ences cited in the previous reviews will not be duplicated unless it is necessary to use them to illustrate specific points in the discussion. Nomenclature is based on *Chemical Abstracts* usage (54).

II. UNSYMMETRICAL 1,6-ADDITIONS TO 2,4-PENTADIENENITRILE

The reactive compound 2,4-pentadienenitrile (VI) (18) will add a number of reagents in a 1,6-process. When Y is hydrogen, or is replaced by hydrogen in

$$\underset{\text{VI}}{CH_2{=}CH{-}CH{=}CH{-}C{\equiv}N} + YZ \rightarrow (ZCH_2{-}CH{=}CH{-}CH{=}C{=}NY)$$

the isolation of the product, the imine form changes to the more stable 5-substituted 3-pentenenitrile (VII). Under more vigorous catalysis with reactive ad-

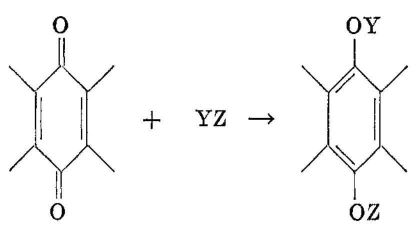
$$\underset{\text{VII}}{ZCH_2{-}CH{=}CH{-}CH_2{-}C{\equiv}N} + HZ \rightarrow \underset{\text{VIII}}{ZCH_2{-}CH_2{-}CH(Z)CH_2{-}C{\equiv}N}$$

denda, the double bond shifts into conjugation and a 1,4-addition of HZ produces the 3,5-disubstituted pentanenitrile (VIII). The products derived from 1,6-addition of reagents to 2,4-pentadienenitrile are tabulated in table 1.

2,4-Pentadienenitrile has a remarkable facility to add a wide range of compounds by a 1,6-process. There is no indication of a 1,4-addition competing with the 1,6-addition. Less reactive addenda such as benzyl cyanide, desoxybenzoin, acetophenone, cyclopentadiene (17), ammonia, and aniline (67) do not form stable adducts. There is indirect evidence for the formation of an unstable 1,6-adduct with ammonia (48). Reduction of a mixture of ammonia and 2,4-pentadienenitrile with hydrogen and Raney nickel produced 5-aminopentanenitrile and pentamethylenediamine in low yield.

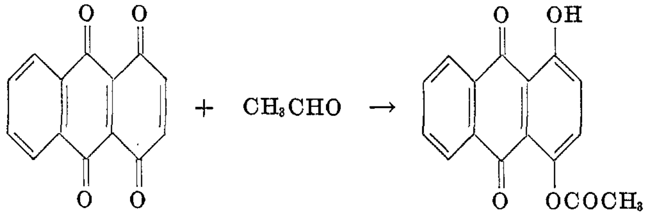
III. UNSYMMETRICAL 1,6-ADDITIONS TO 1,4-QUINONES

There are a number of reactions of 1,4-quinones which take place by a 1,6-process of unsymmetrical addition to the oxygens at the ends of the conjugated quinoidal system.



These reactions require participation by complexes or involve activated states; they are facilitated by the increased resonance energy of the aromatic products.

There are several examples of the reaction of aldehydes with quinones under illumination to produce esters of hydroquinones. An example of this type of addition is reported in the reaction of 1,4,9,10-anthracenetetrone (IX) with acetal-

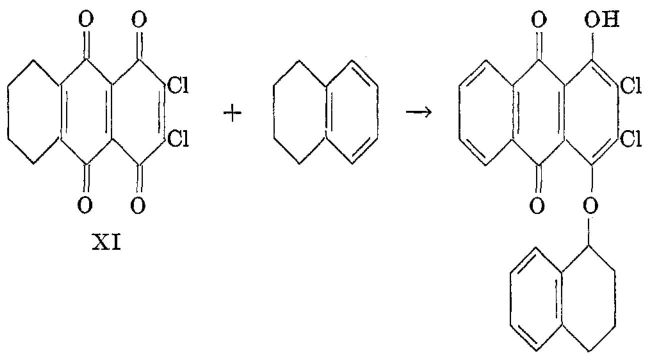


IX X

dehyde to produce X in 49 per cent yield (26). *p*-Benzoquinone (9) and 2-methyl-*p*-benzoquinone (7) react with cinnamaldehyde to produce the corresponding hydroquinone cinnamates. The reaction of 2,3,5,6-tetrachloro-*p*-benzoquinone with benzaldehyde, resulting in tetrachlorohydroquinone benzoate, has been formulated as a radical chain process (53). The production of 2-methylhydroquinone, benzoic acid, and a small amount of 2-methylhydroquinone dibenzoate from a mixture of 2-methyl-*p*-benzoquinone and benzaldehyde was interpreted as evidence for oxidation of the aldehyde, reduction of the quinone, and reaction of these two products to form the ester (7).

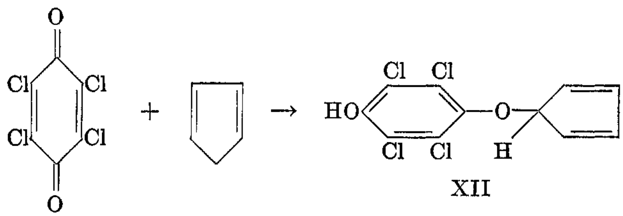
The reaction of *p*-benzoquinone and acetaldehyde takes a different course and the product is 2-acetylhydroquinone in a 1,4-addition (46).

An unusual reaction takes place with 2,3-dichloro-1,4,9,10-anthracenetetrone (XI) and tetralin or cyclohexene to produce hydroquinone ethers (23), for example:



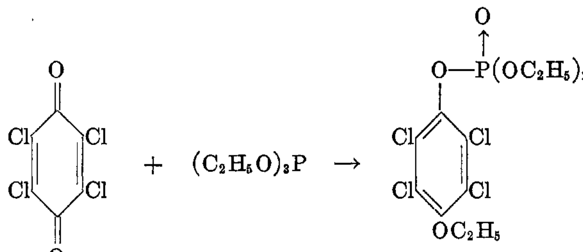
XI

The products from the reactions of dienes and enynes with highly substituted quinones have been formulated (15) as hydroquinone monoethers produced by a 1,6-addition process. The structure of the product (72 per cent yield) from the reaction of 2,3,5,6-tetrachloro-*p*-benzoquinone with cyclopentadiene has not been established; the data suggest the structure XII (2, 69). However, a recent communication implies a normal diene adduct structure (21). The reaction of 2,5-dimethyl-1,5-hexadien-3-yne with 2,3,5,6-tetrachloro-*p*-benzoquinone results in a 2 per cent yield of a product formulated as a hydroquinone ether (14).



XII

A recent discovery of a 1,6-addition process is the reaction of 2,3,5,6-tetrachloro-*p*-benzoquinone with triethyl phosphite to produce a 90 per cent yield of the ethyl ether of 4-hydroxy-2,3-5,6-tetrachlorophenyldiethyl phosphate (XIII) (59). The scope of the reaction was extended to include *p*-benzoquinone (60), 2,3,5,6-



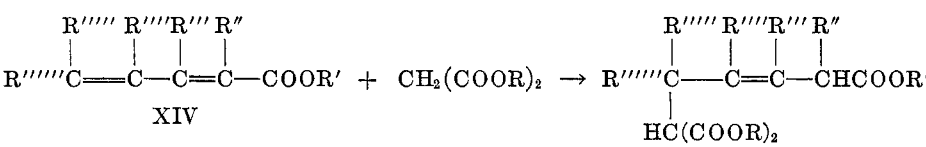
XIII

tetramethyl-*p*-benzoquinone, 2,5-dimethyl-*p*-benzoquinone, and 2,5-dichloro-*p*-benzoquinone (58) with trimethyl and triethyl phosphites. The reaction is general for trialkyl phosphites derived from primary alcohols. When trialkyl phosphites derived from secondary alcohols are employed, the reaction takes a different course, and with 2,3,5,6-tetrachloro-*p*-benzoquinone the products are di-*sec*-alkyl *p*-benzoquinone-2,3,5,6-tetraphosphonates (61).

IV. OTHER UNSYMMETRICAL 1,6-ADDITIONS

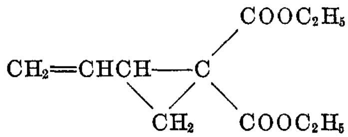
A. Active methylene compounds

The most familiar addition reaction of multiple conjugated systems is the Michael reaction, the base-catalyzed addition of compounds with reactive carbon–hydrogen bonds to carbon–carbon double bonds activated by electron-withdrawing groups (19). Considerable data have accumulated for the Michael reaction of substituted alkyl 2,4-pentadienoates (XIV) with alkyl malonates or alkyl cyanoacetates. These data are tabulated in table 2 and discussed in Section VI.



A more involved 1,6-addition is the reaction of ethyl malonate with ethyl 2-vinylcyclopropane-1,1-dicarboxylate (XV) to produce ethyl 3-hexene-1,1,6,6-

tetraoate (XVI) in 12 per cent yield (45). Formally, this is a 1,7-addition due to the insertion in the chain of the methylene group from the opening of the cyclo-



XV

$$\rightarrow (C_2H_5OOC)_2CHCH_2CH{=}CHCH_2CH(COOC_2H_5)_2$$

XVI

propane ring. However, the mechanism of the addition is similar to that of the reaction between methyl 2,4-hexadienoate and methyl sodiomalonate (31). The major product (64 per cent yield) of the reaction is ethyl 2-keto-4-vinylcyclopentane-1,3-dicarboxylate from the cyclization and elimination of the 1,5-adduct (1,4-mechanism), ethyl 4-pentene-1,1,3,3-tetraoate.

TABLE 1

1,6-Additions to 2,4-pentadienenitrile

Addendum	Product	Yield	Reference
		per cent	
Ethyl malonate	Ethyl bis(4-cyano-2-butenyl)malonate	13	(17)
		—	(4)
Ethyl acetoacetate	Ethyl 2-(4-cyano-2-butenyl)acetoacetate	11	(13)
	Ethyl 2,2-bis(4-cyano-2-butenyl)acetoacetate	56	(17)
		74	(13)
Ethyl cyanoacetate	Ethyl 2,2-bis(4-cyano-2-butenyl)cyanoacetate	60	(17)
Acetylacetone	3,3-Bis(4-cyano-2-butenyl)-2,4-pentanedione	45	(17)
Nitromethane	Nitrotris(4-cyano-2-butenyl)methane	—	(16)
Nitroethane	6-Nitro-3-heptenenitrile	73	(16)
	6-Nitro-6-(4-cyano-2-butenyl)-3-heptenenitrile	65	(16)
1-Nitropropane	6-Nitro-3-octenenitrile	—	(16)
2-Nitropropane	6-Nitro-6-methyl-3-heptenenitrile	58	(16)
Nitrocyclohexane	1-Nitro-1-(4-cyano-2-butenyl)cyclohexane	—	(16)
Ethylamine	5-Ethylamino-3-pentenenitrile	45–56	(67)
Isopropylamine	5-Isopropylamino-3-pentenenitrile	69–80	(67)
n-Butylamine	5-*n*-Butylamino-3-pentenenitrile	46–50	(67)
Cyclohexylamine	5-Cyclohexylamino-3-pentenenitrile	26	(67)
Dimethylamine	5-Dimethylamino-3-pentenenitrile	80	(67)
Diethylamine	5-Diethylamino-3-pentenenitrile	80	(34)
Di-*n*-butylamine	5-Di(*n*-butylamino)-3-pentenenitrile	30	(67)
Morpholine	5-Morpholino-3-pentenenitrile	90	(34)
Piperidine	5-Piperidino-3-pentenenitrile	83	(34)
Piperazine	5-Piperizino-3-pentenenitrile	17	(67)
Ethylenimine	5-Ethylenimino-3-pentenenitrile	90	(67)
Methanol	5-Methoxy-3-pentenenitrile	—	(18)
	3,5-Dimethoxypentanenitrile	39	(48)
Ethyl mercaptoacetate	Ethyl *S*-(4-cyano-2-butenyl)mercaptoacetate	10	(48)
Methyl *N*-methylaminoacetate	Methyl *N*-methyl-*N*-(4-cyano-2-butenyl)aminoacetate	—	(48)
Hydrogen chloride (with ethanol)	Ethyl 5-chloro-3-pentenoate	25	(18)
Hydrogen chloride (concentrated acid)	5-Chloro-3-pentenamide	—	(52)
Hydrogen cyanide	3-Hexene-1,6-dinitrile	Trace	(48)
Hydrogen sulfide	Bis(4-cyano-2-butenyl) sulfide	—	(48)
Thiophenol	5-Phenylmercapto-3-pentenenitrile	—	(68)
Hydrazine	5-Hydrazino-3-pentenenitrile	41	(48)
Sodium bisulfite	Sodium 4-cyano-2-butene-1-sulfonate	—	(48)

B. Nitroalkanes

The addition of nitromethane to alkyl 2,4-pentadienoates produces alkyl 6-nitro-3-hexenoates (5) (also, see table 1).

C. Amines

The addition of ammonia to 2,4-pentadienoic acid (XVII) was reported to produce a diaminovaleric acid (80 per cent yield) with one amino group in the 4- or 5-position (lactam formation) (32). Subsequently, it was shown that the melting points of the mono- and dipicrates of the diaminovaleric acid corresponded to those of ornithine (2,5-diaminovaleric acid) (XVIII) (64).

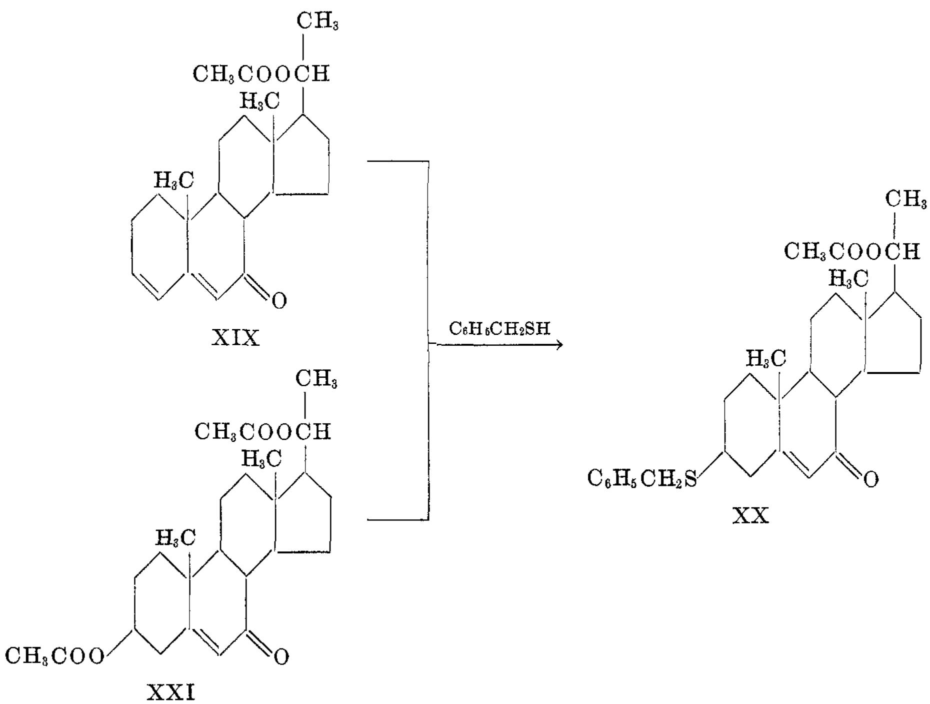
$$\underset{\text{XVII}}{CH_2{=}CHCH{=}CHCOOH} + NH_3 \rightarrow (H_2NCH_2CH{=}CHCH_2COOH) \rightarrow \underset{\text{XVIII}}{H_2N(CH_2)_3CH(NH_2)COOH}$$

The structure of the adduct cannot be considered as definitely established. Substantial theoretical arguments would predict that the actual product is 3,5-diaminovaleric acid.

Methyl 5-phenyl-2,4-pentadienoate does not add ammonia or amines (63).

D. Mercaptans

The addition of benzyl mercaptan to 20β-acetoxypregna-3,5-dien-7-one (XIX) produces 3-benzylmercapto-20β-acetoxypreg-5-en-7-one (XX) in 49 per cent



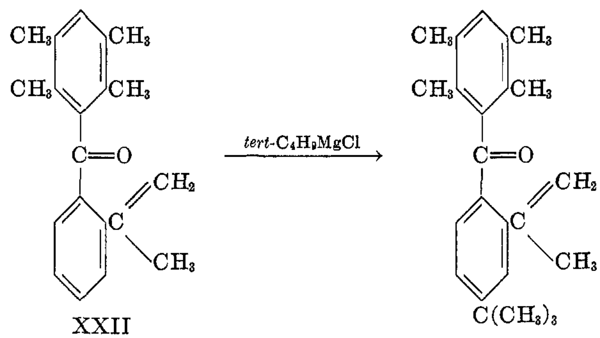
yield. The same product results in 45 per cent yield when the starting material is 3β,20β-diacetoxypreg-5-en-7-one (XXI), the first step being the elimination of acetic acid to form XIX, followed by addition of benzyl mercaptan. No assignment of configuration was made for the 3-benzylmercapto group (65).

E. Hydrogen halides

A novel 1,6-addition of hydrogen chloride is proposed in the reaction of furfural anil with aniline hydrochloride (33). This formulation of the reaction is preferred over an earlier proposal (12) because of the vinyl chloride intermediate involved, which would have too low a reactivity to explain the observed rate.

F. Grignard reagents

The addition of Grignard reagents to fuchsones and to highly hindered diaryl ketones provides the largest number of examples of a single type of 1,6-addition reaction. This subject has been reviewed (39) and is discussed in a recent book (44). A current example of the addition of Grignard reagents to hindered diaryl ketones had the possibility of two different 1,6-additions (38). The addition of *tert*-butylmagnesium chloride to XXII took place in the aromatic ring instead of to the double bond of the isopropenyl substituent on the ring. The ketone analo-



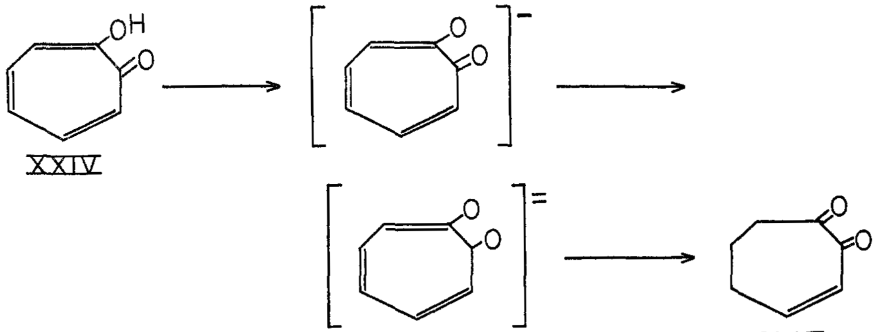
XXII XXIII

gous to XXIII, but with an isopropyl group in place of the isopropenyl group, was produced in 78 per cent yield.

G. Lithium aluminum hydride

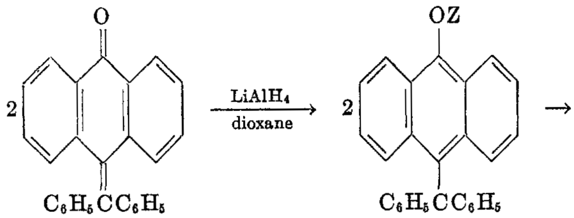
There are two examples of the reduction of organic compounds with lithium aluminum hydride which result in products explained on the assumption of 1,6-addition processes. The reduction of tropolone (XXIV) with lithium aluminum hydride produces 3-cycloheptene-1,2-dione (XXV) in 11 per cent yield (20). The first step in the reduction is the formation of the divalent anion, which is further reduced by a 1,4- or a 1,6-reduction. The reduction of the unsubstituted tropolone does not allow a distinction to be made between a 1,4- and a 1,6-reduction, since both processes would lead to the same product.

The reduction of benzhydrylidenanthrone (XXVI) by lithium aluminum hydride has been explained as a 1,6-reduction (10). The final product, *sym*-tetra-

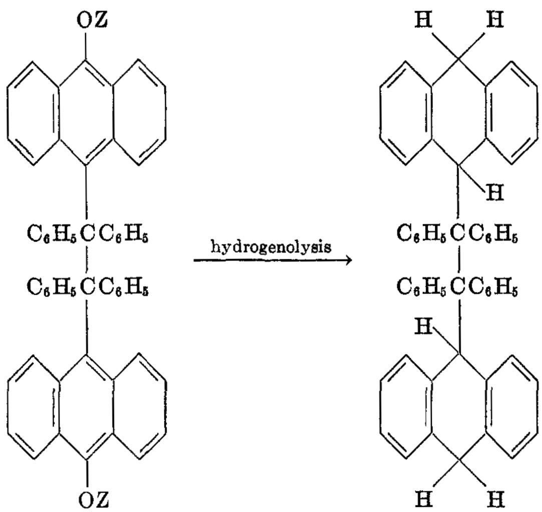


XXIV XXV

phenylbis(9,10-dihydro-9-anthryl)methane (XXVII) was isolated in 51 per cent yield. There has been no previous report of free-radical intermediates in lithium

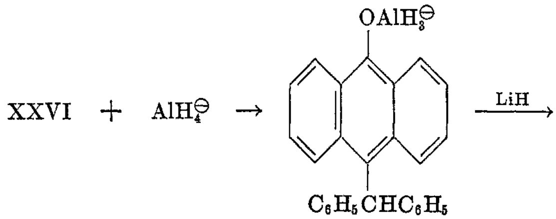


XXVI (Z = Li or H)

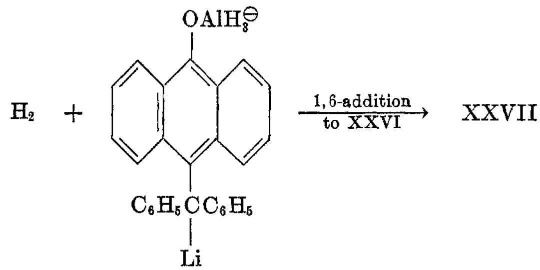


XXVII

aluminum hydride reductions (40) and an alternative explanation for the dimerization is more probable. The primary reduction product to be expected is XXVIII, which has a triphenylmethyl type structure and could be metalated through the agency of lithium hydride. The organolithium derivative XXIX could then add



XXVIII



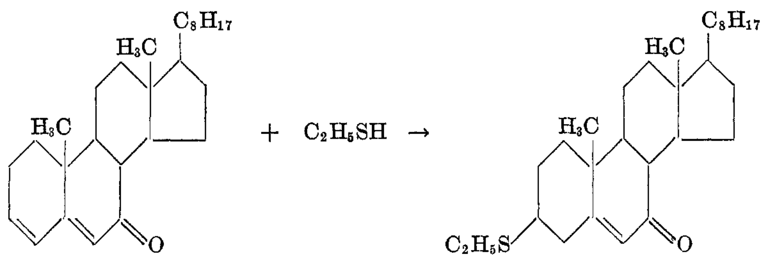
XXIX

1,6 to the starting material (XXVI), and the resulting intermediate would be converted to the observed product (XXVII) by hydrogenolysis.

V. STEREOCHEMISTRY OF 1,6-ADDITIONS

There are only three 1,6-additions where the stereochemistry of the product is defined. This situation of limited stereochemical information is not surprising, since the majority of 1,6-addition reactions do not produce an asymmetric atom. Compounds with long conjugated systems generally have few or no asymmetric centers and asymmetric induction is not operating.

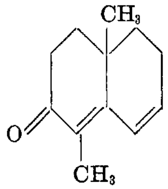
The steroid dienone 3,5-cholestadien-7-one (XXX) provides an excellent model to evaluate the stereochemistry of 1,6-additions. The 1,6-addition of ethanethiol produces a single product, 3β-ethylthio-5-cholesten-7-one (XXXI) in 91



XXX XXXI

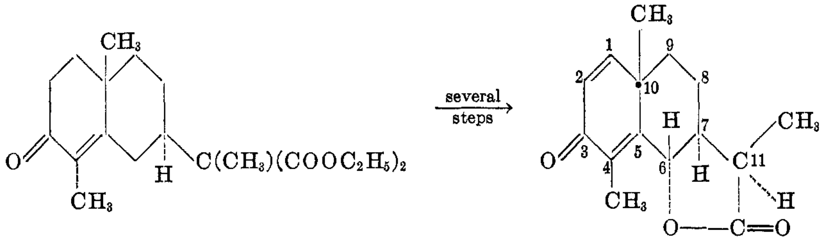
per cent yield (56). A single isomer is also produced by the addition of ethyl malonate to XXX; the adduct isolated in 87 per cent yield (50 per cent conversion) (55) was correlated with the known (8, 43, 66) 3β-cholesterylmalonic acid. The above two additions demonstrate that the 1,6-addition to dienones results in products with equatorial conformation of the entering groups.

The stereochemical results in the steroid series have been used to help define the stereochemistry of santonin (XXXII) (22, 24, 25, 70). The key step in the total synthesis of santonin (1, 50, 51) is the 1,6-addition of ethyl methylmalonate to 2-keto-1,4*a*-dimethyl-2,3,4,4*a*,5,6-hexahydronaphthalene (XXXIII); this addition establishes the configuration of the C_7—C_{11} bond in (−)β-santonin as shown in XXXII.



$+ \ CH_3CH(COOC_2H_5)_2 \ \rightarrow$

XXXIII



XXXII

VI. FACTORS FAVORING 1,6-ADDITION

It is premature to try to define in detail the steric and electronic factors which favor 1,6-addition over the equally possible 1,4-addition. There has been no kinetic study of any of the known 1,6-additions and only speculative mechanisms can be written. A treatment of part of the information on conjugate addition in terms of modern theoretical organic chemistry appears in a recent book (42).

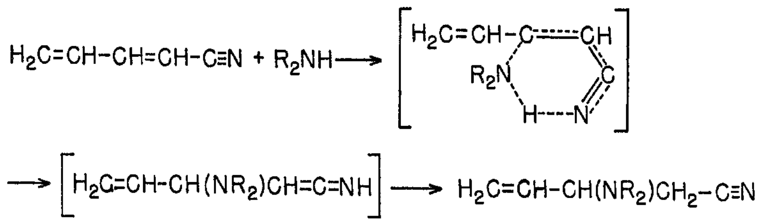
There is enough information on 1,6-additions to formulate qualitative concepts which aid in correlating the facts available at present. For any system there are three principal factors involved: (*a*) steric effects, (*b*) electronic effects, and (*c*) nature of the addenda; any one of these may predominate and control the course of the reaction.

The primary electronic factor which promotes 1,6-addition over 1,4-addition is the operation of terminal polarization of a freely conducting conjugated system. The facility with which 2,4-pentadienenitrile (VI) undergoes 1,6-addition, to the total exclusion of 1,4-addition, is due largely to this phenomenon. The terminal polarization of the system puts the major share of positive charge on the 5-position and facilitates nucleophilic attack at this position:

$$\underset{\text{VI}}{H_2C{=}CH{-}CH{=}CH{-}C{\equiv}N} \longrightarrow \overset{\delta^+}{H_2C}{\cdots}C{\cdots}C{\cdots}C{\equiv}\overset{\delta^-}{N}$$

$$\xrightarrow{R_2NH} \left[\underset{\oplus}{\overset{H}{R_2N}}{-}CH_2{-}CH{=}CH{-}CH{=}C{=}\underset{\ominus}{N}\right] \longrightarrow R_2N{-}CH_2{-}CH{=}CH{-}CH_2{-}C{\equiv}N$$

The operation of terminal polarization is sufficient to overcome the favorable energetics of cyclic transition states possible in 1,4-addition (49), but not likely



in 1,6-addition where an eight-membered ring would be required. All of the valid 1,6-addition reactions have as their main driving force the operation of terminal polarization.

Interesting results show up when the long conjugated system is substituted by replacing hydrogen atoms with methyl groups. The data in table 2 illustrate the effect of such substitution of alkyl 2,4-pentadienoates on the proportion of 1,4- and 1,6-addition. Substitution at the 3-position has little effect, but a substitution at the 4-position gives equal amounts of the 1,4- and 1,6-adducts. This result must be due to hyperconjugation, which reduces the degree of terminal polarization until addition at the 3- and at the 5-position is equally favored. When the methyl group is at the 5-position, hyperconjugation is operating to facilitate terminal polarization. However, a greater steric requirement for addition at the 5-position reduces the proportion of 1,6-adduct. The steric factor predominates when the 5-position is substituted with two methyl groups. Although terminal polarization is enhanced (so that no 1,4-addition takes place), the steric hindrance to attachment at the 5-position is large enough to prohibit addition.

In the series where the 5-position bears two methyl groups, substitution of the 2-position with an additional electron-withdrawing group does not activate the system sufficiently for addition until the groups on the 2-position are identical.

TABLE 2

Addition of alkyl malonates or ethyl cyanoacetate to substituted alkyl 2,4-pentadienoates

$$R'''''\!-\!\overset{R''''}{\underset{|}{C}}\!=\!\overset{R'''}{\underset{|}{C}}\!-\!\overset{R''}{\underset{|}{C}}\!=\!\overset{R'}{\underset{|}{C}}\!-\!COOR$$

Structure	Per Cent of Addition		Reference
	1,4	1,6	
R = CH_3, R′ = R″ = R‴ = R⁗ = R′′′′′ = H	0	75	(29)
R = R′′′′′ = CH_3, R′ = R″ = R‴ = R⁗ = H	7–10	70–73	(31)
R = C_2H_5, R′′′′′ = CH_3, R′ = R″ = R‴ = R⁗ = H	10 ± 2	66 ± 2	(11)
R = C_2H_5, R′ = R′′′′′ = CH_3, R″ = R‴ = R⁗ = H	2	65	(11)
R = C_2H_5, R″ = R′′′′′ = CH_3, R′ = R‴ = R⁗ = H	2	63	(11)
R = R‴ = R′′′′′ = CH_3, R′ = R″ = R⁗ = H	ca. 50	ca. 50	(31)
R = R⁗ = R′′′′′ = CH_3, R′ = R″ = R‴ = H	0	0	(62)
R = R⁗ = R′′′′′ = CH_3, R′ = C≡N, R″ = R‴ = H	0	0	(62)
R = R⁗ = R′′′′′ = CH_3, R′ = $COOCH_3$, R″ = R‴ = H	80	0	(62)

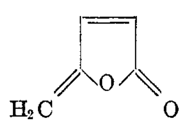
The symmetrical substitution provides extra resonance with increasing polarization. The steric effect of the two methyl groups at the 5-position prohibits 1,6-addition, but the shorter 3-position to oxygen polarization is increased enough to produce high yields of the 1,4-adduct.

Substitution at the 5-position of conjugated dienecarbonyl systems with aromatic groups interrupts the freely conducting conjugated system and promotes 1,4-addition. The compound 1,5-diphenyl-2,4-pentadien-1-one (cinnamylacetophenone) always undergoes conjugate addition by a 1,4-process (3). The resonance energy of the phenyl-vinyl conjugation is high enough to limit polarization at the 5-position; the 3-position to oxygen polarization predominates with the resulting 1,4-addition.

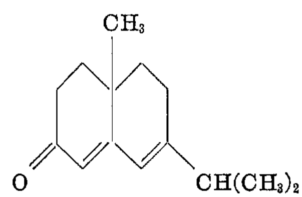
The principal steric factor which favors 1,6- or 1,4-addition is the failure of the latter to take place at a bridgehead double bond in polycyclic systems. This is best illustrated in the steroids. Steroid-4-en-3-ones do not add mercaptans by a 1,4-process under any conditions yet reported (41, 57). The facile 1,6-addition of mercaptans to steroid-3,5-dien-7-ones has been discussed earlier in this review.

There has been no systematic study of the role of the addenda in determining the proportion of 1,6- and 1,4-addition. The majority of addenda are nucleophilic reagents and would be expected to react more readily as their nucleophilicity increased and lead to a higher proportion of 1,6-addition.

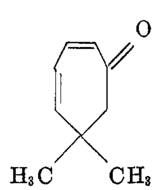
The number of natural products having multiple conjugated systems is impressive. Among the more familiar examples are vitamin A, many carotenoids, the D vitamins, thujic acid, and sorbic acid. Less familiar examples of natural products having conjugated systems capable of 1,6-addition are protoanemonin (XXXIV), β-cyperone (XXXV), eucarvone (XXXVI), lachnophyllum (XXXVII), and anacylin (XXXVIII). It is tempting to speculate that these exotic



XXXIV
Protoanemonin



XXXV
β-Cyperone



XXXVI
Eucarvone

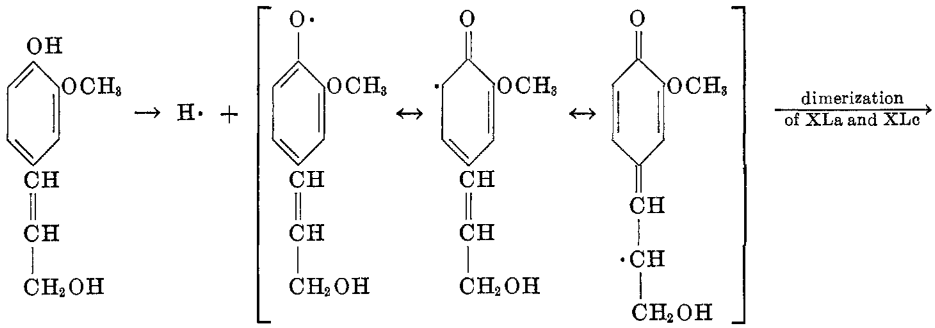
$C_3H_7(C\equiv C)_2CH=CHCOOCH_3$

XXXVII
Lachnophyllum

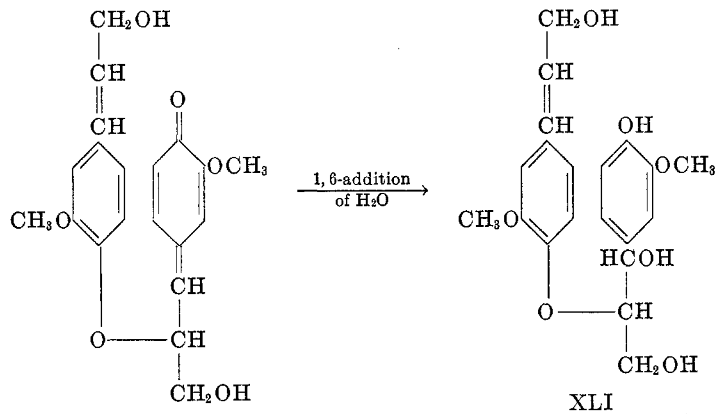
$HC\equiv CCH_2CH_2CH=CHCH=CHCONHC_4H_9$

XXXVIII
Anacylin

structures may owe their biological activity to enzyme-substrate interactions involving the conjugated system acting by a 1,6-process. The only example of a biologically significant 1,6-addition appears in an explanation of the lignification process (28, 35). Among the products from the treatment of coniferyl alcohol (XXXIX) with mushroom extract is α-guaiacylglycerol β-coniferyl ether (XLI) (36, 37), the formation of which is rationalized on the basis of the sequence illustrated by formulas XXXIX to XLI.



XXXIX XLa XLb XLc



XLI

The author is indebted to John F. Carson, Frank C. Lamb, Byron Riegel, and H. William Sause for critical reading of the manuscript. The drawings were made by Mrs. N. Floy Bracelin.

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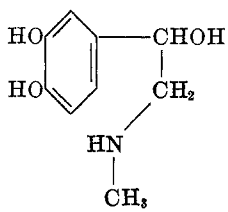
I. Introduction

The development of characteristic colors during the oxidation of aqueous extracts of mammalian suprarenal capsules was first observed over a century ago. In 1856 Vulpian reported that (*a*) on standing in air, the extract soon became rose-carmine in color, (*b*) the colors could also be produced by the action of certain oxidizing agents, and (*c*) although small quantities of alkali facilitated the reaction, larger quantities apparently hindered it (258, 259). It was nearly forty years after these observations were made that the powerful physiological activity of the extracts was first demonstrated (188). At the turn of the century the active principle was isolated, first as its benzoyl derivative (1, 4) and then in crystalline form (244, 245). The structure of the active molecule was shown to be β-hydroxy-β-(3,4-dihydroxyphenyl)-*N*-methylethylamine (I), and this was soon confirmed by an unambiguous synthesis (71, 241). Abel gave the name



I

"epinephrine" to the active substance that was liberated from the benzoate by saponification with dilute sulfuric acid (1, 2). Takamine named the active principle that he isolated from the suprarenal gland "adrenaline" (244), and about the same time von Fürth isolated a physiologically active iron derivative of the substance and called it "suprarenin" (102, 103, 104). Later these products were shown to be more or less pure varieties of the one active constituent (3). Throughout this review the term "adrenaline" will be used. [See Aldrich (6) for a review of the early literature on adrenaline.]

The formation of highly colored oxidation products from adrenaline was reported in the early investigations into the chemistry of this substance. These observations rapidly led to the development of empirical assay methods for this physiologically important compound (see Section VIII,B). The strong yellow-green fluorescence developed during the oxidation of adrenaline in alkaline solution, first noted in 1918 (157), has led to the present-day chemical estimations of adrenaline based on spectrofluorimetric methods (see Section VIII,B). The oxidation products mentioned above were in fact adrenochrome [i.e., 2,3-dihydro-3-hydroxy-*N*-methylindole-5,6-quinone (II) or its 2-iodo derivative, the former being deep red and the latter violet in solution]; the fluorescent material was

THE CHEMISTRY OF ADRENOCHROME AND RELATED COMPOUNDS

R. A. HEACOCK

Psychiatric Research Unit, University Hospital, Saskatoon, Saskatchewan, Canada

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