished by Roe and Swern, who employed methanesulfonic acid in place of sulfuric acid.¹⁹

Similar investigations showed that C¹⁴-labeled 1,2,2-triphenylethanol, when treated with acetonitrile and sulfuric acid, led to a mixture of substituted amides resulting from a carbonium ion equilibrium.^{20, 21}



From data obtained in a kinetic study of the reaction between *t*-butyl alcohol and acrylonitrile in 20–69% sulfuric acid solutions Deno concluded that the transition state was composed of acrylonitrile and protonated *t*-butyl alcohol.²² This concept of a loosely solvated carbonium ion was also advanced by other investigators.²³ In a subsequent study using the α -olefin, 1-hexadecene, Weil and co-workers postulated a cyclic transition state which then proceeded to the "Ritter intermediate";²⁴ however, their



work was in agreement with a carbonium ion process. They formulated an irreversible reaction with water, leading to a stable intermediate, 2, whose precise nature they were unable to determine. (See p. 219.)

Extension of the Ritter reaction to *t*-carboxylic acids furnished additional evidence for a carbonium ion process. Haaf showed that acids having this structure could be reversibly converted to *t*-alkylamido

¹⁹ E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **75**, 5479 (1953).

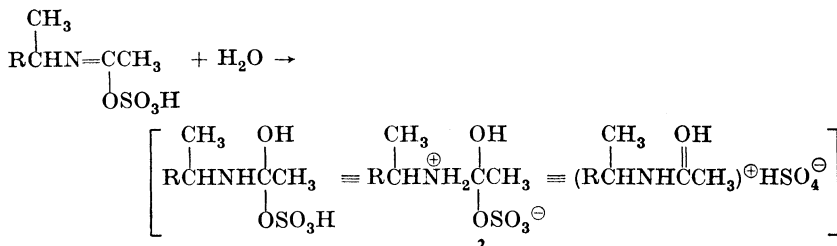
²⁰ A. Laurent, E. Laurent-Dieuzeide, and P. Mison, *Bull. Soc. Chim. France*, 945 (1965).

²¹ A. Laurent and P. Mison, *Bull. Soc. Chim. France*, 956 (1962).

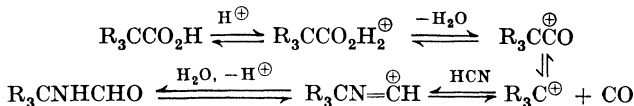
²² N. C. Deno, T. Edwards, and C. Perizzolo, *J. Am. Chem. Soc.*, **79**, 2108 (1957).

²³ C. W. Roberts and N. F. Nuenke, *J. Org. Chem.*, **24**, 1907 (1959).

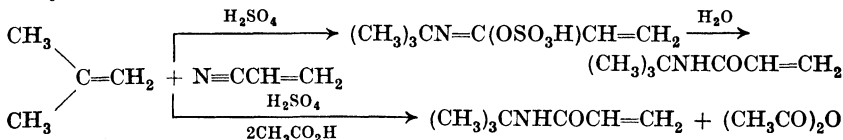
²⁴ I. Weil, R. G. Goebel, E. R. Tulp, and A. Cahn, *Am. Chem. Soc., Div. Petrol. Chem., Preprints*, **8**, (2) B95 (1963).



compounds since treatment of the *t*-alkylamides with carbon monoxide in concentrated sulfuric acid yielded *t*-carboxylic acids.²⁵

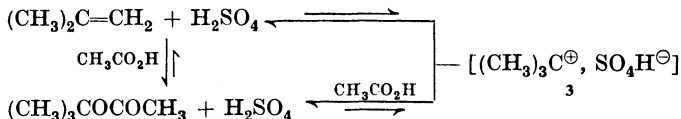


After unsuccessful attempts by various workers^{26, 27} to isolate and characterize the alkyl iminosulfate intermediate suggested by Ritter,⁴ Glikmans and co-workers were able to verify its existence by showing that it is susceptible to hydrolysis in anhydrous acetic acid, obtaining the necessary water from the solvent with concomitant generation of acetic anhydride.^{28, 29}



An earlier attempt to produce N-cumylacrylamide by this route was unsuccessful.²³

Glikmans also showed that the alkene could be replaced by the corresponding alcohol or acetate and suggested the presence of an ion pair such as **3**, which would assist in the electronic transfer as indicated in formula 4.



²⁵ W. Haaf, *Chem. Ber.*, **96**, 3359 (1963).

²⁶ T. Clarke, J. Devine, and D. W. Dicker, *J. Am. Oil Chemists Soc.*, **41**, 78 [*C.A.*, **60**, 6733h (1964)].

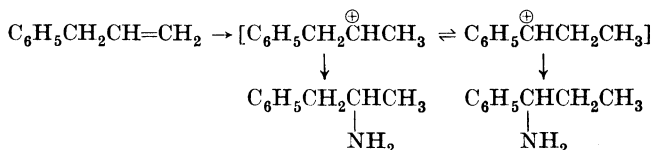
²⁷ R. L. Holmes, J. P. Moreau, and G. Sumrell, *J. Am. Oil Chemists Soc.*, **42**, 922 (1965) [*C.A.*, **63**, 17892c (1965)].

²⁸ G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 1376 (1966).

²⁹ G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 1383 (1966).

Alkenes (Tables II and III)

The addition of hydrogen cyanide and nitriles to alkenes has been investigated by numerous workers (Refs. 24, 26, 28, 29, 32, 33). At an early stage the reaction was elucidated for a variety of nitriles using diisobutylene.¹ As described for isobutene (p. 216), the reaction usually gives the alkylamido addition product corresponding to the carbonium ion initially formed by Markownikoff addition of a proton to the alkene. There are, however, several reports of products resulting from rearrangement of the incipient carbonium ion. Thus 1-phenylpropylamine is obtained from allylbenzene when operating in di-*n*-butyl ether.⁸ On the other hand, in the absence of solvent the expected 2-phenylisopropylamine is obtained.^{4, 34}



It is noteworthy that the carbonium ion from 3-methyl-1-phenylbutene did not undergo a similar rearrangement.⁸ The initial secondary carbonium ion is stabilized to a greater extent by the adjacent phenyl group than is the tertiary carbonium ion that would result from a prototropic shift.

Conflicting results with camphene were reported by several groups of workers. Ritter and Minieri isolated the N-acylisobornylamines, a result of the Wagner rearrangement, when employing hydrogen cyanide or simple nitriles.¹ Other investigators also obtained N-acylisobornylamines from simple nitriles but found that hydrogen cyanide gave the unrearranged norcamphane derivative.³⁵ This anomaly was resolved by Kochetkov and co-workers who made a detailed study of the behavior of camphene. They showed that, when the reaction is conducted at temperatures in the -15° to -20° range, the formation of the isobornyl derivative with hydrogen cyanide is reduced to a minimum.³⁶ Similar results were obtained when 3-formamido-2,2,3-trimethylnorcamphane was formed by treating racemic camphene with hydrogen cyanide at $0-3^\circ$.³⁷

³² C. Malen and J. R. Boissier, *Bull. Soc. Chim. France*, 923 (1956).

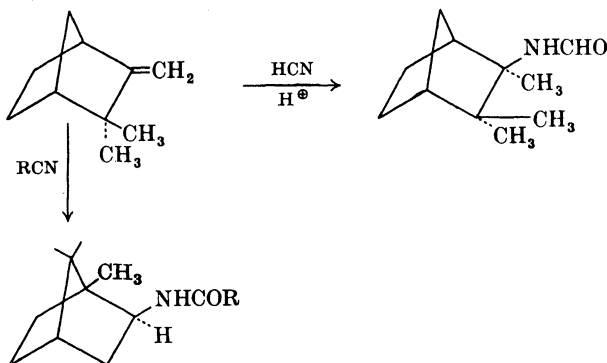
³³ R. Maugé, C. Malen, and J. R. Boissier, *Bull. Soc. Chim. France*, 926 (1956).

³⁴ J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952).

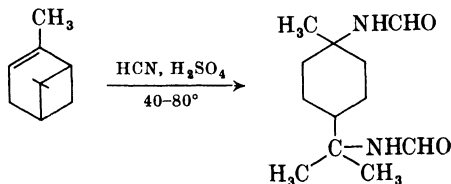
³⁵ G. A. Stein, M. Sletzing, H. Arnold, D. Reinhold, and K. Pfister, III, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

³⁶ N. K. Kochetkov, A. Ya. Khorlin, and K. I. Lopatina, *J. Gen. Chem. USSR (Eng. Transl.)*, **29**, 77 (1959) [*C.A.*, **53**, 22058i (1959)].

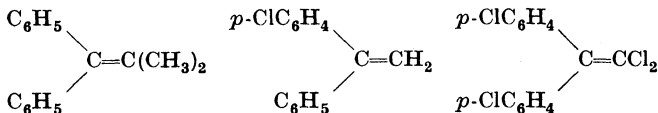
³⁷ C. A. Stone, M. L. Torchiana, K. L. Meekelnburg, J. Stavorski, M. Sletzing, G. A. Stein, W. V. Ruyle, D. F. Reinhold, W. A. Gaines, H. Arnold, and K. Pfister, III, *J. Med. Pharm. Chem.*, **5**, 665 (1962) [*C.A.*, **57** 12341c (1962)].



Kochetkov also showed that the highly active trichloro- and dichloro-acetonitrile reacted with camphene at a reduced temperature without rearrangement, but even at -50° the rearranged products were obtained with aceto- and benzo-nitrile.³⁶ Rearrangement also occurs with α -pinene when it is treated with hydrogen cyanide at slightly elevated temperatures, giving 1,8-diformamido-*p*-menthane.^{38,39}



The failure of the reaction with alkenes has been noted in relatively few instances. The only structural similarity in these cases is the presence of one or two phenyl groups on the double-bonded carbon atom. The failure of 1,1-diphenyl-2,2-dimethylethylene to undergo the reaction was explained on the basis of the high stability of the derived carbonium ion and hence its lack of reactivity toward nitriles.¹⁰ Similar reasoning could rationalize the failure of 1-(*p*-chlorophenyl)-1-phenylethylene and 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene.⁴⁰



Although Ritter reported the successful addition of acetonitrile to α -methylstyrene,⁵ other investigators reported that α -methylstyrene and

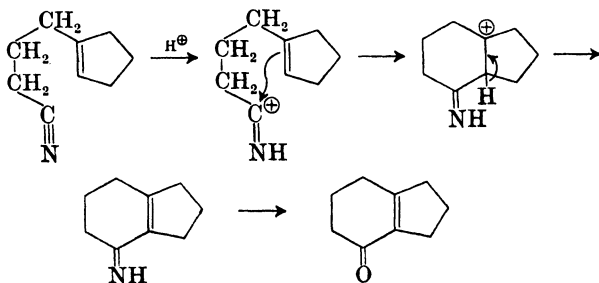
³⁸ N. M. Bortnick, Brit. pat. 681,688 [C.A., **48**, 727f (1954)].

³⁹ N. M. Bortnick, U.S. pat. 2,632,022 [C.A., **48**, 4003h (1954)].

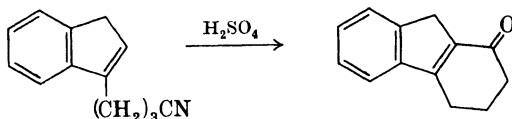
⁴⁰ A. Kluszyner, S. Blum, and E. D. Bergmann, *J. Org. Chem.*, **28**, 3588 (1963).

$$3,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CH}=\text{C}(\text{CH}_3)_2 \xrightarrow[\text{H}_2\text{SO}_4]{\text{KCN, (n-C}_4\text{H}_9)_2\text{O}} 3,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CH}_2\text{C}(\text{CH}_3)_2\text{NHCHO}$$
$$\begin{array}{c} \text{CH}_3(\text{CH}_2)_x\text{CHNHCO}(\text{CH}_2)_4\text{CONHC}(\text{CH}_2)_x\text{CH}_3 \\ | \qquad \qquad \qquad | \\ (\text{CH}_2)_y\text{CO}_2\text{H} \qquad (\text{CH}_2)_y\text{CO}_2\text{H} \\ \mathbf{5,} \ x + y = 15 \end{array}$$
$$\text{RR}_1\text{C}(\text{NHCOR})\text{CH}_2\text{X} \xrightarrow{\text{OH}^\ominus} \text{RR}_1\text{C}(\text{N}=\text{C}(\text{OR})\text{CH}_2)\text{O} + \text{H}_2\text{O}$$

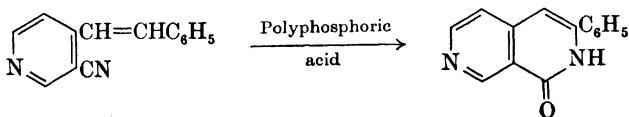
⁴⁶ R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).



An analogous reaction had been reported earlier for γ -3-indenylbutyronitrile and described as a failure of the Ritter reaction.⁴⁷



Conley suggested that these unsaturated nitriles do not react in the usual manner because the cyano group cannot approach the intermediate carbonium ion.^{46,48-50} This proposal, however, was in disagreement with the results of Bobbitt and Doolittle who were able to cyclize 3-cyano-4-stilbazole to the lactam, 1-oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine, in 90% yield.⁵¹



Bobbitt attributed the lactam formation to the electron-withdrawing effect of the pyridinium nucleus on the double bond. This electron deficiency allows the lactam formation and inhibits the acylation reaction which would lead to the ketone.

Alkadienes (Table IV)

The extension of the Ritter reaction to dienes to give dialkylamido derivatives has met with some success. Bortnick prepared 1,8-diamino-*p*-methane^{38, 39} and 2,5-diamino-2,5-dimethylhexane⁵² from limonene and

⁴⁷ F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).

⁴⁸ R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

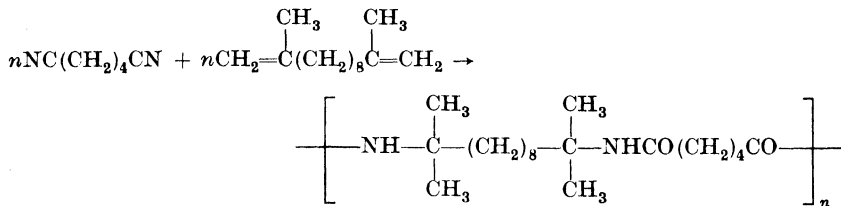
⁴⁹ R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **27**, 1965 (1962).

⁵⁰ R. T. Conley and R. J. Lange, *J. Org. Chem.*, **28**, 210 (1963).

⁵¹ J. M. Bobbitt and R. E. Doolittle, *J. Org. Chem.*, **29**, 2298 (1964).

⁵² N. M. Bortnick, U.S. pat. 2,632,023 [*C.A.*, **49**, 1782a (1955)].

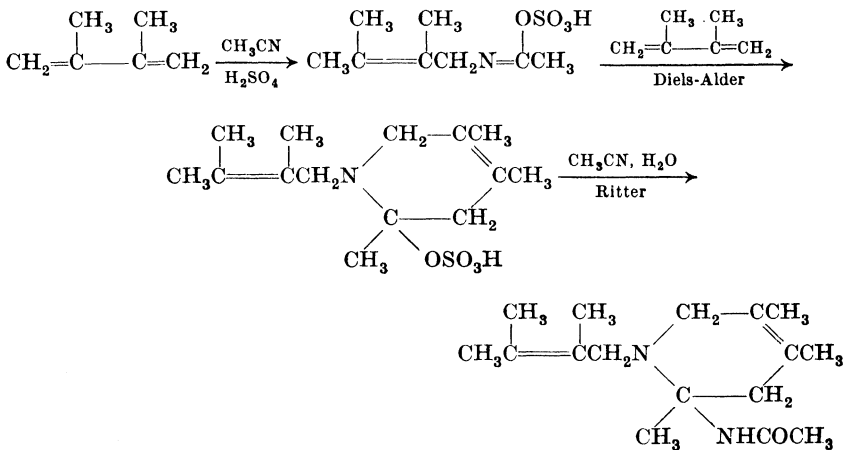
bimethallyl, respectively. Although the reactions attempted with dipentene and 2,5-dimethyl-1,5-hexadiene gave nitrogen-containing materials only in low yield along with substantial amounts of polymeric material, and butadiene reacted explosively,²⁶ Magat prepared a number of synthetic linear polyamides from ditertiary diolefins and dinitriles.⁵³ For example, the polymer, poly($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl)decamethyleneadipamide was prepared from adiponitrile and 2,11-dimethyl-1,11-dodecadiene.



The participation of a conjugated diene in combined Ritter and Diels-Alder reactions has been reported.⁵⁴ 2,3-Dimethyl-1,3-butadiene and acetonitrile furnish the substituted tetrahydropyridine. It was proposed that the diene reacted with 1 mole of acetonitrile to give the iminosulfate intermediate. The $-\text{N}=\text{C}-$ grouping then behaved as a dienophile,



adding another mole of butadiene and acetonitrile, to give the product.



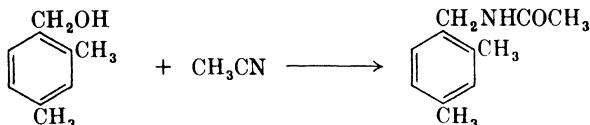
⁵³ E. E. Magat, U.S. pat. 2,628,219 [C.A., **47**, 5130c (1953)].

⁵⁴ M. Lora-Tamayo, G. Gancía Muñoz, and R. Madroñero, *Bull. Soc. Chim. France*, **1334** (1958).

Alcohols (Tables V-VIII)

The use of primary, secondary, and tertiary alcohols, alicyclic and spiro alcohols, glycols, heterocyclic alcohols, and halohydrins in the Ritter reaction has been investigated.

The failure of primary aliphatic alcohols to react with nitriles even at elevated temperatures or on prolonged heating, or with fuming sulfuric acid was reported by Ritter.⁵⁵ Other investigators⁵⁶⁻⁵⁸ observed, however, that primary aralkyl alcohols and glycols condensed smoothly with nitriles under mild conditions to give N-aralkylamides and N,N'-bis-aralkylamides in good yields. N-(2,4-Dimethylbenzyl)acetamide was obtained from 2,4-dimethylbenzyl alcohol and acetonitrile in 87% yield. An exception



to the reactivity of benzyl alcohols is shown by *p*-nitrobenzyl alcohol, which is inert to nitriles in concentrated sulfuric acid.¹⁴

Glikmans found that alcohols, in general, gave lower yields than the corresponding olefins and required the use of concentrated sulfuric acid.²⁸ On the other hand, there are reports that the reverse is true because polymerization of olefin competes with the Ritter reaction.⁵⁹

From studies of a number of alcohols of varied structure Christol, Jacquier, and their associates concluded that tertiary alcohols react with hydrogen cyanide without rearrangement;^{13, 15} for example, methylcyclohexanol gives the corresponding amine in 60% yield.⁶⁰ Although most secondary cycloalkanols react without rearrangement, the yields are somewhat lower; thus cyclohexanol gives only a 4% yield of cyclohexylamine.^{14, 15}

It is an oversimplification to conclude that the reaction product always corresponds to the most stable incipient carbonium ion, yet this conclusion is valid for a majority of the cases.

In a study of the reaction of substituted cycloalkanols it was learned that the yields decrease with increasing separation of the alcohol function

⁵⁵ F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949).

⁵⁶ C. L. Parris, *Org. Syntheses*, **42**, 16 (1962).

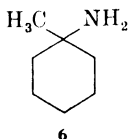
⁵⁷ C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 331 (1960).

⁵⁸ J. A. Sanguigni and R. Levine, *J. Med. Chem.*, **7**, 573 (1964).

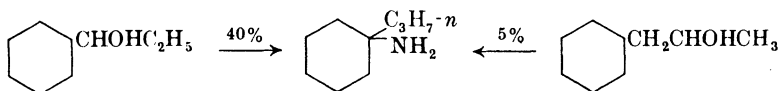
⁵⁹ A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1960).

⁶⁰ L. I. Krimen, unpublished results.

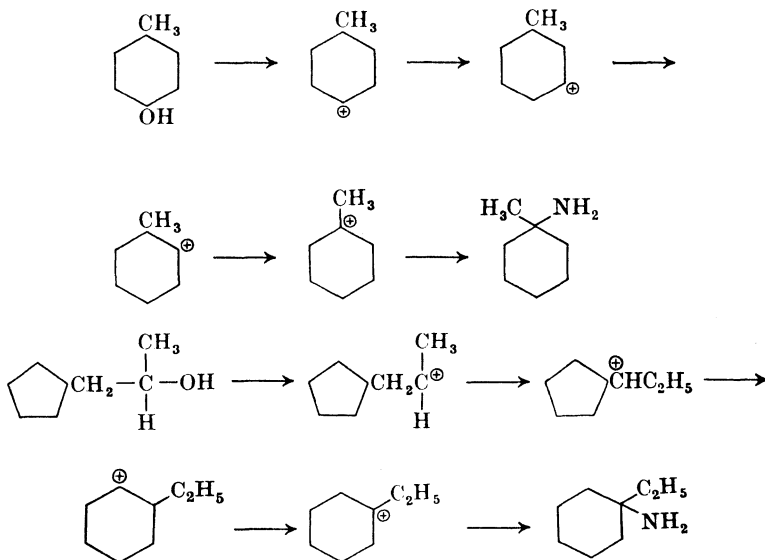
and the substituent.¹⁶ 1- and 2-Methylcyclohexanol gave 1-methylcyclohexylamine (**6**) in 60% yield, whereas the yield from the 4-methyl derivative was only 5%.



Similarly, when the ring is "farther away" from the alcohol as in the cyclohexylpropanols, the yields decrease. For example, ethylcyclohexylcarbinol and 1-cyclohexyl-2-propanol give 1-*n*-propylcyclohexylamine in yields of 40% and 5%, respectively.

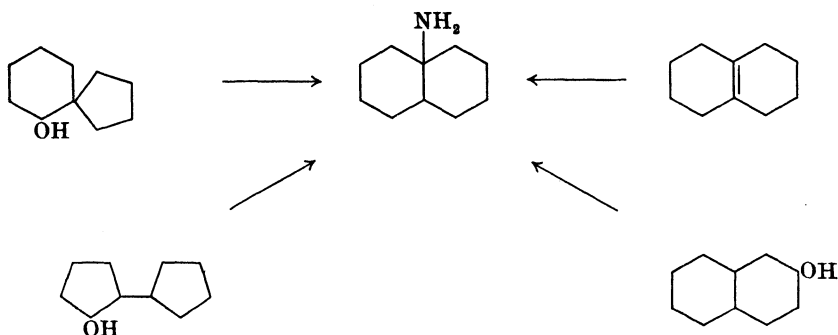


This effect of the separation of hydroxyl group and substituent is a characteristic specific to the Ritter reaction, and not necessarily a function of the number of successive prototropic rearrangements. 4-Methylcyclohexanol and 1-cyclopentyl-2-propanol rearrange, by means of three transitory carbonium ions, to methylcyclohexylamine and ethylcyclohexylamine in yields of 5% and 45%, respectively.

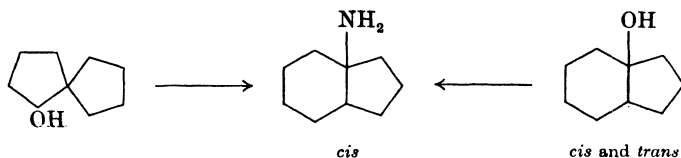


Christol and Jacquier also reported a number of alcohols which did not undergo a Ritter reaction, whereas their position or structural isomers did. Thus 2,2-dimethylcyclohexanol gave 1,2-dimethylcyclohexylamine in 20% yield, but 3,3-dimethylcyclohexanol failed to react. The absence of any reaction was also observed for 2-butanol. The authors attribute the failure of reaction to the difficulty of forming the corresponding ions rather than to the lack of reactivity of these ions.^{14, 16}

Extending their investigations to alicyclic and spiro alcohols, Christol and co-workers found that most Ritter reactions were accompanied by a retropinacol rearrangement.^{6, 14} When spiro[4.5]-6-decanol was subjected to the conditions of the Ritter reaction, ring expansion occurred and *trans*-9-aminodecalin was obtained. The stereospecific nature of the reaction was also noted with other bicyclic and spiro alcohols. For example, a mixture of *cis*- and *trans*-2-cyclopentylcyclopentanol, the diastereoisomers of β -decalol, and $\Delta^{9,10}$ -octalin all gave *trans*-9-aminodecalin when subjected to the Ritter reaction.^{6, 11, 17}

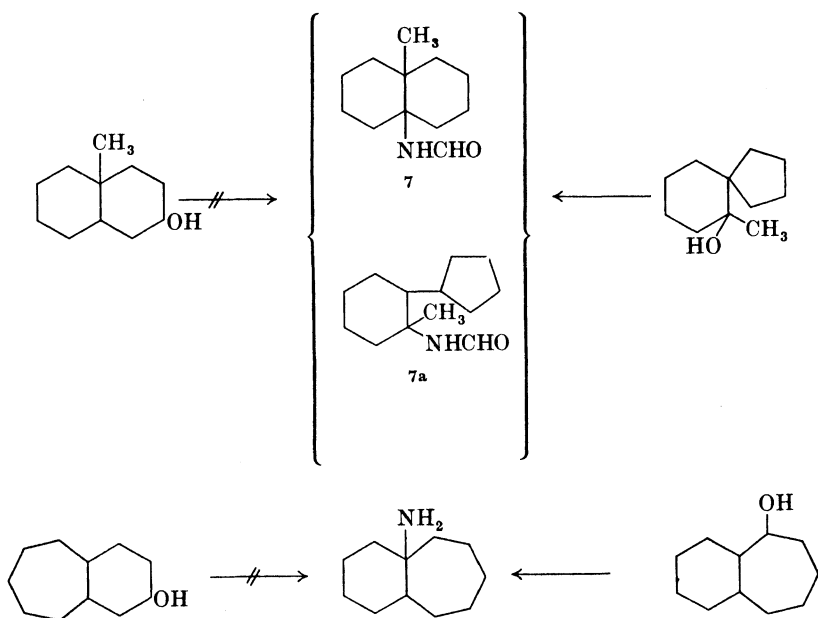


Similar stereospecificity was exhibited by spiro[4.4]-1-nonanol and *cis*- and *trans*-8-hydroxyhydrindane, which reacted to give only the *cis*-8-aminohydrindane. Only the thermodynamically more stable isomer of



1,2-dimethylcyclohexylamine, with the methyl groups *trans* in equatorial positions, was obtained from 1,2- and 2,2-dimethylcyclohexanol.¹³

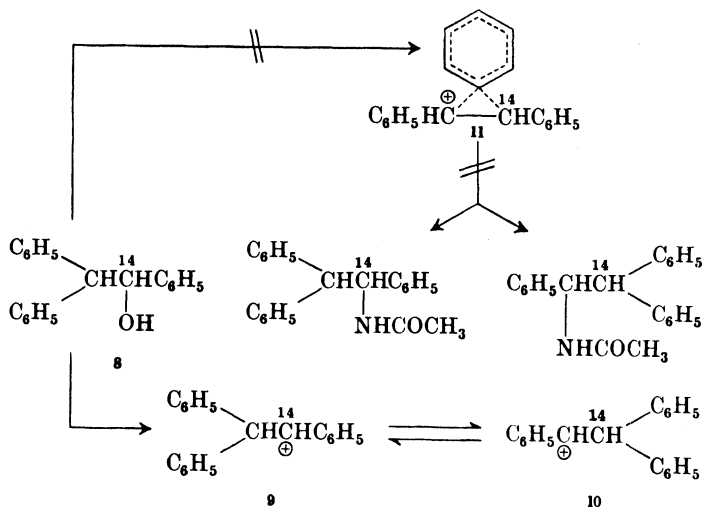
Differences in behavior were also noted in the spiro and bicyclic alcohols.⁶ For example, 4a-methyl-2-decahydronaphthol and bicyclo[5.4.0]-9-undecanol failed to react, but their isomers, 6-methylspiro[4.5]-6-decanol and bicyclo[5.4.0]-2-undecanol did react, to give in one case an angular amine, 1-aminobicyclo[5.4.0]undecane and in the other case a mixture of formamides **7** and **7a** that could not be hydrolyzed to the free amines.



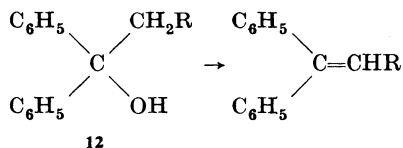
The extension of the Ritter reaction to secondary benzylic alcohols and benzylcarbinols,⁸ tertiary benzylic alcohols,⁹ diphenyl-carbinols and -propanols¹⁰ enabled Christol and co-workers to establish the relative reactivities of the various derived carbonium ions and their susceptibility to prototropic rearrangements.

Further insight into the mode of these carbonium ion rearrangements was reported by Laurent,^{20, 21} who employed C¹⁴-labeled triphenylethanols and showed that the Ritter reaction of triphenylethanol **8** with alkyl or aryl nitriles proceeded via a rearrangement of **9** to **10** before the substitution occurred, thus ruling out the formation of the bridged phenonium ion **11**. (See p. 230.)

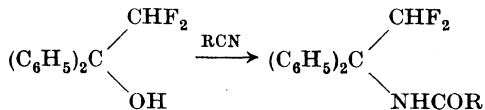
It is noteworthy that diphenylcarbinols such as **12**, when R is CH₃, C₂H₅, C₃H₇-i, CH₂Cl, or CHCl₂, yield only the corresponding 1,1-diphenylethylenes.^{10, 40} A similar dehydration followed by dimerization was



described for 2-phenyl-2-propanol, indicating that the cumyl cation undergoes nucleophilic attack by α -methylstyrene more readily than by



the nitrile.²³ However, diphenylcarbinol itself and difluoromethyldiphenylcarbinol react with various nitriles to give the amides in yields ranging from 68% to 100%.^{10, 40, 58} Magat was able to prepare linear



polyamides from disecundary alcohols and dinitriles. For example, adiponitrile and 1,10-dimethyl-1,10-decanediol yielded a polymer capable of being melt-spun to form fibers.⁵³

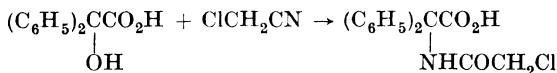
The reaction has also been extended to acids and esters containing the hydroxy group. Both α - and β -acylamine derivatives have been prepared by this route.⁶¹⁻⁶³ The reaction of diphenylhydroxyacetic acid

⁶¹ K. Hohenlohe-Oehringen, *Monatsh.*, **93**, 639 (1962).

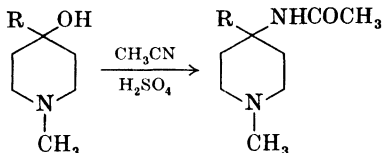
⁶² G. Jansen and W. Taub, *Acta. Chem. Scand.*, **19**, 1772 (1965).

⁶³ L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949).

(benzilic acid) with chloroacetonitrile gave the chloroacetamidodiphenylacetic acid in 82% yield.⁶⁴



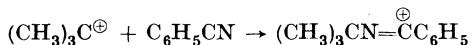
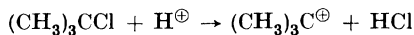
In the only study using heterocyclic alcohols Zagorevskii and Lopatina obtained 4-acetamido-4-alkyl-1-methylpiperidines from the corresponding 4-alkyl-1-methyl-4-piperidinols.⁶⁵



The Ritter reaction with halohydrins proceeds in a manner similar to that described for haloalkenes to give halogen-substituted amides.⁴⁴

Alkyl Chlorides (Table IX)

The use of a tertiary alkyl halide in place of the corresponding alcohol was reported by Magat.⁶⁶ A carbonium ion initially is generated by the abstraction of the halogen atom, and then the reaction proceeds as with alcohols. Both formic and sulfuric acids were employed as reaction media,



and in both reactions the yields were lower than when the corresponding alkenes or alcohols were used.

Aldehydes and Ketones (Tables X, XI, XIII)

The reaction of aldehydes with nitriles to give methylene-*bis*-amides and with dinitriles to yield polyamides was studied by Mowry and Ringwald⁶⁷ and by Magat and co-workers.^{68, 69} These investigators suggested

⁶⁴ K. Hohenlohe-Oehringen and H. Bretschneider, *Monatsh.*, **93**, 645 (1962).

⁶⁵ V. A. Zagorevskii and K. I. Lopatina, *J. Gen. Chem. USSR*, **33**, 2461 (1963) [*C.A.*, **60**, 495f (1964)].

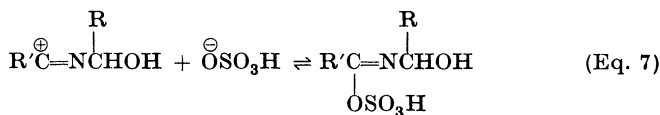
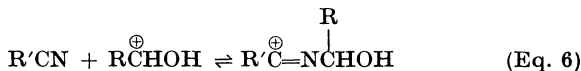
⁶⁶ E. E. Magat, U.S. pat. 2,628,217 [*C.A.*, **47**, 5129g (1953)].

⁶⁷ D. T. Mowry and E. L. Ringwald, *J. Am. Chem. Soc.*, **72**, 4439 (1950).

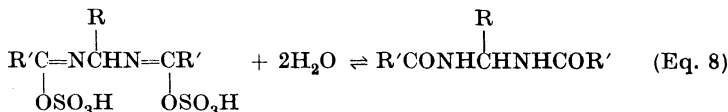
⁶⁸ E. E. Magat, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951).

⁶⁹ E. E. Magat, L. B. Chandler, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1031 (1951).

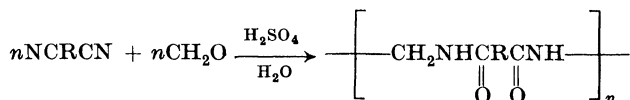
a mechanism in which the nitrile adds to the protonated aldehyde (equation 6) and formation of the iminosulfate follows (equation 7). Subsequent protonation produces a new carbonium ion which undergoes



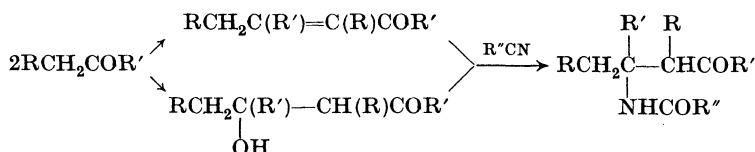
reaction analogous to equations 6 and 7. Hydrolysis (equation 8) gives the methylene-*bis*-amides.



Yields in excess of 90% are often obtained with formaldehyde, but other aldehydes such as acetaldehyde, butyraldehyde, and chloral can be used.⁶⁸ If a dinitrile is treated with formaldehyde, a polymer is formed which corresponds to the polyamide from monomethylenediamine and the parent acid of the dinitrile.^{67, 69}



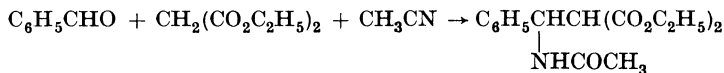
The reaction of nitriles with ketones provides another route to the difficultly accessible β -acylamino ketones (see α,β -unsaturated ketones, p. 234). In a detailed study of this reaction, Khorlin and co-workers showed that positive results were obtained with ketones that readily undergo acid-catalyzed condensations to ketols or α,β -unsaturated ketones.⁷⁰ They suggested that the reaction could proceed by a route similar to that described above for aldehydes or, more reasonably, that the ketal or the α,β -unsaturated ketone or both reacted with the nitrile.



⁷⁰ A. Ya. Khorlin, O. S. Chizhov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **29**, 3411 (1959) [*C.A.*, **54**, 16418h (1960)].

The best results were given by methyl ketones (acetone, 62%; acetophenone, 74%). With an increase in the size of the alkyl group, the yields decrease (methyl ethyl ketone, 16%), and negative results are obtained with propiophenone and butyrone. Among cyclic ketones, only cyclohexanone gave the desired product.

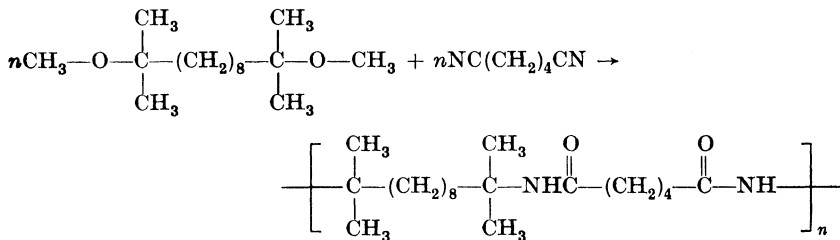
In an unusual variation of this reaction Khorlin carried out a cross reaction in which the compound with the active methylene unit was not a ketone. Instead an aldehyde was the carbonyl component. Benzaldehyde and malonic ester condensed with acetonitrile to give the ethyl ester of 1-carbethoxy-2-phenyl-2-acetamidopropionic acid in 55% yield.⁷⁰



Further reactions of ketones involving intramolecular Ritter reactions are described under Heterocyclic Syntheses (p. 236).

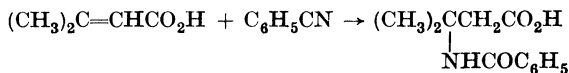
Ethers (Table XII)

The use of secondary and tertiary alkyl ethers as carbonium ion sources has received very limited attention. The only report to date describes the preparation of polyadipamides from the dimethyl ether of α,α' -tetramethyldecamethylene glycol and adiponitrile.⁷¹



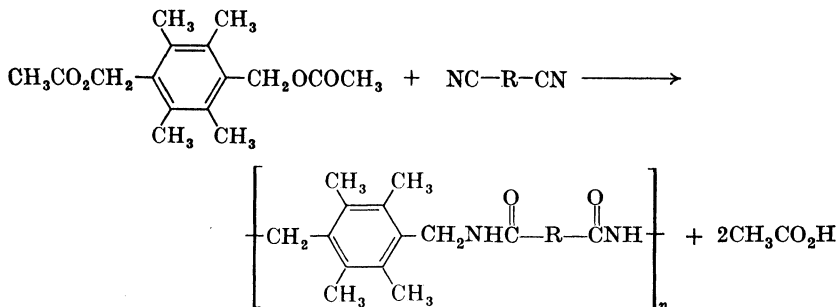
α,β -Unsaturated Carbonyl Compounds (Table XIII)

The scope of the reaction was further broadened when Ritter found that α,β -unsaturated acids and esters having two alkyl groups or one aryl group on the β -carbon atom were very reactive. The reaction of benzonitrile



⁷¹ E. E. Magat, U.S. pat. 2,518,156 [C.A., **45**, 661a (1951)].

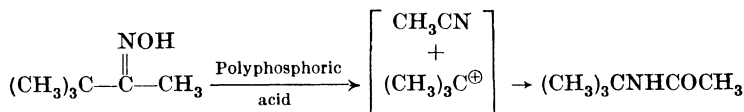
and *t*-butyl acetate²⁸ gave the corresponding N-trialkyl- or triaryl-acetamides. Ramp showed that *bis*(acetoxymethyl) alkylated benzenes could be used as carbonium ion sources.⁷⁷ *Bis*(acetoxymethyl)durene condenses



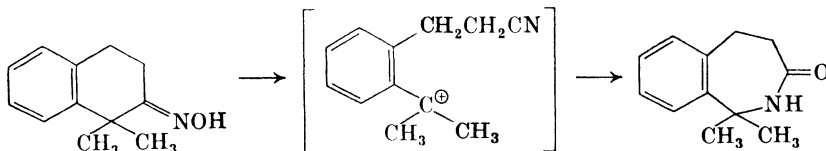
with dinitriles to yield polyamides. Similar polyamides have been prepared from dinitriles and esters of dissecondary alcohols.⁵³

Oximes

While studying the course of the migrating group during the Beckmann rearrangement Hill⁷⁸ and Conley^{49, 79, 80} discovered that α -trisubstituted and α,α' -tetrasubstituted oximes undergo an initial fragmentation to give an intermediate nitrile and a carbonium ion. The two fragments recombine in a Ritter reaction to form an amide. In the case of a cyclic



ketoimine, fragmentation yielded an unsaturated nitrile which on recombination produced a lactam.^{49, 80-82} Treatment of 1,1-dimethyl-2-tetralone oxime with hot polyphosphoric acid resulted in the formation of 2-aza-1,1-dimethyl-3-benzosuberone in 24% yield.⁵⁰



⁷⁷ F. L. Ramp, *J. Polymer Sci.*, **3**, 1877 (1965).

⁷⁸ R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).

⁷⁹ R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).

⁸⁰ R. T. Conley and W. N. Knopka, *Abstr.*, ACS Meeting, 57c (Jan. 1964).

⁸¹ R. K. Hill and R. T. Conley, *Chem. Ind. (London)*, 1314 (1956).

⁸² K. Morita and Z. Suzuki, *J. Org. Chem.*, **31**, 233 (1966).

Heterocyclic Syntheses (Table XVII)

The discovery of Ritter and Tillmanns that the interaction of a suitably substituted diol with a nitrile resulted in the formation of a dihydro-1,3-oxazine, instead of the expected diamide, stimulated research in the synthesis of a variety of heterocyclic systems.⁸³

In addition to dihydro-1,3-oxazines⁸³⁻⁸⁸ the Ritter procedure has been successfully employed in the preparation of oxazolines,⁸⁹ pyrrolines,^{90, 91} dihydropyridines,^{86, 90, 92} Δ^2 -thiazolines,^{59, 90, 93, 94} thiazines,^{59, 87, 95, 96} isoquinolines,³⁴ 2-quinolones,⁹⁷ 2-pyridones,⁹⁷⁻⁹⁹ triazines,¹⁰⁰ azabicycloalkanes,¹⁰¹⁻¹⁰³ bis(heterocyclyl)alkanes,¹⁰⁴ and an oxazolone.¹⁰⁵

Dihydro-1,3-oxazines. The synthesis of oxazines from a diol containing both a tertiary and a secondary hydroxyl group is illustrated in the reaction shown on p. 237; treatment of 2-methyl-2,4-pentanediol with acetonitrile gave the 1,3-oxazine 13 in 44 % yield.⁸³

Aryl,⁸³ aralkyl,⁸³ and unsaturated nitriles⁸⁸ and dinitriles⁸⁵ have also been successfully employed. Unsaturated tertiary alcohols permit the synthesis of spirooxazines.^{84, 86} This unusual ring closure reaction was observed when either of the isomeric tertiary alcohols 13a and 13b was allowed to react with simple nitriles. A possible mechanism for the formation of 2,4,4-trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine

⁸³ E.-J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

⁸⁴ L. M. Trefonas, J. Schneller, and A. I. Meyers, *Tetrahedron Letters*, **22**, 785 (1961).

⁸⁵ A. I. Meyers, *J. Org. Chem.*, **25**, 145 (1960).

⁸⁶ A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963).

⁸⁷ A. I. Meyers, *J. Org. Chem.*, **26**, 218 (1961).

⁸⁸ J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

⁸⁹ S. Julia and C. Papantoniou, *Compt. rend.*, **260**, 1440 (1965).

⁹⁰ A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

⁹¹ A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

⁹² A. I. Meyers, B. J. Betrus, N. K. Ralhan, and K. B. Rao, *J. Heterocyclic Chem.*, **1**, 13 (1964).

⁹³ J. R. Lowell, Jr., and G. K. Helmkamp, *J. Am. Chem. Soc.*, **88**, 768 (1966).

⁹⁴ G. K. Helmkamp, D. J. Pettit, J. R. Lowell, Jr., W. R. Mabey, and R. G. Wolcott, *J. Am. Chem. Soc.*, **88**, 1030 (1966).

⁹⁵ D. S. Tarbell, D. A. Buckley, P. P. Brownlee, R. Thomas, and J. S. Todd, *J. Org. Chem.*, **29**, 3314 (1964).

⁹⁶ A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966).

⁹⁷ A. I. Meyers and G. García-Muñoz, *J. Org. Chem.*, **29**, 1435 (1964).

⁹⁸ A. Vigier and J. Dreux, *Bull. Soc. Chim. France*, 2292 (1963).

⁹⁹ O. Yu. Magidson, *Zh. Obshch. Khim.*, **33**, 2173 (1963) [*C.A.*, **59**, 13942f (1963)].

¹⁰⁰ D. L. Trepanier and co-workers, *J. Med. Chem.*, **9**, 881 (1966).

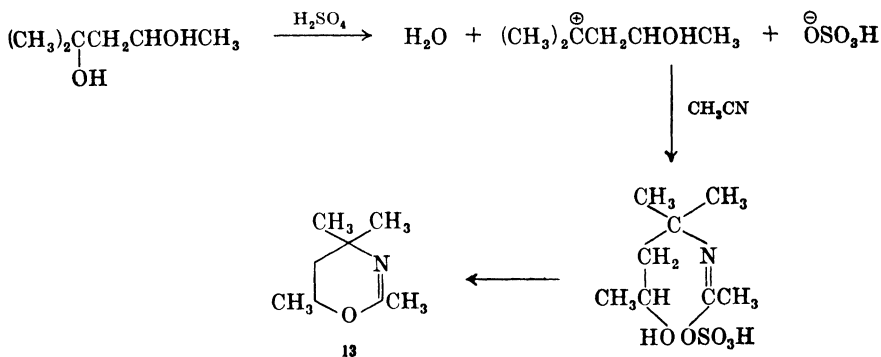
¹⁰¹ A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 4399 (1961).

¹⁰² A. I. Meyers and N. K. Ralhan, *J. Org. Chem.*, **28**, 2950 (1963).

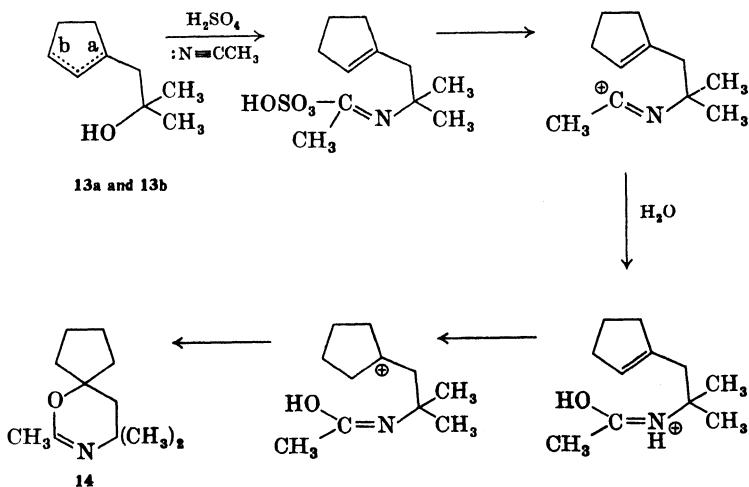
¹⁰³ A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 1682 (1961).

¹⁰⁴ A. I. Meyers, *J. Org. Chem.*, **25**, 2231 (1960).

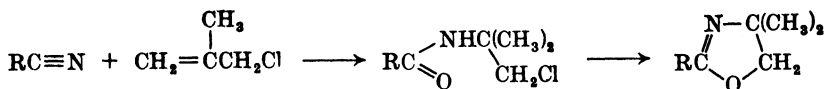
¹⁰⁵ C. W. Bird, *J. Org. Chem.*, **27**, 4091 (1962).



(14) follows. The yields from the 3-cyclopentenyl derivative, 13b, were approximately 20–30% higher than those from the 1-cyclopentenyl compound, 13a.⁸⁶

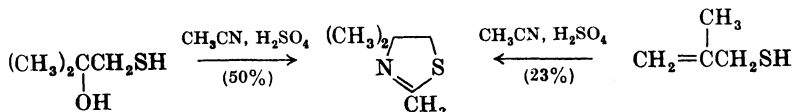


Oxazolines. Julia and Papantoniou prepared a series of β -chloroamides from methallyl chloride and various nitriles.⁸⁹ The amides could be cyclized easily by either potassium ethoxide or silver fluoroborate to give oxazolines.



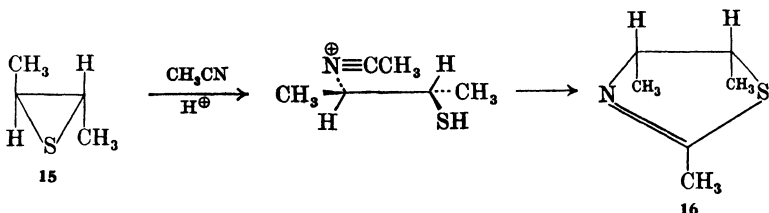
Dihydro-1,3-thiazines and Δ^2 -Thiazolines. Substitution of mercapto alcohols^{89, 87, 95, 96} or methallyl mercaptan⁹⁰ for the diols used in the

oxazine synthesis provided a new route to dihydro-1,3-thiazines and Δ^2 -thiazolines, respectively. The addition of 2-methyl-2-hydroxypropane-thiol or methallyl mercaptan to a cold solution of acetonitrile in concentrated sulfuric acid leads to the formation of 2,4,4-trimethyl- Δ^2 -thiazoline.

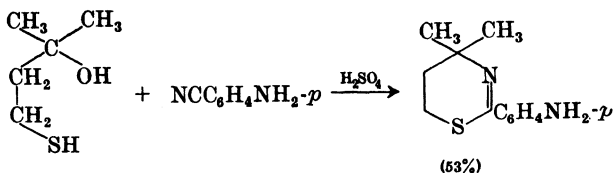


The higher yield obtained by using the mercapto alcohol was attributed to the fact that methallyl mercaptan polymerizes more readily than the alcohol in concentrated sulfuric acid.⁵⁹

A stereospecific synthesis of Δ^2 -thiazolines from episulfides has been reported.^{93,94} The proposed mechanism for this reaction involves protonation of the episulfide, ring opening by nucleophilic attack by the nitrile, and ring closure to form the thiazoline. The preparation of (4R:5S)-(-)-*cis*-2,4,5-trimethyl- Δ^2 -thiazoline (**16**) from (SS)-(-)-*trans*-2-butene episulfide (**15**) demonstrated that the reaction proceeds without racemization.⁹³

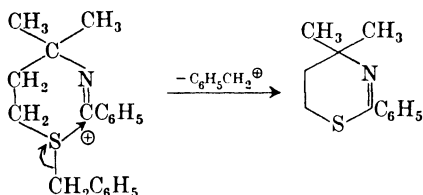


When butanethiol is employed, a dihydro-1,3-thiazine is obtained.^{59, 87} *p*-Aminobenzonitrile reacted with 3-methyl-3-hydroxy-*n*-butanethiol to give 2-(*p*-aminophenyl)-4,4-dimethyl-5,6-dihydro-1,3-thiazine. With



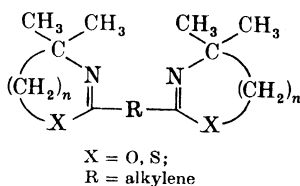
boron trifluoride etherate as catalyst for the formation of the thiazine, yields of 75% were reported.⁹⁵

Benzylmercaptobutanols have also been used to give the dihydro-1,3-thiazine with concomitant debenzoylation of the sulfide. The reaction probably involves attack by the nitrilium ion on the sulfide with expulsion of the benzyl cation. The existence of this cation has been verified by the isolation of *N*-benzylbenzamide.⁹⁵

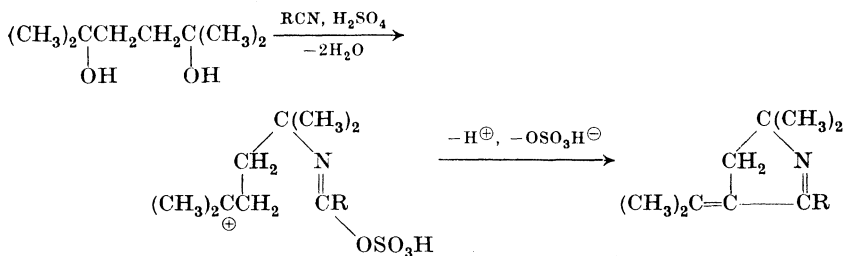


Bis(heterocyclyl)alkanes. The reactions leading to the heterocycles described in the preceding paragraphs can be made to furnish *bis*(heterocyclyl)alkanes by employing dinitriles. The ring closure may be directed to the formation of a mono- or di-cyclic product by utilizing the proper quantities of dinitrile and alcohol.

The addition of 2,5-dimethyl-2,5-hexanediol, 2-methyl-2,4-pentanediol, or 4-mercapto-2-methyl-2-butanol to a dinitrile in sulfuric acid yielded N-heterocyclic bases of the following type.¹⁰⁴



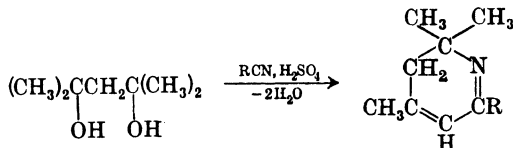
1-Pyrrolines and 5,6-Dihydropyridines. A series of 1-pyrrolines was prepared by heating 1,4-diols with various nitriles.^{90, 91} The yields



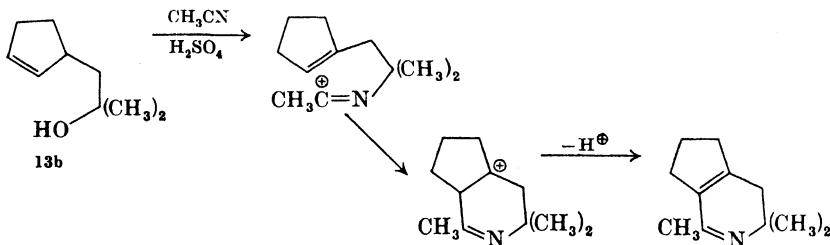
are 60–80% with the diols. Under the same conditions, however, 2,5-dimethyl-2,5-hexadiene gave the corresponding pyrroline in a much smaller yield (28%) as a consequence of a competing polymerization.⁹⁰

Replacement of the 1,4-diols by 1,3-diol 2,4-dimethylpentane-2,4-diol permits the preparation of a variety of 5,6-dihydropyridines. The yields are considerably lower (~20%) because of cleavage of the diol to acetone

and isobutene. From the 1,3-diol and acetonitrile the *N*-*t*-butylacetamide was isolated in 50–55 % yield.⁹⁰



In the course of their studies on oxazine preparation Meyers and co-workers discovered that by controlling the water activity the reaction could be modified to give dihydropyridines exclusively.⁸⁶ Treatment of α -(3-cyclopentenyl)-*t*-butyl alcohol (**13b**) with acetonitrile in sulfuric acid concentrations above 93 % led to an azocarbonium ion that lost a proton to give 3,4-cyclopenteno-5,6-dihydropyridine.



A similar reaction with α -(1-cyclohexenyl)-*t*-butyl alcohol (**15a**) gave the spirodihydropyridine **18** (see Chart I) along with an isoquinoline **17**.⁹²

Isoquinolines. 3,4-Dihydroisoquinolines have been obtained by the reaction of methyleugenol with alkoxyarylnitriles³⁴ and of isosafrol or methylisoeugenol with a variety of nitriles.⁵⁴ For example, veratronitrile and methyleugenol give 1-(3',4'-dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in 53 % yield.³⁴

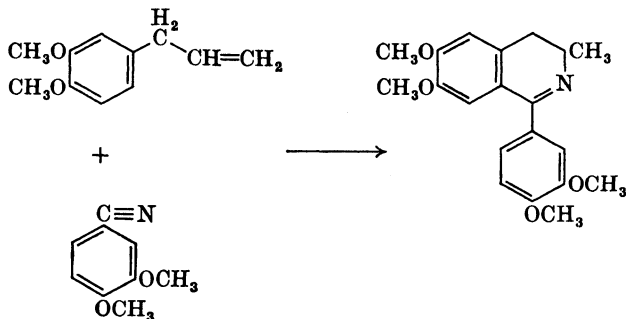
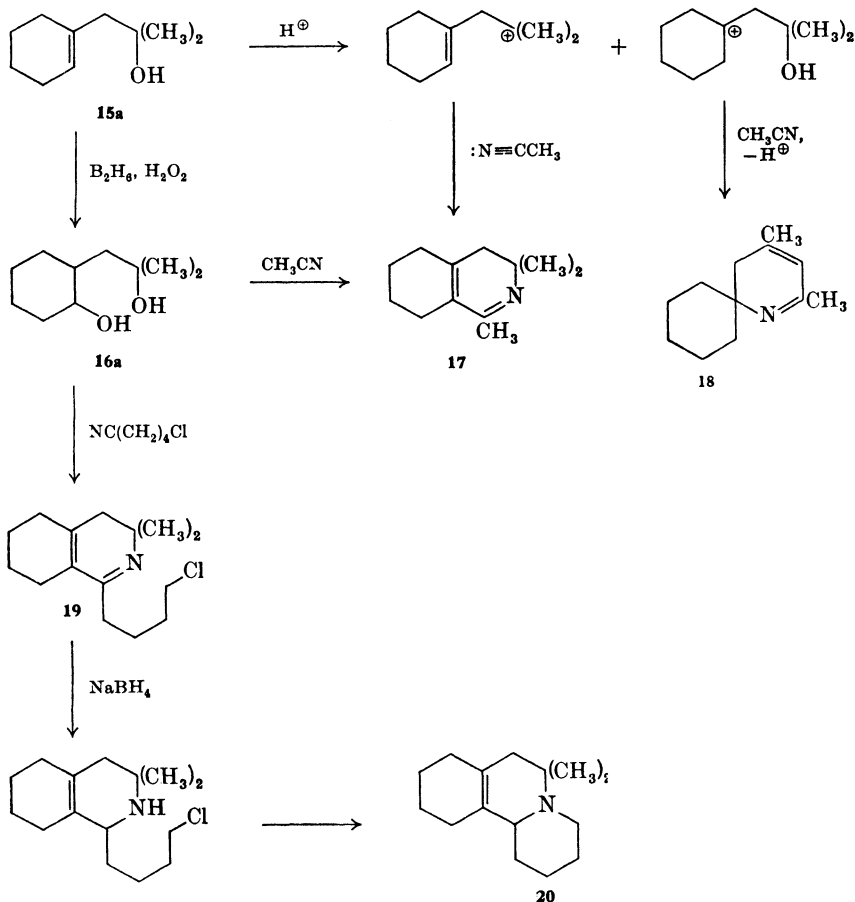


CHART I

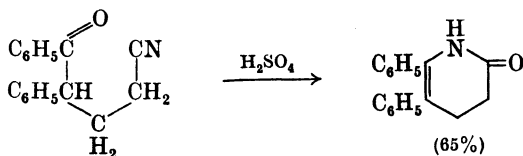


In an attempt to circumvent the formation of the spiro base **18** (Chart I) Meyers utilized the glycol **16a**; however, the desired isoquinoline **17** was obtained in only 30% yield.

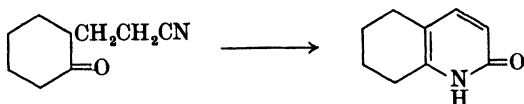
In another modification the same glycol, **16a**, was treated with δ -chlorovaleronitrile to give the hexahydroisoquinoline **19**. Reduction followed by cyclization afforded the quinolizine **20**.

2-Pyridones and 2-Quinolones. The use of keto nitriles in the Ritter reaction provides a direct route to 3,4-dihydro-2-pyridones^{98, 99} and 2-quinolones.⁹⁷ (The synthesis of 5,6-dihydro-2-pyridones is discussed on p. 246.) An example of the dihydropyridone synthesis is given in the

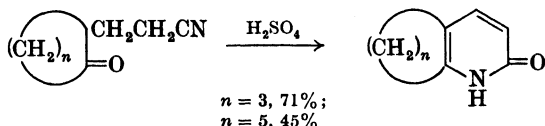
accompanying equation.⁹⁹ A similar approach was applied to 2-(2-cyano-



alkyl)cyclohexanones, which formed the corresponding cycloalkano[e]-2-pyridones by means of a consecutive cyclization-aromatization. When 2-(2-cyanoethyl)cyclohexanone was allowed to stand in sulfuric acid for 3 hours at room temperature, 5,6,7,8-tetrahydro-2-quinolone was formed.⁹⁷



Aromatization also occurred when the corresponding cyclopentanone and cycloheptanone nitriles were cyclized in sulfuric acid.⁹⁷

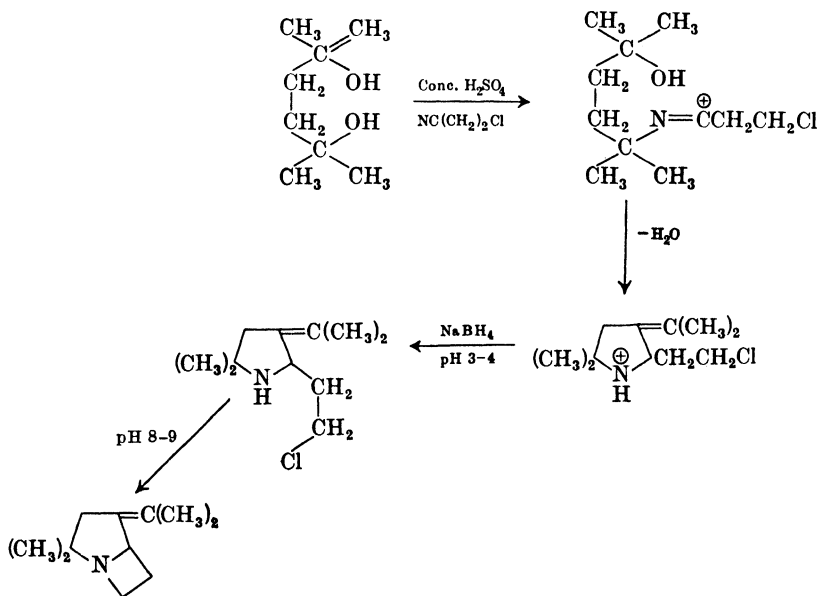


1-Azabicycloalkanes. A new approach to polycyclic bases utilizing the Ritter reaction was investigated by Meyers and co-workers.^{101-103, 106} The method involves the treatment of a ditertiary glycol with an ω -chloronitrile to give an ω -chloroalkyl-1-pyrroline. Subsequent reduction and cyclization via intramolecular alkylation yields the 1-azabicycloalkane.

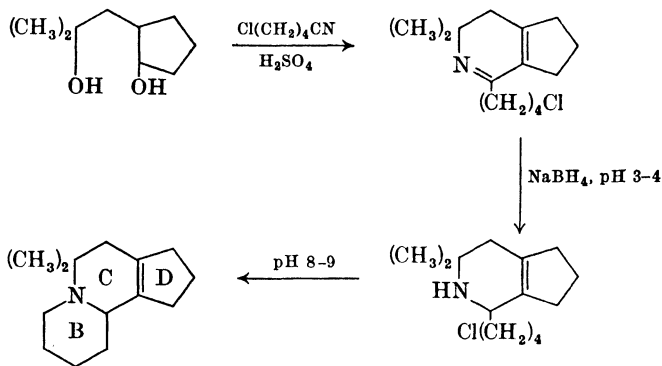
The formation of 1-azabicyclo[3.2.0]heptane in 30% yield is illustrative of this unique reaction which takes place in a single step without isolation of the intermediate 2-chloroethyl-1-pyrroline. By substituting 4-chlorobutyronitrile or 5-chlorovaleronitrile the analogous 1-azabicyclo[3.3.0]- or [4.3.0]-cycloalkanes can be obtained in equally good yields¹⁰¹ (p. 243).

Cyclopenteno[d]-1-azabicycloalkanes have also been synthesized by this procedure from α -(2-hydroxycyclopentyl)-*t*-butyl alcohol and the appropriate chloronitrile.¹⁰² The route outlined below affords the final tricyclic

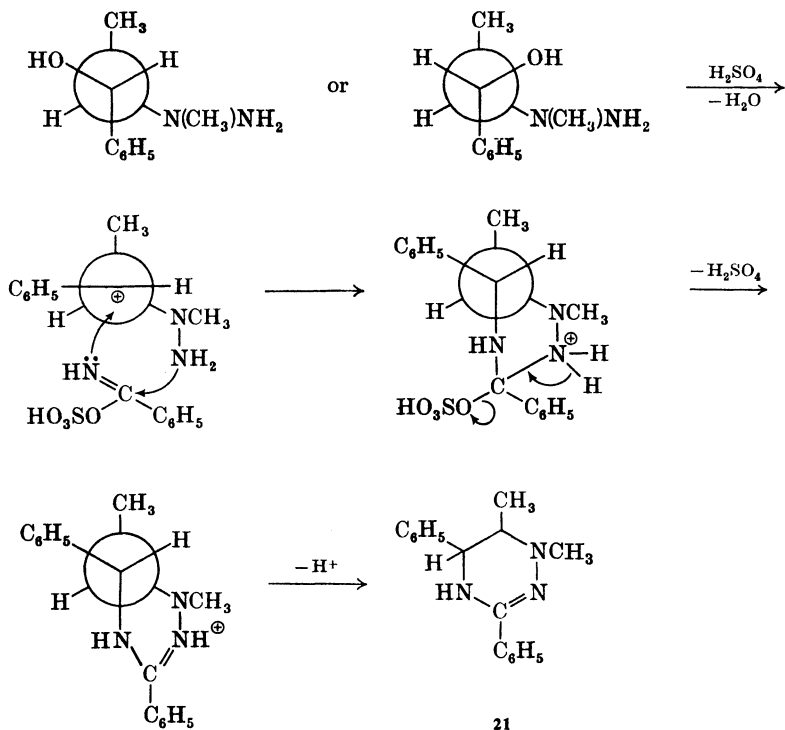
¹⁰⁶ A. I. Meyers and H. Singh, to be published.



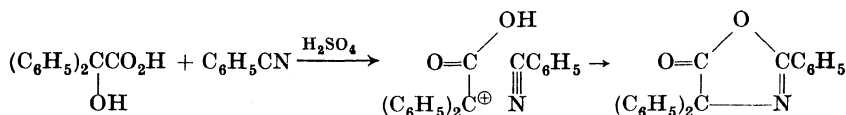
compound in 46% overall yield and represents the formation of rings B, C, and D of an azasteroid nucleus.



1,4,5,6-Tetrahydro-*as*-triazines.¹⁰⁰ Hydrazino alcohols containing a tertiary aliphatic or secondary benzylic hydroxyl group condense with a variety of nitriles to give triazines. N-Amino-(—)-ephedrine reacted with benzonitrile to give *trans*-(+)-1,6-dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine (**21**). The reaction appears to proceed by attack of the nitrilium sulfate on the carbonium ion resulting from the dehydration of the hydrazino alcohol.



2,4,4-Triphenyl-5-oxazolone. The treatment of benzoic acid and benzonitrile with concentrated sulfuric acid by Japp and Findlay represents the earliest report of a reaction of the Ritter type.¹⁰⁷ Reinvestigation of this reaction confirmed the participation of the $(\text{C}_6\text{H}_5)_2\text{CCO}_2\text{H}^+$ cation to give 2,4,4-triphenyl-5-oxazolone.¹⁰⁵



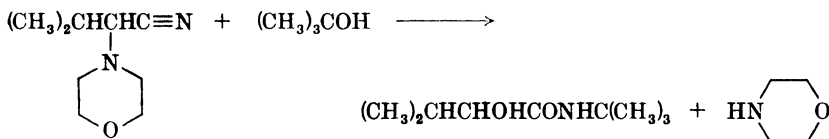
The Nitrile Source

The general applicability of the reaction to nitriles of various structures is evident from Ritter's original investigation.¹ The reactions described in the preceding sections and those referred to in the tables further exemplify the great variety of compounds which have been utilized as a source of the $\text{C}\equiv\text{N}$ group.

¹⁰⁷ F. R. Japp and A. Findlay, *J. Chem. Soc.*, 75, 1027 (1899).

Although the yields of *t*-alkylamides are not markedly affected by the nitrile structure, there is a decrease in the sequence, $\text{CH}_2=\text{CHCN} > \text{C}_6\text{H}_5\text{CN} > \text{CH}_3\text{CN}$ in the reaction with isobutene,²⁸ methylbutene, and isooctene.¹ Thus a phenyl group or a double bond in conjugation with the nitrile exerts a favorable but not a major influence.²⁸ The effect of strongly electronegative substituents in the α position was described for camphene (p. 221); however, there is insufficient experimental evidence to extend this to other alkenes that undergo Wagner rearrangements.

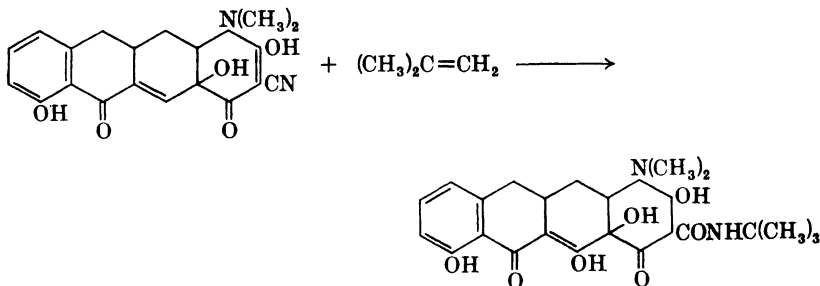
An unexpected result was obtained with α -morpholinyl nitriles.¹⁰⁸ When the β -carbon atom is tertiary, an α -hydroxyamide is produced.



Similar products are obtained if the α -amino substituent contains groups larger than methyl.

Some unusual sources of the nitrile group have been reported. In an attempt to prepare alkyl isonitriles, Heldt obtained the corresponding N-alkylformamides from hexacyanoferric(II) acid and *t*-butyl alcohol, *t*-amyl alcohol, or 1-butene. It is not certain that this acid furnished the $\text{—C}\equiv\text{N}$ group, since gaseous hydrogen cyanide was present during the reaction.¹⁰⁹

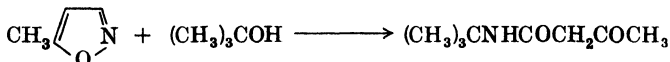
The acid stability of 6-deoxytetracyclines has made possible the conversion of the 2-cyano compound to the corresponding carboxamide by means of the Ritter reaction. For example, the reaction of isobutene with 6-demethyl-6-deoxytetracyclinonitrile gave N²-*t*-butyl-6-demethyl-6-deoxytetracycline.



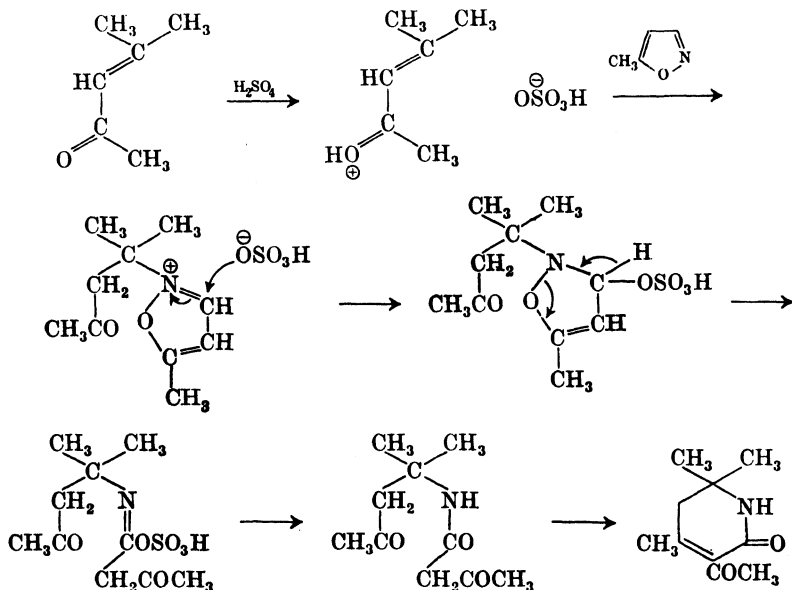
¹⁰⁸ D. Giraud-Clenet and J. Anatol, *Compt. Rend.*, **262**, 224 (1966).

¹⁰⁹ W. Z. Heldt, *J. Org. Chem.*, **26**, 3226 (1961).

Eugster and co-workers employed 5-methyl- and 5-phenyl-isoxazole in an unusual extension of the Ritter reaction.¹¹⁰ Under acid conditions these compounds behave as cyanoacetones and give the corresponding Ritter products. The reaction of 5-methylisoxazole with *t*-butyl alcohol yields *N*-*t*-butylacetoacetamide.



With α,β -unsaturated ketones, the isoxazole forms 5,6-dihydro-2-pyridones. The proposed mechanism follows.



Cyanogen chloride was found to react under Ritter conditions with olefins containing internal or substituted terminal double bonds. Although the yields are considerably lower, the amine is obtained directly without the hydrolysis required when hydrogen cyanide is used.¹¹¹

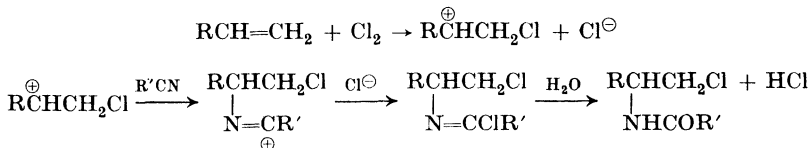
RELATED SYNTHETIC PROCESSES

Halogens and Halogen Acids as Catalysts. A similar reaction has been conducted in media other than strong acids. These modifications of the Ritter reaction conditions have added to the general applicability of this procedure for the preparation of *N*-substituted amides.

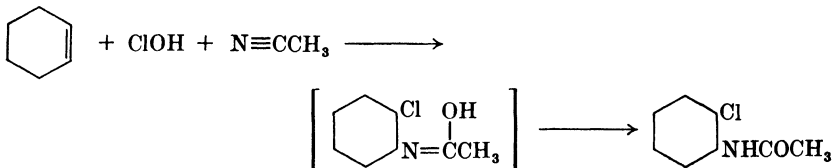
¹¹⁰ C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta.*, **46**, 543 (1963).

¹¹¹ E. M. Smolin, *J. Org. Chem.*, **20**, 295 (1955).

Cairns and co-workers showed that the interaction of chlorine and an olefin in the presence of a nitrile yielded an imidoyl chloride which could be hydrolyzed readily to an N-(2-chloroalkyl)amide.¹¹² 2-Haloalkylamines were obtained when hydrogen cyanide was the nitrile source. A comparable reaction was described by Theilacker who added hypochlorous

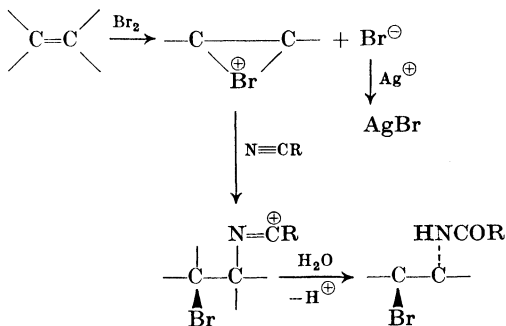


acid to cyclohexene and used aqueous acetonitrile as a solvent.¹¹³ The unexpected participation of acetonitrile yielded N-(2-chlorocyclohexyl)-acetamide. When α,β -unsaturated acids are used in place of olefins,



hydrolysis yields the β -amino α -hydroxy-carboxylic acids in yields up to 70%.

The use of bromine has also been reported.¹¹⁴ In this case the nitrile opens the intermediate cyclic bromonium ion and incorporates itself into the molecule in a stereospecific manner. The reaction proceeds only when the halide anion liberated from the original halogen is removed from solution.

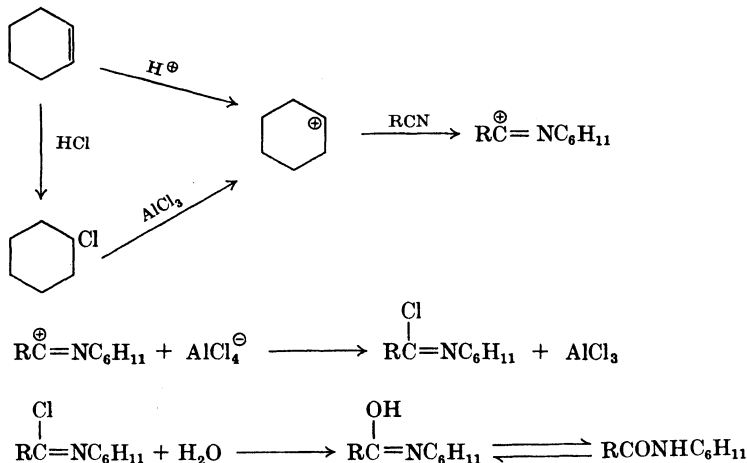


¹¹² T. L. Cairns, P. J. Graham, P. L. Barrick, and R. S. Schreiber, *J. Org. Chem.*, **17**, 751 (1952).

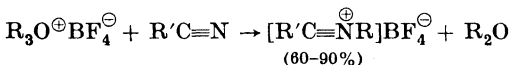
¹¹³ W. Theilacker, *Angew. Chem., Intern. Ed. Engl.*, **6**, 94 (1967).

¹¹⁴ A. Hassner, L. Levy, and R. Gault, *Chem. Eng. News*, **44**, 44 (April 11, 1966).

Friedel-Crafts Catalysts. *N*-Cyclopentyl- and cyclohexyl-amide were prepared in 5–55 % yields by the reaction of nitriles with cyclopentene and cyclohexene under conditions of the Gattermann aldehyde reaction.¹¹⁵ Bromine and iodine were also used to facilitate the aluminum chloride-catalyzed reaction.



The results indicated that the Ritter method is superior with respect to both yields and simplicity. It is noteworthy that primary and tertiary alkyl halides failed to give isolable amides.¹¹⁵ The reactions of trialkyl oxonium fluoborate salts with nitriles to give nitrilium salts have been described.¹¹⁶ Subsequent hydrolysis yields the corresponding *N*-alkyl acid amides.



The synthesis of heterocyclic compounds from nitrilium salts has been investigated by Lora-Tamayo and co-workers.^{117–122} They were able to prepare 3,4-dihydro-isoquinolines,¹¹⁸ -papaverines,¹¹⁹ -quinazolines,¹²⁰ 4,5-diphenyloxazoles,¹²¹ and 4,4,6-trimethyl-4H-1,3-oxazines¹²² by cyclization of suitable nitrilium intermediates. The nitrilium salts were formed

¹¹⁵ G. W. Cannon, K. K. Grebker, and Y. Hsu, *J. Org. Chem.*, **18**, 516 (1953).

¹¹⁶ H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).

¹¹⁷ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ind.*, (London) 657 (1959).

¹¹⁸ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ber.*, **93**, 289 (1960).

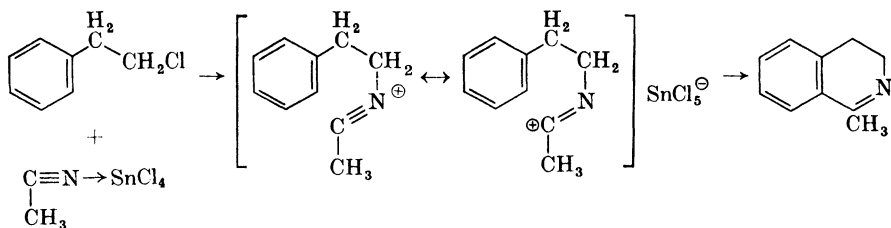
¹¹⁹ M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, J. M. Marzal, and M. Stud, *Chem. Ber.*, **94**, 199 (1961).

¹²⁰ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ber.*, **94**, 208 (1961).

¹²¹ M. Lora-Tamayo, R. Madroñero, and H. Leipprand, *Chem. Ber.*, **97**, 2230 (1964).

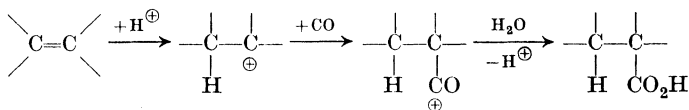
¹²² M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, and H. Leipprand, *Chem. Ber.*, **97**, 2234 (1964).

by the action of a metal halide-nitrile complex. Thus, by heating equimolecular amounts of β -chloroethylbenzene and the tin tetrachloride-acetonitrile complex, a 91% yield of 1-methyl-3,4-dihydroisoquinoline



was obtained.¹¹⁸ Although the yields vary considerably, the method provides a facile route to the heterocycles cited.

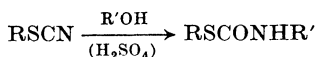
Koch-Haaf Reaction. The reaction of carbonium ions with carbon monoxide in sulfuric acid followed by hydrolysis to give carboxylic acids is known as the Koch-Haaf reaction. Carbon monoxide, either generated *in situ* from formic acid¹²³ or supplied as the gas under pressure,¹²⁴ has been used to produce branched carboxylic acids in good yields from alkenes.



The reaction has been extended to include alcohols, alkyl chlorides, esters, and paraffins as the carbonium ion source.^{123, 124}

In a comparative study of the Koch-Haaf and Ritter reactions Christol and Solladie furnished evidence that the nucleophilic reagent, carbon monoxide, has greater reactivity than its counterpart, the nitrile, particularly with the compounds containing a phenyl group.¹² Indeed, whereas the Ritter reaction failed with diphenylmethylcarbinol,⁴⁰ the Koch-Haaf reaction furnishes the corresponding carboxylic acid in 18% yield.¹²

Thiocarbamate Synthesis. The preparation of *N*-substituted thiocarbamates from thiocyanates, using methods analogous to that of the Ritter reaction, was described by Riemschneider.¹²⁵ He found that thiocyanates react with alcohols and olefins in the presence of sulfuric acid to give products which, on hydrolysis, yield *N*-substituted thiocarbamates.

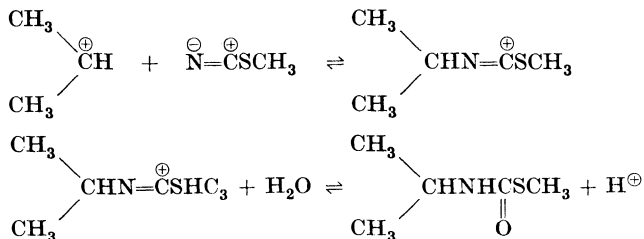


¹²³ H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958).

¹²⁴ W. Haaf and H. Koch, *Ann.* **638**, 122 (1960).

¹²⁵ R. Riemschneider, *J. Am. Chem. Soc.*, **78**, 844 (1956).

The formation of these thiocarbamates from a carbonium ion may be formulated in the following way. Primary alkyl thiocyanates react with



alcohols and olefins to give the desired thiocarbamates in good yields; 1,4-dithiocyanatobutane and 1,5-dithiocyanatopentane yielded the expected N,N'-substituted *bis*-thiocarbamates.

EXPERIMENTAL CONDITIONS

Nature of the Acid. Perchloric,¹⁹ phosphoric,⁵⁷ polyphosphoric^{45, 46, 49-51} formic,^{68, 69} substituted sulfonic acids,^{5, 26, 111} and boron trifluoride⁹⁶ have been used as reagents in the Ritter reaction. The best yields have been reported for the reactions which were conducted in 85-90% sulfuric acid.

A detailed study of the effect of various mineral acids on the formation of N-*t*-butylacrylamide in acetic anhydride showed that the highest yields resulted from the use of sulfuric acid.²⁸ This report and others^{19, 24, 26, 68, 70} describe lower yields when other acids are substituted for sulfuric acid, thus supporting the particular role of sulfuric acid or the bisulfate anion in the Ritter reaction.

Glacial acetic acid has frequently been employed as a diluent; however, Benson and Ritter reported that secondary alcohols would not react under these conditions.⁵⁵ It is noteworthy that esterification competes with amide formation yielding acetates and giving lower yields.^{28, 57}

Nature of the Solvent. In addition to glacial acetic acid, other polar and non-polar solvents have been used. They include acetic anhydride, di-*n*-butyl ether, chloroform, carbon tetrachloride, hexane, and nitrobenzene.

Christol and Solladie made a comparison of products using 96% sulfuric acid with and without solvent.¹¹ They concluded that in highly polar solvents the attacking nitrile is strongly polarized and becomes solvated, resulting in enhancement of its nucleophilic reactivity. On the other hand, in non-polar solvents such as carbon tetrachloride the solvation phenomena are less important since the medium is less polar. In this case the yields are generally lower.

A related study by Glikmans and co-workers employing di-*n*-butyl ether and dioxane gave similar results, and the Ritter reaction failed completely in the presence of methanol or ethanol.²⁸

Reaction Time and Temperature. An examination of the experimental data clearly demonstrates that there is no rigid pattern, but a great number of variations both in reaction time and temperatures. Generally the reaction temperatures are mild; that is, in the 25–50° range. The use of liquid hydrogen cyanide, of course, necessitates temperature in the 0–10° range, and there are a few examples of the reaction proceeding at lower temperatures.³⁶

The reaction time is also quite variable. Swern reported times as brief as 15 minutes, and related time to reaction size.^{19, 42} With lower temperatures, longer reaction times have been used. A study of the influence of time versus yield was reported for the reaction of isobutene with acrylonitrile at 25°. The results show that the reaction is 96.5% complete after 3 hours and that extending the reaction time to 16 hours provides only an increase of 1.9% in the yield of *N*-*t*-butylacrylamide.²⁸

EXPERIMENTAL PROCEDURES

N-Benzylacrylamide. Preparation from acrylonitrile and benzyl alcohol in 59–62% yield is described in *Organic Syntheses*.⁵⁶

***N*-*t*-Butylacetamide.**¹ Gaseous isobutene (12 g., 0.21 mole) is led into a solution of 4.5 g. (0.11 mole) of acetonitrile in 50 ml. of glacial acetic acid containing 10 g. (0.1 mole) of concentrated sulfuric acid while the temperature is maintained at about 20°. The reaction vessel is then stoppered loosely and allowed to stand overnight. The reaction mixture is poured into 200 ml. of water, neutralized with sodium carbonate, and extracted with five 50-ml. portions of diethyl ether. The combined extracts are dried over anhydrous potassium carbonate, most of the ether is removed at 50°, and the remainder is evaporated at room temperature. The residue (11 g., 85%) is recrystallized from hexane as needles, m.p. 97–98°, b.p. 194° (cor.).

1-Methylcyclohexylamine.⁶⁰ 1-Methylcyclohexanol (114 g., 1.0 mole) is slowly added to a previously cooled mixture of 122 g. (4.5 moles) of liquid hydrocyanic acid in 131 g. (1.34 moles) of concentrated sulfuric acid, the temperature being maintained below 0°. This temperature is maintained for 1 hour after completion of the addition. The reaction mixture is then allowed to stand at 25–30° for 24 hours, after which it is cooled and 250 g. of ice and 250 g. of 50% aqueous sodium hydroxide are added. The mixture should be at pH 9; if not, additional sodium hydroxide solution is added.

The reaction mixture is then heated at 50–60° for 4 hours. Sodium hydroxide pellets (50 g.) are added, and the mixture is steam-distilled. The organic distillate is separated and dried over potassium hydroxide. Distillation at 31–38°/8–10 mm. gives 70 g. (60%) of 1-methylcyclohexylamine.

1-Phenylethylamine.⁸ Concentrated sulfuric acid (30 ml.) is added dropwise with stirring to a solution of 12.2 g. (0.1 mole) of 1-phenylethanol in 75 ml. of di-*n*-butyl ether in which is suspended 16.25 g. (0.25 mole) of potassium cyanide. The temperature rises rapidly but is maintained between 60° and 80° by external cooling. After the addition, agitation is continued for 1 hour at 50°. The reaction mixture is then poured onto 300 g. of ice, made alkaline with 20% aqueous sodium hydroxide, and extracted with diethyl ether. The ethers are removed, and the resulting oil is heated under reflux for 3 hours with twice its volume of concentrated hydrochloric acid. After the solution has cooled, it is extracted with ether to remove any impurities. The water layer is made alkaline, and the amine extracted with ether. The ether extracts are dried over anhydrous potassium carbonate and fractionally distilled; the yield is 70.2 g. (60%) of a colorless oil, b.p. 91°/20 mm.

Ethyl 3-propionamido-3-phenylbutyrate.⁶² Concentrated sulfuric acid (10 ml.) is added dropwise with stirring to a mixture of 0.05 mole of ethyl 3-hydroxy-3-phenylbutyrate and 0.06 mole of propionitrile at 0° over a period of 30 minutes. The mixture, which becomes viscous after about half of the sulfuric acid is added, is left standing overnight at room temperature and is then poured into 100 ml. of ice water. The amido ester is collected by filtration and crystallized from methylcyclohexane. The yield of crystals, m.p. 83°, is 73%.

Di-N-*t*-butyladipamide.⁷¹ A solution of 0.05 mole of adiponitrile and 0.1 mole of methyl *t*-butyl ether in 10 ml. of glacial acetic acid is added with stirring and cooling (30°) to a solution of 10 g. of 100% sulfuric acid in 20 ml. of glacial acetic acid. After 3 hours the reaction mixture is poured into water. The di-N-*t*-butyladipamide that precipitates is isolated by filtration. The yield of the diamide, m.p. 212°, is 75%.

Methylene-*bis-p*-toluamide.⁶⁸ A solution of 1.5 g (0.05 mole) of trioxane in 11.7 g. (0.1 mole) of *p*-tolunitrile is added slowly with stirring to 38 ml. of 85% sulfuric acid in a 125-ml. three-necked flask. The temperature is maintained at 30° by cooling with an ice bath. After 3 hours the solution is poured into 300 ml. of ice and water. Methylene-*bis-p*-toluamide separates as white crystals which are filtered and recrystallized from 95% ethanol. The yield is 12.4 g. (83%) of crystals melting at 209–210°.

N-(Benzamidomethyl)acrylamide.⁷⁵ A mixture of 7.6 g. (0.05

mole) of *N*-methylolbenzamide and 3.7 g. (0.07 mole) of acrylonitrile is added slowly to 50 ml. of 96% sulfuric acid with stirring. The temperature is kept at 30° by cooling. At the end of 1 hour the reaction mixture is poured into 200 g. of ice and water. The crystalline product which precipitates is filtered and recrystallized from water to give 6.0 g. (60%) of *N*-(benzamidomethyl)acrylamide. This compound polymerizes in the melting-point tube when it is heated above 150°.

***N*-*t*-Butylphenylacetamide.**⁶⁶ A mixture of 11.7 g. (0.1 mole) of benzyl cyanide, 9.25 g. (0.1 mole) of *t*-butyl chloride, and 24 g. of 90% formic acid is heated under reflux for 5 hours and poured into a mixture of ice and water. The solid that precipitates is filtered and dried. The yield of amide melting at 111–113° is 4.3 g. (23%).

Acetamidostearic Acid.¹⁹ A mixture of 282 g. (1.0 mole) of oleic acid and 123 g. (3.0 moles) of acetonitrile in a cylindrical dropping funnel is stirred vigorously and added during 35 minutes to 338 ml. (6 moles) of 95% sulfuric acid in a 2-l. three-necked flask fitted with a thermometer and an efficient stirrer. The reaction temperature is maintained between 27° and 30° by external cooling. Fifteen minutes after addition is complete, the mixture is poured with stirring onto approximately 2 l. of chopped ice and water. The soft, sirupy, insoluble mass is stirred occasionally and then allowed to stand overnight in the dilute acid. The following morning, stirring is continued until the product hardens to a crumbly, wax-like solid which is filtered, washed several times with cold water, and dried; the yield of crude acetamidostearic acid, m.p. 56–58°, is 339 g. (99%).

4-Methyl-4-benzamido-2-pentanone.⁷² To a solution of 19.6 g. (0.2 mole) of mesityl oxide and 22.0 g. (0.21 mole) of benzonitrile is added 20 ml. of concentrated sulfuric acid. The temperature is kept below 30° by means of an ice bath. After addition is complete, the reaction mixture is warmed to 50° and is kept at this temperature for 1 hour. The dark, viscous liquid is poured into 300 ml. of ice cold water. The resulting solid is filtered and washed with 10% aqueous potassium carbonate, then with water. The yield, m.p. 98–100°, is 20–24 g. (45–55%). Recrystallization from cyclohexene and dilute ethanol furnishes white needles, m.p. 100–101°.

3-Dichloroacetamidoisocamphane.³⁶ Sulfuric acid (20 ml., 98%) is added with stirring, at a temperature below –15°, over a period of 1 to 1½ hours to a solution of 44.3 g. of camphene and 43.0 g. of dichloroacetonitrile in 20 ml. of propionic acid. The reaction mixture is kept for 2 days at –20° to –15°; then it is poured onto 300 ml. of ice water, the aqueous solution neutralized with sodium carbonate, the crystalline precipitate collected by filtration and dried in a vacuum desiccator over phosphorus

pentoxide. After recrystallization from 150 ml. of petroleum ether (b.p. 70–100°), 50.2 g. of material (m.p. 106–108°) is obtained; a further 10 g. of the material is isolated from the mother liquor by evaporation of part of the solvent and recrystallization. The total yield is 60.2 g. (69.7%).

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine.⁸³ Benzonitrile (20.6 g., 0.2 mole) is added dropwise with stirring to 100 g. of 92% sulfuric acid at 2–4° over 20 minutes. Then 23.6 g. (0.2 mole) of 2-methyl-2,4-pentanediol is added dropwise with stirring at 3–6° during 2 hours. The resulting solution is poured with stirring on 1 kg. of cracked ice, and the mixture is half-neutralized with 40% aqueous sodium hydroxide, then extracted with several portions of diethyl ether. The combined ether extracts are dried over anhydrous potassium carbonate and, after removal of the ether, the residual oil is distilled through a 30-cm. vacuum-jacketed Vigreux column. Two recrystallizations from ethanol-water (the compound is dissolved at room temperature, and the solution is then strongly cooled) give colorless crystals, m.p. 34–35°.

2-(*p*-Aminophenyl)-4,4-dimethyl- Δ^2 -thiazoline.⁵⁹ To a solution of 3.5 g. (0.03 mole) of *p*-aminobenzonitrile in 25 ml. of concentrated sulfuric acid previously cooled to 3° is added with stirring 2.1 g. (0.02 mole) of 2-hydroxy-2-methylpropanethiol during 30 minutes. The reaction mixture, which is golden yellow, is stirred at 3–5° for an additional hour; then it is poured on 300 g. of chipped ice. The cold, aqueous acid solution is then extracted with chloroform until the chloroform layer is colorless. After the aqueous solution has been poured through fluted filter paper to remove the excess chloroform, it is carefully neutralized with 30% aqueous sodium hydroxide. The heterocyclic base appears as a crude brown solid which is collected in a Buchner funnel and then washed several times with hot water to remove any unchanged nitrile. Recrystallization from aqueous ethanol yields 2.3 g. (55%) of a very light yellow crystalline material, m.p. 162–164°. The picrate melts at 91–93°.

2-Vinyl-1-pyrroline.¹⁰⁴ To a cold solution of 14.0 g. (0.10 mole) of 3,3'-thiodipropionitrile¹²⁶ in 100.0 ml. of concentrated sulfuric acid is added with stirring 29.6 g. (0.20 mole) of 2,5-dimethyl-2,5-hexanediol. The temperature of the reaction is kept below 10° by employing an ice bath. After the glycol addition has been completed, the mixture is stirred for an additional hour at 4–6° and then slowly poured over 300 g. of chipped ice. The aqueous acid solution, after it has been shaken several times with 75-ml. portions of chloroform to extract polymeric material, is cautiously neutralized with 30% aqueous sodium hydroxide. The heterocyclic base, which separates, is taken up in diethyl ether and dried overnight with potassium carbonate. After the ether is removed at atmospheric pressure,

¹²⁶ F. M. Cowen, *J. Org. Chem.*, **20**, 287 (1955).

the residual oil is distilled under reduced pressure to give a light yellow oil, b.p. 86–87°/1.25 mm.; n_D^{30} 1.5019.

1-(3',4'-Dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline.³⁴ Veratronitrile (9.8 g., 0.06 mole) is added portionwise to concentrated sulfuric acid (15 ml.) in an ice bath with rapid stirring. Methyleugenol (10.2 ml., 0.06 mole) is then added during 2 minutes. The cooling bath is removed before addition of the methyleugenol, and the temperature, which rises rapidly during the addition, is maintained around 80° by intermittent cooling. After it has stood at room temperature for 3 days, the reaction mixture is poured into water and neutralized with sodium carbonate. A yellow mass separates which gradually crystallizes on stirring in warm water. It is filtered, washed with water, and dried. The crude dihydroisoquinoline (11.5 g., 53 %) is crystallized from aqueous ethanol as yellow crystals (6.7 g.) melting at 134–137°. Recrystallization yields a product melting at 138–139°.

5,6-Diphenyl-1,2,3,4-tetrahydro-2-pyridone.⁹⁹ In a flask fitted with a mechanical stirrer is placed 20 ml. of 90 % sulfuric acid, and 10 g. (0.04 mole) of γ -benzoyl- γ -phenylbutyronitrile is added in 5 minutes at 25–27°. Solution is quite rapid with the evolution of a little heat. The stirring is continued for 3 hours, after which the mixture is allowed to stand overnight. The next day, the viscous, brownish-red solution is poured with stirring over 200 g. of cracked ice. The precipitate forms as a whitish lump. The dilute acid is decanted, the lump is treated with 150 ml. of water, and the mixture is heated on the steam bath. The mass disintegrates and becomes crystalline. It is crushed, filtered, washed with water to remove the acid, treated with 3 % aqueous ammonia; after it has stood in the ammonia solution for an hour, it is filtered, washed with water, and dried. Recrystallization from ethyl Cellosolve gives 6.0 g., and an additional 0.5 g. is isolated from the mother liquors. The yield, m.p. 218–219°, is 65 %.

2,2-Dimethylcyclopenteno(d)-1-azabicyclo[4.4.0]decane.¹⁰² To a cold (0–3°) solution of 9.05 g. (0.077 mole) of δ -chlorovaleronitrile in 150 ml. of 98 % sulfuric acid is added dropwise 11.06 g. (0.07 mole) of α -(2-hydroxycyclopentyl)-*t*-butyl alcohol. During the addition efficient stirring is maintained and the temperature of the mixture is kept below 10°. The time required for the complete addition of the glycol under these conditions is approximately 1½ hours.

The deep reddish reaction mixture is slowly poured over 500 g. of chipped ice in a 2-l. beaker. (The following two reactions, i.e., the sodium borohydride reduction and the intramolecular alkylation, are carried out in this vessel.) The aqueous acid solution is extracted several times with chloroform to remove insoluble polymeric material and then partially

neutralized (to pH 2-4) with 35% aqueous sodium hydroxide. The temperature is maintained below 40° during the neutralization with the aid of external cooling. The electrodes of a pH meter (Beckman Zero-matic) are inserted into the solution and the acidity is adjusted to pH 3-4 by the addition of 4*M* sulfuric acid and 6*M* sodium hydroxide which are contained in burets situated above the beaker. The clear solution is cooled to room temperature, and a freshly prepared solution of sodium borohydride (2.66 g., 30 ml. of water, and one drop of 35% sodium hydroxide) is added dropwise with stirring supplied by a magnetic stirrer.

The pH of the reaction during the borohydride addition is constantly kept between 3 and 4 by the periodic addition of sulfuric acid or sodium hydroxide. The sodium borohydride addition is complete after 1 hour at 25°. The solution is allowed to stir at room temperature overnight and is then acidified to pH 1 and stirred for 1 hour to destroy the excess sodium borohydride. After addition of 300 ml. of water the pH is again adjusted to 8-8.5 and the solution is stirred for 5 hours. The oil that separates is extracted with diethyl ether, and the extract is dried over potassium carbonate. Removal of the ether on a steam bath and distillation of the residual oil given 6.6 g. (46%) of the tricyclic base, b.p. 100-102°/1.0 mm., n_D^{30} 1.5062. The infrared spectrum (carbon tetrachloride) shows only strong absorption at 3.4 μ (CH), 6.9 μ (CH₂ bending), and ring skeletal vibrations above 8 μ .

***trans*-1,6-Dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine.**¹⁰⁰ A solution of 36 g. (0.2 mole) of *N*-amino-(+)-pseudoephedrine in 50 ml. of chloroform is added dropwise to cooled (5°), stirred, concentrated sulfuric acid (250 ml.). After the addition is complete, 20.6 g. (0.2 mole) of benzonitrile is added, and the mixture is stirred at ambient temperature overnight. The mixture is poured onto crushed ice, washed with chloroform, made basic with sodium carbonate solution, and the precipitated solid is removed by suction filtration. The solid is recrystallized from isopropyl alcohol to yield 18.5 g. (35%) of white crystalline product, m.p. 146-147°.

TABULAR SURVEY

The tables include reactions compiled from the literature through December 1966. The authors feel that the data are reasonably complete, but some publications were undoubtedly missed.

The tables are arranged in the order in which different sources of the carbonium ion are discussed in the text. The reactants within a table are, in general, listed in order of increasing size and complexity.

CHAPTER 3

THE RITTER REACTION

L. I. KRIMEN AND DONALD J. COTA

Abbott Laboratories

CONTENTS

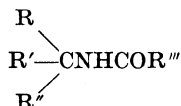
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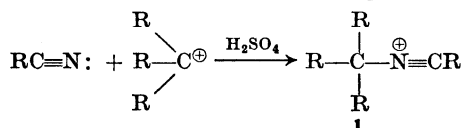
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INTRODUCTION

The formation of N-substituted amides by the addition of nitriles to alkenes in the presence of concentrated sulfuric acid, described first by Ritter in 1948,¹ is one of the newer synthetic reactions available to the organic chemist. The reaction has since been extended to the addition of nitriles to a wide variety of compounds capable of forming a carbonium ion, and it constitutes the only really useful procedure for the preparation of amides of tertiary carbinamines,

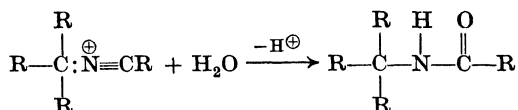


In its most general form the Ritter reaction involves the nucleophilic addition of a nitrile to a carbonium ion in the presence of sulfuric acid.

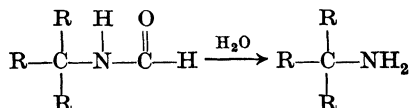


¹ J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).

Subsequent dilution with water yields the amide. When hydrogen cyanide is employed as the nitrile, the resulting N-alkylformamide can be



readily hydrolyzed to the corresponding carbinamine; thus the tertiary carbinamines are readily available.



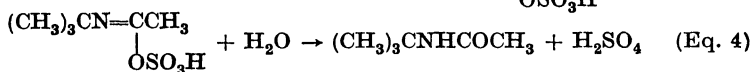
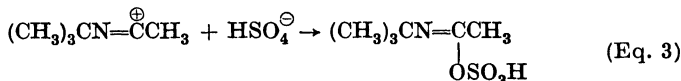
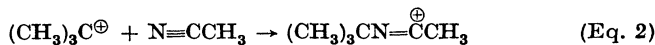
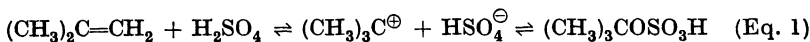
If a nucleophilic center is suitably placed in the primary adduct 1, a wide variety of heterocyclic compounds can be prepared.

Attention has been given primarily to reactions in which the carbonium ion is generated in sulfuric acid or, less commonly, in sulfonic acids, phosphoric acid, or boron trifluoride. For comparison analogous reactions which are initiated by a nitrilium ion, formed from a nitrile and a Friedel-Crafts catalyst, have been included in the discussion of related reactions.

Cursory surveys of the Ritter reaction have appeared in *Russian Chemical Reviews* where Zil'berman dealt with the formation of new nitrogen-carbon bonds² and in *Advances in Heterocyclic Chemistry* in which Johnson reviewed its utility in heterocyclic syntheses.³

MECHANISM

The mechanism suggested by Ritter and his associates in their initial papers is illustrated in the following scheme for the reaction between isobutene and acetonitrile.^{1, 4, 5}



² E. N. Zil'bermann, *Usp. Khim.*, **29**, 709 (1960) [*Russ. Chem. Rev.*, English Transl., 311 (1960)].

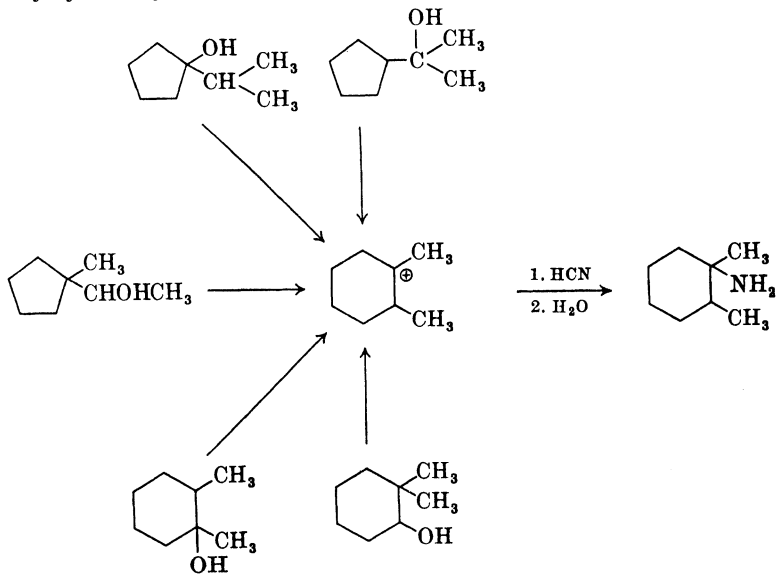
³ F. Johnson and R. Madroñero, in A. R. Katritzky and A. J. Boulton, eds., *Advances in Heterocyclic Chemistry*, Vol. 6, pp. 95-146, Academic Press, New York, 1966.

⁴ J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

⁵ J. J. Ritter, U.S. pat. 2,573,673 [*C.A.*, **46**, 9584h (1952)].

The possibility that the reaction could proceed by the addition of acetamide under acid conditions was discounted when substitution of acetamide for acetonitrile gave no reaction product.¹

Ritter's proposal that the reaction proceeds via a carbonium ion intermediate has been substantially supported by the studies of Jacquier and Christol.⁶⁻¹⁷ They described the synthesis of amines by the reaction of cycloalkanol, secondary aliphatic alcohols, cyclosubstituted alcohols, and alicyclic alcohols containing a spiro structure with potassium cyanide in sulfuric acid. In many reactions there is an intramolecular rearrangement of the Meerwein type,¹⁸ including ring expansion or contraction, leading to the amine resulting from the reaction of hydrogen cyanide with the most stable carbonium ion. For example, 1-isopropylcyclopentanol, 1-methylcyclopentylmethylcarbinol, cyclopentyl dimethylcarbinol, 1,2-dimethylcyclohexanol, and 2,2-dimethylcyclohexanol all yield 1,2-dimethylcyclohexylamine.¹⁶



⁶ H. Christol, R. Jacquier, and M. Mousseron, *Bull. Soc. Chim. France*, 1027 (1957).

⁷ H. Christol and A. Laurent, *Bull. Soc. Chim. France*, 920 (1958).

⁸ H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. France*, 2313 (1961).

⁹ H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. France*, 2319 (1961).

¹⁰ H. Christol, A. Laurent, and G. Solladie, *Bull. Soc. Chim. France*, 877 (1963).

¹¹ H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 1299 (1966).

¹² H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 1307 (1966).

¹³ H. Christol and G. Solladie, *Bull. Soc. Chim. France*, 3193 (1966).

¹⁴ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 556 (1954).

¹⁵ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 596 (1957).

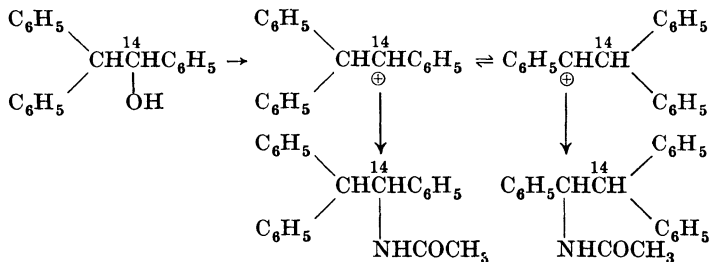
¹⁶ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 600 (1957).

¹⁷ R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 917 (1953).

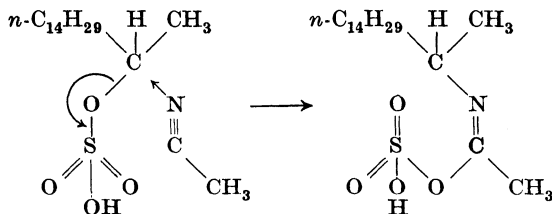
¹⁸ H. Meerwein, *Ann.*, **417**, 255 (1918).

Further support for a carbonium ion mechanism was furnished by Roe and Swern, who employed methanesulfonic acid in place of sulfuric acid.¹⁹

Similar investigations showed that C¹⁴-labeled 1,2,2-triphenylethanol, when treated with acetonitrile and sulfuric acid, led to a mixture of substituted amides resulting from a carbonium ion equilibrium.^{20, 21}



From data obtained in a kinetic study of the reaction between *t*-butyl alcohol and acrylonitrile in 20–69% sulfuric acid solutions Deno concluded that the transition state was composed of acrylonitrile and protonated *t*-butyl alcohol.²² This concept of a loosely solvated carbonium ion was also advanced by other investigators.²³ In a subsequent study using the α -olefin, 1-hexadecene, Weil and co-workers postulated a cyclic transition state which then proceeded to the "Ritter intermediate";²⁴ however, their



work was in agreement with a carbonium ion process. They formulated an irreversible reaction with water, leading to a stable intermediate, 2, whose precise nature they were unable to determine. (See p. 219.)

Extension of the Ritter reaction to *t*-carboxylic acids furnished additional evidence for a carbonium ion process. Haaf showed that acids having this structure could be reversibly converted to *t*-alkylamido

¹⁹ E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **75**, 5479 (1953).

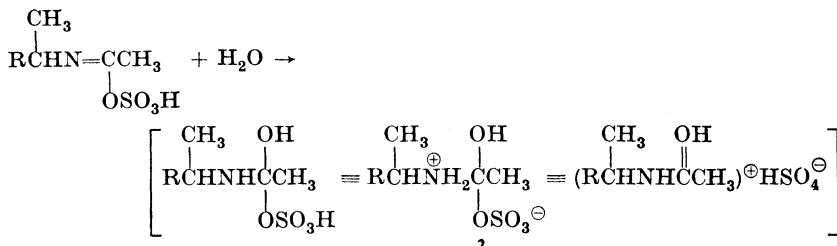
²⁰ A. Laurent, E. Laurent-Dieuzeide, and P. Mison, *Bull. Soc. Chim. France*, 945 (1965).

²¹ A. Laurent and P. Mison, *Bull. Soc. Chim. France*, 956 (1962).

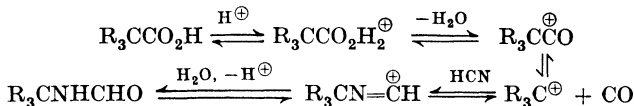
²² N. C. Deno, T. Edwards, and C. Perizzolo, *J. Am. Chem. Soc.*, **79**, 2108 (1957).

²³ C. W. Roberts and N. F. Nuenke, *J. Org. Chem.*, **24**, 1907 (1959).

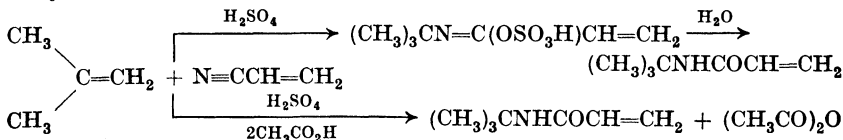
²⁴ I. Weil, R. G. Goebel, E. R. Tulp, and A. Cahn, *Am. Chem. Soc., Div. Petrol. Chem., Preprints*, **8**, (2) B95 (1963).



compounds since treatment of the *t*-alkylamides with carbon monoxide in concentrated sulfuric acid yielded *t*-carboxylic acids.²⁵

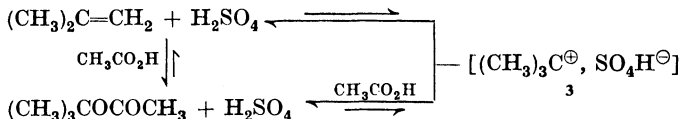


After unsuccessful attempts by various workers^{26, 27} to isolate and characterize the alkyl iminosulfate intermediate suggested by Ritter,⁴ Glikmans and co-workers were able to verify its existence by showing that it is susceptible to hydrolysis in anhydrous acetic acid, obtaining the necessary water from the solvent with concomitant generation of acetic anhydride.^{28, 29}



An earlier attempt to produce N-cumylacrylamide by this route was unsuccessful.²³

Glikmans also showed that the alkene could be replaced by the corresponding alcohol or acetate and suggested the presence of an ion pair such as **3**, which would assist in the electronic transfer as indicated in formula 4.



²⁵ W. Haaf, *Chem. Ber.*, **96**, 3359 (1963).

²⁶ T. Clarke, J. Devine, and D. W. Dicker, *J. Am. Oil Chemists Soc.*, **41**, 78 [*C.A.*, **60**, 6733h (1964)].

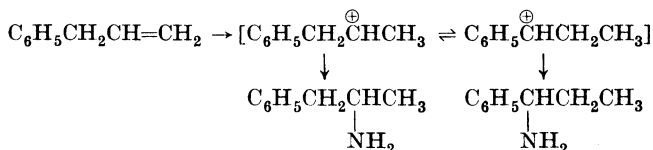
²⁷ R. L. Holmes, J. P. Moreau, and G. Sumrell, *J. Am. Oil Chemists Soc.*, **42**, 922 (1965) [*C.A.*, **63**, 17892c (1965)].

²⁸ G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 1376 (1966).

²⁹ G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 1383 (1966).

Alkenes (Tables II and III)

The addition of hydrogen cyanide and nitriles to alkenes has been investigated by numerous workers (Refs. 24, 26, 28, 29, 32, 33). At an early stage the reaction was elucidated for a variety of nitriles using diisobutylene.¹ As described for isobutene (p. 216), the reaction usually gives the alkylamido addition product corresponding to the carbonium ion initially formed by Markownikoff addition of a proton to the alkene. There are, however, several reports of products resulting from rearrangement of the incipient carbonium ion. Thus 1-phenylpropylamine is obtained from allylbenzene when operating in di-*n*-butyl ether.⁸ On the other hand, in the absence of solvent the expected 2-phenylisopropylamine is obtained.^{4, 34}



It is noteworthy that the carbonium ion from 3-methyl-1-phenylbutene did not undergo a similar rearrangement.⁸ The initial secondary carbonium ion is stabilized to a greater extent by the adjacent phenyl group than is the tertiary carbonium ion that would result from a prototropic shift.

Conflicting results with camphene were reported by several groups of workers. Ritter and Minieri isolated the N-acylisobornylamines, a result of the Wagner rearrangement, when employing hydrogen cyanide or simple nitriles.¹ Other investigators also obtained N-acylisobornylamines from simple nitriles but found that hydrogen cyanide gave the unrearranged norcamphane derivative.³⁵ This anomaly was resolved by Kochetkov and co-workers who made a detailed study of the behavior of camphene. They showed that, when the reaction is conducted at temperatures in the -15° to -20° range, the formation of the isobornyl derivative with hydrogen cyanide is reduced to a minimum.³⁶ Similar results were obtained when 3-formamido-2,2,3-trimethylnorcamphane was formed by treating racemic camphene with hydrogen cyanide at $0-3^\circ$.³⁷

³² C. Malen and J. R. Boissier, *Bull. Soc. Chim. France*, 923 (1956).

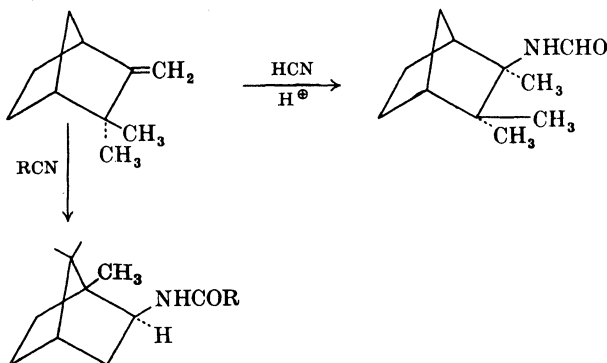
³³ R. Maugé, C. Malen, and J. R. Boissier, *Bull. Soc. Chim. France*, 926 (1956).

³⁴ J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952).

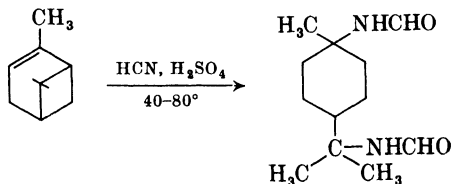
³⁵ G. A. Stein, M. Sletzing, H. Arnold, D. Reinhold, and K. Pfister, III, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

³⁶ N. K. Kochetkov, A. Ya. Khorlin, and K. I. Lopatina, *J. Gen. Chem. USSR (Eng. Transl.)*, **29**, 77 (1959) [*C.A.*, **53**, 22058i (1959)].

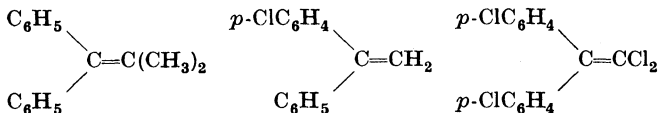
³⁷ C. A. Stone, M. L. Torchiana, K. L. Meekelnburg, J. Stavorski, M. Sletzing, G. A. Stein, W. V. Ruyle, D. F. Reinhold, W. A. Gaines, H. Arnold, and K. Pfister, III, *J. Med. Pharm. Chem.*, **5**, 665 (1962) [*C.A.*, **57** 12341c (1962)].



Kochetkov also showed that the highly active trichloro- and dichloro-acetonitrile reacted with camphene at a reduced temperature without rearrangement, but even at -50° the rearranged products were obtained with aceto- and benzo-nitrile.³⁶ Rearrangement also occurs with α -pinene when it is treated with hydrogen cyanide at slightly elevated temperatures, giving 1,8-diformamido-*p*-menthane.^{38,39}



The failure of the reaction with alkenes has been noted in relatively few instances. The only structural similarity in these cases is the presence of one or two phenyl groups on the double-bonded carbon atom. The failure of 1,1-diphenyl-2,2-dimethylethylene to undergo the reaction was explained on the basis of the high stability of the derived carbonium ion and hence its lack of reactivity toward nitriles.¹⁰ Similar reasoning could rationalize the failure of 1-(*p*-chlorophenyl)-1-phenylethylene and 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene.⁴⁰



Although Ritter reported the successful addition of acetonitrile to α -methylstyrene,⁵ other investigators reported that α -methylstyrene and

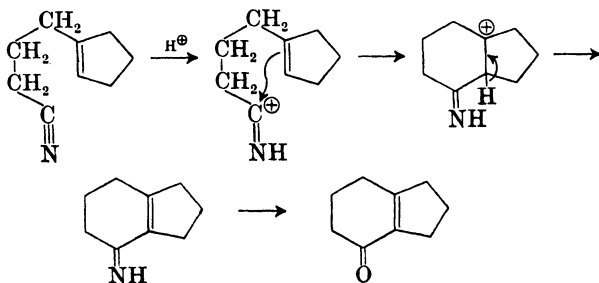
³⁸ N. M. Bortnick, Brit. pat. 681,688 [C.A., **48**, 727f (1954)].

³⁹ N. M. Bortnick, U.S. pat. 2,632,022 [C.A., **48**, 4003h (1954)].

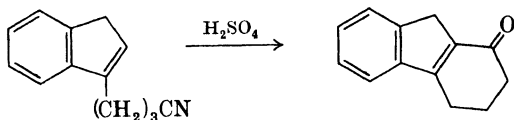
⁴⁰ A. Kluszyner, S. Blum, and E. D. Bergmann, *J. Org. Chem.*, **28**, 3588 (1963).

$$3,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CH}=\text{C}(\text{CH}_3)_2 \xrightarrow[\text{H}_2\text{SO}_4]{\text{KCN, (n-C}_4\text{H}_9)_2\text{O}} 3,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CH}_2\text{C}(\text{CH}_3)_2\text{NHCHO}$$
$$\begin{array}{c} \text{CH}_3(\text{CH}_2)_x\text{CHNHCO}(\text{CH}_2)_4\text{CONHC}(\text{CH}_2)_x\text{CH}_3 \\ | \qquad \qquad \qquad | \\ (\text{CH}_2)_y\text{CO}_2\text{H} \qquad (\text{CH}_2)_y\text{CO}_2\text{H} \\ \mathbf{5,} \ x + y = 15 \end{array}$$
$$\text{RR}_1\text{C}(\text{NHCOR})\text{CH}_2\text{X} \xrightarrow{\text{OH}^\ominus} \text{RR}_1\text{C}(\text{N}=\text{C}(\text{OR})\text{CH}_2)\text{O} + \text{H}_2\text{O}$$

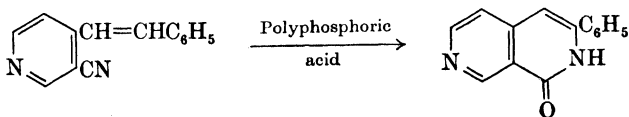
⁴⁶ R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).



An analogous reaction had been reported earlier for γ -3-indenylbutyronitrile and described as a failure of the Ritter reaction.⁴⁷



Conley suggested that these unsaturated nitriles do not react in the usual manner because the cyano group cannot approach the intermediate carbonium ion.^{46,48-50} This proposal, however, was in disagreement with the results of Bobbitt and Doolittle who were able to cyclize 3-cyano-4-stilbazole to the lactam, 1-oxo-3-phenyl-1,2,3,4-tetrahydrocyclopenta[b]indene, in 90% yield.⁵¹



Bobbitt attributed the lactam formation to the electron-withdrawing effect of the pyridinium nucleus on the double bond. This electron deficiency allows the lactam formation and inhibits the acylation reaction which would lead to the ketone.

Alkadienes (Table IV)

The extension of the Ritter reaction to dienes to give dialkylamido derivatives has met with some success. Bortnick prepared 1,8-diamino-*p*-methane^{38, 39} and 2,5-diamino-2,5-dimethylhexane⁵² from limonene and

⁴⁷ F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).

⁴⁸ R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

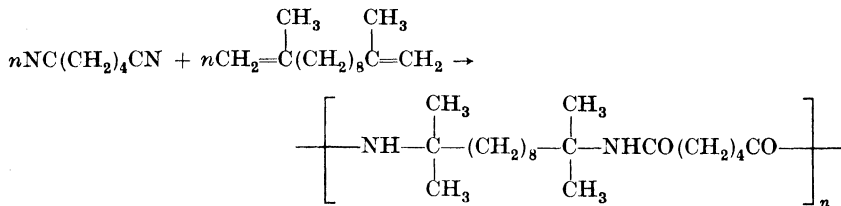
⁴⁹ R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **27**, 1965 (1962).

⁵⁰ R. T. Conley and R. J. Lange, *J. Org. Chem.*, **28**, 210 (1963).

⁵¹ J. M. Bobbitt and R. E. Doolittle, *J. Org. Chem.*, **29**, 2298 (1964).

⁵² N. M. Bortnick, U.S. pat. 2,632,023 [*C.A.*, **49**, 1782a (1955)].

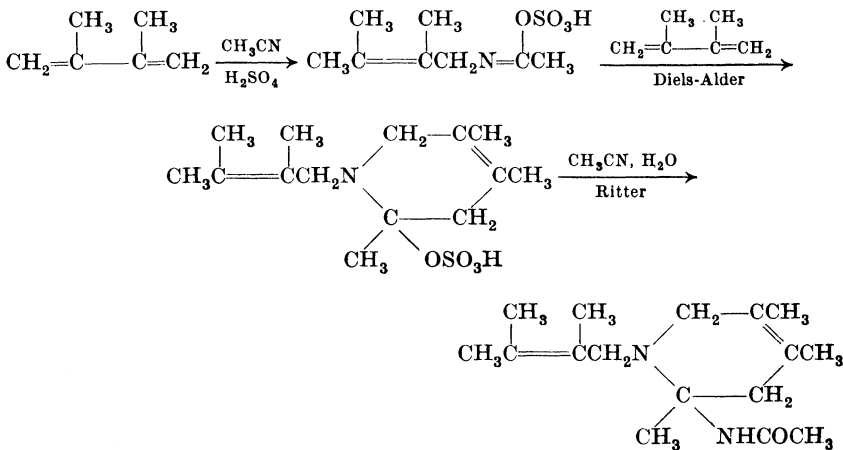
bimethallyl, respectively. Although the reactions attempted with dipentene and 2,5-dimethyl-1,5-hexadiene gave nitrogen-containing materials only in low yield along with substantial amounts of polymeric material, and butadiene reacted explosively,²⁶ Magat prepared a number of synthetic linear polyamides from ditertiary diolefins and dinitriles.⁵³ For example, the polymer, poly($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl)decamethyleneadipamide was prepared from adiponitrile and 2,11-dimethyl-1,11-dodecadiene.



The participation of a conjugated diene in combined Ritter and Diels-Alder reactions has been reported.⁵⁴ 2,3-Dimethyl-1,3-butadiene and acetonitrile furnish the substituted tetrahydropyridine. It was proposed that the diene reacted with 1 mole of acetonitrile to give the iminosulfate intermediate. The $-\text{N}=\text{C}-$ grouping then behaved as a dienophile,



adding another mole of butadiene and acetonitrile, to give the product.



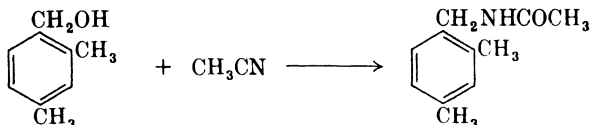
⁵³ E. E. Magat, U.S. pat. 2,628,219 [C.A., **47**, 5130c (1953)].

⁵⁴ M. Lora-Tamayo, G. Gancía Muñoz, and R. Madroñero, *Bull. Soc. Chim. France*, **1334** (1958).

Alcohols (Tables V-VIII)

The use of primary, secondary, and tertiary alcohols, alicyclic and spiro alcohols, glycols, heterocyclic alcohols, and halohydrins in the Ritter reaction has been investigated.

The failure of primary aliphatic alcohols to react with nitriles even at elevated temperatures or on prolonged heating, or with fuming sulfuric acid was reported by Ritter.⁵⁵ Other investigators⁵⁶⁻⁵⁸ observed, however, that primary aralkyl alcohols and glycols condensed smoothly with nitriles under mild conditions to give N-aralkylamides and N,N'-bis-aralkylamides in good yields. N-(2,4-Dimethylbenzyl)acetamide was obtained from 2,4-dimethylbenzyl alcohol and acetonitrile in 87% yield. An exception



to the reactivity of benzyl alcohols is shown by *p*-nitrobenzyl alcohol, which is inert to nitriles in concentrated sulfuric acid.¹⁴

Glikmans found that alcohols, in general, gave lower yields than the corresponding olefins and required the use of concentrated sulfuric acid.²⁸ On the other hand, there are reports that the reverse is true because polymerization of olefin competes with the Ritter reaction.⁵⁹

From studies of a number of alcohols of varied structure Christol, Jacquier, and their associates concluded that tertiary alcohols react with hydrogen cyanide without rearrangement;^{13, 15} for example, methylcyclohexanol gives the corresponding amine in 60% yield.⁶⁰ Although most secondary cycloalkanols react without rearrangement, the yields are somewhat lower; thus cyclohexanol gives only a 4% yield of cyclohexylamine.^{14, 15}

It is an oversimplification to conclude that the reaction product always corresponds to the most stable incipient carbonium ion, yet this conclusion is valid for a majority of the cases.

In a study of the reaction of substituted cycloalkanols it was learned that the yields decrease with increasing separation of the alcohol function

⁵⁵ F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949).

⁵⁶ C. L. Parris, *Org. Syntheses*, **42**, 16 (1962).

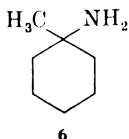
⁵⁷ C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 331 (1960).

⁵⁸ J. A. Sanguigni and R. Levine, *J. Med. Chem.*, **7**, 573 (1964).

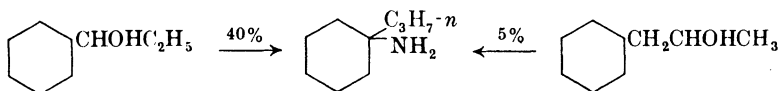
⁵⁹ A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1960).

⁶⁰ L. I. Krimen, unpublished results.

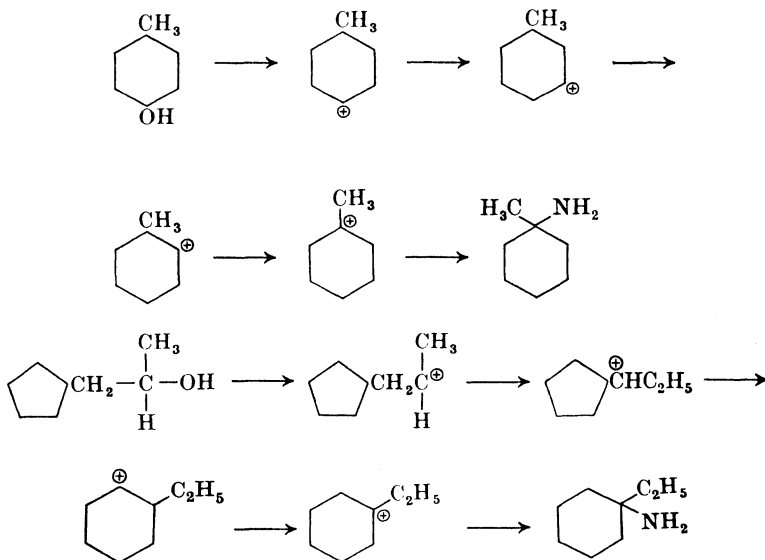
and the substituent.¹⁶ 1- and 2-Methylcyclohexanol gave 1-methylcyclohexylamine (**6**) in 60% yield, whereas the yield from the 4-methyl derivative was only 5%.



Similarly, when the ring is "farther away" from the alcohol as in the cyclohexylpropanols, the yields decrease. For example, ethylcyclohexylcarbinol and 1-cyclohexyl-2-propanol give 1-*n*-propylcyclohexylamine in yields of 40% and 5%, respectively.

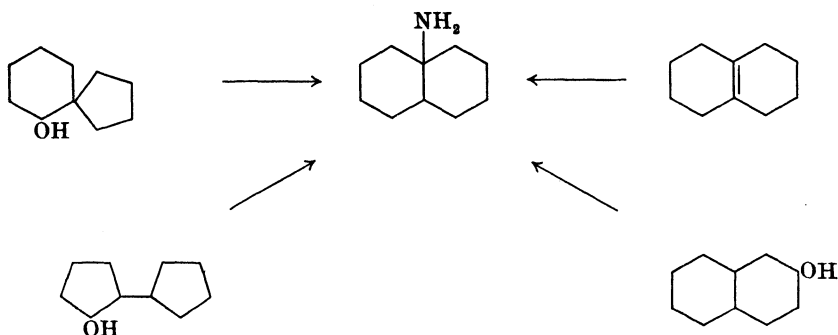


This effect of the separation of hydroxyl group and substituent is a characteristic specific to the Ritter reaction, and not necessarily a function of the number of successive prototropic rearrangements. 4-Methylcyclohexanol and 1-cyclopentyl-2-propanol rearrange, by means of three transitory carbonium ions, to methylcyclohexylamine and ethylcyclohexylamine in yields of 5% and 45%, respectively.

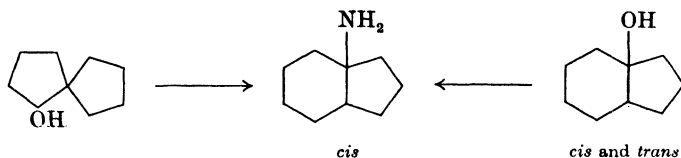


Christol and Jacquier also reported a number of alcohols which did not undergo a Ritter reaction, whereas their position or structural isomers did. Thus 2,2-dimethylcyclohexanol gave 1,2-dimethylcyclohexylamine in 20% yield, but 3,3-dimethylcyclohexanol failed to react. The absence of any reaction was also observed for 2-butanol. The authors attribute the failure of reaction to the difficulty of forming the corresponding ions rather than to the lack of reactivity of these ions.^{14, 16}

Extending their investigations to alicyclic and spiro alcohols, Christol and co-workers found that most Ritter reactions were accompanied by a retropinacol rearrangement.^{6, 14} When spiro[4.5]-6-decanol was subjected to the conditions of the Ritter reaction, ring expansion occurred and *trans*-9-aminodecalin was obtained. The stereospecific nature of the reaction was also noted with other bicyclic and spiro alcohols. For example, a mixture of *cis*- and *trans*-2-cyclopentylcyclopentanol, the diastereoisomers of β -decalol, and $\Delta^{9,10}$ -octalin all gave *trans*-9-aminodecalin when subjected to the Ritter reaction.^{6, 11, 17}

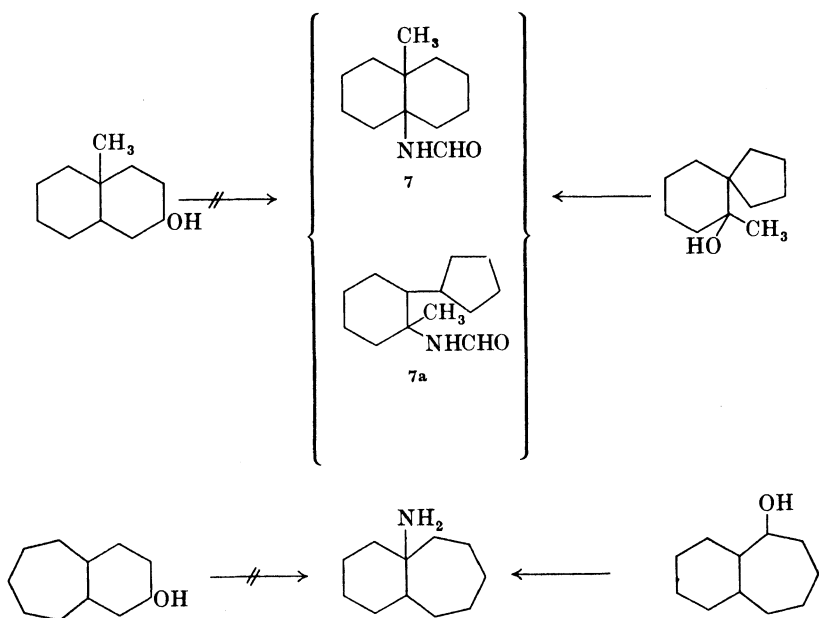


Similar stereospecificity was exhibited by spiro[4.4]-1-nonanol and *cis*- and *trans*-8-hydroxyhydrindane, which reacted to give only the *cis*-8-aminohydrindane. Only the thermodynamically more stable isomer of



1,2-dimethylcyclohexylamine, with the methyl groups *trans* in equatorial positions, was obtained from 1,2- and 2,2-dimethylcyclohexanol.¹³

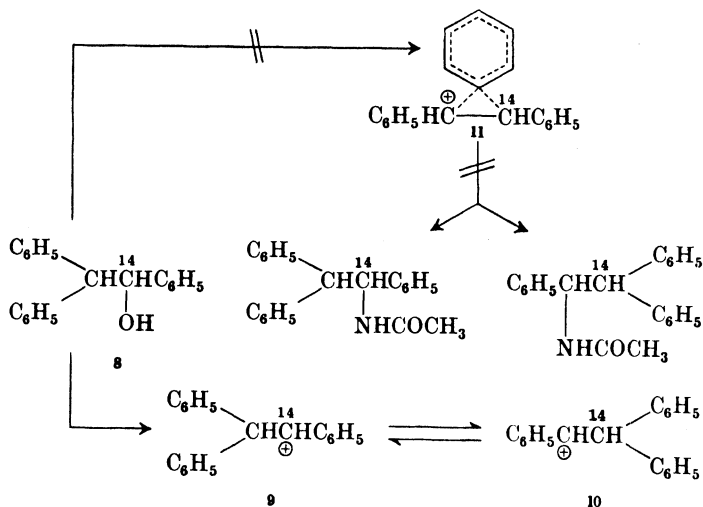
Differences in behavior were also noted in the spiro and bicyclic alcohols.⁶ For example, 4a-methyl-2-decahydronaphthol and bicyclo[5.4.0]-9-undecanol failed to react, but their isomers, 6-methylspiro[4.5]-6-decanol and bicyclo[5.4.0]-2-undecanol did react, to give in one case an angular amine, 1-aminobicyclo[5.4.0]undecane and in the other case a mixture of formamides **7** and **7a** that could not be hydrolyzed to the free amines.



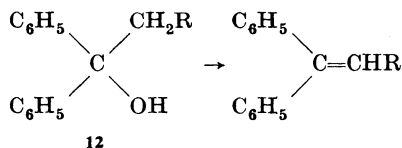
The extension of the Ritter reaction to secondary benzylic alcohols and benzylcarbinols,⁸ tertiary benzylic alcohols,⁹ diphenyl-carbinols and -propanols¹⁰ enabled Christol and co-workers to establish the relative reactivities of the various derived carbonium ions and their susceptibility to prototropic rearrangements.

Further insight into the mode of these carbonium ion rearrangements was reported by Laurent,^{20, 21} who employed C¹⁴-labeled triphenylethanol and showed that the Ritter reaction of triphenylethanol **8** with alkyl or aryl nitriles proceeded via a rearrangement of **9** to **10** before the substitution occurred, thus ruling out the formation of the bridged phenonium ion **11**. (See p. 230.)

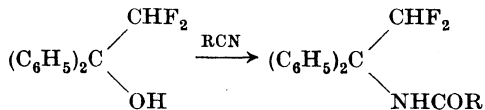
It is noteworthy that diphenylcarbinols such as **12**, when R is CH₃, C₂H₅, C₃H₇-i, CH₂Cl, or CHCl₂, yield only the corresponding 1,1-diphenylethylenes.^{10, 40} A similar dehydration followed by dimerization was



described for 2-phenyl-2-propanol, indicating that the cumyl cation undergoes nucleophilic attack by α -methylstyrene more readily than by



the nitrile.²³ However, diphenylcarbinol itself and difluoromethyl-diphenylcarbinol react with various nitriles to give the amides in yields ranging from 68% to 100%.^{10, 40, 58} Magat was able to prepare linear



polyamides from dissecondary alcohols and dinitriles. For example, adiponitrile and 1,10-dimethyl-1,10-decanediol yielded a polymer capable of being melt-spun to form fibers.⁵³

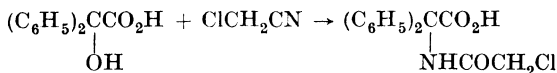
The reaction has also been extended to acids and esters containing the hydroxy group. Both α - and β -acylamine derivatives have been prepared by this route.⁶¹⁻⁶³ The reaction of diphenylhydroxyacetic acid

⁶¹ K. Hohenlohe-Oehringen, *Monatsh.*, **93**, 639 (1962).

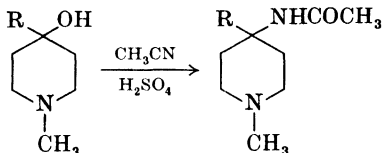
⁶² G. Jansen and W. Taub, *Acta. Chem. Scand.*, **19**, 1772 (1965).

⁶³ L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949).

(benzilic acid) with chloroacetonitrile gave the chloroacetamidodiphenylacetic acid in 82% yield.⁶⁴



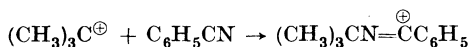
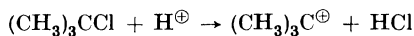
In the only study using heterocyclic alcohols Zagorevskii and Lopatina obtained 4-acetamido-4-alkyl-1-methylpiperidines from the corresponding 4-alkyl-1-methyl-4-piperidinols.⁶⁵



The Ritter reaction with halohydrins proceeds in a manner similar to that described for haloalkenes to give halogen-substituted amides.⁴⁴

Alkyl Chlorides (Table IX)

The use of a tertiary alkyl halide in place of the corresponding alcohol was reported by Magat.⁶⁶ A carbonium ion initially is generated by the abstraction of the halogen atom, and then the reaction proceeds as with alcohols. Both formic and sulfuric acids were employed as reaction media,



and in both reactions the yields were lower than when the corresponding alkenes or alcohols were used.

Aldehydes and Ketones (Tables X, XI, XIII)

The reaction of aldehydes with nitriles to give methylene-*bis*-amides and with dinitriles to yield polyamides was studied by Mowry and Ringwald⁶⁷ and by Magat and co-workers.^{68, 69} These investigators suggested

⁶⁴ K. Hohenlohe-Oehringen and H. Bretschneider, *Monatsh.*, **93**, 645 (1962).

⁶⁵ V. A. Zagorevskii and K. I. Lopatina, *J. Gen. Chem. USSR*, **33**, 2461 (1963) [*C.A.*, **60**, 495f (1964)].

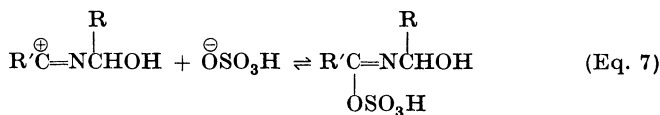
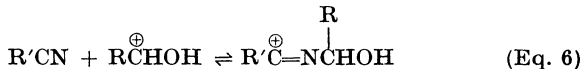
⁶⁶ E. E. Magat, U.S. pat. 2,628,217 [*C.A.*, **47**, 5129g (1953)].

⁶⁷ D. T. Mowry and E. L. Ringwald, *J. Am. Chem. Soc.*, **72**, 4439 (1950).

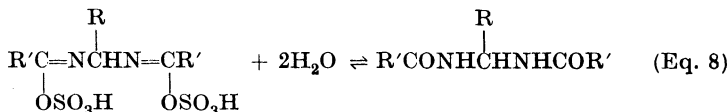
⁶⁸ E. E. Magat, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951).

⁶⁹ E. E. Magat, L. B. Chandler, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1031 (1951).

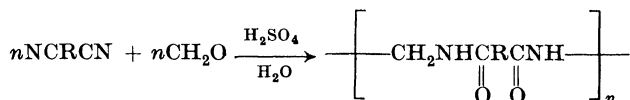
a mechanism in which the nitrile adds to the protonated aldehyde (equation 6) and formation of the iminosulfate follows (equation 7). Subsequent protonation produces a new carbonium ion which undergoes



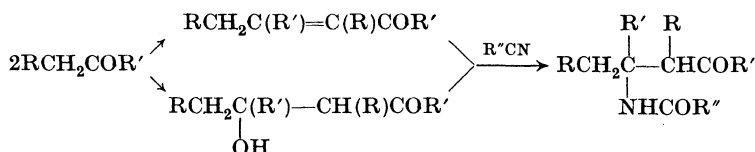
reaction analogous to equations 6 and 7. Hydrolysis (equation 8) gives the methylene-*bis*-amides.



Yields in excess of 90 % are often obtained with formaldehyde, but other aldehydes such as acetaldehyde, butyraldehyde, and chloral can be used.⁶⁸ If a dinitrile is treated with formaldehyde, a polymer is formed which corresponds to the polyamide from monomethylenediamine and the parent acid of the dinitrile.^{67, 69}



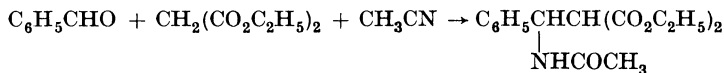
The reaction of nitriles with ketones provides another route to the difficultly accessible β -acylamino ketones (see α,β -unsaturated ketones, p. 234). In a detailed study of this reaction, Khorlin and co-workers showed that positive results were obtained with ketones that readily undergo acid-catalyzed condensations to ketols or α,β -unsaturated ketones.⁷⁰ They suggested that the reaction could proceed by a route similar to that described above for aldehydes or, more reasonably, that the ketal or the α,β -unsaturated ketone or both reacted with the nitrile.



⁷⁰ A. Ya. Khorlin, O. S. Chizhov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **29**, 3411 (1959) [*C.A.*, **54**, 16418h (1960)].

The best results were given by methyl ketones (acetone, 62%; acetophenone, 74%). With an increase in the size of the alkyl group, the yields decrease (methyl ethyl ketone, 16%), and negative results are obtained with propiophenone and butyrone. Among cyclic ketones, only cyclohexanone gave the desired product.

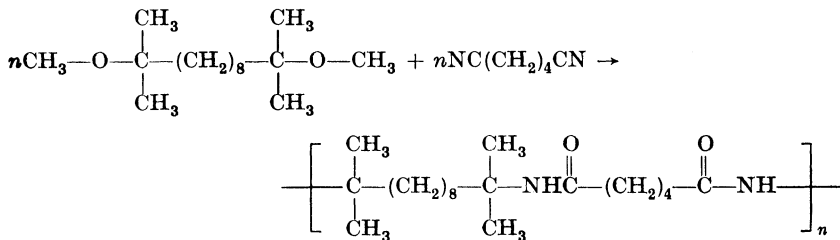
In an unusual variation of this reaction Khorlin carried out a cross reaction in which the compound with the active methylene unit was not a ketone. Instead an aldehyde was the carbonyl component. Benzaldehyde and malonic ester condensed with acetonitrile to give the ethyl ester of 1-carbethoxy-2-phenyl-2-acetamidopropionic acid in 55% yield.⁷⁰



Further reactions of ketones involving intramolecular Ritter reactions are described under Heterocyclic Syntheses (p. 236).

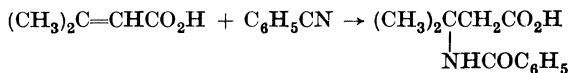
Ethers (Table XII)

The use of secondary and tertiary alkyl ethers as carbonium ion sources has received very limited attention. The only report to date describes the preparation of polyadipamides from the dimethyl ether of α, α' -tetramethyldecamethylene glycol and adiponitrile.⁷¹



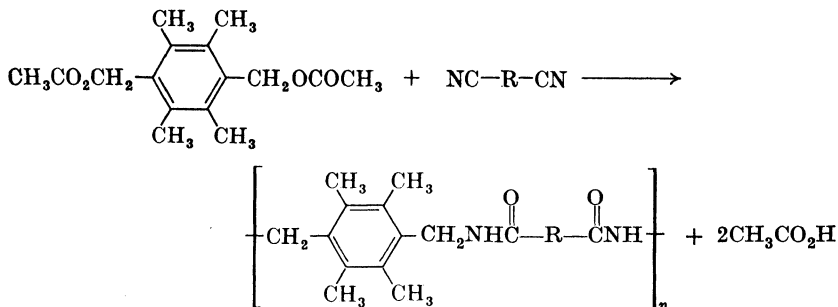
α, β -Unsaturated Carbonyl Compounds (Table XIII)

The scope of the reaction was further broadened when Ritter found that α, β -unsaturated acids and esters having two alkyl groups or one aryl group on the β -carbon atom were very reactive. The reaction of benzonitrile



⁷¹ E. E. Magat, U.S. pat. 2,518,156 [C.A., **45**, 661a (1951)].

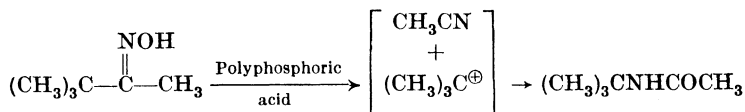
and *t*-butyl acetate²⁸ gave the corresponding N-trialkyl- or triaryl-acetamides. Ramp showed that *bis*(acetoxymethyl) alkylated benzenes could be used as carbonium ion sources.⁷⁷ *Bis*(acetoxymethyl)durene condenses



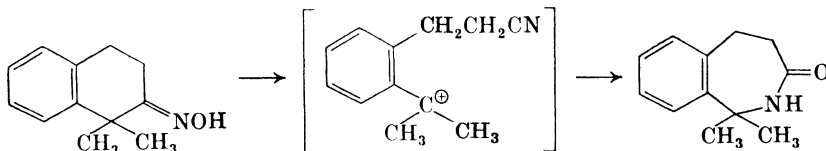
with dinitriles to yield polyamides. Similar polyamides have been prepared from dinitriles and esters of dissecondary alcohols.⁵³

Oximes

While studying the course of the migrating group during the Beckmann rearrangement Hill⁷⁸ and Conley^{49, 79, 80} discovered that α -trisubstituted and α,α' -tetrasubstituted oximes undergo an initial fragmentation to give an intermediate nitrile and a carbonium ion. The two fragments recombine in a Ritter reaction to form an amide. In the case of a cyclic



ketoxime, fragmentation yielded an unsaturated nitrile which on recombination produced a lactam.^{49, 80-82} Treatment of 1,1-dimethyl-2-tetralone oxime with hot polyphosphoric acid resulted in the formation of 2-aza-1,1-dimethyl-3-benzosuberone in 24% yield.⁵⁰



⁷⁷ F. L. Ramp, *J. Polymer Sci.*, **3**, 1877 (1965).

⁷⁸ R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).

⁷⁹ R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).

⁸⁰ R. T. Conley and W. N. Knopka, *Abstr.*, ACS Meeting, 57c (Jan. 1964).

⁸¹ R. K. Hill and R. T. Conley, *Chem. Ind. (London)*, 1314 (1956).

⁸² K. Morita and Z. Suzuki, *J. Org. Chem.*, **31**, 233 (1966).

Heterocyclic Syntheses (Table XVII)

The discovery of Ritter and Tillmanns that the interaction of a suitably substituted diol with a nitrile resulted in the formation of a dihydro-1,3-oxazine, instead of the expected diamide, stimulated research in the synthesis of a variety of heterocyclic systems.⁸³

In addition to dihydro-1,3-oxazines⁸³⁻⁸⁸ the Ritter procedure has been successfully employed in the preparation of oxazolines,⁸⁹ pyrrolines,^{90, 91} dihydropyridines,^{86, 90, 92} Δ^2 -thiazolines,^{59, 90, 93, 94} thiazines,^{59, 87, 95, 96} isoquinolines,³⁴ 2-quinolones,⁹⁷ 2-pyridones,⁹⁷⁻⁹⁹ triazines,¹⁰⁰ azabicycloalkanes,¹⁰¹⁻¹⁰³ bis(heterocyclyl)alkanes,¹⁰⁴ and an oxazolone.¹⁰⁵

Dihydro-1,3-oxazines. The synthesis of oxazines from a diol containing both a tertiary and a secondary hydroxyl group is illustrated in the reaction shown on p. 237; treatment of 2-methyl-2,4-pentanediol with acetonitrile gave the 1,3-oxazine 13 in 44 % yield.⁸³

Aryl,⁸³ aralkyl,⁸³ and unsaturated nitriles⁸⁸ and dinitriles⁸⁵ have also been successfully employed. Unsaturated tertiary alcohols permit the synthesis of spirooxazines.^{84, 86} This unusual ring closure reaction was observed when either of the isomeric tertiary alcohols 13a and 13b was allowed to react with simple nitriles. A possible mechanism for the formation of 2,4,4-trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine

⁸³ E.-J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

⁸⁴ L. M. Trefonas, J. Schneller, and A. I. Meyers, *Tetrahedron Letters*, **22**, 785 (1961).

⁸⁵ A. I. Meyers, *J. Org. Chem.*, **25**, 145 (1960).

⁸⁶ A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963).

⁸⁷ A. I. Meyers, *J. Org. Chem.*, **26**, 218 (1961).

⁸⁸ J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

⁸⁹ S. Julia and C. Papantoniou, *Compt. rend.*, **260**, 1440 (1965).

⁹⁰ A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

⁹¹ A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

⁹² A. I. Meyers, B. J. Betrus, N. K. Ralhan, and K. B. Rao, *J. Heterocyclic Chem.*, **1**, 13 (1964).

⁹³ J. R. Lowell, Jr., and G. K. Helmkamp, *J. Am. Chem. Soc.*, **88**, 768 (1966).

⁹⁴ G. K. Helmkamp, D. J. Pettit, J. R. Lowell, Jr., W. R. Mabey, and R. G. Wolcott, *J. Am. Chem. Soc.*, **88**, 1030 (1966).

⁹⁵ D. S. Tarbell, D. A. Buckley, P. P. Brownlee, R. Thomas, and J. S. Todd, *J. Org. Chem.*, **29**, 3314 (1964).

⁹⁶ A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966).

⁹⁷ A. I. Meyers and G. García-Muñoz, *J. Org. Chem.*, **29**, 1435 (1964).

⁹⁸ A. Vigier and J. Dreux, *Bull. Soc. Chim. France*, 2292 (1963).

⁹⁹ O. Yu. Magidson, *Zh. Obshch. Khim.*, **33**, 2173 (1963) [*C.A.*, **59**, 13942f (1963)].

¹⁰⁰ D. L. Trepanier and co-workers, *J. Med. Chem.*, **9**, 881 (1966).

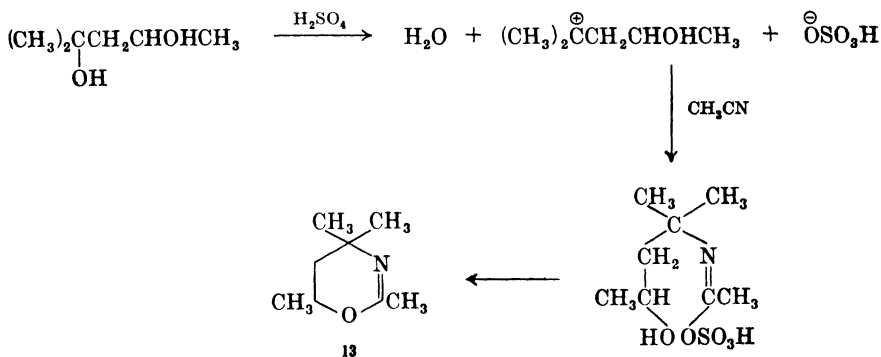
¹⁰¹ A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 4399 (1961).

¹⁰² A. I. Meyers and N. K. Ralhan, *J. Org. Chem.*, **28**, 2950 (1963).

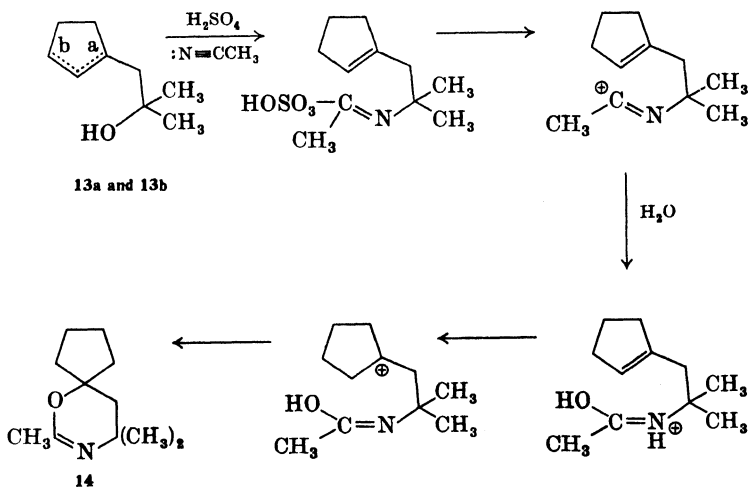
¹⁰³ A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 1682 (1961).

¹⁰⁴ A. I. Meyers, *J. Org. Chem.*, **25**, 2231 (1960).

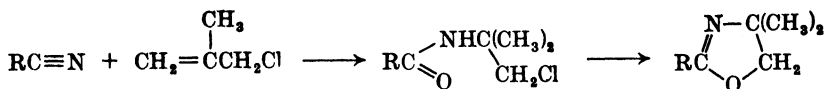
¹⁰⁵ C. W. Bird, *J. Org. Chem.*, **27**, 4091 (1962).



(14) follows. The yields from the 3-cyclopentenyl derivative, 13b, were approximately 20–30% higher than those from the 1-cyclopentenyl compound, 13a.⁸⁶

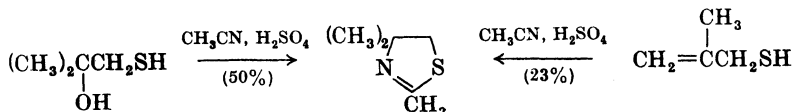


Oxazolines. Julia and Papantoniou prepared a series of β -chloroamides from methallyl chloride and various nitriles.⁸⁹ The amides could be cyclized easily by either potassium ethoxide or silver fluoroborate to give oxazolines.



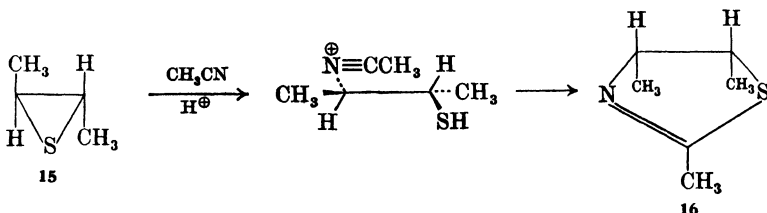
Dihydro-1,3-thiazines and Δ^2 -Thiazolines. Substitution of mercapto alcohols^{89, 87, 95, 96} or methallyl mercaptan⁹⁰ for the diols used in the

oxazine synthesis provided a new route to dihydro-1,3-thiazines and Δ^2 -thiazolines, respectively. The addition of 2-methyl-2-hydroxypropane-thiol or methallyl mercaptan to a cold solution of acetonitrile in concentrated sulfuric acid leads to the formation of 2,4,4-trimethyl- Δ^2 -thiazoline.

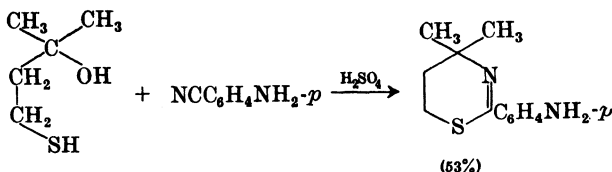


The higher yield obtained by using the mercapto alcohol was attributed to the fact that methallyl mercaptan polymerizes more readily than the alcohol in concentrated sulfuric acid.⁵⁹

A stereospecific synthesis of Δ^2 -thiazolines from episulfides has been reported.^{93,94} The proposed mechanism for this reaction involves protonation of the episulfide, ring opening by nucleophilic attack by the nitrile, and ring closure to form the thiazoline. The preparation of (4R:5S)-(-)-*cis*-2,4,5-trimethyl- Δ^2 -thiazoline (**16**) from (SS)-(-)-*trans*-2-butene episulfide (**15**) demonstrated that the reaction proceeds without racemization.⁹³

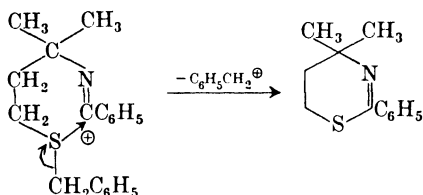


When butanethiol is employed, a dihydro-1,3-thiazine is obtained.^{59, 87} *p*-Aminobenzonitrile reacted with 3-methyl-3-hydroxy-*n*-butanethiol to give 2-(*p*-aminophenyl)-4,4-dimethyl-5,6-dihydro-1,3-thiazine. With



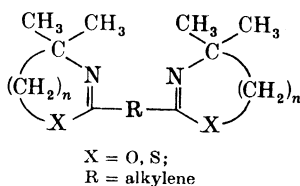
boron trifluoride etherate as catalyst for the formation of the thiazine, yields of 75% were reported.⁹⁵

Benzylmercaptobutanols have also been used to give the dihydro-1,3-thiazine with concomitant debenzylation of the sulfide. The reaction probably involves attack by the nitrilium ion on the sulfide with expulsion of the benzyl cation. The existence of this cation has been verified by the isolation of *N*-benzylbenzamide.⁹⁵

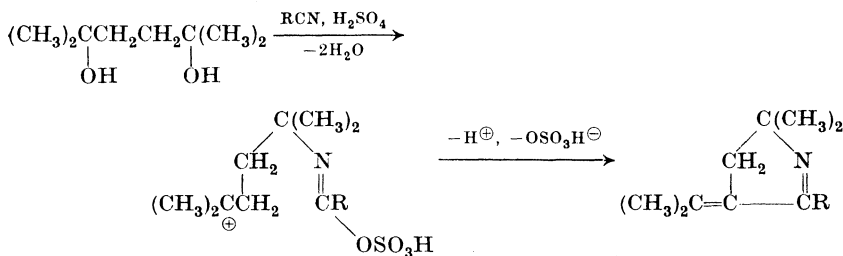


Bis(heterocyclyl)alkanes. The reactions leading to the heterocycles described in the preceding paragraphs can be made to furnish *bis*(heterocyclyl)alkanes by employing dinitriles. The ring closure may be directed to the formation of a mono- or di-cyclic product by utilizing the proper quantities of dinitrile and alcohol.

The addition of 2,5-dimethyl-2,5-hexanediol, 2-methyl-2,4-pentanediol, or 4-mercapto-2-methyl-2-butanol to a dinitrile in sulfuric acid yielded N-heterocyclic bases of the following type.¹⁰⁴



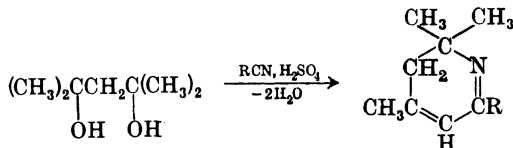
1-Pyrrolines and 5,6-Dihydropyridines. A series of 1-pyrrolines was prepared by heating 1,4-diols with various nitriles.^{90, 91} The yields



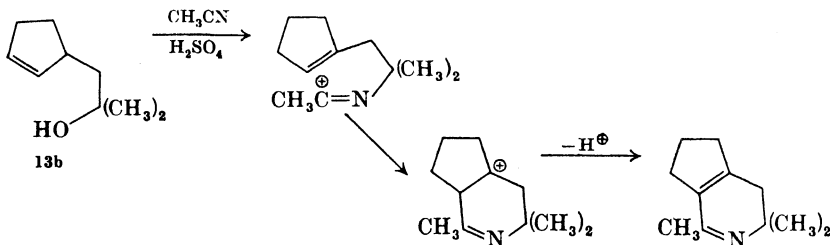
are 60–80% with the diols. Under the same conditions, however, 2,5-dimethyl-2,5-hexadiene gave the corresponding pyrroline in a much smaller yield (28%) as a consequence of a competing polymerization.⁹⁰

Replacement of the 1,4-diols by 1,3-diol 2,4-dimethylpentane-2,4-diol permits the preparation of a variety of 5,6-dihydropyridines. The yields are considerably lower (~20%) because of cleavage of the diol to acetone

and isobutene. From the 1,3-diol and acetonitrile the *N*-*t*-butylacetamide was isolated in 50–55 % yield.⁹⁰



In the course of their studies on oxazine preparation Meyers and co-workers discovered that by controlling the water activity the reaction could be modified to give dihydropyridines exclusively.⁸⁶ Treatment of α -(3-cyclopentenyl)-*t*-butyl alcohol (**13b**) with acetonitrile in sulfuric acid concentrations above 93 % led to an azocarbonium ion that lost a proton to give 3,4-cyclopenteno-5,6-dihydropyridine.



A similar reaction with α -(1-cyclohexenyl)-*t*-butyl alcohol (**15a**) gave the spirodihydropyridine **18** (see Chart I) along with an isoquinoline **17**.⁹²

Isoquinolines. 3,4-Dihydroisoquinolines have been obtained by the reaction of methyleugenol with alkoxyarylnitriles³⁴ and of isosafrol or methylisoeugenol with a variety of nitriles.⁵⁴ For example, veratronitrile and methyleugenol give 1-(3',4'-dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in 53 % yield.³⁴

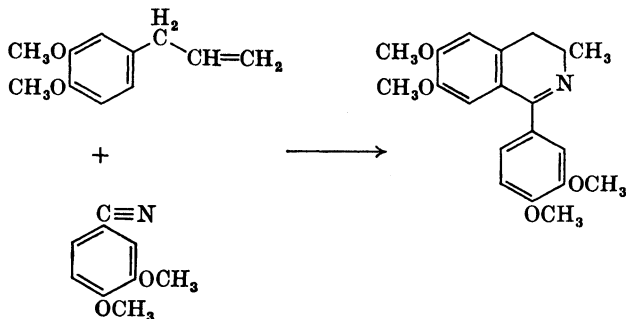
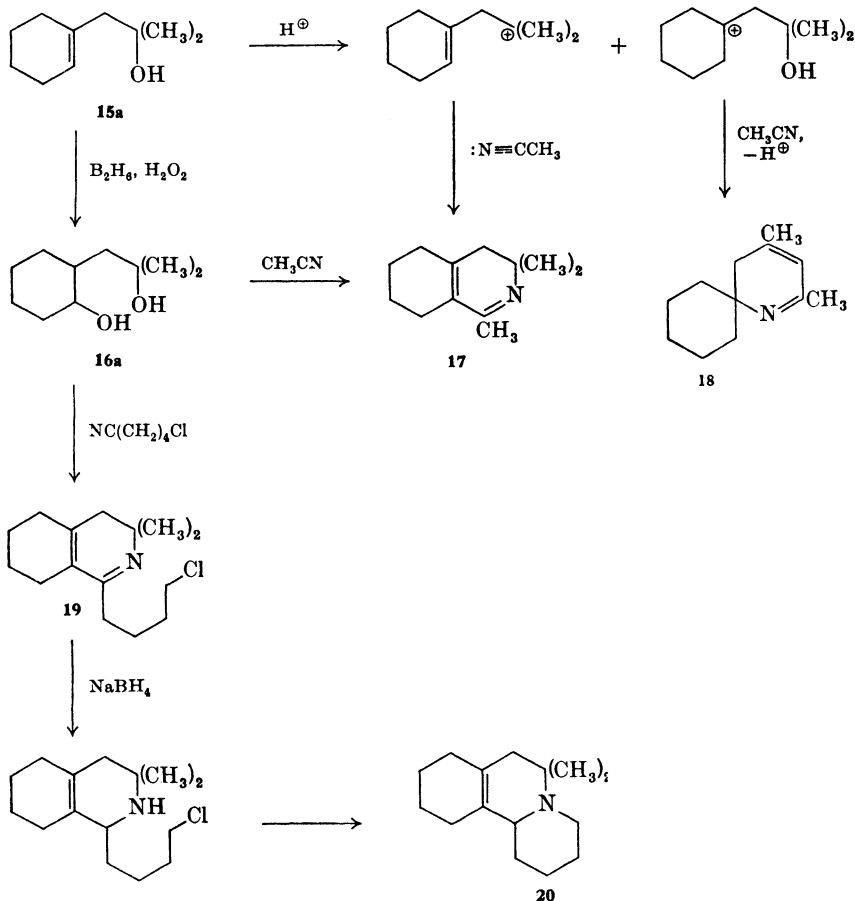


CHART I

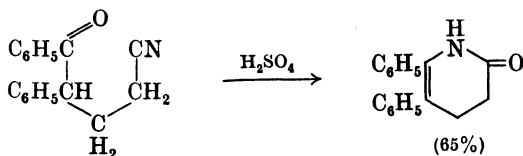


In an attempt to circumvent the formation of the spiro base **18** (Chart I) Meyers utilized the glycol **16a**; however, the desired isoquinoline **17** was obtained in only 30% yield.

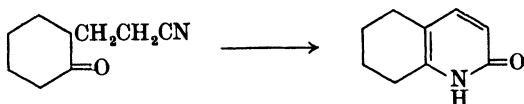
In another modification the same glycol, **16a**, was treated with δ -chloro-valeronitrile to give the hexahydroisoquinoline **19**. Reduction followed by cyclization afforded the quinolizine **20**.

2-Pyridones and 2-Quinolones. The use of keto nitriles in the Ritter reaction provides a direct route to 3,4-dihydro-2-pyridones^{98, 99} and 2-quinolones.⁹⁷ (The synthesis of 5,6-dihydro-2-pyridones is discussed on p. 246.) An example of the dihydropyridone synthesis is given in the

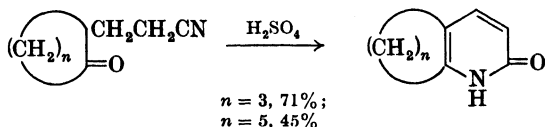
accompanying equation.⁹⁹ A similar approach was applied to 2-(2-cyano-



alkyl)cyclohexanones, which formed the corresponding cycloalkano[e]-2-pyridones by means of a consecutive cyclization-aromatization. When 2-(2-cyanoethyl)cyclohexanone was allowed to stand in sulfuric acid for 3 hours at room temperature, 5,6,7,8-tetrahydro-2-quinolone was formed.⁹⁷



Aromatization also occurred when the corresponding cyclopentanone and cycloheptanone nitriles were cyclized in sulfuric acid.⁹⁷

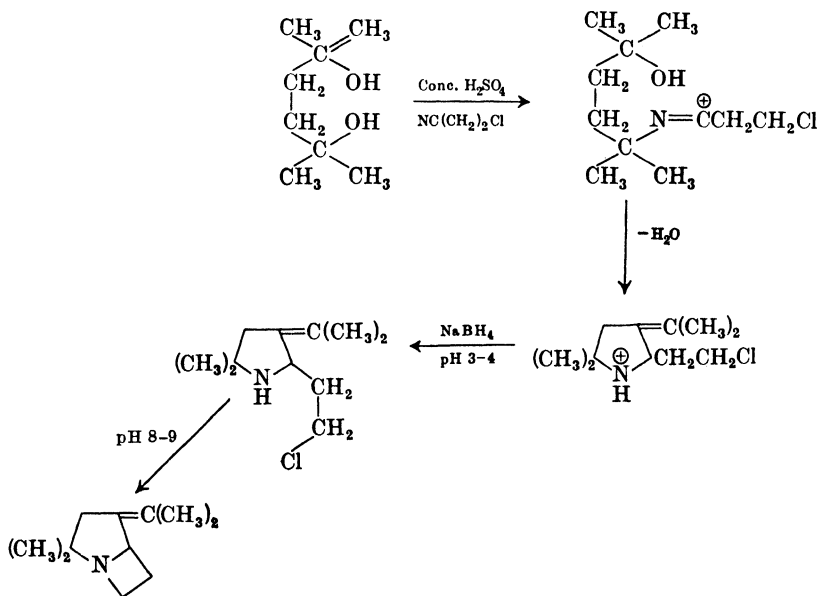


1-Azabicycloalkanes. A new approach to polycyclic bases utilizing the Ritter reaction was investigated by Meyers and co-workers.^{101-103, 106} The method involves the treatment of a ditertiary glycol with an ω -chloronitrile to give an ω -chloroalkyl-1-pyrroline. Subsequent reduction and cyclization via intramolecular alkylation yields the 1-azabicycloalkane.

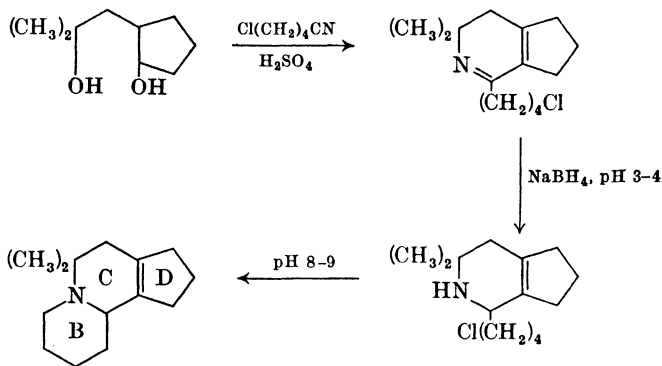
The formation of 1-azabicyclo[3.2.0]heptane in 30% yield is illustrative of this unique reaction which takes place in a single step without isolation of the intermediate 2-chloroethyl-1-pyrroline. By substituting 4-chlorobutyronitrile or 5-chlorovaleronitrile the analogous 1-azabicyclo[3.3.0]- or [4.3.0]-cycloalkanes can be obtained in equally good yields¹⁰¹ (p. 243).

Cyclopenteno[d]-1-azabicycloalkanes have also been synthesized by this procedure from α -(2-hydroxycyclopentyl)-*t*-butyl alcohol and the appropriate chloronitrile.¹⁰² The route outlined below affords the final tricyclic

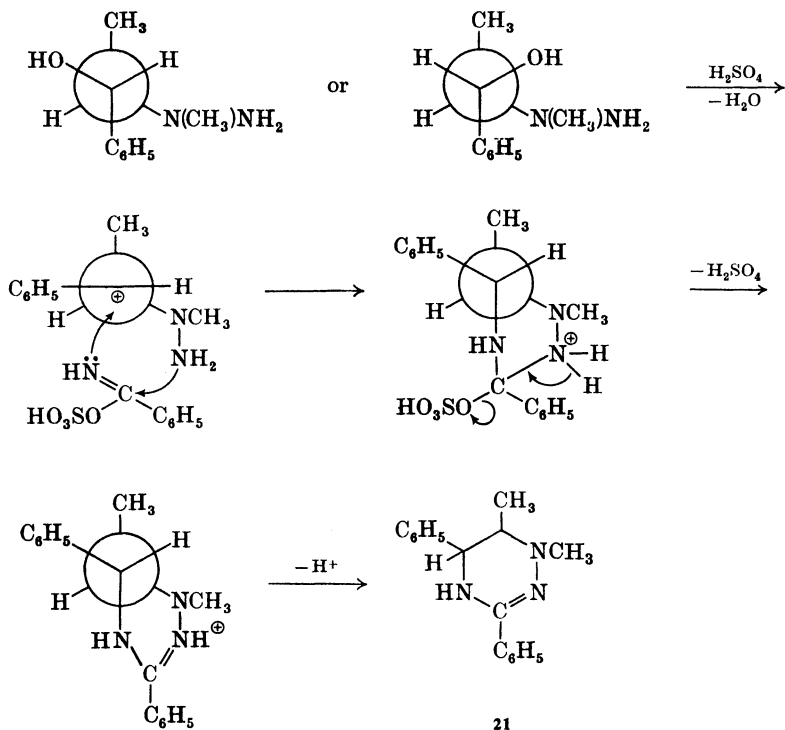
¹⁰⁶ A. I. Meyers and H. Singh, to be published.



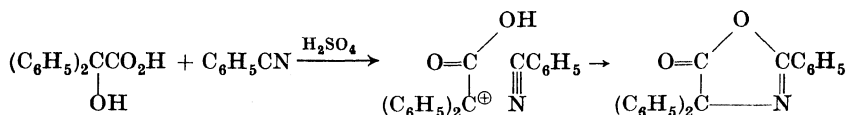
compound in 46% overall yield and represents the formation of rings B, C, and D of an azasteroid nucleus.



1,4,5,6-Tetrahydro-*as*-triazines.¹⁰⁰ Hydrazino alcohols containing a tertiary aliphatic or secondary benzylic hydroxyl group condense with a variety of nitriles to give triazines. N-Amino-(—)-ephedrine reacted with benzonitrile to give *trans*-(+)-1,6-dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine (**21**). The reaction appears to proceed by attack of the nitrilium sulfate on the carbonium ion resulting from the dehydration of the hydrazino alcohol.



2,4,4-Triphenyl-5-oxazolone. The treatment of benzoic acid and benzonitrile with concentrated sulfuric acid by Japp and Findlay represents the earliest report of a reaction of the Ritter type.¹⁰⁷ Reinvestigation of this reaction confirmed the participation of the $(\text{C}_6\text{H}_5)_2\text{CCO}_2\text{H}^+$ cation to give 2,4,4-triphenyl-5-oxazolone.¹⁰⁵



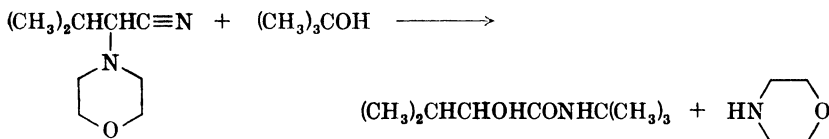
The Nitrile Source

The general applicability of the reaction to nitriles of various structures is evident from Ritter's original investigation.¹ The reactions described in the preceding sections and those referred to in the tables further exemplify the great variety of compounds which have been utilized as a source of the $\text{C}\equiv\text{N}$ group.

¹⁰⁷ F. R. Japp and A. Findlay, *J. Chem. Soc.*, 75, 1027 (1899).

Although the yields of *t*-alkylamides are not markedly affected by the nitrile structure, there is a decrease in the sequence, $\text{CH}_2=\text{CHCN} > \text{C}_6\text{H}_5\text{CN} > \text{CH}_3\text{CN}$ in the reaction with isobutene,²⁸ methylbutene, and isooctene.¹ Thus a phenyl group or a double bond in conjugation with the nitrile exerts a favorable but not a major influence.²⁸ The effect of strongly electronegative substituents in the α position was described for camphene (p. 221); however, there is insufficient experimental evidence to extend this to other alkenes that undergo Wagner rearrangements.

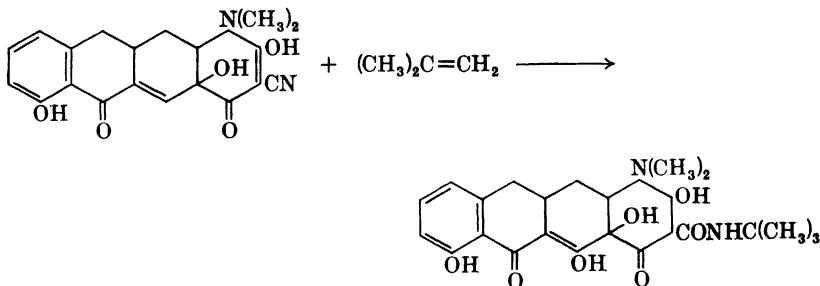
An unexpected result was obtained with α -morpholinyl nitriles.¹⁰⁸ When the β -carbon atom is tertiary, an α -hydroxyamide is produced.



Similar products are obtained if the α -amino substituent contains groups larger than methyl.

Some unusual sources of the nitrile group have been reported. In an attempt to prepare alkyl isonitriles, Heldt obtained the corresponding N-alkylformamides from hexacyanoferric(II) acid and *t*-butyl alcohol, *t*-amyl alcohol, or 1-butene. It is not certain that this acid furnished the $\text{—C}\equiv\text{N}$ group, since gaseous hydrogen cyanide was present during the reaction.¹⁰⁹

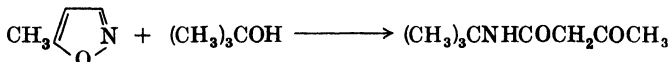
The acid stability of 6-deoxytetracyclines has made possible the conversion of the 2-cyano compound to the corresponding carboxamide by means of the Ritter reaction. For example, the reaction of isobutene with 6-demethyl-6-deoxytetracyclinonitrile gave N²-*t*-butyl-6-demethyl-6-deoxytetracycline.



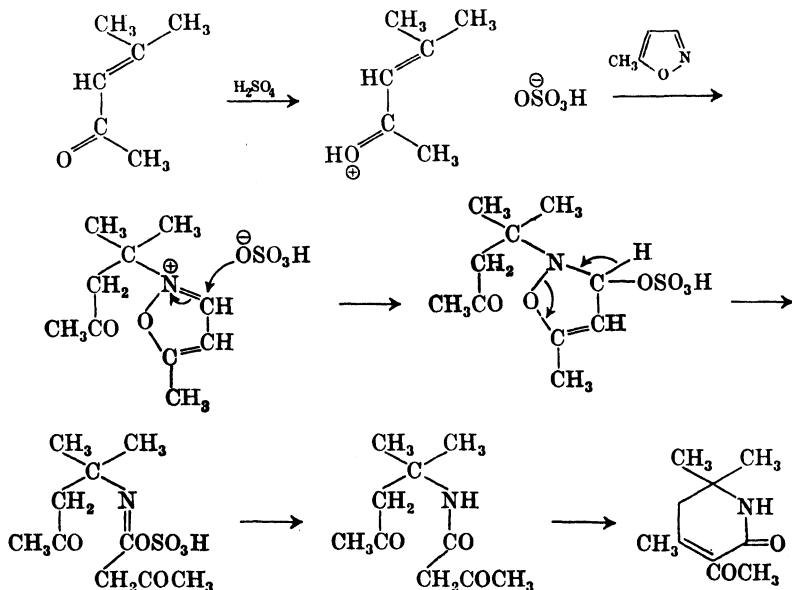
¹⁰⁸ D. Giraud-Clenet and J. Anatol, *Compt. Rend.*, **262**, 224 (1966).

¹⁰⁹ W. Z. Heldt, *J. Org. Chem.*, **26**, 3226 (1961).

Eugster and co-workers employed 5-methyl- and 5-phenyl-isoxazole in an unusual extension of the Ritter reaction.¹¹⁰ Under acid conditions these compounds behave as cyanoacetones and give the corresponding Ritter products. The reaction of 5-methylisoxazole with *t*-butyl alcohol yields *N*-*t*-butylacetoacetamide.



With α,β -unsaturated ketones, the isoxazole forms 5,6-dihydro-2-pyridones. The proposed mechanism follows.



Cyanogen chloride was found to react under Ritter conditions with olefins containing internal or substituted terminal double bonds. Although the yields are considerably lower, the amine is obtained directly without the hydrolysis required when hydrogen cyanide is used.¹¹¹

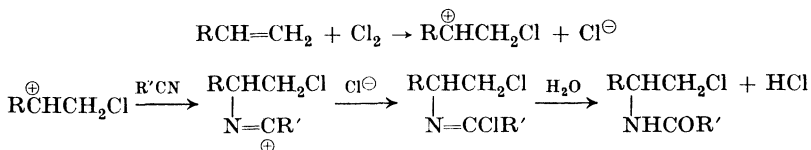
RELATED SYNTHETIC PROCESSES

Halogens and Halogen Acids as Catalysts. A similar reaction has been conducted in media other than strong acids. These modifications of the Ritter reaction conditions have added to the general applicability of this procedure for the preparation of *N*-substituted amides.

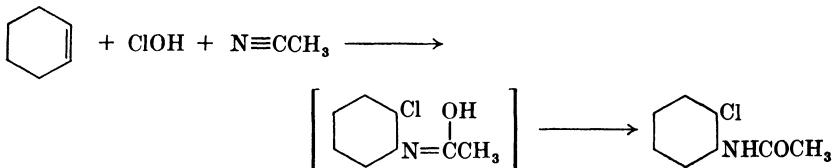
¹¹⁰ C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta.*, **46**, 543 (1963).

¹¹¹ E. M. Smolin, *J. Org. Chem.*, **20**, 295 (1955).

Cairns and co-workers showed that the interaction of chlorine and an olefin in the presence of a nitrile yielded an imidoyl chloride which could be hydrolyzed readily to an N-(2-chloroalkyl)amide.¹¹² 2-Haloalkylamines were obtained when hydrogen cyanide was the nitrile source. A comparable reaction was described by Theilacker who added hypochlorous

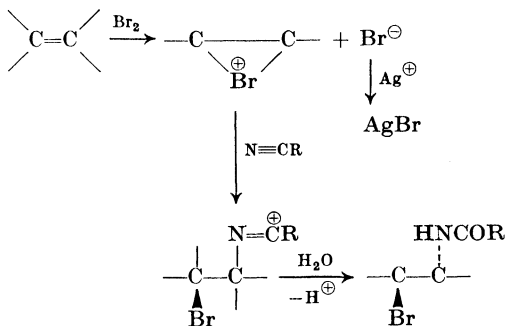


acid to cyclohexene and used aqueous acetonitrile as a solvent.¹¹³ The unexpected participation of acetonitrile yielded N-(2-chlorocyclohexyl)-acetamide. When α,β -unsaturated acids are used in place of olefins,



hydrolysis yields the β -amino α -hydroxy-carboxylic acids in yields up to 70%.

The use of bromine has also been reported.¹¹⁴ In this case the nitrile opens the intermediate cyclic bromonium ion and incorporates itself into the molecule in a stereospecific manner. The reaction proceeds only when the halide anion liberated from the original halogen is removed from solution.

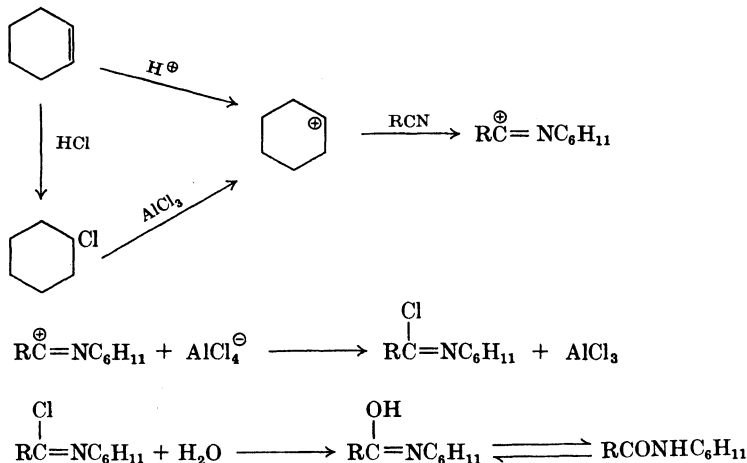


¹¹² T. L. Cairns, P. J. Graham, P. L. Barrick, and R. S. Schreiber, *J. Org. Chem.*, **17**, 751 (1952).

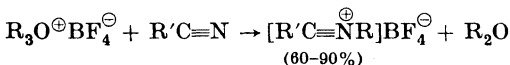
¹¹³ W. Theilacker, *Angew. Chem., Intern. Ed. Engl.*, **6**, 94 (1967).

¹¹⁴ A. Hassner, L. Levy, and R. Gault, *Chem. Eng. News*, **44**, 44 (April 11, 1966).

Friedel-Crafts Catalysts. *N*-Cyclopentyl- and cyclohexyl-amide were prepared in 5–55 % yields by the reaction of nitriles with cyclopentene and cyclohexene under conditions of the Gattermann aldehyde reaction.¹¹⁵ Bromine and iodine were also used to facilitate the aluminum chloride-catalyzed reaction.



The results indicated that the Ritter method is superior with respect to both yields and simplicity. It is noteworthy that primary and tertiary alkyl halides failed to give isolable amides.¹¹⁵ The reactions of trialkyl oxonium fluoborate salts with nitriles to give nitrilium salts have been described.¹¹⁶ Subsequent hydrolysis yields the corresponding *N*-alkyl acid amides.



The synthesis of heterocyclic compounds from nitrilium salts has been investigated by Lora-Tamayo and co-workers.^{117–122} They were able to prepare 3,4-dihydro-isoquinolines,¹¹⁸ -papaverines,¹¹⁹ -quinazolines,¹²⁰ 4,5-diphenyloxazoles,¹²¹ and 4,4,6-trimethyl-4H-1,3-oxazines¹²² by cyclization of suitable nitrilium intermediates. The nitrilium salts were formed

¹¹⁵ G. W. Cannon, K. K. Grebker, and Y. Hsu, *J. Org. Chem.*, **18**, 516 (1953).

¹¹⁶ H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).

¹¹⁷ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ind.*, (London) 657 (1959).

¹¹⁸ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ber.*, **93**, 289 (1960).

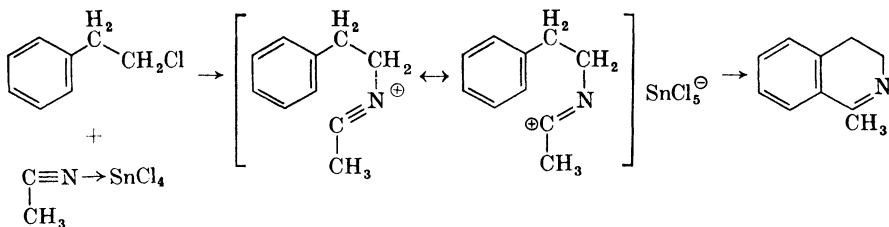
¹¹⁹ M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, J. M. Marzal, and M. Stud, *Chem. Ber.*, **94**, 199 (1961).

¹²⁰ M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ber.*, **94**, 208 (1961).

¹²¹ M. Lora-Tamayo, R. Madroñero, and H. Leipprand, *Chem. Ber.*, **97**, 2230 (1964).

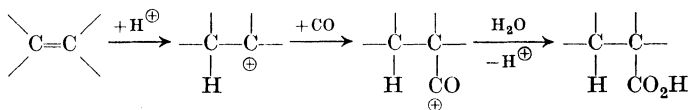
¹²² M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, and H. Leipprand, *Chem. Ber.*, **97**, 2234 (1964).

by the action of a metal halide-nitrile complex. Thus, by heating equimolecular amounts of β -chloroethylbenzene and the tin tetrachloride-acetonitrile complex, a 91% yield of 1-methyl-3,4-dihydroisoquinoline



was obtained.¹¹⁸ Although the yields vary considerably, the method provides a facile route to the heterocycles cited.

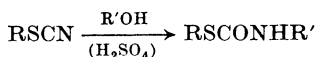
Koch-Haaf Reaction. The reaction of carbonium ions with carbon monoxide in sulfuric acid followed by hydrolysis to give carboxylic acids is known as the Koch-Haaf reaction. Carbon monoxide, either generated *in situ* from formic acid¹²³ or supplied as the gas under pressure,¹²⁴ has been used to produce branched carboxylic acids in good yields from alkenes.



The reaction has been extended to include alcohols, alkyl chlorides, esters, and paraffins as the carbonium ion source.^{123, 124}

In a comparative study of the Koch-Haaf and Ritter reactions Christol and Solladie furnished evidence that the nucleophilic reagent, carbon monoxide, has greater reactivity than its counterpart, the nitrile, particularly with the compounds containing a phenyl group.¹² Indeed, whereas the Ritter reaction failed with diphenylmethylcarbinol,⁴⁰ the Koch-Haaf reaction furnishes the corresponding carboxylic acid in 18% yield.¹²

Thiocarbamate Synthesis. The preparation of *N*-substituted thiocarbamates from thiocyanates, using methods analogous to that of the Ritter reaction, was described by Riemschneider.¹²⁵ He found that thiocyanates react with alcohols and olefins in the presence of sulfuric acid to give products which, on hydrolysis, yield *N*-substituted thiocarbamates.

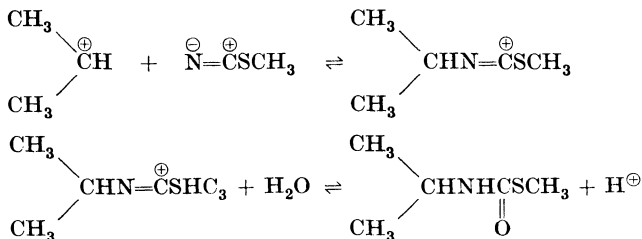


¹²³ H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958).

¹²⁴ W. Haaf and H. Koch, *Ann.* **638**, 122 (1960).

¹²⁵ R. Riemschneider, *J. Am. Chem. Soc.*, **78**, 844 (1956).

The formation of these thiocarbamates from a carbonium ion may be formulated in the following way. Primary alkyl thiocyanates react with



alcohols and olefins to give the desired thiocarbamates in good yields; 1,4-dithiocyanatobutane and 1,5-dithiocyanatopentane yielded the expected N,N'-substituted *bis*-thiocarbamates.

EXPERIMENTAL CONDITIONS

Nature of the Acid. Perchloric,¹⁹ phosphoric,⁵⁷ polyphosphoric^{45, 46, 49-51} formic,^{68, 69} substituted sulfonic acids,^{5, 26, 111} and boron trifluoride⁹⁶ have been used as reagents in the Ritter reaction. The best yields have been reported for the reactions which were conducted in 85-90 % sulfuric acid.

A detailed study of the effect of various mineral acids on the formation of N-*t*-butylacrylamide in acetic anhydride showed that the highest yields resulted from the use of sulfuric acid.²⁸ This report and others^{19, 24, 26, 68, 70} describe lower yields when other acids are substituted for sulfuric acid, thus supporting the particular role of sulfuric acid or the bisulfate anion in the Ritter reaction.

Glacial acetic acid has frequently been employed as a diluent; however, Benson and Ritter reported that secondary alcohols would not react under these conditions.⁵⁵ It is noteworthy that esterification competes with amide formation yielding acetates and giving lower yields.^{28, 57}

Nature of the Solvent. In addition to glacial acetic acid, other polar and non-polar solvents have been used. They include acetic anhydride, di-*n*-butyl ether, chloroform, carbon tetrachloride, hexane, and nitrobenzene.

Christol and Solladie made a comparison of products using 96 % sulfuric acid with and without solvent.¹¹ They concluded that in highly polar solvents the attacking nitrile is strongly polarized and becomes solvated, resulting in enhancement of its nucleophilic reactivity. On the other hand, in non-polar solvents such as carbon tetrachloride the solvation phenomena are less important since the medium is less polar. In this case the yields are generally lower.

A related study by Glikmans and co-workers employing di-*n*-butyl ether and dioxane gave similar results, and the Ritter reaction failed completely in the presence of methanol or ethanol.²⁸

Reaction Time and Temperature. An examination of the experimental data clearly demonstrates that there is no rigid pattern, but a great number of variations both in reaction time and temperatures. Generally the reaction temperatures are mild; that is, in the 25–50° range. The use of liquid hydrogen cyanide, of course, necessitates temperature in the 0–10° range, and there are a few examples of the reaction proceeding at lower temperatures.³⁶

The reaction time is also quite variable. Swern reported times as brief as 15 minutes, and related time to reaction size.^{19, 42} With lower temperatures, longer reaction times have been used. A study of the influence of time versus yield was reported for the reaction of isobutene with acrylonitrile at 25°. The results show that the reaction is 96.5% complete after 3 hours and that extending the reaction time to 16 hours provides only an increase of 1.9% in the yield of *N*-*t*-butylacrylamide.²⁸

EXPERIMENTAL PROCEDURES

N-Benzylacrylamide. Preparation from acrylonitrile and benzyl alcohol in 59–62% yield is described in *Organic Syntheses*.⁵⁶

***N*-*t*-Butylacetamide.**¹ Gaseous isobutene (12 g., 0.21 mole) is led into a solution of 4.5 g. (0.11 mole) of acetonitrile in 50 ml. of glacial acetic acid containing 10 g. (0.1 mole) of concentrated sulfuric acid while the temperature is maintained at about 20°. The reaction vessel is then stoppered loosely and allowed to stand overnight. The reaction mixture is poured into 200 ml. of water, neutralized with sodium carbonate, and extracted with five 50-ml. portions of diethyl ether. The combined extracts are dried over anhydrous potassium carbonate, most of the ether is removed at 50°, and the remainder is evaporated at room temperature. The residue (11 g., 85%) is recrystallized from hexane as needles, m.p. 97–98°, b.p. 194° (cor.).

1-Methylcyclohexylamine.⁶⁰ 1-Methylcyclohexanol (114 g., 1.0 mole) is slowly added to a previously cooled mixture of 122 g. (4.5 moles) of liquid hydrocyanic acid in 131 g. (1.34 moles) of concentrated sulfuric acid, the temperature being maintained below 0°. This temperature is maintained for 1 hour after completion of the addition. The reaction mixture is then allowed to stand at 25–30° for 24 hours, after which it is cooled and 250 g. of ice and 250 g. of 50% aqueous sodium hydroxide are added. The mixture should be at pH 9; if not, additional sodium hydroxide solution is added.

The reaction mixture is then heated at 50–60° for 4 hours. Sodium hydroxide pellets (50 g.) are added, and the mixture is steam-distilled. The organic distillate is separated and dried over potassium hydroxide. Distillation at 31–38°/8–10 mm. gives 70 g. (60%) of 1-methylcyclohexylamine.

1-Phenylethylamine.⁸ Concentrated sulfuric acid (30 ml.) is added dropwise with stirring to a solution of 12.2 g. (0.1 mole) of 1-phenylethanol in 75 ml. of di-*n*-butyl ether in which is suspended 16.25 g. (0.25 mole) of potassium cyanide. The temperature rises rapidly but is maintained between 60° and 80° by external cooling. After the addition, agitation is continued for 1 hour at 50°. The reaction mixture is then poured onto 300 g. of ice, made alkaline with 20% aqueous sodium hydroxide, and extracted with diethyl ether. The ethers are removed, and the resulting oil is heated under reflux for 3 hours with twice its volume of concentrated hydrochloric acid. After the solution has cooled, it is extracted with ether to remove any impurities. The water layer is made alkaline, and the amine extracted with ether. The ether extracts are dried over anhydrous potassium carbonate and fractionally distilled; the yield is 70.2 g. (60%) of a colorless oil, b.p. 91°/20 mm.

Ethyl 3-propionamido-3-phenylbutyrate.⁶² Concentrated sulfuric acid (10 ml.) is added dropwise with stirring to a mixture of 0.05 mole of ethyl 3-hydroxy-3-phenylbutyrate and 0.06 mole of propionitrile at 0° over a period of 30 minutes. The mixture, which becomes viscous after about half of the sulfuric acid is added, is left standing overnight at room temperature and is then poured into 100 ml. of ice water. The amido ester is collected by filtration and crystallized from methylcyclohexane. The yield of crystals, m.p. 83°, is 73%.

Di-N-*t*-butyladipamide.⁷¹ A solution of 0.05 mole of adiponitrile and 0.1 mole of methyl *t*-butyl ether in 10 ml. of glacial acetic acid is added with stirring and cooling (30°) to a solution of 10 g. of 100% sulfuric acid in 20 ml. of glacial acetic acid. After 3 hours the reaction mixture is poured into water. The di-N-*t*-butyladipamide that precipitates is isolated by filtration. The yield of the diamide, m.p. 212°, is 75%.

Methylene-*bis-p*-toluamide.⁶⁸ A solution of 1.5 g (0.05 mole) of trioxane in 11.7 g. (0.1 mole) of *p*-tolunitrile is added slowly with stirring to 38 ml. of 85% sulfuric acid in a 125-ml. three-necked flask. The temperature is maintained at 30° by cooling with an ice bath. After 3 hours the solution is poured into 300 ml. of ice and water. Methylene-*bis-p*-toluamide separates as white crystals which are filtered and recrystallized from 95% ethanol. The yield is 12.4 g. (83%) of crystals melting at 209–210°.

N-(Benzamidomethyl)acrylamide.⁷⁵ A mixture of 7.6 g. (0.05

mole) of *N*-methylolbenzamide and 3.7 g. (0.07 mole) of acrylonitrile is added slowly to 50 ml. of 96% sulfuric acid with stirring. The temperature is kept at 30° by cooling. At the end of 1 hour the reaction mixture is poured into 200 g. of ice and water. The crystalline product which precipitates is filtered and recrystallized from water to give 6.0 g. (60%) of *N*-(benzamidomethyl)acrylamide. This compound polymerizes in the melting-point tube when it is heated above 150°.

***N*-*t*-Butylphenylacetamide.**⁶⁶ A mixture of 11.7 g. (0.1 mole) of benzyl cyanide, 9.25 g. (0.1 mole) of *t*-butyl chloride, and 24 g. of 90% formic acid is heated under reflux for 5 hours and poured into a mixture of ice and water. The solid that precipitates is filtered and dried. The yield of amide melting at 111–113° is 4.3 g. (23%).

Acetamidostearic Acid.¹⁹ A mixture of 282 g. (1.0 mole) of oleic acid and 123 g. (3.0 moles) of acetonitrile in a cylindrical dropping funnel is stirred vigorously and added during 35 minutes to 338 ml. (6 moles) of 95% sulfuric acid in a 2-l. three-necked flask fitted with a thermometer and an efficient stirrer. The reaction temperature is maintained between 27° and 30° by external cooling. Fifteen minutes after addition is complete, the mixture is poured with stirring onto approximately 2 l. of chopped ice and water. The soft, sirupy, insoluble mass is stirred occasionally and then allowed to stand overnight in the dilute acid. The following morning, stirring is continued until the product hardens to a crumbly, wax-like solid which is filtered, washed several times with cold water, and dried; the yield of crude acetamidostearic acid, m.p. 56–58°, is 339 g. (99%).

4-Methyl-4-benzamido-2-pentanone.⁷² To a solution of 19.6 g. (0.2 mole) of mesityl oxide and 22.0 g. (0.21 mole) of benzonitrile is added 20 ml. of concentrated sulfuric acid. The temperature is kept below 30° by means of an ice bath. After addition is complete, the reaction mixture is warmed to 50° and is kept at this temperature for 1 hour. The dark, viscous liquid is poured into 300 ml. of ice cold water. The resulting solid is filtered and washed with 10% aqueous potassium carbonate, then with water. The yield, m.p. 98–100°, is 20–24 g. (45–55%). Recrystallization from cyclohexene and dilute ethanol furnishes white needles, m.p. 100–101°.

3-Dichloroacetamidoisocamphane.³⁶ Sulfuric acid (20 ml., 98%) is added with stirring, at a temperature below –15°, over a period of 1 to 1½ hours to a solution of 44.3 g. of camphene and 43.0 g. of dichloroacetonitrile in 20 ml. of propionic acid. The reaction mixture is kept for 2 days at –20° to –15°; then it is poured onto 300 ml. of ice water, the aqueous solution neutralized with sodium carbonate, the crystalline precipitate collected by filtration and dried in a vacuum desiccator over phosphorus

pentoxide. After recrystallization from 150 ml. of petroleum ether (b.p. 70–100°), 50.2 g. of material (m.p. 106–108°) is obtained; a further 10 g. of the material is isolated from the mother liquor by evaporation of part of the solvent and recrystallization. The total yield is 60.2 g. (69.7%).

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine.⁸³ Benzonitrile (20.6 g., 0.2 mole) is added dropwise with stirring to 100 g. of 92% sulfuric acid at 2–4° over 20 minutes. Then 23.6 g. (0.2 mole) of 2-methyl-2,4-pentanediol is added dropwise with stirring at 3–6° during 2 hours. The resulting solution is poured with stirring on 1 kg. of cracked ice, and the mixture is half-neutralized with 40% aqueous sodium hydroxide, then extracted with several portions of diethyl ether. The combined ether extracts are dried over anhydrous potassium carbonate and, after removal of the ether, the residual oil is distilled through a 30-cm. vacuum-jacketed Vigreux column. Two recrystallizations from ethanol-water (the compound is dissolved at room temperature, and the solution is then strongly cooled) give colorless crystals, m.p. 34–35°.

2-(*p*-Aminophenyl)-4,4-dimethyl- Δ^2 -thiazoline.⁵⁹ To a solution of 3.5 g. (0.03 mole) of *p*-aminobenzonitrile in 25 ml. of concentrated sulfuric acid previously cooled to 3° is added with stirring 2.1 g. (0.02 mole) of 2-hydroxy-2-methylpropanethiol during 30 minutes. The reaction mixture, which is golden yellow, is stirred at 3–5° for an additional hour; then it is poured on 300 g. of chipped ice. The cold, aqueous acid solution is then extracted with chloroform until the chloroform layer is colorless. After the aqueous solution has been poured through fluted filter paper to remove the excess chloroform, it is carefully neutralized with 30% aqueous sodium hydroxide. The heterocyclic base appears as a crude brown solid which is collected in a Buchner funnel and then washed several times with hot water to remove any unchanged nitrile. Recrystallization from aqueous ethanol yields 2.3 g. (55%) of a very light yellow crystalline material, m.p. 162–164°. The picrate melts at 91–93°.

2-Vinyl-1-pyrroline.¹⁰⁴ To a cold solution of 14.0 g. (0.10 mole) of 3,3'-thiodipropionitrile¹²⁶ in 100.0 ml. of concentrated sulfuric acid is added with stirring 29.6 g. (0.20 mole) of 2,5-dimethyl-2,5-hexanediol. The temperature of the reaction is kept below 10° by employing an ice bath. After the glycol addition has been completed, the mixture is stirred for an additional hour at 4–6° and then slowly poured over 300 g. of chipped ice. The aqueous acid solution, after it has been shaken several times with 75-ml. portions of chloroform to extract polymeric material, is cautiously neutralized with 30% aqueous sodium hydroxide. The heterocyclic base, which separates, is taken up in diethyl ether and dried overnight with potassium carbonate. After the ether is removed at atmospheric pressure,

¹²⁶ F. M. Cowen, *J. Org. Chem.*, **20**, 287 (1955).

the residual oil is distilled under reduced pressure to give a light yellow oil, b.p. 86–87°/1.25 mm.; n_D^{30} 1.5019.

1-(3',4'-Dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisquinoline.³⁴ Veratronitrile (9.8 g., 0.06 mole) is added portionwise to concentrated sulfuric acid (15 ml.) in an ice bath with rapid stirring. Methyleugenol (10.2 ml., 0.06 mole) is then added during 2 minutes. The cooling bath is removed before addition of the methyleugenol, and the temperature, which rises rapidly during the addition, is maintained around 80° by intermittent cooling. After it has stood at room temperature for 3 days, the reaction mixture is poured into water and neutralized with sodium carbonate. A yellow mass separates which gradually crystallizes on stirring in warm water. It is filtered, washed with water, and dried. The crude dihydroisquinoline (11.5 g., 53 %) is crystallized from aqueous ethanol as yellow crystals (6.7 g.) melting at 134–137°. Recrystallization yields a product melting at 138–139°.

5,6-Diphenyl-1,2,3,4-tetrahydro-2-pyridone.⁹⁹ In a flask fitted with a mechanical stirrer is placed 20 ml. of 90 % sulfuric acid, and 10 g. (0.04 mole) of γ -benzoyl- γ -phenylbutyronitrile is added in 5 minutes at 25–27°. Solution is quite rapid with the evolution of a little heat. The stirring is continued for 3 hours, after which the mixture is allowed to stand overnight. The next day, the viscous, brownish-red solution is poured with stirring over 200 g. of cracked ice. The precipitate forms as a whitish lump. The dilute acid is decanted, the lump is treated with 150 ml. of water, and the mixture is heated on the steam bath. The mass disintegrates and becomes crystalline. It is crushed, filtered, washed with water to remove the acid, treated with 3 % aqueous ammonia; after it has stood in the ammonia solution for an hour, it is filtered, washed with water, and dried. Recrystallization from ethyl Cellosolve gives 6.0 g., and an additional 0.5 g. is isolated from the mother liquors. The yield, m.p. 218–219°, is 65 %.

2,2-Dimethylcyclopenteno(d)-1-azabicyclo[4.4.0]decane.¹⁰² To a cold (0–3°) solution of 9.05 g. (0.077 mole) of δ -chlorovaleronitrile in 150 ml. of 98 % sulfuric acid is added dropwise 11.06 g. (0.07 mole) of α -(2-hydroxycyclopentyl)-*t*-butyl alcohol. During the addition efficient stirring is maintained and the temperature of the mixture is kept below 10°. The time required for the complete addition of the glycol under these conditions is approximately 1½ hours.

The deep reddish reaction mixture is slowly poured over 500 g. of chipped ice in a 2-l. beaker. (The following two reactions, *i.e.*, the sodium borohydride reduction and the intramolecular alkylation, are carried out in this vessel.) The aqueous acid solution is extracted several times with chloroform to remove insoluble polymeric material and then partially

neutralized (to pH 2-4) with 35% aqueous sodium hydroxide. The temperature is maintained below 40° during the neutralization with the aid of external cooling. The electrodes of a pH meter (Beckman Zero-matic) are inserted into the solution and the acidity is adjusted to pH 3-4 by the addition of 4*M* sulfuric acid and 6*M* sodium hydroxide which are contained in burets situated above the beaker. The clear solution is cooled to room temperature, and a freshly prepared solution of sodium borohydride (2.66 g., 30 ml. of water, and one drop of 35% sodium hydroxide) is added dropwise with stirring supplied by a magnetic stirrer.

The pH of the reaction during the borohydride addition is constantly kept between 3 and 4 by the periodic addition of sulfuric acid or sodium hydroxide. The sodium borohydride addition is complete after 1 hour at 25°. The solution is allowed to stir at room temperature overnight and is then acidified to pH 1 and stirred for 1 hour to destroy the excess sodium borohydride. After addition of 300 ml. of water the pH is again adjusted to 8-8.5 and the solution is stirred for 5 hours. The oil that separates is extracted with diethyl ether, and the extract is dried over potassium carbonate. Removal of the ether on a steam bath and distillation of the residual oil given 6.6 g. (46%) of the tricyclic base, b.p. 100-102°/1.0 mm., n_D^{30} 1.5062. The infrared spectrum (carbon tetrachloride) shows only strong absorption at 3.4 μ (CH), 6.9 μ (CH₂ bending), and ring skeletal vibrations above 8 μ .

***trans*-1,6-Dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine.**¹⁰⁰ A solution of 36 g. (0.2 mole) of *N*-amino-(+)-pseudoephedrine in 50 ml. of chloroform is added dropwise to cooled (5°), stirred, concentrated sulfuric acid (250 ml.). After the addition is complete, 20.6 g. (0.2 mole) of benzonitrile is added, and the mixture is stirred at ambient temperature overnight. The mixture is poured onto crushed ice, washed with chloroform, made basic with sodium carbonate solution, and the precipitated solid is removed by suction filtration. The solid is recrystallized from isopropyl alcohol to yield 18.5 g. (35%) of white crystalline product, m.p. 146-147°.

TABULAR SURVEY

The tables include reactions compiled from the literature through December 1966. The authors feel that the data are reasonably complete, but some publications were undoubtedly missed.

The tables are arranged in the order in which different sources of the carbonium ion are discussed in the text. The reactants within a table are, in general, listed in order of increasing size and complexity.