DIELS-ALDER SYNTHESES WITH HETEROATOMIC COMPOUNDS

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CONTENTS

I. INTRODUCTION

The diene synthesis or Diels–Alder reaction, as commonly formulated, consists in the addition of a compound containing a double or triple bond to the 1,4-positions of a conjugated diene system with the formation of a six-membered hydroaromatic ring. The mechanism of this reaction has received considerable attention (39, 55, 87, 101, 178, 205) and will not be elaborated upon here. The present article is restricted to those systems in which one or more atoms of the dienophile or of the diene are something other than carbon. The reaction proceeds most readily in the case where the dienophile is activated by a strong electronegative group in conjugation with the double or triple bond. The activating moiety generally found may be —C=O, —C≡N, —NO_2, —SO_2R, *etc.* Because such systems often contain the activating group as part of a suitable 1,3-diene arrangement of bonds, many compounds of this class have been used successfully as dienes leading to the formation of heterocyclic systems through self-condensation.

The earliest examples of reactions following the general mechanism of the diene synthesis were based on the work of Zincke and co-workers and dealt with the self-condensation of 1,2,4,5,5-pentachlorocyclopenten-3-one to give tetrachlorocyclopentadienone (293–295).

The formal development of the Diels–Alder reaction followed the recognition by Diels (77) that the reaction between *p*-benzoquinone and isoprene observed by Euler and Josephson (98) was very similar to his reaction between azocarboxylic esters and isoprene derivatives or cyclopentadiene (84). The diene synthesis then underwent extensive development in the hands of Diels and Alder and others and gave rise to a long series of papers which continue to the present time. Staudinger (241) and Albrecht (9) laid the groundwork for much of our understanding as to the nature and mechanism of the diene synthesis.

The formation of the heterocyclic system from cyclopentadiene and azocarboxylic ester is one of the earliest examples of synthesis by the Diels–Alder

reaction but at the same time represents a departure from what has become the common form of the reaction, that giving rise to the all-carbon hydroaromatic cyclic structure. Preparation of commercially useful organic intermediates as well as the continuing search for routes to substances of potential interest (23, 89, 128, 243, 291) as medicinals has led to the investigation

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of the Diels–Alder reaction as a means of producing the requisite heterocyclic structures or carbocyclic systems.

The experimental work in the diene synthesis up to the last ten to fifteen years has been extensively reviewed (57, 132, 150, 181) in its many ramifications. A number of other papers, of a more limited scope, appeared sporadically in a variety of journals during the past decade and have carried the survey of the literature pertinent to the general Diels–Alder reaction almost to the present time (10–13, 138, 166, 182, 190, 268).

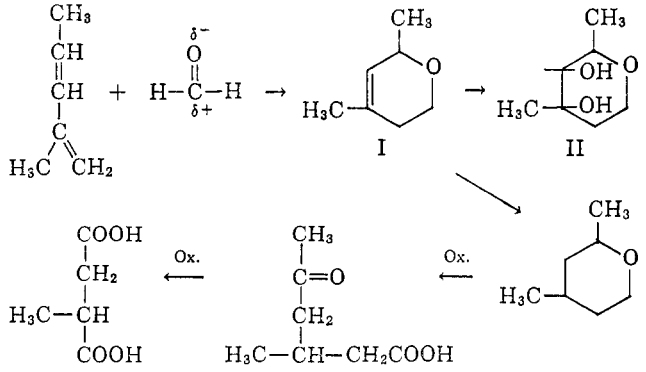
The present survey will be limited to those systems in which one or both of the atoms of the dienophile is N, O or S, or, where one or both of the atoms in the 1 and 4 position of the diene are N or O. Although the reaction products of dienophiles with furan, pyrrole, or thiophene may be envisioned as containing a heterocyclic atom, they are specifically excluded in that they do not fit within the interest of this paper, that the heteroatom directly enter into *de novo* heterocyclic formation. The survey of the literature is limited to the period from 1947 to March, 1960.

II. Dienophiles

A. Carbonyl Compounds as Dienophiles

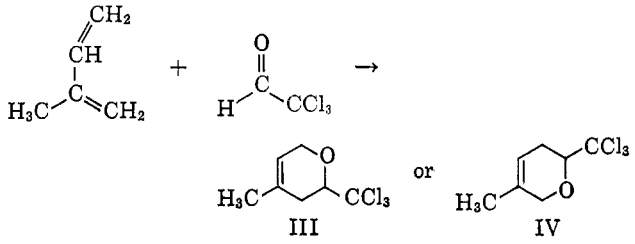
Syntheses of substituted 3,4-dihydro-1,2-pyrans from the self-condensation of α,β-unsaturated carbonyl compounds or from reaction with other dienophiles through the Diels–Alder mechanism are numerous. However, the formations of substituted 5,6-dihydro-1,2-pyrans by the direct 1,4-addition of a carbonyl group to conjugated dienes are less common.

Gresham and Steadman, using formaldehyde as the dienophile, condensed it with 2-methylpentadiene in a sealed container for several hours at 180° to obtain 2,4-dimethyl-5,6-dihydro-1,2-pyran (I) in 60% yield (110).



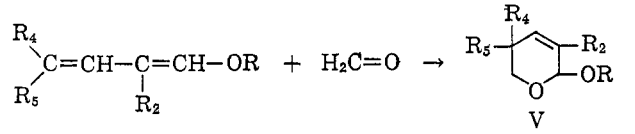
This was identified by the hydroxylation of the double bond with potassium permanganate or *t*-butyl hydroperoxide to form *cis*-3,4-dihydroxy-2,4-dimethyl-5,6-dihydro-1,2-pyran (II) and by hydrogenation followed by oxidative degradation. Formaldehyde could not be condensed with butadiene or piperylene to obtain the expected pyran derivatives. This may be accounted for by the more active nature of 2-methylpenta-1,3-diene toward Diels–Alder synthesis due to favorable polarization induced by the two methyl groups.

The carbonyl group also serves as a dienophile in the reaction of chloral with 1,3-dienes (70). Dale and Sisti condensed chloral with various 1,3-dienes such as 2,3-dimethylbutadiene, isoprene, piperylene, *etc.*, in sealed tubes at 150° for 24 hr. to yield the corresponding substituted 5,6-dihydro-1,2-pyrans in 30% yields. The products were identified by their hydrogenated or brominated derivatives.



The condensation of unsymmetrical dienes such as isoprene and chloral could lead to a mixture of two isomers depending on the direction of polarization of the dienes (III or IV). Only one product, however, was isolated. 4-Methyl-6-trichloromethyl-5,6-dihydro-1,2-pyran (III) is the most probable structure when one takes into consideration hyperconjugation for the polarizability of isoprene. Chloroacetaldehyde also reacted in a similar fashion (71).

Attempts to condense several aromatic aldehydes such as benzaldehyde, anisaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde with isoprene or 2,3-dimethylbutadiene (70) were unsuccessful. Paraformaldehyde reacts with 1-alkoxy or 1-alkoxy-alkoxy-1,3-butadiene in presence of a polymerization inhibitor, to form the 2-alkoxy and 2-alkoxy-alkoxy-5,6-dihydro-1,2-pyran (V) (156). The reaction of carbonyl cyanide

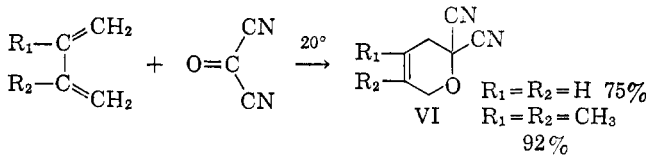


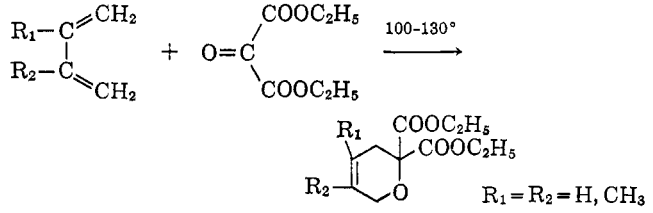
and conjugated dienes is of special interest because the carbonyl group is highly activated by two strongly electropositive cyano groups.

When carbonyl cyanide reacted with butadiene and 2,3-dimethylbutadiene, respectively, at room temperature for 15 min., 6,6-dicyano-5,6-dihydro-1,2-pyran (VI) and 3,4-dimethyl-6,6-dicyano-5,6-dihydro-1,2-pyran were obtained in good yield (7). Contrary to the Diels–Alder reaction of other carbonyl compounds, the ease of this reaction indicates an extraordinarily easy polariza-

tion of the C=O bond, due to the nitrile groups.

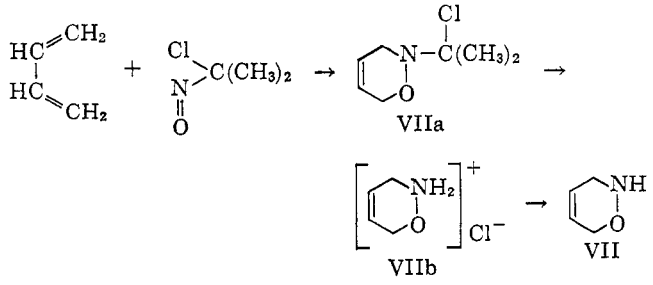
Similar condensations may be expected when other 2-strongly negative groups are attached to the carbonyl group. In fact, diethyl mesoxalate reacted with butadiene and 2,3-dimethylbutadiene at a moderate temperature (100° or 130°) and prolonged time (6 hr.) to give diethyl 5,6-dihydro-1,2-pyran-6,6-dicarboxylate and diethyl 3,4-dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylate, respectively.



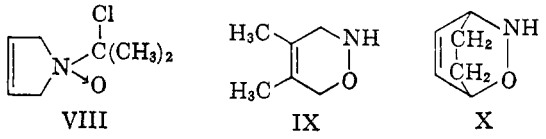


B. NITROSO COMPOUNDS AS THE DIENOPHILE

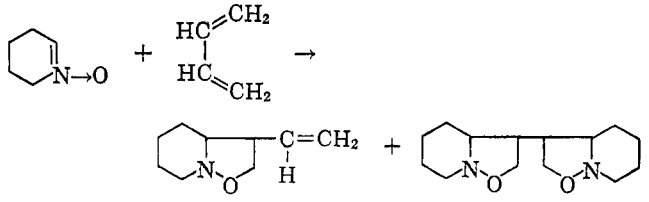
Wichterle (276) obtained a crystalline product, C_4H_8ONCl (m.p. 153°), from an ethanolic solution of buta-1,3-diene and 2-chloro-2-nitrosopropane. This can be obtained through a normal Diels–Alder 1,4-addition to form the six-membered orthoöxazine ring or through the addition of butadiene at the 1,4-positions to the nitrosobenzene nitrogen atom to form the N-oxide of 1-substituted-2,5-dihydropyrrole (VIII) as in the case of reaction between buta-1,3-dienes and sulfur dioxide compounds. The structure of the product was confirmed as 3,6-dihydro-*o*-oxazine (VII) by Raman spectrum showing a frequency corresponding to an isolated C=C bond (102). Thus, it was shown that the Diels–Alder reaction proceeds smoothly using a nitroso compound as the dienophile. It is reasonable to assume that the product of the reaction between butadiene and the initial chloronitroso compound is the normal Diels–Alder adduct which is the N-derivative of 3,6-dihydro-*o*-oxazine (VIIa). The compound undergoes alcoholysis to form 3,6-dihydro-*o*-oxazine hydrochloride (VIIb). When the hydrochloride was liberated, the free base (VII) was obtained.



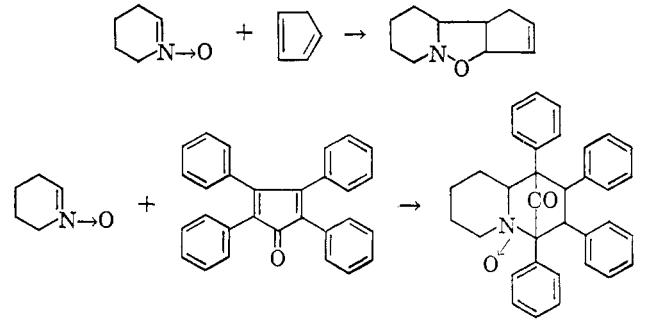
The reactions between 1-chloro-1-nitrosocyclohexane and buta-1,3-diene, 2,3-dimethylbuta-1,3-diene, cyclohexa-1,3-diene and chloroprene, in ethereal solution, in the presence of ethanol, also were investigated (31, 279). 3,6-Dihydro-*o*-oxazine (VII), 4,5-dimethyl-3,6-dihydro-*o*-oxazine hydrochloride (IX) and 3,6-endoethyleno-3,6-dihydro-*o*-oxazine (X), respectively, were obtained in fairly good yield.



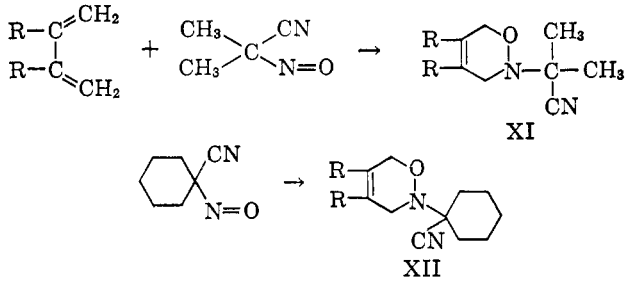
Only those nitroso compounds having a strongly polar bond in the vicinity of the nitroso group to aid in its polarization, are capable of diene addition (278). Wichterle and his co-workers attempted the addition of unsubstituted alkyl nitroso compounds to buta-1,3-diene without success. Brown also tried the 1,4-addition of nitrones to buta-1,3-dienes but only simple 1,2-addition took place with the nitrone, instead of the butadiene, behaving like a pseudodiene.



Cyclopentadiene, used in place of buta-1,3-dienes, gave similar results. However, when nitrone was condensed with tetraphenylcyclopentadienone, a common Diels–Alder synthesis took place (54).



Geminal cyanonitroso compounds would be expected to add to dienes because the C≡N group polarizes a nitroso group in the same direction as chlorine. In fact, geminal cyanonitroso compounds such as α-nitroso isobutyronitrile and 1-nitrosocyclohexyl cyanide undergo diene synthesis smoothly to give compounds as shown in the following equations (277). The products, XI and XII, are much more stable than those obtained from chloronitrosoalkane and are resistant to hydrolysis and alcoholysis. They can be isolated as such.

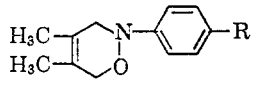


XI

XII

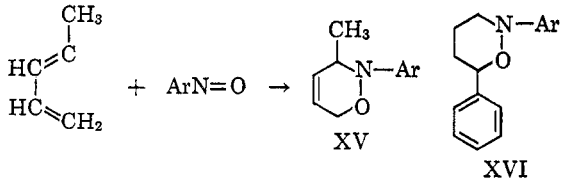
Aromatic nitroso compounds are very reactive dienophiles and add smoothly to substituted dienes at room temperature or at ice bath temperatures to give the corresponding oxazine derivatives. The reaction of aromatic nitroso compounds to various substituted dienes was studied in detail by Arbuzov and co-workers (28, 29) and also by Wichterle and his co-workers (277).

When nitrosobenzene reacted with 2,3-dimethylbutadiene, in addition to the expected 3,6-dihydro-4,5-dimethyl-2-phenyl-1,2-2H-oxazine (XIII) in 66% yield, a small amount of unidentified compound was isolated. However, when *p*-nitrosotoluene was used, 3,6-dihydro-4,5-dimethyl-2-(*p*-tolyl)-1,2-2H-oxazine (XIV) was isolated, as the only product, in 55% yield.



XIII, R = H
XIV, R = CH_3

Nitrosobenzene seems to react with unsymmetrically substituted butadienes in such a way that 3-substituted compounds were obtained as predominant products rather than 6-substituted compounds. For example, nitrosobenzene, with penta-1,3-diene, gives 3,6-dihydro-3-methyl-2-phenyl-1,2-2H-oxazine (XV) as the chief product (33).



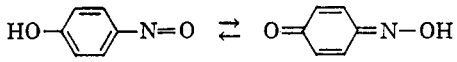
XV XVI

In the reaction of 1-phenylbuta-1,3-diene and nitrosobenzene, 2,6-diphenyl-3,6-dihydro-1,2-oxazine (XVI) was obtained. That the phenyl group is in position six rather than in position three is accounted for by the assumption that the nitroso nitrogen, which is substituted by a bulky group, cannot approach the phenyl substituted end of the diene as readily as the oxygen atom forming the terminal member of the chain (281).

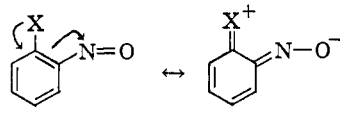
2,3-Diphenylbuta-1,3-diene, 1,2,3,4-tetraphenylbuta-1,3-diene, and 1,4-tetraphenylbuta-1,3-diene do not react with either aromatic nitroso compounds or 1-chloro-1-nitroso-cyclohexane (281). The failure of the Diels–Alder synthesis in these cases is most likely due to the steric hindrance. In each instance, the dienes bear bulky substituents.

In contrast to the reaction between butadiene and benzonitrile, in which the substituent in dienes or polarizability of the dienes influences the reactivity of the Diels–Alder addition, the substituents in the dienes have little influence in the reactivity of the reaction in addition of nitroso compounds to dienes. Under similar conditions, various dienes add smoothly to aromatic nitroso compounds to give the same order of yield of product. Arbuzov and co-workers (33) favor a radical mechanism for this diene reaction rather than an ionic mechanism. However, the nature of the reaction mechanism is still very ambiguous, there being so many contradictory experimental evidences.

The influence of the substituent in the aromatic ring of nitrosobenzene to the Diels–Alder reaction also was investigated. When nitrosophenol was combined with butadiene, a reaction did not take place (151). This probably can be explained by the fact that the nitroso group was stabilized by the tautomeric system which is common in nitrosophenol compounds. It can exist in two structural forms, namely, hydroxynitroso and quinone-oxime. Diene syntheses also were attempted

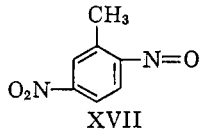


with 2,3-dimethylbutadiene and other aromatic nitrosobenzenes, such as *o*-, *m*-, *p*-nitrosotoluenes (151), *o*-, *m*-, *p*-nitrosochlorobenzenes, other halogenated nitrosobenzenes (152), 3-nitro-6-nitrosotoluene and 3-nitro-4-nitrosotoluene (151). In each case, reaction conditions were kept constant; *o*- and *p*-substituted nitrosobenzenes were found to react sluggishly over a long period of time, while *m*-substituted nitrosobenzenes reacted with butadiene violently with the evolution of heat as in the case of the nitrosobenzene itself. Apparently *o*- and *p*-substitutents retard the reaction. Similar effects also were observed for the reaction of halogen-substituted nitrosobenzenes. That is, the *o*- and *p*-halonitroso benzenes retard the reaction considerably while *m*-halonitroso benzenes proceed smoothly. Again, all of the retarding effects of *o*- and *p*-substituents probably are due to stabilization of the nitroso group through resonance effects. Both methyl groups and halogens are electron releasing groups which may resonate effectively with the nitroso group through conjugation when situated in the *o*- or *p*-positions. In the *meta*-position, this kind of resonance stabilization cannot take place. In the case of reaction between 3-

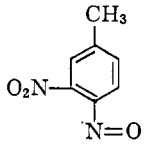


X = CH_3 or halogens

nitro-6-nitrosotoluene and 3-nitro-4-nitrosotoluene and butadiene, the former shows more retardation than the latter. It is also interesting to note that the difference in reactivity between *o*-nitrosotoluene and *p*-nitrosotoluene is not significant. However, when a nitro group is substituted in the position *meta* to a methyl group, the retarding effect of the methyl group disappears (XVII, XVIII). This may be accounted for by the fact



XVII

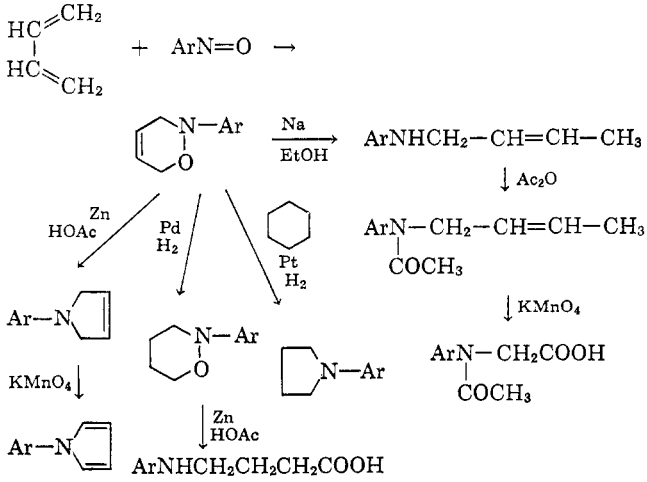


XVIII

that the inductive effect of a nitro group toward a nitroso group effectively compensates the conjugative effect of a methyl group toward a nitroso group allowing the reaction to proceed smoothly without interference of the methyl group.

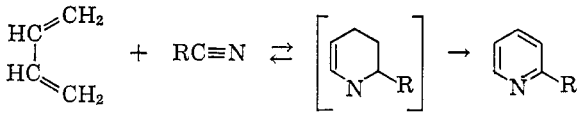
The reactivity of nitroso compounds as dienophiles in the formation of oxazole derivatives can be summarized by the following: Only those nitroso alkyl compounds in which the electron density on the nitroso group is decreased by neighboring groups such as a chloro- or nitrile group (inductive effect) can undergo diene synthesis. Nitroso aromatic compounds are, in general, more reactive dienophiles and the diene synthesis of 2-aryl-1,2-oxazine failed only with dienes where a steric factor is involved. However, electron releasing substituents in the *o*- or *p*-position of nitrosobenzene retards its activity considerably through conjugation effect.

Oxazine formation by condensing nitroso compounds and dienes is of particular interest because it could be used as the intermediate for the synthesis of 4-aminobuten-2-ol, 4-aminobutene, pyrrole, and N-phenylglycine as shown in the scheme (121).



C. THE NITRILE GROUP AS THE DIENOPHILE

Prior to the work of Janz and his co-workers (126) on cyanogen and its derivatives, little appears in the literature on the use of nitriles as dienophiles. In most cases, the cyanogen derivatives were treated with simple dienes such as butadienes, isoprenes, *etc.*, to form pyridine derivatives. For example, butadiene and hydrogen cyanide, acetonitrile, ethyl nitrile, cyanogen, acrylonitrile, and benzonitrile react according to the following equation to give the intermediate 2,5-dihydropyridine derivatives which lose hydrogen easily under the experimental conditions giving the corresponding pyridine derivatives. The thermodynamic

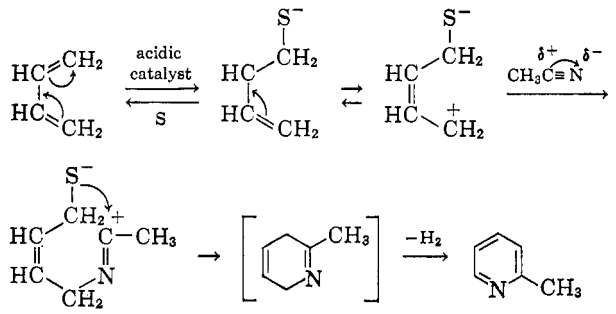


properties of these reactions have been estimated and a general trend in this series of reactions is indicated: (1) in each case, the log K_p equilibrium constant for reaction decreased as the temperature increased. Accordingly, the thermodynamic conditions are more favorable at lower temperatures. (2) The free energy change (ΔF) for the reaction is greatest for the case of cyanogen and decreases for HCN, CH_3CN and benzonitrile, in that order.

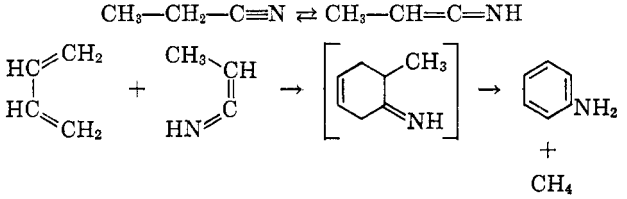
Actually, most of the reactions were run in the gaseous phase in the temperature range of 300 and 500°. Over-all yield was low even in the presence of a catalyst (127, 145). Of the catalysts tested, a mixture of chromium oxide and activated alumina was most promising.

The dienes used also extended to isoprene, chloroprene, 2-methylpentadiene and hexachlorobutadiene. It has been demonstrated that, with the exception of cyanogen, the relative reactivities of the nitriles ($CH_3C{\equiv}N$, $C_2H_5{-}C{\equiv}N$, $C_6H_5{-}C{\equiv}N$, HCN) are all of the same order of magnitude. This suggests that the energy of activation is not greatly influenced by the substituent group of the nitriles and, apparently, the internal electronic polarizability within the nitrile has little influence in the reaction mechanism. On the contrary, by changing the polarizability of dienes, the polarizability reaction rate is greatly influenced (147). When acetonitrile reacted with butadiene, isoprene or 2-methylbuta-1,3-diene at 400°, 2-methylpyridine, 2,4-dimethylpyridine, and 2,4,6-trimethylpyridine, respectively, were obtained. The relative reactivity of the above dienes was found to be 1:6:8 in the presence of the catalyst. These facts indicate that the mode of action is to promote the electron displacement in the diene leading to polar structures important in the transition state of the reaction. This reaction mechanism is in accord with a semi-ionic Diels–Alder type

reaction mechanism. It can be written as:

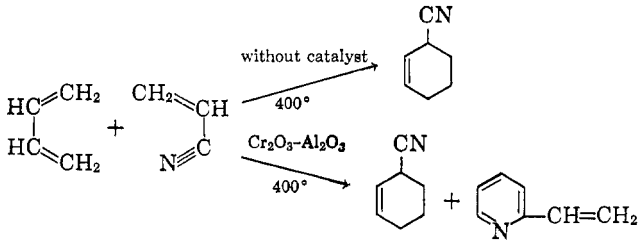


When butadiene was treated with propionitrile, both Janz and Meyer (146) and Marvel and Hwa (171) obtained aniline as a by-product in addition to the expected 2-ethylpyridine. Formation of aniline was rather surprising. Since further experimentation showed that methane was also a product, Hwa, *et al.*, postulated a probable intermediate for aniline formation. Propionitrile was first rearranged to the imine type of compound which cyclized and rearranged subsequently to give aniline. The reaction between butadiene and



acrylonitrile is of particular interest, since acrylonitrile possesses two dienophilic groups, namely, the vinyl group and the cyano group. Relative activity again was studied in detail by Janz and Duncan (142) and V. G. Yashunskii and his co-workers (290). Acrylonitrile belongs to the group of dienophiles having the greatest reactivity in the Diels–Alder reaction. The unsaturated vinyl (C=C) bond is highly activated in this instance by an effective electronegative cyano (C≡N) group. However, under certain suitable conditions, not the vinyl group but the cyano group adds to butadiene to yield 2-substituted pyridine derivatives as the product. In the homogeneous gas phase at 400° and short contact time of the reactants, the vinyl group reacts as the principal dienophile. The yield of cyanocyclohexene is good; the presence of vinylpyridine is not detected. In the presence of catalyst under the same conditions, both vinylpyridine and cyanocyclohexene were obtained as reaction products.

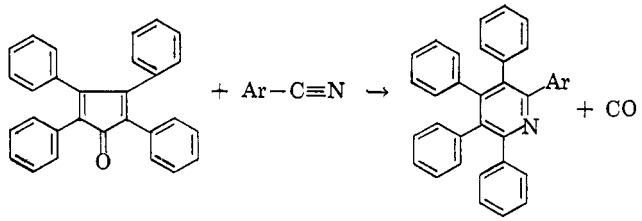
The relative reactivity of these bonds (C=C and C≡N) in acrylonitrile can be considered from both the thermodynamic and the kinetic points-of-view. Thermodynamically, Janz and co-workers have shown that the free energy changes for cyanocyclohexene and vinylpyridine formation from acrylonitrile and butadiene at 650°K. are −22 and −15 kcal./mole, respectively. This shows that both reactions are thermodynamically favored and one might expect two products in about the same ratio from thermodynamic considerations alone. Hence, the predominant yield of cyanocylohexene can only be explained by the kinetic factor. In fact, with the assumption that the rate determining step in each reaction is the cyclization step, it is shown (143) that, without the presence of the catalyst, vinylcyclohexene formation is 5800 times faster than vinylpyridine, while, in the presence of the catalyst, the vinyl (C=C) group is only 9–15 times more reactive than the nitrile (C≡N) group of acrylonitrile in the Diels–Alder reaction. The effect of the catalyst in lowering the energy of activation apparently is more effective for the pyridinic cyclization, as the presence of vinylpyridine was shown in the Diels–Alder reaction in the presence of catalyst even though it is in only small quantities. When benzonitrile as a dienophile



reacted with dienes involving the aromatic double bonds, the pyridine ring was formed with difficulty. For example, benzonitrile with anethole, isosafrole, isoeugenol, or anisylcyclone, respectively, gave only polymerization of the dienes. When the reaction mixture was heated in a sealed tube (164) in toluene or without solvent no Diels–Alder reaction takes place. When the reactants were allowed to react in nitrobenzene with activated alumina, benzonitrile–isosafrole, and benzonitrile–isoeugeneol adducts, which behave as quinoline or isoquinoline derivatives, were isolated only in 8% yield. It was not surprising that the reaction proceeds with difficulty when one considers that the Diels–Alder addition would destroy the more stable electron resonance system of the benzene ring.

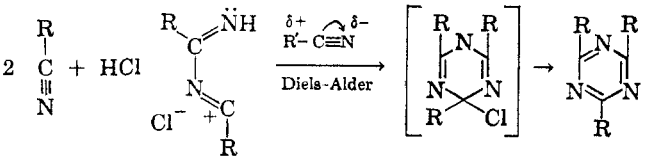
The reaction between trifluoroacetonitrile and butadiene was also tried at 350° and 2-trifluoromethylpyridine was isolated as product (141).

It might be worth mentioning that the diene reaction of tetraphenylcyclopentadienone and substituted aromatic nitrile gives pentasubstituted pyridine systems (193) depending on the nature of arylonitrile. The reaction proceeds by an ionic mechanism. The rate of the



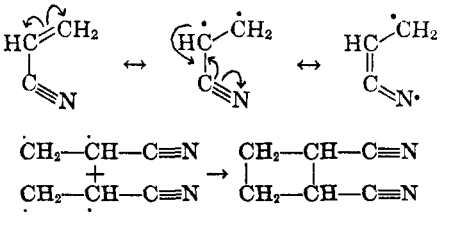
reaction is proportional to the extent that the molecular structure increases the negative character of the cyano nitrogen atom. Tetraphenylcyclopentadiene condenses nicely with *p*-toluonitrile or *p*-halobenzonitrile to give pyridine derivatives. However, when *p*-hydroxy, *p*-N,N-dimethylamino-, *p*-acetamido- or *p*-nitrobenzonitrile is used as dienophile, no condensation takes place and tetraphenylcyclopentadienone is reduced to tetraphenylcyclopentenone. *o*-Toluonitrile fails to react with tetraphenylcyclopentadienone, probably because of steric interference.

In elucidating the mechanism of nitrile trimerization to *s*-triazine compounds, Grundmann and his co-workers suggested that diene synthesis may be involved in the final step (112). Since the commonly used catalyst for this trimerization was hydrochloric acid, they tried and were able to isolate the intermediate reaction product of nitriles with hydrochloric acid [$(RCN)_2 \cdot HCl$]. In the presence of additional nitrile, the same or a different one, hydrogen chloride was evolved and the triazine compound was formed as shown in the equation



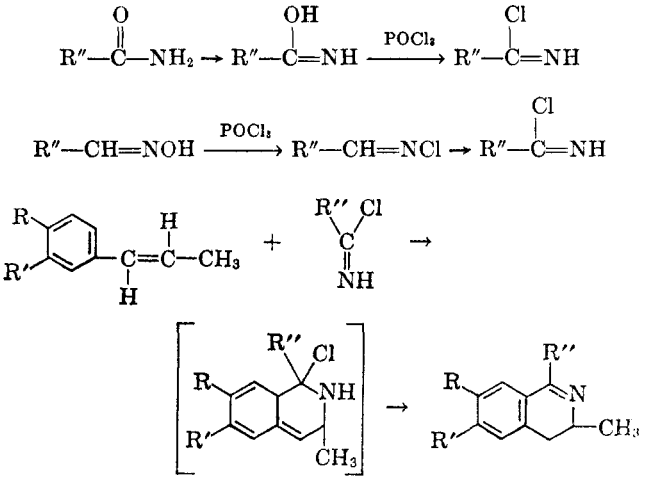
However, when the trichloroacetonitrile–hydrogen chloride adduct was treated with acetonitrile, no 2-methyl-4,6-bistrichloromethyl-*s*-triazine was obtained. A mixture of trichloroacetonitrile and acetonitrile treated with HCl, however, gave a 90% yield of the expected product. Hence, the Diels–Alder mechanism for trimerization of a nitrile might be an over-simplication.

It has been established that acrolein and methyl vinyl ketone undergo thermal dimerization to give up to 50% yield of dihydropyran (18). In the same way, one would expect the dimerization of acrylonitrile to give dihydropyridine derivatives. From such attempts, however, only *cis*- and *trans*-1,2-dicyanocyclobutane were obtained (63). The mechanism shown was proposed by Coyner and Hillman for the formation of 1,2-dicyanocyclobutane



D. IMINO GROUPS AS DIENOPHILES

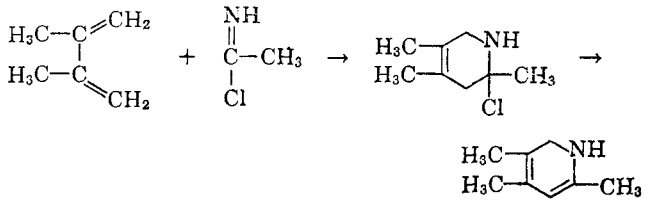
Through condensation of isosafrol or methyl isoeugenol with amides or oximes, in the presence of phosphorous oxychloride, Tamayo and co-workers obtained dihydroisoquinoline (165, 256, 257). The proposed reaction mechanism suggests a normal Diels–Alder synthesis in which the iminochloride produced as an intermediate behaves as a dienophile and adds to the 1,4-position of the diene system to produce the dihydroisoquinoline ring. The dienophilic character of imino-



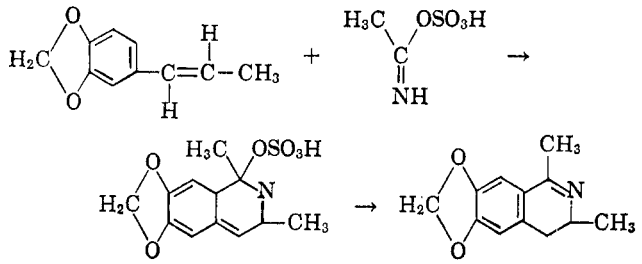
chloride has been suggested by Grundmann and his co-workers in their elucidation of the mechanism for the trimerization of nitriles in the presence of hydrochloric acid to form 1,3,5-*s*-triazine (112). From formamide, acetamide, benzamide, and phenylacetamide, as well as acetaldoxime, benzaldoxime, piperonaldoxime, and cinnamic aldoxime aromatic dienes, the corresponding dihydroisoquinolines were obtained. The products were characterized by dehydrogenation to the corresponding isoquinoline derivatives.

When aliphatic dienes were employed in place of aromatic dienes, the hydropyridines were obtained as the result of a regular Diels–Alder reaction.

For example, when 2,3-dimethylbuta-1,3-diene was condensed with acetamide in the presence of phosphorous oxychloride, 2,4,5-trimethyl-1,2-dihydropyridine was obtained. The reaction of imino hydrosulfate



with conjugated dienes also has been studied by Tamayo and co-workers, who condensed nitriles with dienes in the presence of fuming sulfuric acid (112). The same result was obtained as when iminochloride was employed. The condensation of acetonitrile and isosafrol gave 1,3-dimethyl-6,7-methylenedioxy-3,4-dihydroisoquinoline. Several derivatives were prepared in a similar fashion.

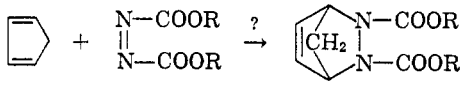


E. ALKYL AZODICARBOXYLATES AS DIENOPHILES

The use of alkyl azodicarboxylate as a dienophile in the Diels–Alder reaction was first reported by Diels, Blom, and Koll (84) in 1924, this being one of the earliest examples of the diene synthesis. Since then, further contributions have been made by various workers in regard to the activity of these esters as dienophiles and to the reaction mechanism. Alkyl azodicarboxylate in the diene synthesis is of particular interest in that it leads to pyridazine heterocyclic systems; these can be converted to other useful compounds by dehydrogenation, rearrangement, or decarboxylation.

The additions of alkyl azodicarbozylate may be conveniently classified according to the following scheme:

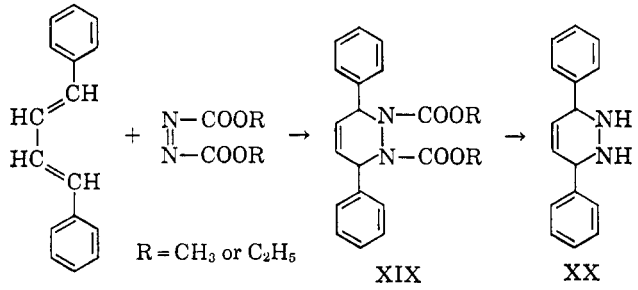
1. *Addition to Simple Aliphatic or Cycloaliphatic Dienes.*—The addition of alkyl azodicarboxylate to simple aliphatic or cycloaliphatic dienes such as isoprene, 1,3-hexadiene or pentadiene, in nonpolar solvents or without solvent, was reported by Diels, Blum, and Koll (84) to give almost quantitative yields of addition products. No adduct was obtained in methanol or ethanol from cyclopentadiene. This was



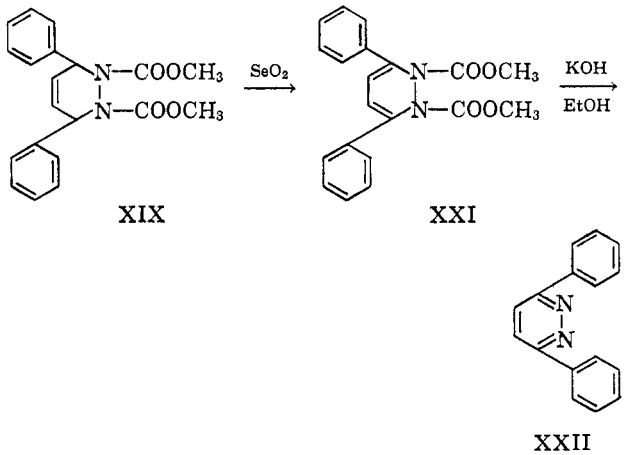
explained as involving the slow addition of methanol or ethanol to dimethyl azodicarboxylate. These two competing reactions led to two different products. In

contrast to this, MacKenzie, Rodgman, and Wright (163) were able to obtain the expected adduct in high yield from alcoholic media. The addition reaction also occurs in alcohol with buta-1,3-diene and substituted butadienes and diethyl or dimethyl azodicarboxylate. The yield in methanol or ethanol was as good as may be obtained in nonpolar solvents. The yield of the alternative addition product of solvents to dialkyl dicarboxylate was negligible in every instance. Later evidence attributes to the impurity of azodicarboxylate esters used, the failure of Diels and his co-workers to isolate the adduct. Dialkyl azodicarboxylate, prepared by the oxidation of diethyl hydrazocarboxylate with hypochlorite solution as specified by Rabjohn (182a), might be contaminated with hydrogen chloride, which might inhibit the addition of azoesters to cyclopentadiene and accelerate the gaseous decomposition of the dialkyl azodicarboxylate.

2. *Addition to 1,4-Aromatic Butadienes.*—The addition of methyl or ethyl azodicarboxylate to *trans-trans*-1,4-diphenylbutadiene was described by Diels and Alder. 1,4-Addition led to 3,6-diphenyl-N,N′-dicarbomethoxy or (ethoxy)-Δ^4-tetrahydropyridazine (XIX) which was assumed to be saponified to 3,6-diphenyl-Δ^4-tetrahydropyridazine (XX). The proof of the structure was given only by the existence of a double bond and the absence of benzoic acid after degradation with ozone. Further investigation carried

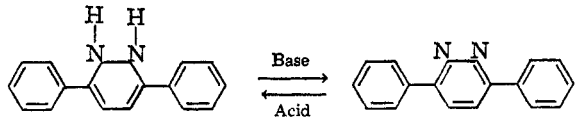


out by Alder and Niklas (20), Cohen and his co-workers (269) and Baranger and Levisalles (36) clarified the nature of Diels–Alder adduct. 3,6-Diphenyl-N,N-dicarbomethoxy-Δ^4-tetrahydropyridazine was oxidized with selenium oxide to 3,6-diphenyl-N,N-dicarbomethoxydihydropyridazine (XXI). This yielded an unstable base after saponification and decarboxylation. Dehydrogenation transforms it to 3,6-diphenyl-pyridazine (XXII). The unstable base obtained from



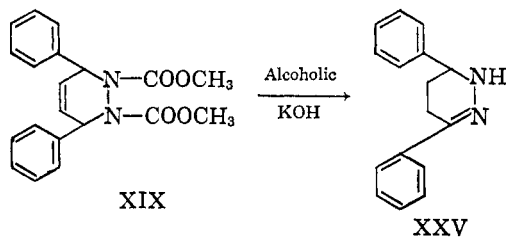
saponification and decarboxylation of the Diels–Alder adduct was found to exist in a second stable, isomeric form. The structure of the unstable base was shown as XXIII and the stable form as XXIV. The stable isomer is an azine compound which can be derived from the respective hydrazine derivatives. The structure of the saponification product (XX) of the Diels–Alder adduct, assumed to be 3,6-diphenyl-Δ^4-tetrahydropyridazine

(XX), was proved to be incorrect as regards the position of the double bond. Nitrosation studies support the



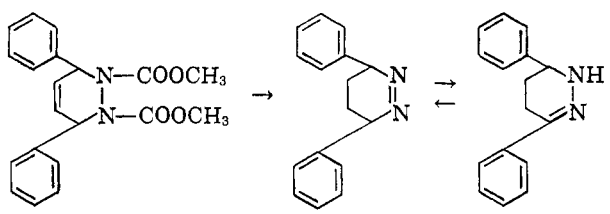
XXIII, Unstable XXIV, Stable

view that during saponification of the adduct, a shift of the double bond takes place so that the actual compound isolated is the hydrazo compound of structure XXV instead of the compound XX. Cohen and his



XIX XXV

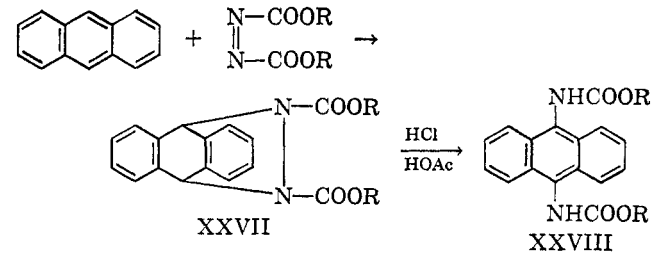
co-workers prepared the 3,6-diphenyl-N,N′-dicarboethoxy-Δ^4-tetrahydropyridazine (XIX) in a similar manner (269). The product was then converted to 3,6-diphenyl-3,4,5,6-tetrahydropyridazine (XXVI) by hydrogenation, saponification, and decarboxylation, then autoxidation. Here, again, it was found that compound XXVI was tautomerized very easily to its hydrazo form (XXV). In investigation of the condensation of



XXVI

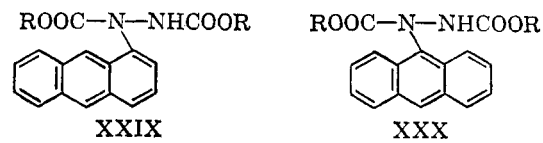
substituted dienes and alkyl azodicarboxylate (36), generally tetrahydropyridazine derivatives were obtained. Transformation of these to pyridazine was realized only in a few instances. Where transformation was not successful, shift of the double bond could take place leading to hydrazo compounds rather than tetrahydropyridazines.

3. *Addition to Aromatic Compounds.*—The addition of azodicarboxylic acid ester to anthracene (20, 163) is the most well-studied example of this class of reactions. The typical Diels–Alder 1,4-addition presumably takes place at the C_9 and C_{10} of the center ring to give the expected Diels–Alder adduct (XXVII). However, this is not isolated as such. Compound XXVII is unstable but is stabilized under the influence of hydrogen chloride in glacial acetic acid solution. The structure XXVIII is tentatively assigned for the stable product. Normal 9,10-addition gives the unstable compound XXVII which then undergoes a benzidine type re-



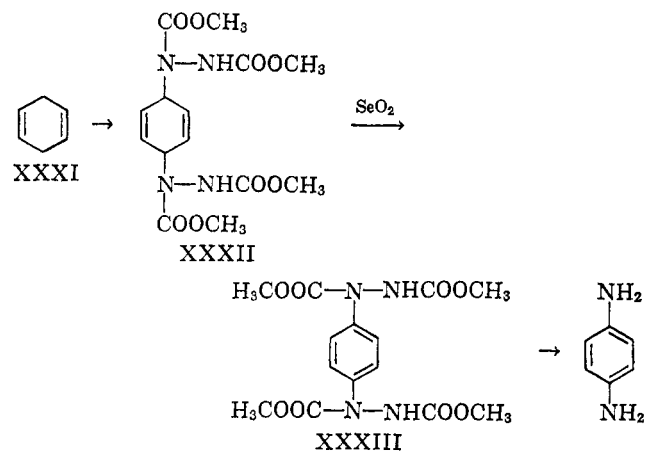
XXVII XXVIII

arrangement under the influence of hydrochloric acid in glacial acetic acid to give the stable product XXVIII. The instability of compound XXVII probably is due to the strained bridge structure. Later evidence proved that the compound is identical with one isolated by Stalle and Adams from a similar reaction. From its chemical behavior and ultraviolet absorption spectra, it was reported that stable adduct has neither structure XXVIII nor structure XXIX, which was assigned by Stalle and Adams, but possesses the structure which can be written as XXX (20). In regard to the validity of struc-



XXIX XXX

ture XXX assigned for a stable adduct, a few similar types of reaction can be given as examples. Dialkyl azodicarboxylate also adds to diphenylmethane, fluorene, and 1,4-dihydrobenzene in a fashion analogous to that for the stable adduct. 1,4-Dihydrobenzene, XXXI, adds two moles of azodicarboxylate to give compound XXXII which was dehydrogenated by selenium dioxide in glacial acetic acid to give compound XXXIII. The structure of compound XXXIII is established by the fact that the decomposition leads to *p*-phenylenediamine. MacKenzie and his co-workers, in



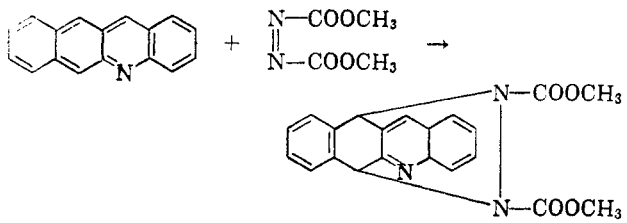
XXXI XXXII XXXIII

repeating the addition of dialkyl azodicarboxylate to anthracene, were unable to hydrolyze a similar labile product (XXVII) to 9,10-diaminoanthracene.

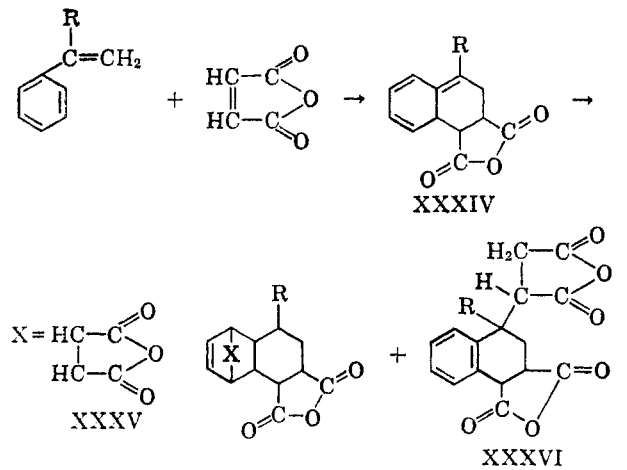
The reaction mechanism for the addition of azodicarboxylic acid ester to anthracene is closely related to the

addition of maleic anhydride, molecular oxygen, and many other dienophiles. The initial product, no doubt, possesses the structure XXVII as suggested by Diels. It is, however, so labile that stabilization of the Diels–Alder adduct takes place in the direction of transformation from XXVII to XXX.

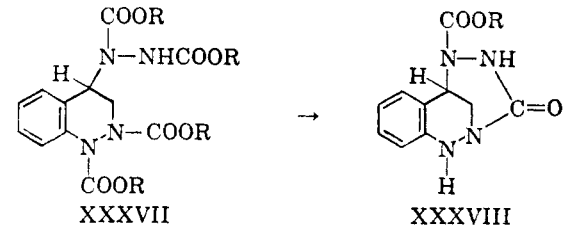
2,3-Benzoacridine reacts like anthracene with methyl azodicarboxylate to yield the corresponding adduct (21). Unlike the case for anthracene, the bridge structure is stable enough to permit its isolation without rearrangement. Attempts to combine methyl azodicarboxylate with acridine were unsuccessful. The addition of methyl acetylenedicarboxylate to 2,3-benzacridine in benzene solution and in methanol solution gave different results which will be discussed in a later section.



Styrene and its α-substituted derivative may add two mole of maleic anhydride to give compound XXXV, XXXVI or both, depending on the nature of substituents and experimental conditions. The addition

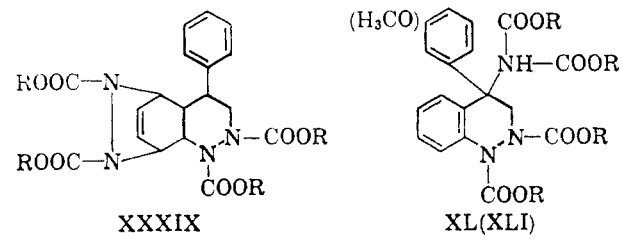


takes place according to the scheme XXXIV to XXXV or by a second mechanism, in which the Diels–Alder addition was followed by "substituting addition" (XXXIV to XXXVI). The latter is more probable and predominates. Since the same mechanism was involved in the addition of azodicarboxylate and maleic anhydride to anthracene, one might expect the azodicarboxylate to react with α-substituted styrenes in a similar fashion. Addition of two moles of alkyl azodicarboxylate to styrene gives a product having structure XXXVII. The product loses two carbomethoxy groups through saponification and dicarboxylation by aqueous potassium hydroxide. The third carboxyl group was unaffected and the fourth carboxyl group was stabilized



by loss of one mole of water. This intramolecular loss of water was interpreted as in XXXVII to XXXVIII.

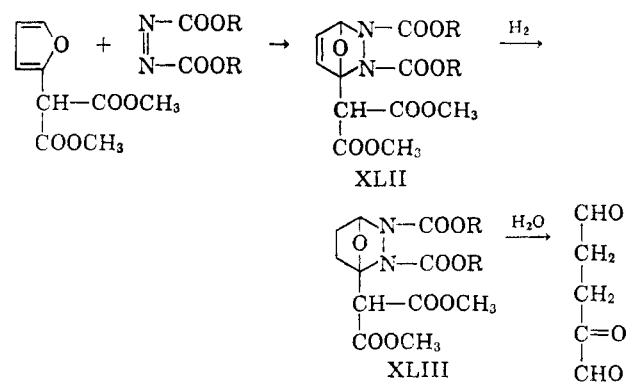
When α-phenylstyrene reacts with alkyl azodicarboxylate, two structures may be assigned to the resulting product. One involves two consecutive diene syntheses giving the structure as XXXIX. The other is the result of a primary diene synthesis followed by an indirect substituting addition with the structure of XL.



The driving force for the latter reaction is the reconstruction of the stable benzene resonance system. Hence, compound XL is the more likely Diels–Alder adduct (21). Similarly, α-methoxystyrene reacts with two moles of alkyl azodicarboxylate to give the compound XLI (21).

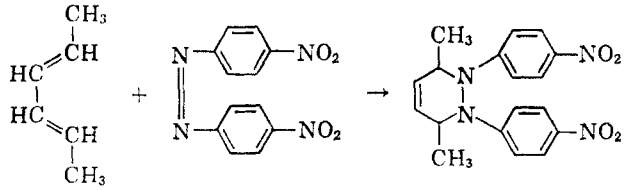
Further development of the 1,2-benzopyridazine derivatives has been greatly stimulated because some compounds in this series possess anti-malarial activities.

4. *Addition to Furan Derivatives.*—Furan derivatives with dialkyl azodicarboxylate react in a normal 1,4-addition manner to give bicyclic systems. Thus, furfuryl diacetate and azodicarboxylate react readily at room temperature in an equivalent molar ratio to yield the Diels–Alder adduct (XLII) which is labile and absorbs one mole of hydrogen to form the saturated bicyclic system (XLIII). Because of bifunctionality of additional center the compound hydrolyzes easily to form dihydrazodicarboxylate and α-ketoglutaric dialdehyde. Condensation of alkyl azodicarboxylate with



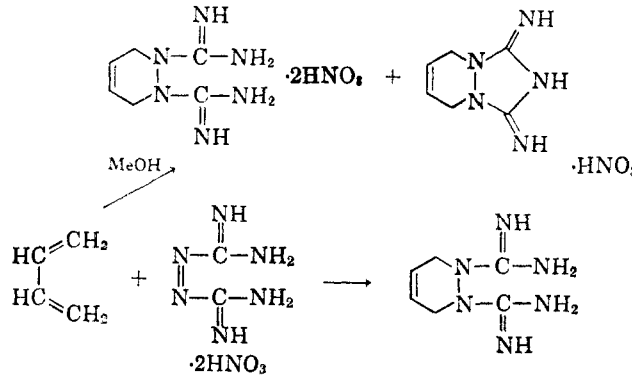
furan, 2-methylfuran and 2,5-dimethylfuran was reported to give an unstable product which yielded only a resin on either acid or base hydrolysis (36).

5. *Addition of Dienes and Compounds Related to Dialkyl Azodicarboxylate.*—In closely related reactions, *p*-nitrophenylazobenzene has reacted with 2,4-hexadiene (37) to yield 1,2-bisnitrophenyl-3,6-dimethyl-1,2,3,6-tetrahydropyridazines. 1,2-Dicarbamyl-1,2,3,6-



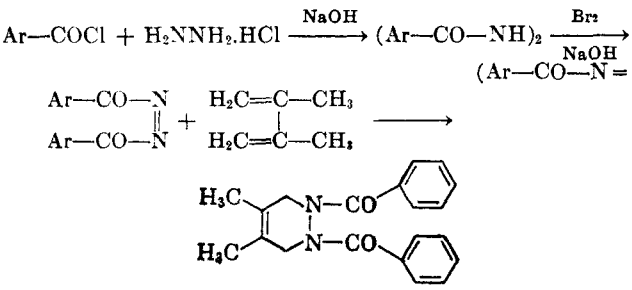
tetrahydropyridazine and its derivatives substituted in the 3, the 6 or in both positions are prepared in a similar way by condensing azodicarboxamide and an alkadiene having a conjugated double bond (137).

No reaction takes place with buta-1,3-diene and azo-bis-formamidine dinitrate unless azo-bis-formamidine is freed by a pyridine base. N,N'-Diguanyl-1,2,3,6-tetrahydropyridazine dinitrate was obtained in a quantitative yield without solvent and in 74% yield with methanol as a solvent (163). The lower yield in meth-



anolic solution was attributed to the instability of the Diels-Alder adduct in this solvent. MacKenzie, Rodgman, and Wright were able to isolate a 20% yield of 1,3-diimino-2,8,9-triazo-4,6,8,9-tetrahydroindan nitrate by recrystallization from hot methanol (163).

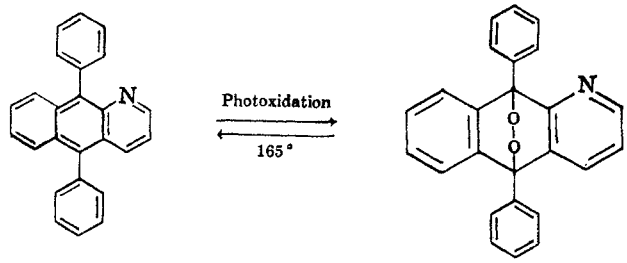
Levina and co-workers (221, 226) successfully condensed azobenzoyl and substituted dienes to isolate the expected Diels-Alder adducts in a good yield. Thus, by the reaction of 2,3-dimethylbutadiene with



azodibenzoyl was obtained 1,2-dibenzoyl-4,5-dimethyl-Δ^4-tetrahydropyridazine in 70% yield. Nitrogen bridge tricyclodecenes have been prepared in a two-step process by the Diels-Alder reaction of dialkyl azodicarboxylate and cyclopentadiene, then addition of tetrachlorocyclopentadiene to the resulting intermediate (157).

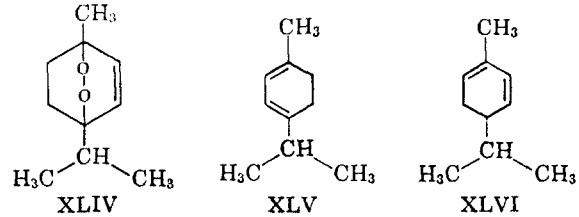
F. MISCELLANEOUS

1. *Oxygen.*—The reaction of oxygen as a dienophile in the diene synthesis has been investigated. Due to the structural similarity between benzo[g]quinoline and anthracene, similar photochemical reactions have been shown with regard to their Diels-Alder addition of molecular oxygen (94). When a carbon disulfide solution of 5,10-diphenylbenzo[g]quinoline was irradiated by sunlight, it was transformed to its photoxide in 90% yield by the 1,4-addition of molecular oxygen. The compound liberates practically all of its oxygen at 165–170° with regeneration of 5,10-diphenylbenzo[g]-quinoline.



Under similar conditions 2-phenylbenzo[g]quinoline also undergoes photoöxidation to give the corresponding oxygenated compounds. However, on being heated, alone or in solution, 2-phenyl-1-azanthraquinone is obtained as the product. From 2-phenyl-10-chlorobenzo[g]quinoline and 10-chlorobenzo[g]quinoline, no intermediate Diels-Alder adducts, *i.e.*, photoxides were isolated, these being oxidized directly to the corresponding 1-azanthraquinones.

The conditions for the preparation of ascaridole (XLIV) from oxygen and α-terpinene (XLV) were applied to the addition of molecular oxygen to α-phellandrene (XLVI) and 1,3-cyclohexadiene yielding the corresponding endoxides. A detailed discussion re-



XLIV XLV XLVI

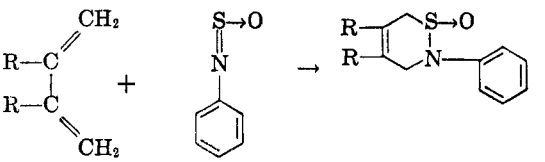
garding the influence of solvent, photosensitization and other physical conditions is beyond the scope of this review and may be referred to in the original literature (210–214).

2. *Sulfur Compounds.*—In a few instances, sulfur-

containing compounds have reacted as dienophiles in the Diels–Alder reaction. The difficulty for sulfur atoms to participate in diene syntheses probably results from its poorly polarizable character.

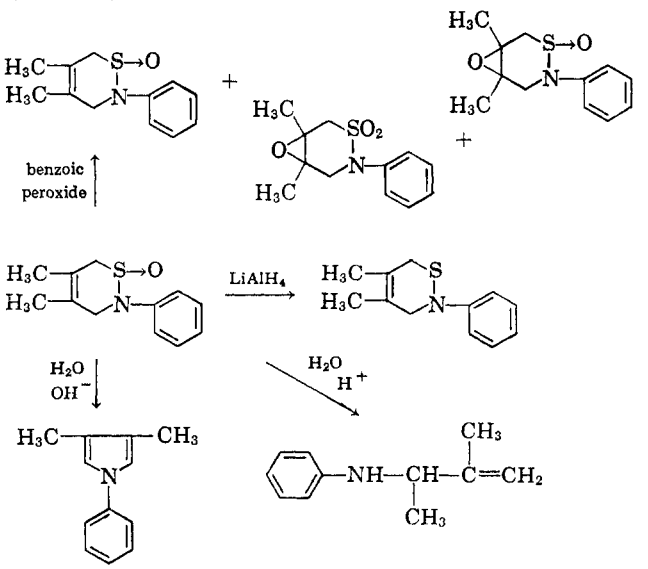
(a) An example of a pseudo Diels–Alder type of reaction is the condensation of 2-chlorobuta-1,3-diene with sulfur dioxide in the presence of pyrogallol to give 2-chloro-1-thia-3-cyclopentene dioxide (chloroprene sulfone). The yield is very low (2.5%) when the mixture is heated for only 12 hr. However, when buta-1,3-diene and sulfur dioxide react for several weeks, 1-thia-3-cyclopentenedioxide is obtained in 70% yield (35).

(b) The addition of butadiene or 2,3-dimethylbuta-1,3-diene to aromatic thionylamines ($C_6H_5N{=}S{\rightarrow}O$) represents a new type of Diels–Alder reaction, discovered by Wichterle and co-workers (280), leading to a new type of heterocyclic compound, 2,3-dihydro-6H-1,2-thiazine-1-oxide (XLVII) or its substituted derivatives. This new heterocyclic system can lead to many other interesting compounds. For example, upon acid



XLVII
R = H or CH_3

hydrolysis, 4,5-dimethyl-2-phenyl-2,3-dihydro-6H-1,2-thiazine was converted to but-3-enylphenylamine and on alkaline hydrolysis 1-phenyl-3,4-dimethylpyrrole was the product. Lithium aluminum hydride reduction gives 2-phenyl-4,5-dimethyl-2,3-dihydro-1,2-thiazine and oxidation with benzoic peroxide yielded 4,5-dimethyl - 2 - phenyl - 2,3 - dihydro - 6H - 1,2 - thiazine 1,1-dioxide or its 4,5-epoxy derivatives. Diels–Alder additions do not take place with aliphatic thionylamines. In most cases, the thionylamines were prepared by heating amines with thionyl chloride.



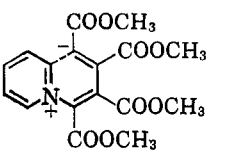
III. DIENES

A. ALKYL ACETYLENE DICARBOXYLATE IN THE DIENE SYNTHESIS

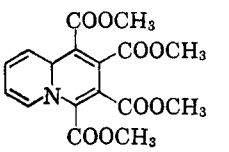
The alkyl acetylenedicarboxylates have been shown as dienophiles in the Diels–Alder reaction for many years. The reaction of the acetylenecarboxylates with conjugated systems containing hetero-atomic bases such as pyridine, quinoline, isoquinoline, acridine, and phenanthridine comprise an unusual class of Diels–Alder reactions. These were investigated by Diels and his co-workers in the 1930's (78–82, 85–86, 90–93). Conclusive experimental evidence, however, regarding the structure of the products and, hence, the nature of the reaction, is lacking. Because of an unusual interest in the value of this reaction toward forming fused ring systems with a nitrogen bridge-head, the mechanism is being investigated further by various workers. It is yet too early to draw specific conclusions from data thus far available.

Diels and Alder (80–82) isolated, from the reaction of pyridine with dimethyl acetylenedicarboxylate, isomeric labile (red) and stable (yellow) adducts and a third fraction called "Kashimoto's compound."

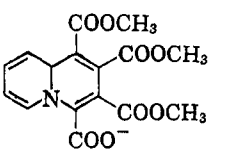
Structures XLVIII, XLIX, and L, respectively, were proposed for the isolated compounds. Structures XLVIII and XLIX were assigned on the basis of the ease with which the labile red compound isomerizes to the stable yellow compound and on the oxidation of the latter to pyridine-2-carboxylic acid N-oxide. Drawing



XLVIII

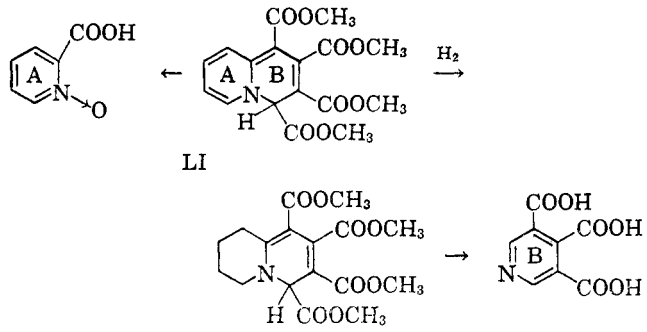


XLIX



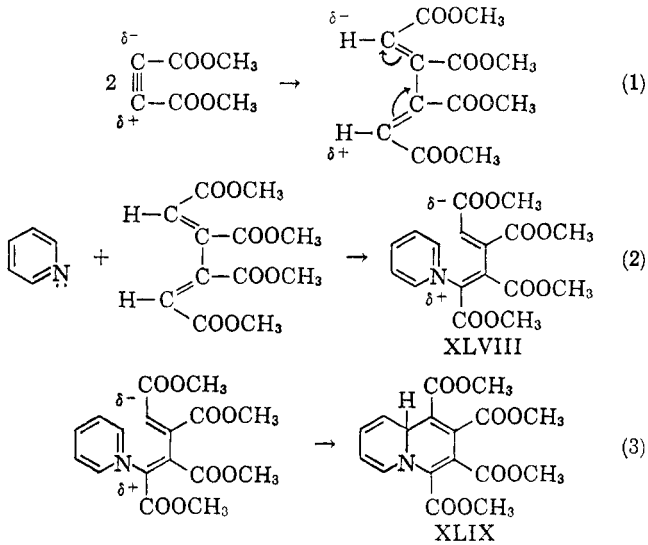
L

analogy to the pyridine studies, Diels and Alder subsequently suggested structures for the corresponding reaction products with quinoline (80, 82), isoquinoline (85), acridine (92) and phenanthridene (91). The reaction of pyridine and related compounds with dialkyl acetylenedicarboxylate has been repeated by various workers in recent years (6, 139, 282). Structure LI now is proposed for the stable pyridine adduct instead of that suggested (XLIX) by Diels and his co-workers (XLIX). Oxidation to pyridine-2-carboxylic acid N-oxide proved the structure of ring A while the expected product from hydrogenation and nitric acid oxidation confirmed ring B (2, 3, 6).



LI

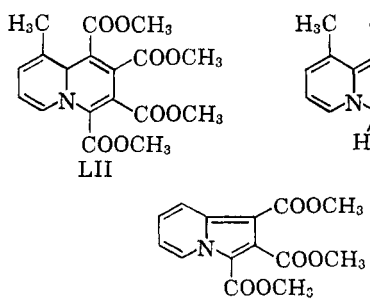
It was suggested that the reaction mechanism of dialkyl acetyldicarboxylate with heterocyclic bases proceeds in three steps: (1) condensation of two moles of acetylenedicarboxylate to form the diene system with charge separation, (2) attack on the ring nitrogen by a carbonium ion to form the labile product, (3) cyclization to form the stable product. Jackman and his co-



XLVIII

XLIX

workers carried out the condensation of dimethyl acetylenedicarboxylate with β-picoline in ether at room temperature. Measurement of the ultraviolet absorption of the reaction mixture at intervals showed no evidence for the existence of the proposed intermediate dimer of acetylene dicarboxylate (139). Structures, LII and LIII, respectively, were proposed for the labile and stable adducts of acetylenedicarboxylate and β-picoline.



LII

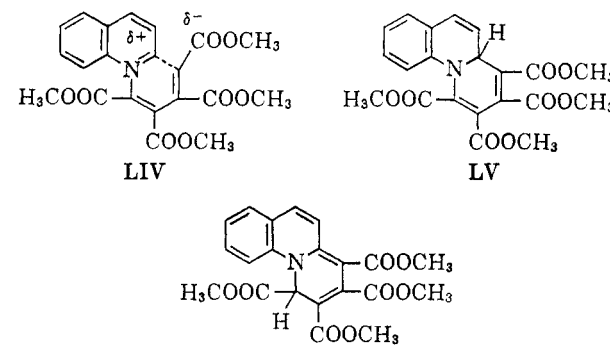
LIII

Strong support for these structures was obtained from magnetic resonance and ultraviolet absorption spectra and from degradation of the products (6, 139).

The ylide type of structure originally suggested by Diels for the labile pyridine adduct might be expected to undergo pyridinium methoxide formation. Since the labile adducts from both 3-methyl and 3,5-dimethylpyridine are stable to methanol, cyclic structure LII rather than XLVIII is more attractive for the labile adduct. Isomerization to LIII with its resonance stabilization, could account for the formation of stable adducts.

Wiley and Knabeschuh, investigating similar reactions, obtained 1,2,3-tricarbomethoxypyrrocoline as the product (282). They favored the free radical mechanism for the reaction because of: (1) the improved yield at low temperatures, (2) the evidence for peroxide initiation, and (3) the influence of trace impurities.

The two structures, LIV and LV, previously proposed for labile and stable adducts of quinoline and dimethyl acetylenedicarboxylate by Diels and Alder, have been revised by Acheson and his co-workers to LV and LVI, respectively (6). Isoquinoline behaves in a similar way

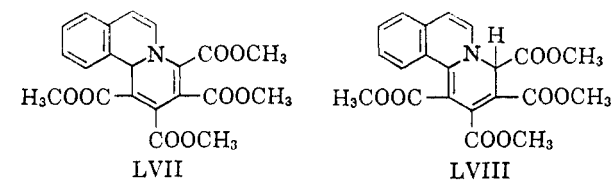


LIV

LV

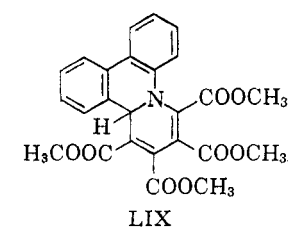
LVI

giving a labile adduct, LVII, which is converted into the corresponding stable adduct, LVIII, by a proton shift in methanolic solution (139). Phenanthridine and



LVII

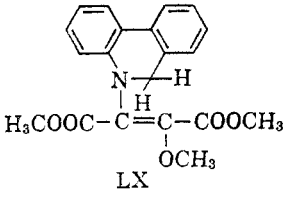
LVIII

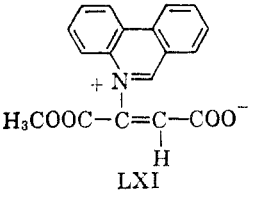


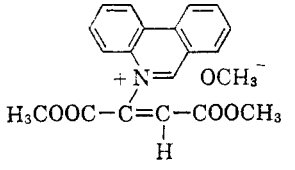
LIX

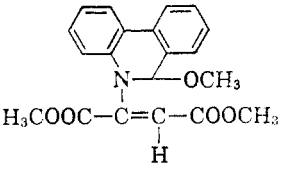
the acetylenedicarboxylate condense in benzene in a typical Diels–Alder fashion to give tetramethyldibenzoquinolinolizinetetracarboxylate (LIX). According to Diels and his co-workers, in methanolic solution, however, 9,10-dihydrophenanthridine, LX, is obtained as a

yellow product, and a phenanthridinium structure, LXI as the colorless component (91).


LX


LXI

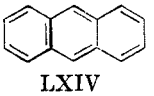

LXII

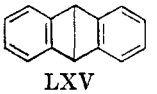

LXIII

Close reinvestigation of the same reaction by Acheson and Bond (I) led to a revision of these structures. The yellow adduct from phenanthridine was suggested as being 10-(*trans*-1,2-dimethoxycarbonyl-vinyl)-phenanthridinium methoxide (LXII) or conjugated 9,10-dihydrophenanthridine (LXIII) (1).

The existence of these structures in the condensation product depends on the acidity or basicity of the reaction media and the structure given is supported by the ultraviolet absorption curve and some chemical reactions undergone by it (1). The considerable differences in ultraviolet absorption spectrum between the phenanthridinium ion and the 9,10-dihydro-9-methoxyphenanthridine enable these species to be identified easily.

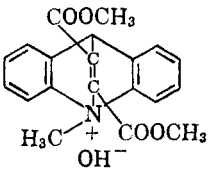
The addition of a variety of dienophiles to the 9,10-positions of anthracene is well known. The relatively nonaromatic character of the middle ring is shown by

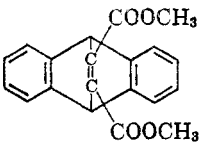

LXIV

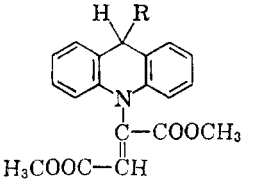

LXV

the easy addition and removal of hydrogen atoms from positions 9 and 10 in a process corresponding to that with quinone. From two of the possible resonating forms shown, it is apparent that addition takes place at 9,10- rather than at 1,4- or 5,8- because the 9,10-positions are alpha to a true aromatic ring in either case. The best argument for the existence of a conjugated system between 9 and 10 (LXIV) rather than a *para* bond (LXV) is the fact that anthracene acts as a typical diene in the Diels–Alder reaction with maleic anhydride.

The evidence for a *para* bond in the middle ring of acridine is about like that for one in anthracene. Comparable additions of dienophiles to acridines, however, are less known. Acridine was reported by Barnett, *et al.*, not to add maleic anhydride (38) though Diels and Thiele (91, 92) assigned the structure, LXVI, to the major compound with methyl acetylenedicarboxylate formed in the presence of methanol, based on the

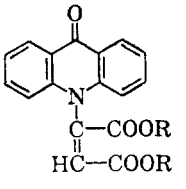

LXVI

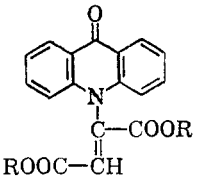

LXVII


LXVIII

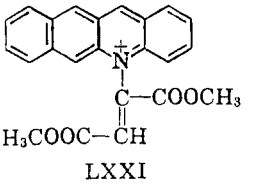
comparable structure for the anthracene adduct (LXVII) (78). The alternate structures for the 9-anthryl fumarate or maleate were excluded on the basis of their ultraviolet absorption being compatible with the 9,10-dihydroanthracene (192), but not the anthracene formulation.

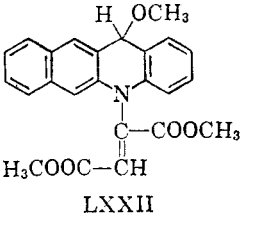
Acheson and Burstall (2) have re-examined the major adduct of Diels and Thiele and found, instead, the structure, LXVIII, to be correct. No minor adduct was obtained. In ether, methyl 5,10-dihydro-5-oxa-acridinyl fumarate and maleate, LXIX and LXX, was obtained. 2,3-Benzacridine combined, like anthracene,

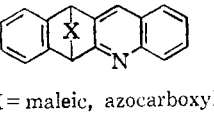




with maleic anhydride and methyl azodicarboxylate to give the corresponding adducts (4). With methyl acetylene dicarboxylate in methanol, however, the product was the N-substituted benzacridinium methoxide, LXXI, or the conjugated methoxyacridan, LXXII, rather than the alternate adduct, LXXIII. The


LXXI

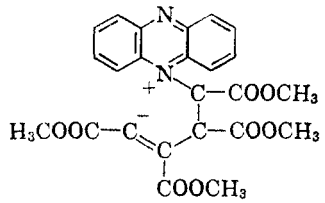

LXXII


X = maleic, azocarboxylate
LXXIII

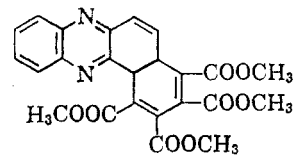
acridinium cation has been found to undergo normal Diels–Alder addition when heated with a variety of dienophiles such as maleic anhydride, maleate, fumarate, or acrylonitrile (46, 47). In no case did adduct

formation take place in which the diene is a quaternary salt.

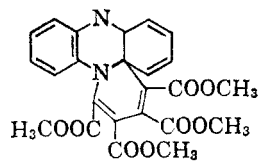
Lora-Tamayo and co-workers, suggest (259) that phenazine adds two moles of methyl acetylenedicarboxylate (LXXIV) by a procedure somewhat reminiscent of the comparable addition with acridine. He does not eliminate the possibility of addition taking place



LXXIV



LXXV



LXXVI

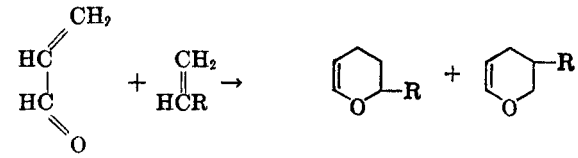
with a dienophilic double bond of the aromatic nucleus giving, instead the adduct, LXXV. This also has been postulated for the acridine adduct following rearrangement of the primary compound. Finally, in analogy with N-methylpyrrole and 1,2-dimethylimidazole, addition may take place in which the —N=C— bond acts as the dienophile (259) LXXVI.

Another interesting dienophile, closely related to acetylenedicarboxylate, is ethoxyacetylene derivatives (117). The electron releasing character of the alkoxy group facilitates the polarization of the acetylene group and makes it possible to undergo the Diels–Alder addition with various conjugated systems. It reacts with aromatic isocyanate, aromatic nitrones, aromatic azides, *etc.*, to yield the corresponding heterocyclic ring systems. It may lead to new preparative methods for various triazoles and oxazole compounds.

B. α,β-UNSATURATED CARBONYLS AS DIENES

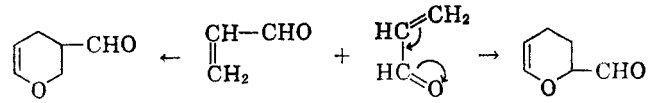
The reactions between α,β-unsaturated carbonyl compounds and suitable dienophiles give rise to the appropriately substituted dihydropyran ring system. This is the most common class of heterocyclic substances formed by means of the diene synthesis and this technique has afforded a convenient route to the commercial preparation of the dihydropyrans and of a large variety of compounds derived from them (205, 231).

α,β-Unsaturated carbonyls enter into dihydropyran formation with one of three major types of dienophiles (134). The diene itself, functioning also as the dienophile, condenses with a second molecule of diene through the olefinic linkage and is an example of the first category. In the reaction shown, R is —CHO. The second



kind includes olefinic ethers where R is an alkoxy or an aryloxy group. The vinyl group in conjugation with an aromatic ring, the styrenes, or other olefins make up the third class of dienophiles most often encountered. As is the case with the holocarbon Diels–Alder system, the dienophile frequently is activated by another functional group, for example, the carbonyl, the alkyl or the aromatic ring, which aids in polarizing the olefin bond. Acetylenes, which are more difficult to polarize, in general, are not equally suited for dienophiles as are the ethylenic compounds.

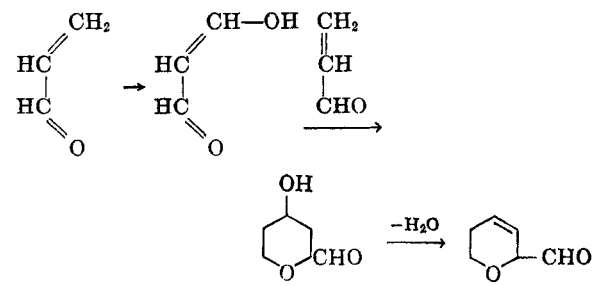
The dimerization of acrolein should lead to 2-formyl-2,3-dihydropyran (4-10) or 3-formyl-2,3-dihydropyran. Mechanistically, the 3-formyl derivative would appear to form favorably, but, from the two possible reaction products, 2-formyl-2,3-dihydropyran is formed exclusively (108, 231). Smith, *et al.*, suggest that this occurs because the reaction mechanism favors the



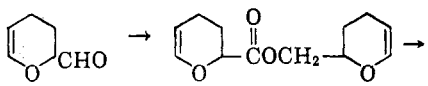
concentration of π electrons with the oxygen of the dienic carbonyl moiety attaching to the more substituted carbon of the dienophile olefinic compound.

The nature of the group activating the ethylenic bond might be expected to vary the direction of addition of the dienophile to the diene. However, this has not been borne out in a study of electron attracting and electron repelling groups, –CN, $-OCH_3$, –CHO, –COOR, $-CH_3$, and $-C_6H_5$ as the olefin activator where the direction of addition has been observed to yield only the 2-substituted product (231).

Heat (103, 271) and dilute acid (219) catalysis as well as neutral milieu at atmospheric conditions for several days (22, 122, 123, 245) generally afford the same product. Acrolein, in the presence of 1.7% H_2SO_4, undergoes oxidation prior to dimerization giving β-oxypropionaldehyde which then cyclizes to 3-formyl-4-hydroxytetrahydropyran (108, 219). Dehydration yields 3-formyl-5,6-dihydropyran in 26–32% yield (60, 111, 129, 159, 207). The 2-formyl-2,3-dihydropy-



rans are very autoxidizable (103, 271). Acid degradation gives α-hydroxy adipic dialdehyde (219) while treatment with aluminum isopropoxide yields alkyl acrylate through the disproportionated dipyran ester intermediate (272).

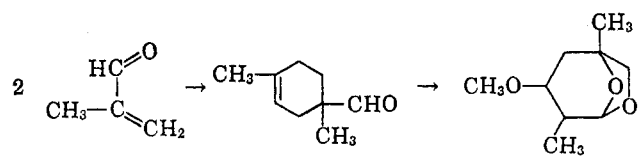


$H_2C{=}CH{-}COOCH_2{-}CH{=}CH_2$

Silver salt oxidation followed by ammonolysis leads to the synthesis of an amino acid derivative, N-benzoyllysine in very low yield according to Whetstone and Ballard (273).

Self-condensation of α-chloroacrolein gives the expected 2-formyl-2,5-dichloro-2,3-dihydropyran (270).

The acid catalyzed dimerization of α-methylacrolein in sealed tubes gives 2-formyl-2,5-dimethyl dihydropyran in 80% yield (242). Cold methanolic hydrochloric acid converts the dimer to 3-methoxy-1,4-dimethyl-6,8-dioxabicyclo[3.2.1]octane (274–275).



Crotonaldehyde undergoes acid catalyzed self-condensation to yield a mixture of dimer as well as what appears to be the trimeric product (140). A similar mixture of products was obtained from the reaction of crotonaldehyde and aldol by way of the β,β'-dibutyraldehyde ether (72–75, 239). Cyclization to dialdon followed by dehydration, gave 3-formyl-2,6-dimethyl-5,6-dihydropyran, the dimer, in 20% yield (265). The trimer was obtained in 8–10% yield.

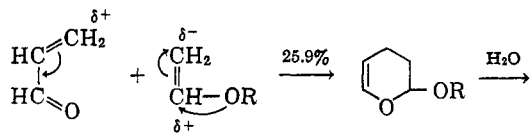
The trisubstituted acrolein derivatives dimerize with heating in the absence (219, 220) or presence (18, 219, 231, 244) of solvent to form the 3,3,4,4,5-pentasubstituted-2-formyl-2,3-dihydropyrans. In general, the α-alkyl substituted aldehydes such as the α-methyl- or α-ethylacroleins dimerize at temperatures of 140–170° in three to five hours while the β-alkyl substituted homologs of acrolein react with much greater difficulty (242). Heating the β-methylacrolein (crotonaldehyde) in benzene solution to 145° gives α-methylacrolein in 45 min. (270).

2,3-Dihydropyran readily reverts to the starting materials by a reverse Diels-Alder thermal splitting at temperatures greater than 400° (48–50, 188, 189, 227, 234, 285–287). From 960 g. of 2,3-dihydropyran at 540° is obtained 260 liters of gases, of which 92.5% is accounted for by ethylene and 577 g. of liquified products. On distillation of the liquid, one gets 539 g. of acrolein and 36 g. of residue, a total of 84.5% of the theoretical value (50). This is analogous to the commercial cracking of cyclohexene to butadiene and ethylene (50). Acrolein and ethylene can be produced from 2,3-dihydropyran or directly from tetrahydrofurfuryl alcohol at 450° over an aluminum silicate catalyst (51, 52, 149, 185–187, 283, 284). The 3-chloro-2,3-dihydropyran yields α-chloroacrolein and ethylene after pyrolysis over pumice stone (134).

Butadiene (34%) and formaldehyde (66%) are obtained from 5,6-dihydro-1,2-pyran (104, 110) while 2,6-dimethyl-3-formyl-5,6-dihydro-1,2-pyranene yields acetaldehyde and vinyl crotonaldehyde at 550° (265).

Vinyl alkyl ethers react rapidly and in high yield with acrolein (18, 19, 22, 124, 125, 160, 229, 230, 239), crotonaldehyde (184, 205) and methyl vinyl ketone (96, 172) to give 2-alkoxy-3,4-dihydropyrans. Divinyl ether, phenyl vinyl ether (160), and phenyl vinyl sulfide react in a fashion similar to acrolein (230). The addition of vinyl alkyl ethers to α,β-unsaturated carbonyl compounds takes place even more readily than does the dimerization of the unsaturated carbonyl compounds themselves. It is suggested that the greater polarization of the vinyl ether promotes this reaction. A possible exception is the case of methacrolein which dimerizes much more readily than other unsaturated carbonyl compounds thereby reducing the yield of vinyl ketone addition products (160).

A commercial synthesis of glutardialdehyde (227, 229) involves the Diels–Alder addition of acrolein and vinyl alkyl ketone followed by hydrolysis. The 2-



$OHCCH_2CH_2CHO + ROH$

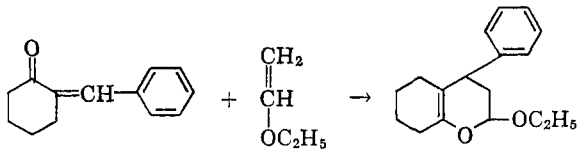
methoxypyran is formed by heating the same reactants to 180° (289). 2-Iso-butoxy-2,3-dihydropyran is formed in 85% yield. α-Methyl glutardialdehyde is obtained by Hall and Howe from the addition product of α-methylacrolein and vinyl alkyl ether (125) while the β-methyl derivative arises from the reaction beginning with crotonaldehyde (184) at moderate temperatures under pressure according to Parham and Holmquist. The α,β-disubstituted dialdehydes and hydroxyaldehydes have been prepared from the corresponding pyran derivatives under pressure without solvent or catalyst (230) and provide a convenient route for a class of compounds which have been previously only difficultly available.

Smith, Norton, and Ballard carried out additions of vinyl ethers to acrolein in steel or glass pressure vessels without solvent for one hour at 180° (230), or for 12–30 hr. at lower reaction temperatures (160). In addition to acrolein and methacrolein, crotonaldehyde (160, 184), cinnamaldehyde, β-furylacrolein, methyl vinyl ketone, benzalacetone and benzalacetophenone have

been used by Smith and Ballard as α,β-unsaturated carbonyl dienes for adduct formation with vinyl alkyl ethers (229).

Following catalytic reduction and hydrolysis is obtained 5-oxo-3-phenylhexanal from benzalacetone and β-phenyl glutardialdehyde from cinnamaldehyde (160).

The successful use of α,β-unsaturated carbonyl compounds as the diene component in the Diels–Alder reaction has been extended to the synthesis of bicyclic hydropyrans. Both 2-benzylidenecyclopentanone and 2-benzylidene hexanone have yielded the corresponding bicyclic pyran after adduct formation with a vinyl ether. Thus, the hexanone gave 2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran in 22–25% yield. From 2-piperonyl-

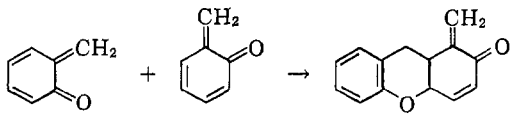


idene-1,3-indandione and 2-veratrylidene-1,3-indandione were prepared the 1-aryl-3-ethoxy-1,2,3,4-tetrahydro-4-oxa-9-fluorenones (95).

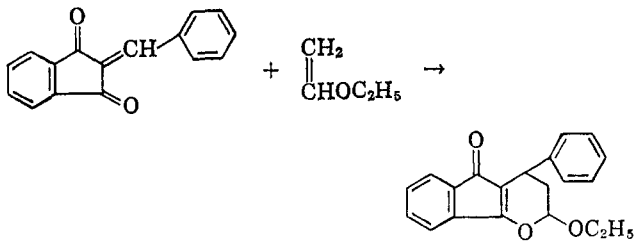
2-Alkoxy-2,3-dihydropyrans have been prepared through the diene synthesis from vinyl methyl ketones (96) and benzalacetophenone (160). α-Methyl methyl vinyl ketone dimerized to form 2,5,6-trimethyl-2-acetyl-2,3-dihydropyran (62). Ethyl propenyl ketone combines with maleic anhydride in a typical Diels–Alder fashion after heating for four days to give 3,6-dimethyl-4-oxohexahydrophthalic anhydride (41).

Catalytic hydrogenation over Raney nickel of 2-alkoxydihydropyran gives 2-alkoxytetrahydropyran. Reduction with copper chromate and water gives instead pentane-1,5-diol (161). Treatment with alumina-silica catalyst afford 5-alkoxypent-4-enal (233). Addition of ROH, RCOOH, C_6H_5OH, and HCN yields the appropriate 6-alkoxy, 6-acyloxy, 6-phenoxy and 6-cyano derivatives of 2-alkoxytetrahydropyran. Several of these compounds are in commercial developmental production (224, 225). Pyridine, in fair yield, is obtained from 2-alkoxy-3,4-dihydropyran and ammonia at 400° over an alumina catalyst (26, 27).

o-Methylenecyclohexanone (167–169) and *o*-methylenequinone (105, 194) dimerize readily to form pyran or chroman ring compounds. From 2-benzylidene

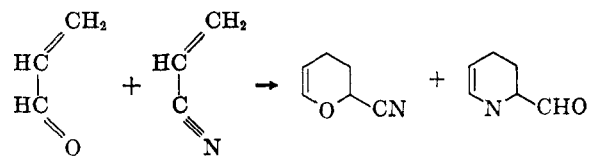


hydrindone and vinyl ethyl ether can be obtained other tricyclic pyrans. *o*-Hydroxybenzyl alcohol adds to styrene, probably through the formation of an intermediate of *o*-methylenequinone, to give *o*-phenyl-

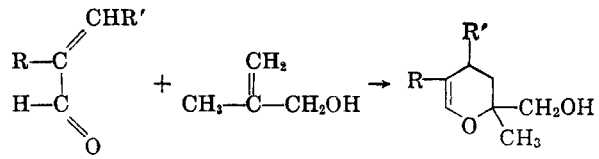


chroman (121). Other chroman derivatives have been prepared from the appropriate *o*-hydroxymethylol compounds and olefins (135, 136).

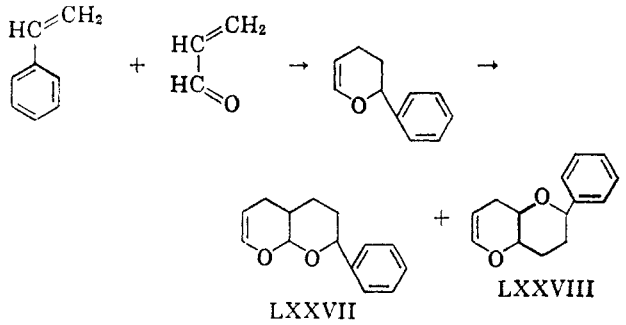
Unsaturated hydrocarbons activated by the phenyl ring, for example styrene, undergo typical Diels–Alder reactions with α,β-unsaturated carbonyl compounds such as acrolein to give dihydropyran derivatives (232). The dihydropyran on warming with 10% H_2SO_4 gave 5-phenyl-5-oxypentanal. In an analogous fashion, Whetstone and Ballard obtained 5-oxy-5,7,7-trimethyloctanal, 5-oxy-5-methylhexanal and 5-oxy-3-methyl-5-phenylhexanal (62). Unsaturated esters such as methyl acrylate and methacrylate, vinyl acetate and methallyl acetate and methacrylonitrile have been added to acrolein, methacrolein and crotonaldehyde to give the appropriately substituted, 3,4-dihydro-2H-pyrans (234). The addition is quite analogous to the addition of vinyl ethers and other olefins and in all cases, the β-carbon of the aldehyde was attached to the unsubstituted olefinic carbon atom. In general, the reaction conditions required heating the reagent under autogenous pressure in the absence of solvents at 170–200° for one to two hours. Conversion to product proceeded to the extent of 3% for the acrolein–methyl acrylate adduct and to 40% for the acrolein–methyl methacrylate product. Only for the addition of methacrylonitrile to acrolein were the conditions critical. At lower temperatures, the yield dropped rapidly while at temperatures greater than 200° an exothermic reaction took place leading to a variety of compounds. Dimerization of the aldehyde, polymerization of either reactants or further addition of the carbonyl compound to the primary adduct reduce the yield. The addition of acrylonitrile and of methyl acrylate to acrolein has been reported (217, 219). The reaction between acrolein and acrylonitrile yielded two products. Compounds re-



lated to phytol and to vitamin A have been synthesized from intermediates formed from the diene synthesis (231). In addition to styrene and α-methylstyrene, isobutylene, diisobutylene and 1-hexene have been added to conjugated unsaturated carbonyl compounds. The conversions to product were of the order of 10–25%.



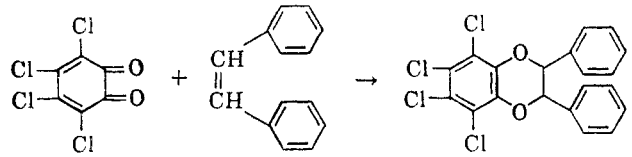
Styrene and acrolein yielded, in addition to the primary product, an adduct resulting from the reaction of a second mole of acrolein to the 2-phenyl-dihydropyran intermediate (LXXVII). The isomeric adduct of two



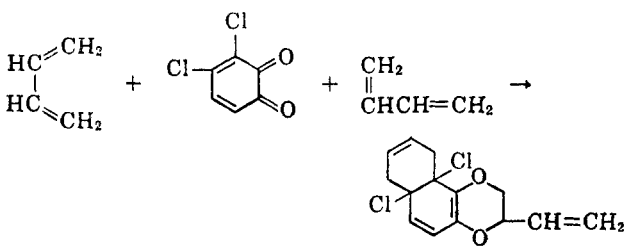
LXXVII LXXVIII

molecules of acrolein and one of styrene (LXXVIII) was present only in very small quantities. Formation of this adduct proceeds by a mechanism not in accord with a polar mechanism similar to that postulated for the Diels–Alder reaction. A "divalent radical" mechanism has been suggested to explain the orientation of reactants determined experimentally (231).

Substituted *o*-quinones also undergo diene synthesis with suitable dienophiles. Thus, the tetrahaloquinone, *o*-benzoquinone, and 3,4-dichloroethyl-β-naphthoquinone have been added to stilbene to give derivatives

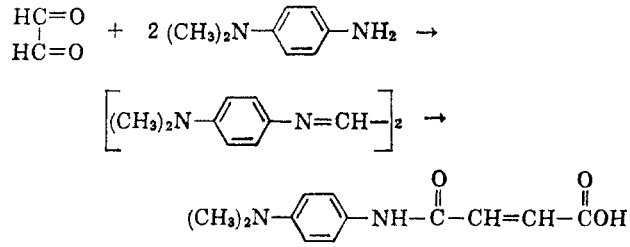


of benzodioxane (133, 215). Similarly two moles of butadiene and one mole of 3,4-dichloro-*o*-benzoquinone underwent a double Diels–Alder addition giving the expected tricyclic dioxane derivative.

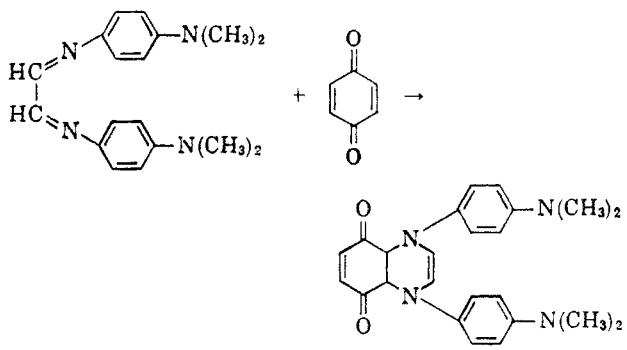


C. MISCELLANEOUS DIENES

Despite the ease with which compounds such as methyl vinyl ketone or acrylonitrile undergo adduct formation in the diene synthesis with suitable dienophiles, their ability to react through self-condensation points to their facile junction as true dienophiles as well. The effect of the electronegative cyano substituent in a strong diene system on the ease of adduct formation was determined for a variety of dienophiles including several "amphoteric" substances. Thus, with 2-cyano-1,3-butadiene was obtained the normal Diels–Alder adduct when the dienophile was methyl vinyl ketone and acrylonitrile as well as ethyl acrylate, *p*-benzoquinone and 1,4-naphthaquinone (246, 247). The use of glyoxal and other α,β-diketoanils as diene systems entails special precautions in experimental procedure. Tomimatsu (261, 262) obtained from glyoxal and *p*-dimethylaminoaniline, followed by maleic anhydride, a product tentatively identified as the half amide of maleic acid and *p*-dimethylaminoaniline.



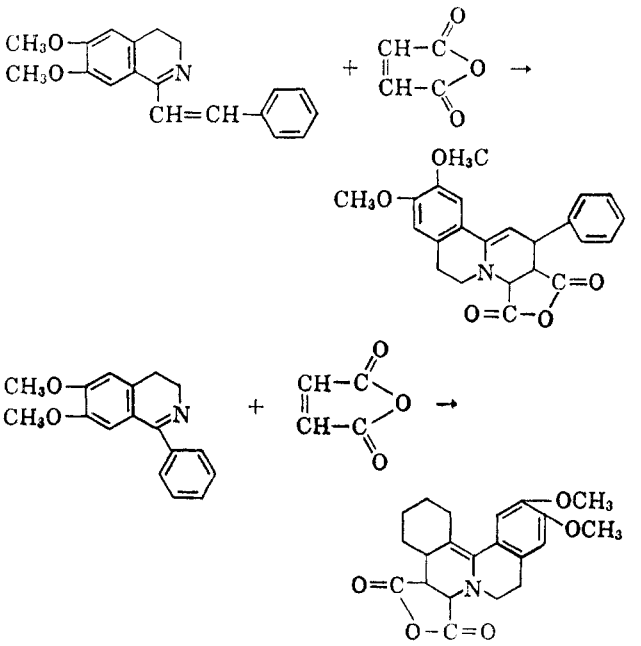
From the same diene intermediate with *p*-quinone was isolated an adduct with a structure thought to be 1,4 - bis - (*p* - dimethylaminophenyl) - 5,8 - dioxo-1,4,4a,5,8,8a-hexahydroquinoxaline, the expected product. Formation of the anil appears to be replete with



difficulty. Tars generally are obtained during the reaction of glyoxal with aniline derivatives in the presence of atmospheric oxygen. In our hands (61), the anils from glyoxal corresponding to aniline, toluidine, *p*-aminobenzoic acid and *p*-chloroaniline were prepared, at 0° under an atmosphere of nitrogen, as tan amorphous solids. Exposure to the atmosphere produced an immediate darkening of the product with formation of a tar. The anils of biacetyl were obtained as crystalline solids in low yield. Identification was made on the basis of infrared absorption analysis. The product from *p*-nitro-aniline and glyoxal could not be obtained because of poor solubility of the reactant (61). The typical Diels–Alder adduct could be obtained most conveniently when the dienophile, maleic anhydride or ester or *p*-quinone, was added directly to the diene with or without solvent.

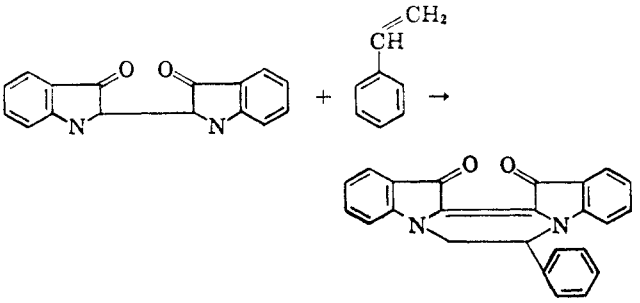
The Schiff base of pyridine-2-aldehyde and hydrazine was found by Needleman and Chang (179) to react smoothly, as a diene, with a number of dienophilic compounds. From several possible modes of addition, only structures III or IV were consistent with the evidence obtained from infrared absorption analysis for the adduct of the Schiff base and acrylonitrile. Adduct formation with cyclopentadiene led to a structure suggestive of an endomethylene bridge compound. No reaction took place between pyridine-2-carboxyhydrazone and azobenzene.

Hydroquinoxazine adduct formation was found, too, by Tomimatsu after the addition of maleic anhydride to the dienes 1-styryl-6,7-dimethoxy-3,4-dihydroisoquinoline and 1-cyclohexenyl-3,4-dihydro-6,7-dimethoxy-3,4-dihydroisoquinoline and 1-cyclohexenyl-3,4-dihydro-6,7-dimethoxyisoquinoline. Pyra-

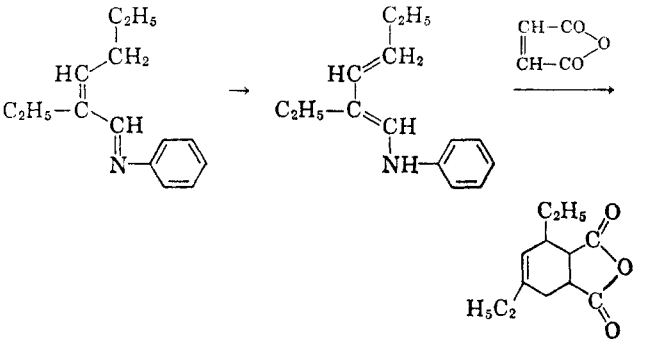


zines, quinoxalines and phenazines have been synthesized as typical Diels–Alder adducts from compounds containing ethylenic linkages in conjugation with an unshared pair of electrons from nitrogen (208).

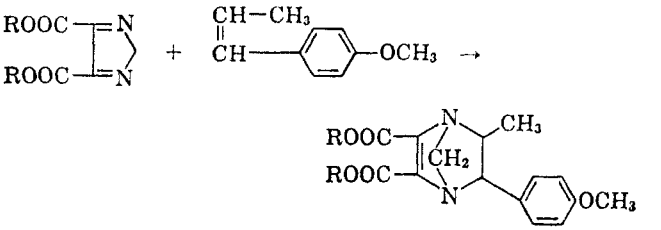
Derivatives of *p*-diazine have been obtained as reaction products from the diene system —N=C—C=N—, and olefins. Thus, a tetrahydropyrazine results from the addition of styrene to dihydroindigo



(10). Attempts at synthesizing pyridine derivatives by the Diels–Alder addition of maleic anhydride to anils were unsuccessful for benzalazine (154, 155, 236, 267), cinnamylidenoaniline (40) and benzalquinaldene (237, 238). Addition of the dienophile does not take place, with the system —N=C—C=C—, but rather with the normal all-carbon diene obtained by rearrangement of the anilide (248, 249). This is in agreement with the results of Tamayo (248, 249) and Ardaszew (34).



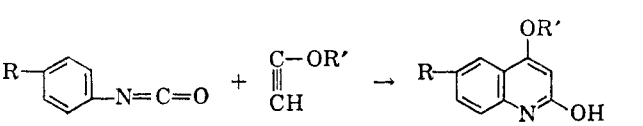
Tamayo has examined the reaction of anethole and other dienophiles to the esters of imidazole-4,5-dicarboxylic acid (248–251, 255) and obtained the ester of



N,N′ - endomethylenetetrahydropyrazino - 2,3 - dicarboxylic acid. Similar findings were obtained by Farina (99) for isoxazole and other imidazole derivatives.

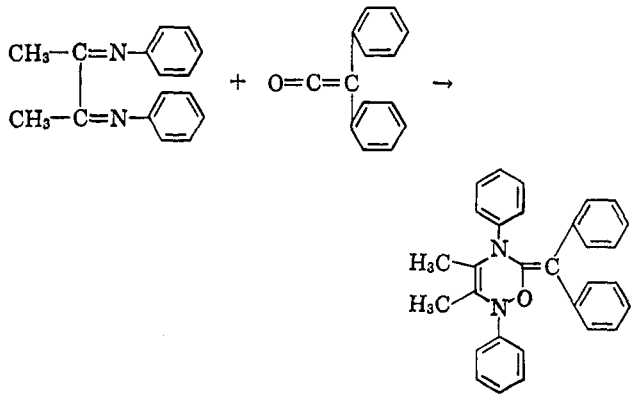
o-Quinone dibenzimides may undergo addition through the ethylene conjugation of the quinone nucleus as well as through the N=C—C=N conjugation. On the basis of chemical properties and infrared and ultraviolet spectra, only the ethylene adduct forms (260).

In analogy to the work of Grünanger who used nitrile oxides as dienes, Nieuwenhuis and Arens (180) investigated the use of aryl isocyanates as dienes leading to hydroxyquinoline adduct formation. Although earlier



studies report that ketenes do not react with dienes in a Diels–Alder fashion (24, 53, 100, 235), Pfleger and Jager (191) have obtained pyridone and pyrazine derivatives from ketenes and the anil diene system. Thus, from ketene and cinnamalanil was isolated 1,4-diphenyl-3,4-dihydro-2-pyridone in 69% yield while

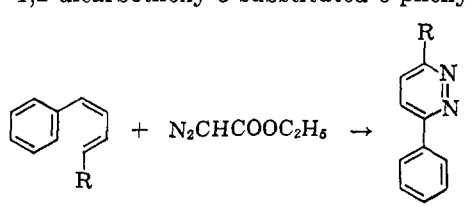
from diacetyldianil and diphenylketene, after 8 days, was recovered 1,3,3,4-tetraphenyl-5,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrazine. Dimerization of ketene in



the presence of a base catalyst affords good yields of dehydroacetic acid (44). Dehydroacetic acid, in turn, under acidic conditions, leads to dimethylpyrone (194) and other intermediates important in the synthesis of dyes and medicinals (195).

IV. Pseudo Diels–Alder Reactions

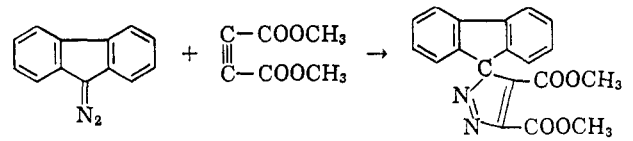
A variety of reactions proceed by a mechanism only indirectly related to that for the normal Diels–Alder synthesis. Replacing the conjugated bonds of the regular diene system are pairs of unshared electrons, often associated with a nitrogen atom but occasionally with oxygen. Thus, hydrazine adds, as a pseudodiene, to an olefinic double bond to form pyridazine derivatives (183). Interestingly, stereo considerations are quite pronounced with respect to adduct formation when using hydrazine as the diene. The *cis*-olefin proceeds almost to quantitative compound formation in the cold while the *trans* isomer gives small amounts of product only after prolonged reaction at elevated temperatures. Diacetylethylene and substituted cyclohexenes, however, did not give a similar product, yielding instead polymers (211). In contrast, ethyl diazocarboxylate reacts as a dienophile in the synthesis of 3-methyl-6-phenylpyridazine and 3,6-diphenylpyridazine (158). Dehydrogenation with nickel of the intermediate compound, 1,2-dicarbethoxy-3-substituted-6-phenyl-1,2,3,-



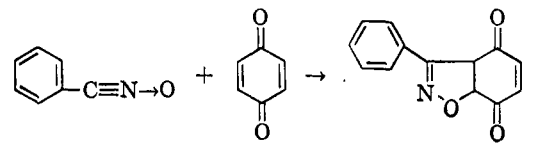
6-tetrahydropyridazine, was not successful, aromatization being effected by bromination and removal of hydrogen bromide with base.

While the Diels–Alder condensation is an important synthesis procedure for the formation of six-membered rings, a consideration of the mechanism for this reaction suggests, too, the possibility of the formation of five- or seven-membered rings.

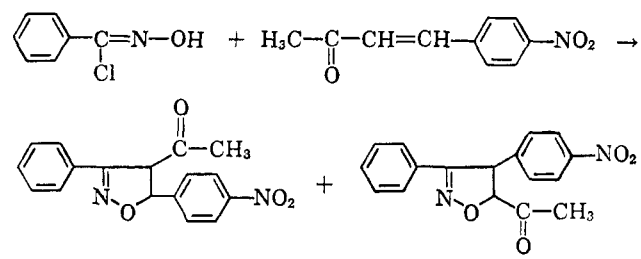
Diazomethane (25) or higher substituted diazo compounds (25) have been added to acetylene esters or acetals to yield dialdehydic or dicarboxylic 1,2-diazoles by a mechanism which can be related to that for the normal diene synthesis. An unusual type of



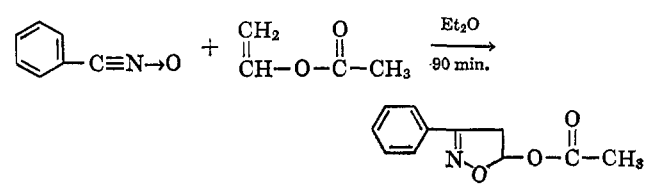
pseudodiene synthesis yields a five-membered 2-isoxazoline ring system rather than the customary six-membered ring compounds. Quilico, d' Alcontres, Grünanger, and co-workers as well as others have treated nitrile oxides with a large number of double bond compounds to obtain the appropriately substituted isoxazolines. Benzonitrile oxide with *p*-quinone (196) gave the expected 3-phenylbenzoisoxazolequinone. Other unsaturated ketones also react with



benzonitrile oxide to form substituted isoxazolines (66). The nature of the ketone chain exerts a steric effect on the course of the reaction, the aromatic group hindering the isoxazoline or isoxazole nucleus and the acetyl group having only little effect. Thus, *p*-nitrobenzylidene acetone with benzonitrile oxide gives a mixture of two isomers with the less sterically hindered one being favored. Other unsaturated aromatic com-

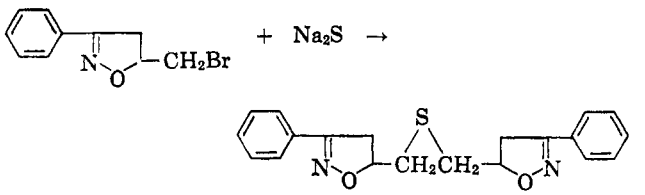


pounds react in the expected fashion (174, 175). Addition of the nitrile of 5-phenylisoxazole (from styrene) (113) or of 5-substituted isoxazole derivatives in general



(68). With allyl compounds were obtained the 5-carboxyl-, 5-methylhalo- or -cyano-derivatives. Reac-

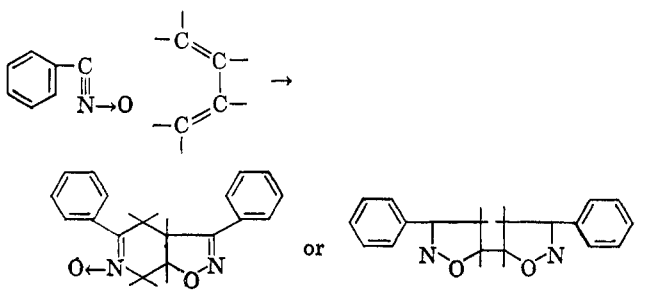
tion of 3-phenyl-5-bromomethylene isoxazoline with sodium sulfide afforded a route to bis-3-phenyl-5-



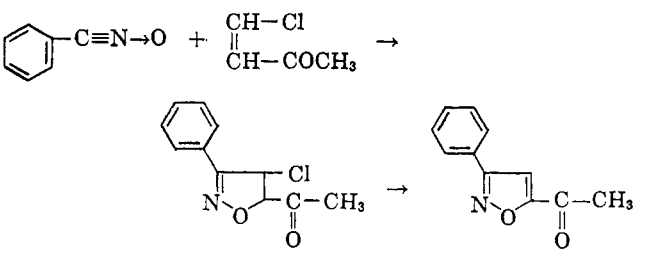
methylene isoxazoline sulfide (68). Substituted styrenes, indenes and unsaturated phenols condense with benzonitrile oxide to give the corresponding 2-isoxazolines (65, 69, 113, 114, 118). No addition occurs to propenylphenols except isoapide (65). With acetylenic ethers (115, 119), oxazole ether adducts are obtained.

Phenyl nitrile oxide reacts readily with conjugated dienes by the addition of one or two moles of the unsaturated compound (64, 201). Thus the ethylenic hydrocarbon reacts with the nitrile as a typical diene to form a six-membered hydropyridine oxide. This may react further with a second mole of diolefin to give 3,5-diphenyldihydroisoxazolinotetrahydropyridine oxides.

Conversely, the olefin may add as the dienophile with the nitrile oxide, yielding the mono- and diisoxazoline adducts (201). Biallyl and fulvenes give both types of isoxazolinic compounds. The reaction is

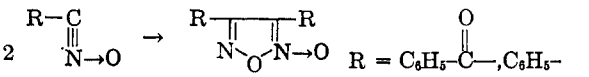


analogous to that of butadiene with diazomethene confirming the general reaction similarities between nitrile oxide and aliphatic diazo compounds (114). With unsaturated esters, the phenylisoxazolinecarboxylic esters are obtained, these in turn being saponified to yield the free acids (66, 198–200). β-Chlorovinyl ketones add with phenyl nitrile oxide through the vinyl group to give the corresponding chloroisoxazolines (120). Loss of hydrogen chloride produces the ketone substituted isoxazole compounds. The isoxazole compounds are obtained

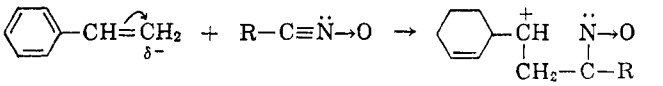


directly by addition of benzonitrile oxide to acetylenic hydrocarbons (116, 202, 203), acetylenic ethers (119) and propargyl derivatives (162, 204).

Dimerization of benzonitrile oxide leads to 1,2,5-oxadiazole compounds rather than the isoxazoles (204, 209). Carbethoxyformonitrile oxide affords a con-

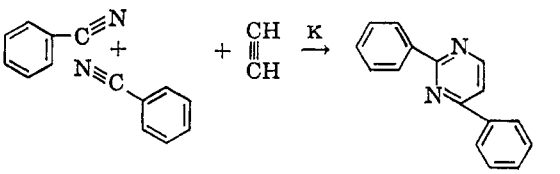


venient starting material to the synthesis of 3-substituted-2-isoxazolines through the Diels–Alder synthesis (266). While methyl styryl carbamate reacted well, cinnamic acid, methyl cinnamate and cinnamonitrile failed to give the expected product. This would suggest that the attack of the nitrile oxide is more electrophilic than nucleophilic in character. The addition of

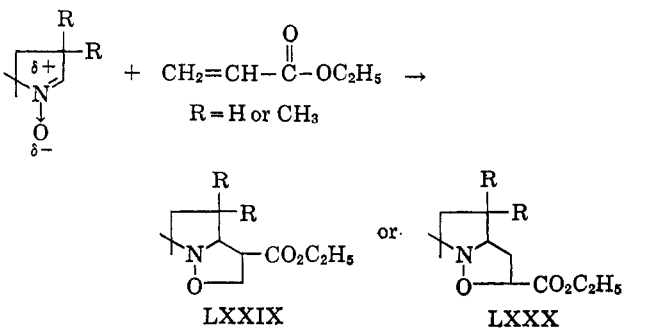


aliphatic diazo compounds, azides and the addition of nitrile oxides to olefins is similar and the orientation follows the Markownikoff rule.

Fulminic acid gives the expected product (196) with the ethylenic double bond (67). Benzonitrile and potassium metal treated with acetylene under pressure and at elevated temperatures yield a product which can be envisaged as proceeding through a Diels–Alder-like mechanism (58). Nitrones were shown to add to olefins



such as α,β-unsaturated esters to give isoxazolidines by 1,3-addition; these undergo thermally catalyzed reversion to the original starting materials even on moderate heating at 100° in vacuum (54, 76). In addition to the

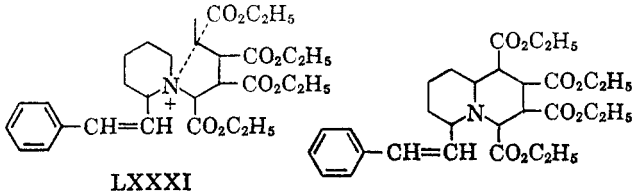


LXXIX LXXX

1,3-Diels–Alder type of adduct formation, it is possible for the reactants to undergo a Michael type of product formation. For the 3,3,5,5-tetramethyl-1-pyrroline-1-oxide reactant, no Michael addition is possible, thereby suggesting the 1,3-addition mechanism (56). Since

nitrones generally undergo nucleophilic attack, structure LXXX is more likely (45).

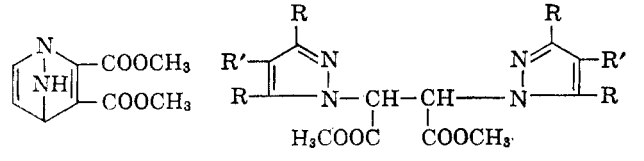
Pyridine reacts with dimethyl acetylenedicarboxylate in a manner similar to benzonitrile and potassium metal (79, 81, 82). Dimerization of the acetylene diester leads to a polarized diene which adds to the ring nitrogen followed by cyclization. From the same reaction was also obtained derivatives of quinolizine. Quinoline (79, 81, 82) or phenanthridine (91) yielded the corresponding adducts. From the same ester and stilbazole (88), LXXXI was obtained in ether solvent and LXXXII in xylene solvent. Pyrazole and its 3,5-



LXXXI LXXXII

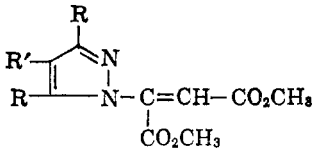
dimethyl and 3,4,5-trimethyl derivatives combine with two moles of dimethyl acetylenedicarboxylate to give adducts which differ with respect to their ultraviolet spectra from the parent pyrazoles. The absorption bonds of *ca.* 3.2 μ, corresponding to a bonded N–H found in the parent compounds, are absent from the spectra of the adducts from the pyrazole derivatives. In spite of repeated crystallizations, a small residual absorption remains for the unsubstituted pyrazole adduct.

While a Diels–Alder addition of dimethyl acetylenedicarboxylate to pyrazole could be expected to yield the structure LXXXIII, degradative studies of the products show the adduct formation to proceed by way of a double Michael addition yielding LXXXIV, LXXXV or LXXXVI, respectively (5). Diels, Alder



LXXXIV, R = R′ = H
LXXXV, R = CH_3; R′ = H
LXXXVI, R = R′ = CH_3

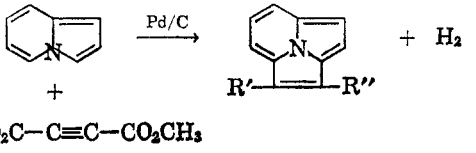
and co-workers earlier reported that dimethyl acetylenedicarboxylate combines with two moles of pyrazole to give two isomeric products (83), while the 3,5-dimethyl derivative gives both a 1:1 and 1:2 adduct. While the isomeric forms of the pyrazole adduct could be ascribed to *cis* and *trans* configurations of the ester groups (LXXXIV), the 1:1 and 1:2 products described by Diels and Alder for 3,5-dimethylpyrazole and the closely related products from the 3,4,5-trimethyl derivatives of Acheson and Poulter, have been shown to bear the relationship given by structures LXXXV and LXXXVI and LXXXVII and LXXXVIII, respectively, with the *trans* configuration in LXXXVII and LXXXVIII being more likely (1, 2). The reaction of pyr-



LXXXVII, R = CH_3; R′ = H
LXXXVIII, R = R′ = CH_3

rocoline with dimethyl acetylenedicarboxylate under dehydrogenation conditions leads to the formation of a five-membered ring compound of the cyclo[3.2.2]-azine series (43, 288).

Godfrey noted that the reaction of 1,2,6,7-dibenzopyrrocoline with dimethyl acetylenedicarboxylate in the presence of a dehydrogenation catalyst gave a product corresponding to the equimolar adduct with loss of hydrogen (109). That addition occurred across the 3- and 5-positions of the pyrrocoline ring was shown by



$CH_3O_2C-C\equiv C-CO_2CH_3$

LXXXIX, R′ = R″ = CO_2CH_3
XC, R′ = R″ = CO_2H
XCI, R′ = R″ = H

comparison of the ultraviolet spectra with those of known cycl[3.2.2]azine derivatives. Boekelheide has verified this mode of reaction for the case of pyrrocoline itself where the initial adduct, LXXXIX, has been degraded to the parent heterocyclic compound, XCI (107). Examination of molecular models of pyrrocoline and of possible Diels–Alder adducts of pyrrocoline indicates that formation of the 3,9- or 5,8- adducts (from 1,4-Diels–Alder addition) should be precluded on steric considerations while the 3,5-adduct (from 1,8- Diels–Alder addition) should be free of strain (109). The resonance energy of the 3,5-adduct should favor formation of this adduct rather than the 3,9- or 5,8- adduct. Further, molecular orbital calculations indicate that the localization energy for simultaneous attack at the 3- and 5- positions is comparable to that of normal Diels–Alder additions (109).

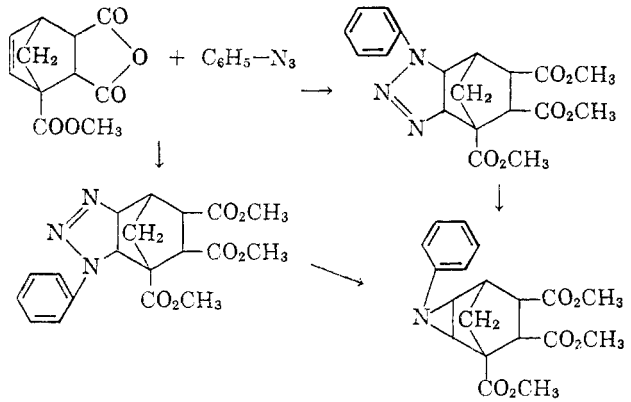
The structure of a number of normal Diels–Alder polycyclic adducts has been proved by reaction with phenyl azide, an addition which itself proceeds through a Diels–Alder like mechanism (14–17, 59, 130). At least two of the possible resonance forms for phenylazide are given by XCII and XCIII. Either form may

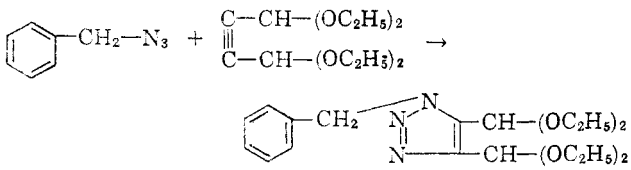
XCII XCIII

proceed to initiate nucleophilic attack, the diene generally being the nucleophilic agent, to give intermediate forms XCIV or XCV which then undergo cyclization

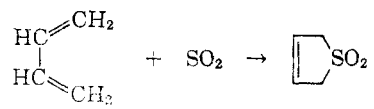
XCIV XCV

to the corresponding triazole (117, 148, 176, 177, 222).





An interesting example of a reaction which may be envisioned as proceeding essentially through a Diels-Alder mechanism is the formation of 3-sulfolene (butadiene sulfone) from butadiene and sulfur dioxide (225).



V. REFERENCES

(1) Acheson, R. M., and Bond, G. J. F., *J. Chem. Soc.*, 246 (1956).
(2) Acheson, R. M., and Burstall, M. L., *J. Chem. Soc.*, 3240 (1954).
(3) Acheson, R. M., Earl, N. T., Higham, P., Richards, R. E., Taylor, G. A., and Vernon, T. M., *Proc. Chem. Soc.*, 281 (1960).
(4) Acheson, R. M., and Jefford, C. W., *J. Chem. Soc.*, 2676 (1956).
(5) Acheson, R. M., and Poulter, P. W., *J. Chem. Soc.*, 2138 (1960).
(6) Acheson, R. M., and Taylor, G. A., *J. Chem. Soc.*, 1691 (1960).
(7) Achmatowicz, O., and Zomajski, A., *Bull. Acad. Polon Sci. Classe III*, **5**, 927–9 (1957); *Chem. Abstracts*, **52**, 6333 (1958).
(8) Agawa, T., and Miller, S. I., *J. Am. Chem. Soc.*, **83**, 449 (1961).
(9) Albrecht, W., *Ann.*, **348**, 31 (1906).
(10) Alder, K., *Diels-Alder Sym. Coloq. Problemas sintesis*, **7** (1953); *Chem. Abstracts*, **47**, 1573 (1953).
(11) Alder, K., *Experientia*, Suppl. No. 2, 14e congr. intern. Chim. pure et appl. Zurich 86 (1955).
(12) Alder, K., "Prix Nobel" 157 (1950).
(13) Alder, K., *Svensk Kem. Tid.*, **62**, 239 (1950).
(14) Alder, K., and Flock, F. H., *Ber.*, **87**, 1916 (1954).
(15) Alder, K., Flock, F., Hunsweiler, A., and Reeber, R., *Ber.*, **87**, 1752 (1954).
(16) Alder, K., Flock, F. H., and Janssen, P., *Ber.* **89**, 2689 (1956).
(17) Alder, K., Kriefer, H., and Weiss, H., *Ber.*, **88**, 144 (1955).
(18) Alder, K., Offermanns, H., and Ruden, E., *Ber.*, **74B**, 905 (1941).
(19) Alder, K., Offermanns, H., and Ruden, E., *Ber.*, **74**, 926 (1941).
(20) Alder, K., and Niklas, H., *Ann.*, **585**, 81, 90 (1954).
(21) Alder, K., and Niklas, H., *Ann.*, **585**, 97 (1954).
(22) Alder, K., and Ruden, E., *Ber.*, **74**, 920 (1941).
(23) Alder, K., and Schmacher, M., *Fortsch. Chem. Org. Naturstoffe*, **10**, 1 (1953).
(24) Allen, C. F. H., and Sheps, L. J., *Can. J. Res.*, **11**, 171 (1934).
(25) von Alphen, J., *Rec. trav. chim.*, **62**, 491 (1943); *Chem. Abstracts*, **38**, 1742 (1944).
(26) *Ann. Repts. on Progr. Chem.*, (Chem. Soc. London), **48**, 211 (1951).
(27) *Ann. Repts. on Progr. Chem.*, (Chem. Soc. London), **47**, 226 (1950).
(28) Arbuzov Yu. A., *Izvest. Akad. Nauk S.S.S.R. Otdel Khim. Nauk*, 344 (1952).
(29) Arbuzov, Yu. A., Fedyukina, N. L., Shavyrina, U. V., and Shepeleva, R. J., *Izvest. Akad. Nauk S.S.S.R. Otdel Khim. Nauk*, 566 (1952).
(30) Arbuzov, Yu. A., Fedyukina, N. L., Shavyrina, U. V., and Shepeleva, R. J., *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 539 (1952).
(31) Arbuzov, Yu. A., and Markovskaya, A., *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk*, 363 (1952).
(32) Arbuzov, Yu. A., and Markovskaya, A., *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 355 (1952).
(33) Arbuzov, Yu. A., and Piska, T. A., *Doklady Akad. Nauk S.S.S.R.*, **116**, 71 (1957); *Chem. Abstracts*, **52**, 6357 (1598).
(34) Ardaszew, B. J., and Markowa, Z. D., *Zurn. Osbszes. Chim.*, **21**, 1505 (1951).
(35) Bacher, H. I., and Bless, T. A. H., *Rec. Trav. Chim.*, **61**, 785 (1942); *Chem. Abstracts*, **38**, 3646 (1944).
(36) Baranger, P., and Levisalles, J., *Bull. Soc. Chim.*, 704 (1957); *Chem. Abstracts*, **51**, 12924 (1957).
(37) Baranger, P., Levisalles, J., and Vuidart, M., *Compt. rend.*, **236**, 1365 (1953); *Chem. Abstracts*, **48**, 2715 (1954).
(38) Barnett, E. B., Goodway, N. F., Higgins, A. G., and Lawrence, C. A., *J. Chem. Soc.*, 1224 (1934).
(39) Benghiat, I., *Diss. Abst.*, **18**, 1611 (1958).
(40) Bergmann, F., *J. Am. Chem. Soc.*, **60**, 2811 (1938).
(41) Berner, E., *Acta Chem. Scand.*, **10**, 268 (1956).
(42) Boekelheide, V., and Fahrenholza, K., *J. Am. Chem. Soc.*, **83**, 458 (1961).
(43) Boekelheide, V., and Windgassen, R. J., Jr., *J. Am. Chem. Soc.*, **80**, 2020 (1958).
(44) Boese, A. B., Jr., *Ind. Eng. Chem.*, **32**, 16 (1950).
(45) Bonnett, Brown, R. D., Clark, Sutherland and Todd, *Biochem. J.*, 2094 (1959).
(46) Bradsher, C. K., Beavers, L. E., and Jones, J. H., *J. Org. Chem.*, **22**, 1740 (1952).
(47) Bradsher, C. K., and Solomons, T. W. G., *J. Am. Chem. Soc.*, **80**, 933 (1958).
(48) Bremner, J. G. M., British Patent 608538 (1945) to Imp. Chem. Ind., Ltd.

(49) Bremner, J. G. M., and Jones, D. G., U.S. Patent 2,451,712 (1944) to Imp. Chem. Ind., Ltd.
(50) Bremner, J. G. M., Jones, D. G., and Beaumont, S., *J. Chem. Soc.*, 1018 (1946).
(51) Bremner, J. G. M., and McNeil, D., British Patent 547334 (1941) to Imp. Chem. Ind., Ltd.
(52) Bremner, J. G. M., and McNeil, D., German Patent 814005 (1949) to Imp. Chem. Ind., Ltd.
(53) Brooks, B. T., and Wilbert, A., *J. Am. Chem. Soc.*, **63**, 870 (1941).
(54) Brown, C. W., Marsden, K., Rogers, M. A. T., Tylor, C. M. B., and Wright, R., *Proc. Chem. Soc.*, 254 (1960).
(55) Brown, R. D., *J. Chem. Soc.*, 2730 (1950).
(56) Brown, R. D., Clark, Lamchen, M., and Todd, *Biochem. J.*, 2116 (1959).
(57) Butz, L. W., and Rytina, A. W., *Org. Reactions*, **5**, 136 (1949).
(58) Cairns, T. L., Sauer, J. C., and Wilkinson, W. K., *J. Am. Chem. Soc.*, **74**, 3989 (1952).
(59) Cava, M. P., and Mitchell, M. J., *J. Am. Chem. Soc.*, **81**, 5409 (1959).
(60) Chalvet, O., Dandel, R., Gouarneaud, R., and Roux, M., *Compt. rend.*, **232**, 2221 (1951).
(61) Chang, M. C., and Needleman, S. B., unpublished data.
(62) Colonge, J., and Dreux, J., *Compt. rend.*, **228**, 582 (1949).
(63) Coyner, E. C., and Hillman, W. S., *J. Am. Chem. Soc.*, **71**, 324 (1949).
(64) d'Alcontres, G. S., *Gazz. chim. ital.*, **82**, 627 (1952); *Chem. Abstracts*, **48**, 5859 (1954).
(65) d'Alcontres, G. S., *Gazz. chim. ital.*, **82**, 823 (1952); *Chem. Abstracts*, **47**, 12354 (1953).
(66) d'Alcontres, G. S., and Fenech, A., *Acta cienc. venezolana*, **4**, 95 (1953); *Chem. Abstracts*, **49**, 1706 (1955); *Chem. Abstracts*, **50**, 305 (1956).
(67) d'Alcontres, G. S., and Fenech, G., *Gazz. chim. ital.*, **82**, 175 (1952); *Chem. Abstracts*, **47**, 8734 (1953).
(68) d'Alcontres, G. S., and Grünanger, P., *Gazz. chim. ital.*, **80**, 741 (1950); *Chem. Abstracts*, **46**, 971 (1952).
(69) d'Alcontres, G. S., and Grünanger, P., *Gazz. chim. ital.*, **80**, 831 (1950); *Chem. Abstracts*, **46**, 4527 (1952).
(70) Dale, W. J., and Sisti, A. J., *J. Am. Chem. Soc.*, **76**, 81 (1954).
(71) Dale, W. J., and Sisti, A. J., *J. Org. Chem.*, **22**, 449 (1957).
(72) Delepine, M., *Ann. de chim.*, **20**, 389 (1910).
(73) Delepine, M., *Compt. rend.*, **150**, 394, 535 (1910).
(74) Delepine, M., and Horeau, A., *Bull. soc. chim. France*, **5**, 339 (1938).
(75) Delepine, M., and Horeau, A., *Compt. rend.*, **206**, 27 (1938).
(76) Delpierre, G. R., and Lamchen, M., *Proc. Chem. Soc.*, 386 (1960).
(77) Diels, O., and Alder, K., *Ann.*, **460**, 98 (1928).
(78) Diels, O., and Alder, K., *Ann.*, **486**, 191 (1931).
(79) Diels, O., and Alder, K., *Ann.*, **498**, 16 (1932).
(80) Diels, O., and Alder, K., *Ann.*, **498**, 31 (1932).
(81) Diels, O., and Alder, K., *Ann.*, **505**, 103 (1933).
(82) Diels, O., and Alder, K., *Ann.*, **510**, 87 (1934).
(83) Diels, O., Alder, K., Winckler, H., and Petersen, E., *Ann.*, **489**, 1 (1932).
(84) Diels, O., Blom, J., and Koll, W., *Ann.*, **443**, 242 (1925).
(85) Diels, O., and Harms, *Ann.*, **525**, 73 (1936).
(86) Diels, O., and Koch, U., *Ann.*, **519**, 140 (1935).
(87) Diels, O., and Koch, U., *Ann.*, **556**, 38 (1944).
(88) Diels, O., and Moller, F., *Ann.*, **516**, 45 (1935).
(89) Diels, O., and Olsen, S., *J. prakt. Chem.*, **156**, 286 (1940).
(90) Diels, O., and Pistron, A., *Ann.*, **530**, 87 (1937).
(91) Diels, O., and Thiele, W. E., *J. prakt. Chem.*, **156**, 195 (1940).
(92) Diels, O., and Thiele, W. E., *Ann.*, **543**, 79 (1939).
(93) Elderfield, R. C., "Heterocyclic Compounds," **4**, 252, 427, 585, John Wiley and Sons, Inc., N. Y., 1952.
(94) Elderfield, "Heterocyclic Compounds," **4**, 657, John Wiley and Sons, Inc., 1952.
(95) Emerson, W. S., Birum, G. H., and Longley, R. I., Jr., *J. Am. Chem. Soc.*, **75**, 1312 (1953).
(96) Emerson, W. S., and Longley, R. I., U. S. Patent 2,624,764 (1949) to Monsanto Chemical Company.
(97) Etienne, A., *Ann. Chim.*, **1**, 5 (1946).
(98) Euler, H., and Josephson, K., *Ber.*, **53B**, 822 (1920).
(99) Farina-Perez, F., *Rev. real acad. cienc. exact. fis. natur.*, **45**, 371 (1951); *Chem. Abstracts*, **47**, 2764 (1953).
(100) Farmer, E. H., and Farooq, M. D., *J. Chem. Soc.*, 1925, (1938).
(101) Fernandez-Alonso, J. I., and Domingo, S. R., *"Selecta Chim.,"* **17**, 13 (1958).
(102) Finkelshtein, A. I., Arbuzov, Yu. A., and Shorygin, P. P., *J. Phys. Chem. (U.S.S.R.)*, **24**, 802 (1950).
(103) Fountaine, E. B., and Sharp, W. H., U. S. Patent 2,537,579 (1949) to Shell Development Company.
(104) Friedrichsen, W., German Patent 800298 (1948) BASF, *Chem. Abstracts*, **45**, 1628 (1951).
(105) Fries, K., and Brandes, E., *Ann.*, **542**, 48 (1939).
(106) Galbraith, A., Small, T., Barnes, A., and Boekelheide, V., *J. Am. Chem. Soc.*, **83**, 453 (1961).
(107) Galbraith, A., Small, T., and Boekelheide, V., *J. Org. Chem.*, **24**, 582 (1959).
(108) Geyer, B. P., and Mortimer, R. H., U. S. Patent 2,514,156 (1949), to Shell Development Company.
(109) Godfrey, J. C., *J. Org. Chem.*, **24**, 581 (1959).
(110) Gresham, T. L., and Steadman, T. R., *J. Am. Chem. Soc.*, **71**, 737 (1949).
(111) Grummitt, O., and Becker, E. J., *J. Am. Chem. Soc.*, **70**, 149 (1949).
(112) Grundmann, A., Weise, G., and Seide, S., *Ann. Chem.*, **577**, 77 (1952).
(113) Grünanger, P., *Atti. accad. Nazl. Lincei Rend. Classe sci. fis. mat. e nat.*, **16**, 726 (1954).
(114) Grünanger, P., *Gazz. chim. ital.*, **84**, 359 (1954); *Chem. Abstracts*, **49**, 5436 (1955).
(115) Grünanger, P., *Rend. accad. Lincei*, **24**, 163 (1958).
(116) Grünanger, P., and Fabbri, E., *Gazz. chim. ital.*, **89**, 598 (1959).
(117) Grünanger, P., Finzi, P. V., and Fabbri, E., *Gazz. chim. ital.*, **90**, 413 (1960).
(118) Grünanger, P., and Grasso, A., *Gazz. chim. ital.*, **85**, 1271 (1955); *Chem. Abstracts*, **50**, 9384 (1956).
(119) Grünanger, P., and Langella, M. R., *Gazz. chim. ital.*, **89**, 1784 (1959).
(120) Grünanger, P., and Mangiapan, S., *Gazz. chim. ital.*, **88**, 149 (1958).
(121) Hahn, W. E., *Wiadomosci Chem.*, **9**, 616 (1955).
(122) Hall, R. H., *J. Chem. Soc.*, 4083 (1942).
(123) Hall, R. H., *J. Chem. Soc.*, 1398 (1953).
(124) Hall, R. H., *J. Chem. Soc.*, 4303 (1954).
(125) Hall, R. H., and Howe, B. K., *J. Chem. Soc.*, 2480 (1951).
(126) Hawkins, P. J., and Janz, G. J., *J. Chem. Soc.*, 1479 (1949).
(127) Hawkins, P. J., and Janz, G. J., *J. Chem. Soc.*, 1485 (1949).
(128) Hauptmann, H., *Bol. Assoc. Quim. Brazil*, **9**, 1 (1951).
(129) Henecka, H., *Z. Naturforsch.*, **46**, 15 (1949); *Chem. Abstracts*, **44**, 1909 (1950).

(130) Henkel, K., and Weygand, F., *Ber.*, **76**, 812 (1943); *Chem. Abstracts*, **38**, 1742 (1944).
(131) Hock, H., and Depke, F., *Ber.*, **84**, 349 (1951).
(132) Holmes, H. L., "Org. Reactions," **4**, 60 (1948).
(133) Homer, L., and Merz, H., *Ann.*, **570**, 89 (1950).
(134) "Methoden der Organischer Chemie," Ed. Houben-Weyl, Vol. **7/1** 253, Georg Thieme Verlag, Stuttgart, 1954.
(135) Hultsch, K., *J. prakt. Chem.*, **158**, 275 (1941).
(136) Hultsch, K., *Ber.*, **74**, 898 (1941).
(137) Hunter, W. T., U. S. Patent 2,813,867 (1957) to Sterling Drug Inc.; *Chem. Abstracts*, **52**, 10220 (1958).
(138) Irie, S., *Kagaku no Rojoikk*, (J. Japan Chem.), **7**, 626 (1953).
(139) Jackman, L. M., Johnson, A. W., and Tebby, T. C., *J. Chem. Soc.*, 1579 (1960).
(140) Jaques, J., *Ann. Chem.*, **20**, 363 (1945).
(141) Jarvice, J. M. S., and Janz, G. J., *J. Phys. Chem.*, **60**, 1430 (1956).
(142) Janz, G. J., and Duncan, N. E., *J. Am. Chem. Soc.*, **75**, 5389 (1953).
(143) Janz, G. J., and Duncan, N. E., *J. Am. Chem. Soc.*, **75**, 5391 (1953).
(144) Janz, G. J., and Duncan, N. E., *Nature*, **171**, 933 (1953).
(145) Janz, G. J., McCulloch, W. J. G., and Timpane, E. F., *Ind. Eng. Chem.*, **45**, 1343 (1953).
(146) Janz, G. J., and Meyers, R. E., *J. Am. Chem. Soc.*, **75**, 1910 (1953).
(147) Janz, G. J., and Wait, S. C., Jr., *J. Am. Chem. Soc.*, **76**, 6377 (1954).
(148) Kirmse, W., and Horner, L., *Ann.*, **614**, 1 (1958).
(149) Kline, C. H., and Turkevich, J., *J. Am. Chem. Soc.*, **67**, 498 (1945).
(150) Kloetzel, M. C., "Org. Reactions," **4**, 1 (1948).
(151) Kojima, S., *Kogyo Kagaku Zasshi*, **58**, 540 (1955).
(152) Kojima, S., *Kogyo Kagaku Zasshi*, **59**, 951 (1956).
(153) Kondrateva, G. Ya., *Khim. Nauka. i Prom.*, **2**, 666 (1957).
(154) Kovacs, J., Bruckner, V., Kandel, I., *Acta Chim. Hung.*, **1**, 230 (1951).
(155) Kovacs, J., *Magyar Kem Folyoirat*, **56**, 74 (1950); *Chem. Abstracts*, **46**, 252, 8649 (1952).
(156) Kubler, D. G., U. S. Patent 2,905,699 (1960) to Union Carbide Corp.
(157) Kuderna, J. G., U. S. Patent 2,802,012 (1957) to Shell Development Company; *Chem. Abstracts*, **52**, 1270 (1958).
(158) Levisalles, J., and Baranger, P., *Compt. rend.*, **238**, 592 (1954).
(159) Littman, E. R., *J. Am. Chem. Soc.*, **50**, 1316 (1936).
(160) Longley, R. I., Jr., and Emerson, W. S., *J. Am. Chem. Soc.*, **72**, 3079 (1950).
(161) Longley, R. I., Emerson, W. S., and Shafer, T. C., *J. Am. Chem. Soc.*, **74**, 2012 (1952).
(162) Lo Vecchio, G., and Monforte, P., *Gazz. chim. ital.*, **86**, 399 (1956).
(163) MacKenzie, J. C. J., Rodgman, A., and Wright, G. F., *J. Org. Chem.*, **17**, 1666 (1954).
(164) Madroñero-Peláez, R., *Rev. real. acad. cienc. exact. fis. y nat.* (Madrid), **47**, 107 (1953); *Chem. Abstracts*, **49**, 3206e (1955).
(165) Madroñero-Peláez, R., Alvarez, E. G., and Tamayo, M. L., *Anal. real. soc. espan. fis. y quimica*, **4B**, 276 (1955).
(166) Mameli, E., *Chimica e industria* (Milan), **32**, 594 (1950).
(167) Mannich, C., *Ber.*, **74**, 557 (1941).
(168) Mannich, C., *Ber.*, **74**, 565 (1941).
(169) Mannich, C., *Ber.*, **74**, 1007 (1941).
(170) Martinez, J. R., *Rev. real acad. cienc. exact. fis. y nat.* (Madrid), **48**, 81 (1952).
(171) Marvel, C. S., and Hwa, J. C. H., *J. Org. Chem.*, **15**, 525 (1950).
(172) Merling, A., German Patent 227,176.
(173) Miller, J. B., *J. Org. Chem.*, **25**, 1279 (1960).
(174) Monforte, F., and Lo Vecchio, G., *Gazz. chim. ital.*, **82**, 130 (1952); *Chem. Abstracts*, **47**, 4876 (1953).
(175) Monforte, F., and Lo Vecchio, G., *Gazz. chim. ital.*, **83**, 416 (1953); *Chem. Abstracts*, **49**, 296 (1955).
(176) Moulin, F., *Helv. Chim. Acta*, **35**, 167 (1952).
(177) Mugnaini, E., and Grünanger, P., *Rend. accad. Lincei*, **14**, 275 (1953).
(178) Nazarov, I. N., Kuznetsova, A. I., and Kuznetsov, N. V., *J. Gen. Chem. (U.S.S.R.)*, **25**, 75 (1955).
(179) Needleman, S. B., and Chang, M. C., unpublished data.
(180) Nieuwenhuis, J., and Arens, J. F., *Rec. trav. chim.*, **76**, 999 (1957).
(181) Norton, J. A., *Chem. Revs.*, **31**, 319 (1942).
(182) Olsen, S., *Tids. Kjemi Bergvesen Met.*, 33 (1950).
(182a) Rabjohn, N., *Org. Syntheses*, **28**, 58 (1948).
(183) Paal, C., and Schulz, H., *Ber.*, **33**, 3800 (1900); *Chem. Abstracts*, **44**, 557 (1950).
(184) Parham, W. E., and Holmquist, H. E., *J. Am. Chem. Soc.*, **73**, 913 (1951).
(185) Paul, R., *Bull. soc. chim. France*, **53**, 1489 (1933).
(186) Paul, R., *Bull. soc. chim. France*, **2**, 745 (1935).
(187) Paul, R., *Org. Syntheses*, **23**, 25 (1943).
(188) Paul, R., and Tchelitcheff, S., *Bull. soc. chim. France*, **14**, 167 (1947).
(189) Paul, R., and Tchelitcheff, S., *Comp. rend.*, **224**, 1722 (1947).
(190) Pelaez, R. M., *Ion*, **13**, 449, 512 (1953).
(191) Pfleger, R., and Jager, A., *Ber.*, **90**, 2460 (1957).
(192) Phillips, D. D., and Cason, J., *J. Am. Chem. Soc.*, **74**, 2934 (1952).
(193) Polaczkowa, W., and Walinski, J., *Roczniki Chem.*, **26**, 407 (1952); *Chem. Abstracts*, **48**, 11359 (1954).
(194) Pummerer, R., and Cherbuliez, E., *Ber.*, **52**, 1392 (1919).
(195) Pummerer, R., and Fieselmann, H., *Ann.*, **544**, 206 (1940).
(196) Quilico, A., and d'Alcontres, G. S., *Gazz. chim. ital.*, **80**, 140 (1950); *Chem. Abstracts*, **45**, 606 (1951).
(197) Quilico, A., d'Alcontres, G. S., and Grünanger, P., *Gazz. chim. ital.*, **80**, 479 (1950); *Chem. Abstracts*, **45**, 3836 (1951).
(198) Quilico, A., and Grünanger, P., *Gazz. chim. ital.*, **82**, 140 (1952); *Chem. Abstracts*, **47**, 6937 (1953).
(199) Quilico, A., and Grünanger, P., *Gazz. chim. ital.*, **25**, 1449 (1955); *Chem. Abstracts*, **50**, 10079 (1956).
(200) Quilico, A., Grünanger, P., and Mangiapon, S., *Gazz. chim. ital.*, **85**, 1250 (1955).
(201) Quilico, A., Grünanger, P., and Mazzini, R., *Gazz. chim. ital.*, **82**, 349 (1952); *Chem. Abstracts*, **48**, 2039 (1954).
(202) Quilico, A., and Simonetta, M., *Gazz. chim. ital.*, **76**, 200 (1946).
(203) Quilico, A., and Simonetta, M., *Gazz. chim. ital.*, **77**, 586 (1947).
(204) Quilico, A., and Speroni, G., *Gazz. chim. ital.*, **76**, 148 (1946).
(205) Reppe, W., *Ann.*, **601**, 81 (1956).
(206) Rubin, W., Steiner, W., and Wasserman, A., *J. Chem. Soc.*, 3046 (1949).
(207) Rubin, W., and Wasserman, A., *J. Chem. Soc.*, 2205 (1950).
(208) Rurato, M. S., *Rev. real acad. cienc.* (Madrid), **49**, 23 (1955).

(209) Scarpati, R., and Rippa, M., *Gazz. chim. ital.*, **88**, 804 (1958).
(210) Schenk, G. O., *Ann.*, **584**, 156 (1953).
(211) Schenk, G. O., *Ber.*, **77B**, 741 (1944).
(212) Schenk, G. O., Eggert, H., and Dink, W., *Ann.*, **584**, 177 (1953).
(213) Schenk, G. O., Kinkel, K. G., and Mertens, H. J., *Ann.*, **584**, 125 (1953).
(214) Schenk, G. O., and Schmidt-Thornec, G. A., *Ann.*, **584**, 199 (1953).
(215) Schonberg, A., Lotif, N., Moubasher, K., and Sina, A., *J. Chem. Soc.*, 136 (1951).
(216) Schultz, H., German Patent 863795 (1953); *Chem. Abstracts*, **52**, 19953 (1958).
(217) Schultz, H., Anzilotti-Fiat Final Report 1157 PB85174, pp. 17–18, U. S. Department of Commerce, January 18, 1948.
(218) Schultz, H., and Wagner, H., *Angew. Chem.*, **62**, 100 (1950).
(219) Schultz, H., and Wagner, H., *Angew. Chem.*, **62**, 112 (1950).
(220) Schultz, H., and Wagner, H., *Ann.*, **566**, 127 (1939).
(221) Shabarov, Yu. S., Vasiley, N. J., and Levina, R. Ya., *Doklady Akad. Nauk S.S.S.R.*, 129, 600 (1959); *Chem. Abstracts*, **54**, 14259 (1960).
(222) Sheehan, J. C., and Robinson, C. A., *J. Am. Chem. Soc.*, **73**, 1207 (1951).
(223) Shell Development Company, Technical Information Bulletin PD 123.
(224) Shell Development Company, Product Development Chemicals Industrial Bulletin, May, 1960.
(225) Data Sheet DS-58:3 (R), Shell Development Company, Emeryville, California.
(226) Skvarchenko, V. R., Kuzimin, M. G., and Levina, R. Ya., *Vestnik Moskov, Univ. 12 Ser. Mat., Mekr., Astron., Fiz., Khim.*, **3**, 169 (1957); *Chem. Abstracts*, **52**, 6358 (1958).
(227) Smith, C. W., Morton, D. G., and Ballard, S. A., U. S. Patent 2,514,168 (1947) to Shell Development Company.
(228) Smith, C. W., U. S. Patent 2,546,019 (1947) to Shell Development Company.
(229) Smith, C. W., and Ballard, S. A., U. S. Patent 2,546,018 (1947) to Shell Development Company.
(230) Smith, C. W., Norton, D. G., and Ballard, S. A., *J. Am. Chem. Soc.*, **73**, 5267 (1951).
(231) Smith, C. W., Norton, D. G., and Ballard, S. A., *J. Am. Chem. Soc.*, **73**, 5273 (1951).
(232) Smith, C. W., Norton, D. G., and Ballard, S. A., *J. Am. Chem. Soc.*, **73**, 5274 (1951).
(233) Smith, C. W., Norton, D. G., and Ballard, S. A., *J. Am. Chem. Soc.*, **74**, 2018 (1952).
(234) Smith, C. W., Norton, D. G., and Ballard, S. A., *J. Am. Chem. Soc.*, **74**, 5267, 5270 (1952).
(235) Smith, L. I., Agre, C. L., Leekley, R. M., and Prichard, W. W., *J. Am. Chem. Soc.*, **61**, 7 (1939).
(236) Snyder, H. R., Levin, R. H., and Wiley, P. F., *J. Am. Chem. Soc.*, **60**, 2025 (1938).
(237) Snyder, H. R., and Robinson, J. C., Jr., *J. Am. Chem. Soc.*, **63**, 3279 (1941).
(238) Snyder, H. R., Hasbrook, R. B., and Richardson, J. F., *J. Am. Chem. Soc.*, **61**, 3558 (1939).
(239) Späth, E., Lorenz, R., and Freund, E., *Monatsh.*, **76**, 297 (1947).
(240) Stagno, G., d'Alcontres, G. S., and DeGiacomo, G., *Atti. Soc. peloritana sci. fis. mat. e nat.*, **5**, 159 (1958).
(241) Staudinger, H., "Die Ketene," F. Enke, Stuttgart, 1912, pp. 11, 23, 59.
(242) Stoner, G. G., and McNulty, J. S., *J. Am. Chem. Soc.*, **72**, 1531 (1950).
(243) Stork, G., van Tamelen, E. E., Friedman, L. J., and Burgstahler, A. W., *J. Am. Chem. Soc.*, **73**, 4501 (1951).
(244) Szherlin, S. M., *Zurn. Obszez. Chim.*, **8**, 15 (1938).
(245) Szherlin, S. M., Berlin, A. J., Serebrennikova, A., and Rabinovich, A., *J. Gen. Chem. (U.S.S.R.)*, **8**, 22 (1938).
(246) Tamaka, M., *J. Ind. Chem. (Japan)*, **60**, 1509 (1957).
(247) Tamaka, M., *J. Ind. Chem. (Japan)*, **60**, 1512 (1957).
(248) Tamayo, M. L., *Ann. real soc. espan. fiz. y quim.*, **47B**, 819 (1952); *Chem. Abstracts*, **46**, 11164 (1952).
(249) Tamayo, M. L., *Ann. real soc. espan. fiz. y quim.*, **48B**, 75 (1952); *Chem. Abstracts*, **47**, 3818 (1953).
(250) Tamayo, M. L., *Ann. real soc. espan. fiz. y quim.*, **48B**, 81 (1952); *Chem. Abstracts*, **47**, 2169 (1953).
(251) Tamayo, M. L., *Ann. real soc. espan. fiz. y quim.*, **48B**, 89 (1952); *Chem. Abstracts*, **47**, 2819 (1953).
(252) Tamayo, M. L., and Alvarez, F., *Ann. real soc. espan. fiz. y quim.*, **48B**, 81 (1952).
(253) Tamayo, M. L., Aparicio, T. Lopez, and Madroñero, R., *Ann. real soc. espan. fiz. y quim.*, **51B**, 567 (1958).
(254) Tamayo, M. L., Madroñero, R., and Munoz, G. G., *Ber.*, **93**, 289 (1960).
(255) Tamayo, M. L., and Madroñero, R., *Rev. real acad. cien. exactas, fis. Natur.*, **53**, 1 (1959).
(256) Tamayo, M. L., and Madroñero, R., "Festschr. Arthur Stoll," pp. 220–226.
(257) Tamayo, M. L., Munoz, G. G., and Madroñero, R., *Bull. soc. chim. Fr.*, 1331 (1958).
(258) Tamayo, M. L., Munoz, G. G., and Madroñero, R., *Bull. soc. chim. Fr.*, 1334 (1958).
(259) Tamayo, M. L., Ossorio, R. P., and Burata, M. S., *Ann. real soc. espan. fiz. y quim.*, **50B**, 865 (1954).
(260) Tamayo, M. L., and Soto Camara, J. L., *Ann. real soc. espan. fiz. y quim.*, **53B**, 27 (1957).
(261) Yomimatsu, Y., *Yakugaku Zasshi*, **77**, 286 (1947); *Chem. Abstracts*, **51**, 11356 (1957).
(262) Tomimatsu, T., *Yakugaku Zasshi*, **77**, 292 (1947).
(263) Tomimatsu, Y., *J. Pharm. Chem.* (Japan), **77**, 7 (1957).
(264) Tomimatsu, Y., *J. Pharm. Chem.* (Japan), **77**, 186 (1957).
(265) Toussaint, W. J., U. S. Patent 2,387,356 (1942) to Union Carbide Chem. Corp.
(266) Vaughan, W. R., and Spencer, J. L., *J. Org. Chem.*, **25**, 1160 (1960).
(267) Wagner-Jauregg, T., *Ber.*, **63**, 3213 (1930).
(268) Walling, C., in "The Chemistry of Petroleum Hydrocarbons," Brooks, B. T., Boord, C. E., Kurtz, S. S., Jr., and Schmerling, L. Editors, Reinhold Publishing Corp., New York, N. Y., Vol. 2, p. 207.
(269) Wang, C. H., Hsiao, S. H., Saklad, E., and Cohen, S. G., *J. Am. Chem. Soc.*, **79**, 2661 (1951).
(270) Whetstone, R. R., U. S. Patent 2,479,283 (1949) to Shell Development Company.
(271) Whetstone, R. R., U. S. Patent 2,514,688 (1949) to Shell Development Company.
(272) Raah, W. J., and Ballard, S. A., U. S. Patent 2,562,849 (1949) to Shell Development Company.
(273) Whetstone, R. R., and Ballard, S. A., *J. Am. Chem. Soc.*, **73**, 5280 (1951).
(274) Whetstone, R. R., and Hall, R. H., U. S. Patent 2,511,891 (1948).
(275) Whetstone, R. R., and Hall, R. H., *J. Chem. Soc.*, 1398 (1953).
(276) Wichterle, O., *Collect. Trav. Chem. Tchecosl.*, **12**, 292 (1947).

(277) Wichterle, O., and Gregor, V., *Coll. Czech. Chem. Comm.*, **24**, 1158 (1959).
(278) Wichterle, O., Gregor, V., Dubansky, A., and Seidl, V., *Chem. Listy*, **51**, 605 (1957).
(279) Wichterle, O., and Kolinsky, M., *Chem. Listy*, **47**, 1787 (1953).
(280) Wichterle, O., and Racek, J., *Chem. Listy*, **47**, 1768 (1953); *Chem. Abstracts*, **49**, 1053 (1955).
(281) Wichterle, O., and Svastal, S., *Coll. Czech. Chem. Communs.*, **16**, 33 (1951).
(282) Wiley, R. H., and Knabeschuh, L. H., *J. Org. Chem.*, **18**, 836 (1953).
(283) Wilson, C. L., British Patent 569,625 (1943) to Revertex, Ltd.
(284) Wilson, C. L., *J. Chem. Soc.*, 53 (1945).
(285) Wilson, C. L., *J. Am. Chem. Soc.*, **68**, 1646 (1946).
(286) Wilson, C. L., *Nature*, **157**, 846 (1946).
(287) Wilson, C. L., *J. Am. Chem. Soc.*, **69**, 3004 (1947).
(288) Windgassen, R. J., Jr., Saunders, W. H., Jr., and Boekelheide, V., *J. Am. Chem. Soc.*, **81**, 1459 (1959).
(289) Woods, G. F., and Sanders, H., *J. Am. Chem. Soc.*, **68**, 2111 (1946).
(290) Yashunskii, V. G., Terent'ev, A. P., and Nekhlin, Ya. G., *J. Gen. Chem. (U.S.S.R.)*, **26**, 831 (1956).
(291) Ziegler, K., *Ann.*, **551**, 1 (1942).
(292) Zincke, T., Bregmann, A., Francke, and Prenntgell, *Ann.*, **296**, 135 (1897).
(293) Zincke, T., and Gunther, H., *Ann.*, **272**, 243 (1893).
(294) Zincke, T., and Meyer, A., *Ann.*, **367**, 1 (1909).
(295) Zincke, T., and Pfaffendorf, W., *Ann.*, **394**, 7 (1912).