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RESPUESTA A ARTICULO 46

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- **Lee et al. Bull. Korean. Chem. Soc. 2002, 23, p. 19-20**
- **Williams et al. Chem Rev. 1981, 81, 589-636**

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Investigation of the Cyclization of *N*-(2-Hydroxyethyl)-*N'*-phenylthioureas: Mitsunobu Conditions vs TsCl/NaOH System

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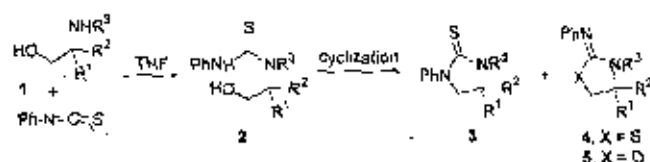
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Keywords: *N*-(2-Hydroxyethyl)-*N'*-phenylthioureas, Mitsunobu reaction, TsCl/NaOH.

The Mitsunobu reaction is a mild way to convert an alcohol into a wide range of functionality.¹ In general, this method proves efficacious for the acidic component ($pK_a \sim 8$) of the form of amides,² phthalimides,³ *N*-alkylsulfonamides,⁴ *N*-methyltrifluoromethanesulfonamides,⁵ or hydrazoic acid,⁶ providing useful yields under neutral reaction conditions. In the intramolecular Mitsunobu reaction of *N*-(2-hydroxyethyl)amides and *N*-(2-hydroxyethyl)thioamides having ambident nucleophile, *O*-cyclized products⁷ and *S*-cyclized product^{7b} are generally obtained in preference to *N*-cyclized products, respectively. Recently we reported that 2-phenylamino-2-oxazolines were prepared by the cyclization of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas using TsCl and NaOH.⁸ This reaction proceeded via cyclodesulfurization to regiocontrolled *O*-alkylation products. To the best of our knowledge, no Mitsunobu reaction of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas has been reported in the literature so far.⁹ Therefore, the behavior of ambident nucleophile in the Mitsunobu-mediated intramolecular cyclization of *N*-(2-hydroxyethyl)thioureas **2** was investigated to compare the results using TsCl and NaOH (Scheme 1). In addition, mechanistic investigation of Mitsunobu conditions and TsCl/NaOH system was also disclosed.

N-(2-hydroxyethyl)thioureas **2** as substrates were readily prepared from reaction of the corresponding 1,2-aminoalcohols with phenyl isothiocyanate in THF at room temperature in good yields.¹⁰ The Mitsunobu reaction was achieved with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF. The reactions were complete within 30 min at room temperature. The intramolecular Mitsunobu reaction of various substrates **2a-2h** was examined. The results are shown in Table 1. The Mitsunobu reaction furnished mainly the mixture of *N*- and *S*-cyclization (entries 1-8). In the case of **2d** and **2e** a small amount of *O*-alkylation products were formed (entries 4-5). On the other hand, using TsCl and NaOH the regioselectivity of cyclization was depending on the *N*-substituted group. That is, **2a-2e**



Scheme 1

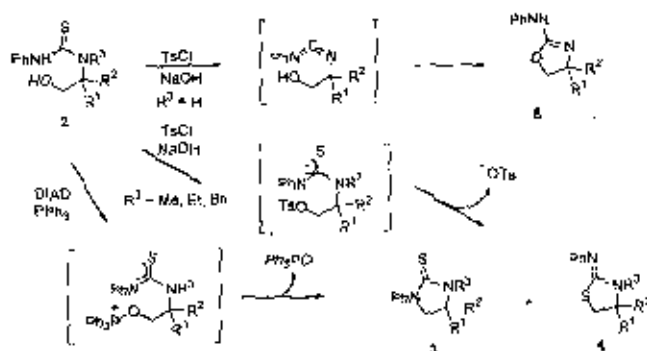
Table 1. Cyclization of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2**

Entry	Substrate	R ¹	R ²	R ³	Product ratios ^a	
					Mitsunobu reaction	TsCl/NaOH ^b
1	2a	H	H	H	3a/4a/5a	69/31/0
2	2a	Me	H	H	3b/4b/5b	72/28/0
3	2c	Et	H	H	3c/4c/5c	79/21/0
4	2d	(S)-i-Pr	H	H	3d/4d/5d	70/13/17
5	2e	Me	Me	H	3e/4e/5e	51/32/17
6	2f	H	H	Me	3f/4f/5f	80/20/0
7	2g	H	H	Et	3g/4g/5g	89/11/0
8	2h	H	H	Bn	3h/4h/5h	95/5/0

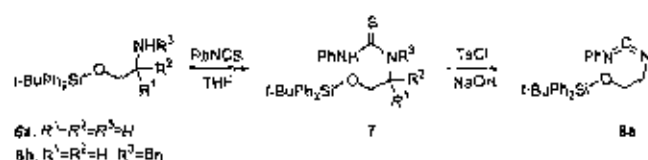
^aThe ratio of the crude mixtures was determined by ¹H NMR. ^bFor isolated yields, see: Ref. 8. ^cFor procedure for Mitsunobu reaction, see: Ref. 14.

prepared from *N*-unsubstituted aminoalcohols ($R^3 = H$) proceeded to the regiocontrolled *O*-cyclization (entries 1-5) and **2f-2h** prepared from *N*-substituted aminoalcohols gave the mixture of *N*- and *S*-cyclization as the Mitsunobu reaction rather than *O*-cyclization (entries 6-8). The significant difference of the reaction pathway of various thioureas **2** was unique to TsCl/NaOH system and was not observed in the Mitsunobu condition.

Mitsunobu of thioureas such as **2** almost might proceed through *N*- or *S*-nucleophilic attack of thiourea upon the oxyphosphonium intermediate to produce the mixture of *N*- and *S*-alkylation product as delineated in Scheme 2. A small amount of *O*-alkylation in **2d-2e** might occur through carbodiimide intermediate.⁹ Using TsCl and NaOH the mechanism



Scheme 2



Scheme 3

for the formations of *O*-, *N*-, and *S*-cyclized products could be proposed as follows. The reaction might proceed to two directions such as the cyclodesulfurization or the cyclodehydration to be strongly influenced by the R^3 group of thioureas (Scheme 2): (i) in the case of 2a-2e ($R^3=H$), the reaction pathway of carbodiimide¹¹ intermediate is leading to oxazoline derivatives 5. (ii) in the case of 2f-2h ($R^3=Me$, Et , and Bn), the tosylate is formed and anion delocalized on nitrogen and sulfur can attack the tosylate to provide the mixture of *N*-cyclized product 3 and *S*-cyclized product 4. The remarkable *O*-cyclization selectivity in *N*-phenylthioureas 2a-2e may be due to a carbodiimide intermediate because a carbodiimide intermediate can be formed only in case of $R^3=H$. To confirm the proposed pathway, *O*-(*t*-butyldiphenylsilyl) (TBDPS) protected thiourea 7 was prepared from *O*-TBDPS protected aminoalcohols 6 and phenyl isothiocyanate,¹² followed by cyclization using $TsCl$ and $NaOH$ (Scheme 3). In the case of 7a the carbodiimide intermediate was isolated as expected.¹³ With 7h no reaction such as tosylation occurred and the starting material was recovered. Thus, 7h prepared from *N*-substituted aminoalcohols did not provide carbodiimide or tosylated thiourea. From these results our proposed reaction mechanism in $TsCl$ and $NaOH$ might be possible.

In conclusion, our study on *N*-(2-hydroxyethyl)-*N'*-phenylthioureas demonstrates the main formation of *N*-cyclized product from thioureas 2 under Mitsunobu conditions. Cyclization of 2a-2e under $TsCl/NaOH$ results in regiocontrolled 2-amino-2-oxazolines via carbodiimide intermediate.

Acknowledgment. This work was supported by the grant No. (2001-1-12300-004-1) from the Basic Research Program of the Korea Science and Engineering Foundation and by the grant from the Brain Korea 21 program of the Ministry of Education.

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- Preparation of *N*-(*t*-butyldiphenylsilyloxyethyl)thiourea 7a. To a stirred solution of 2-(*t*-butyldimethylsilyloxy)ethylamine 6a (0.21 g, 0.63 mmol) in THF (5 mL) under nitrogen at room temperature was added and triethylamine (0.11 mL, 0.76 mmol) and phenyl isothiocyanate (0.08 mL, 0.76 mmol). The reaction mixture was stirred for 5 min and evaporated. The crude product was purified by column chromatography to give the requisite product 7a. Yield 90%; $R_f=0.5$ (ethyl acetate/hexane 1 : 4); 1H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, bs, PhNH), 7.54-7.25 (15H, m, 3Ph), 6.67 (1H, bs, NH), 3.82-3.76 (4H, m, C_2H_4), 0.92 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 136.0, 135.3, 130.2, 129.9, 127.8, 127.3, 125.3, 62.0, 47.5, 26.6, 19.0.
- Phenyl *t*-butyldiphenylsilyloxyethylcarbodiimide 8a. To a stirred solution of thiourea 7a (0.10 g, 0.23 mmol) in THF (5 mL) at room temperature was added a solution of $NaOH$ (0.02 g, 0.55 mmol) in water (1 mL) and $TsCl$ (0.05 g, 0.28 mmol) in THF (2 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 1 h at room temperature, quenched with water (20 mL), and extracted with ether (20 mL $\times$ 3). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the carbodiimide product 8a. Yield 70%; $R_f=0.8$ (ethyl acetate/hexane 1 : 4); IR ($CDCl_3$, cm^{-1}) 2142 (N=C=N); 1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (4H, m, 2Ph), 7.42-7.32 (6H, m, 2Ph), 7.28-7.22 (2H, m, Ph), 7.13-7.08 (3H, m, Ph), 3.84 (2H, t, OCH_2 , $J=5.4$ Hz), 3.48 (2H, t, CH_2N , $J=5.4$ Hz), 1.02 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 136.9, 135.6, 133.3, 129.7, 129.2, 127.7, 124.5, 123.8, 63.8, 49.0, 26.7, 19.1.
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Carbodiimide Chemistry: Recent Advances

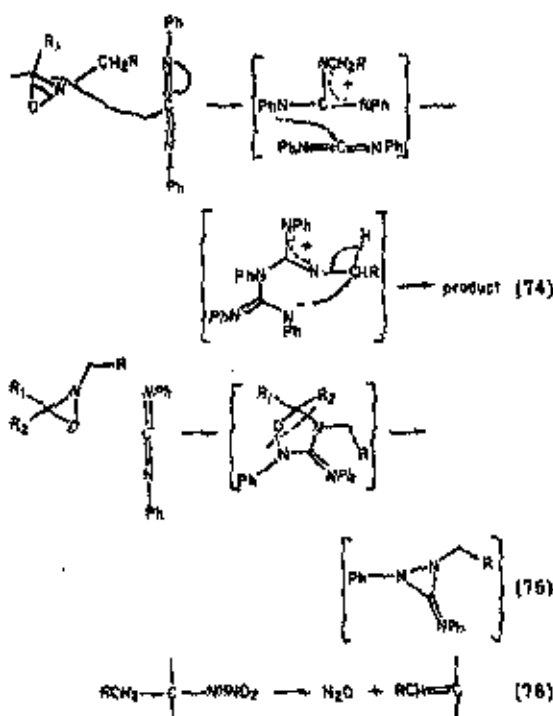
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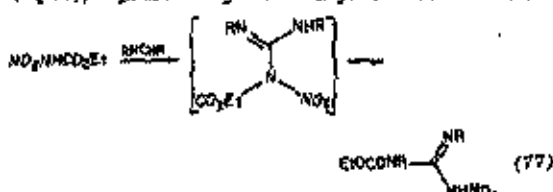
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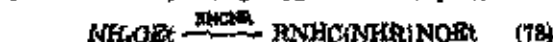
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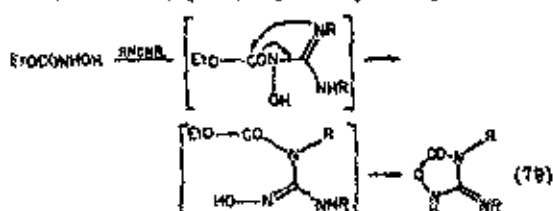
Other reactions with nitramine nucleophiles involve the formation of a nitroguanidine from *N*-nitrourethane (eq 77),²⁴⁴ presumably via an acyl-shift reaction from



the initially formed adduct. *O*-Alkylhydroxylamines yield the corresponding oxyguanidines (eq 78),²⁴⁵ and

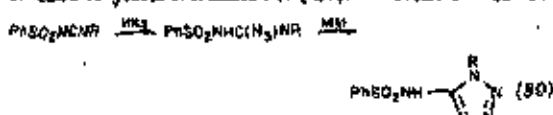


N-(ethoxycarbonyl)hydroxylamine yields a 1,2,4-oxadiazolin-5-one (eq 79),²⁴⁶ probably through attack of

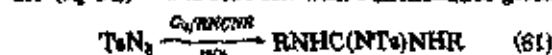


nitrogen on the central carbon followed by an acyl shift and a cyclization. Reactions of carbodiimides with other hydroxylamines are noted.²⁴⁷⁻²⁵⁰

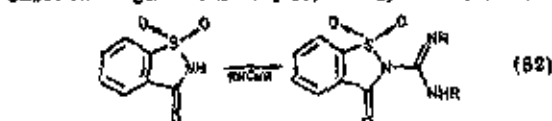
Cyanoguanidines may be formed from cyanamide and carbodiimides.²⁵¹ Hydrazoic acid reacts with carbodiimides to yield tetrazoles (eq 80).²⁵² Reaction of car-



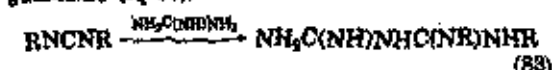
bodiimides with tosylazide is catalyzed by copper powder (eq 81),²⁵³ and reaction with sulfonamides gives



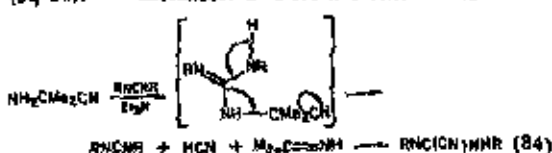
substituted guanidines (eq 82).²⁵⁴ 1,2-Di-substituted



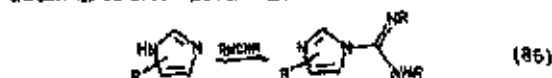
biguanidines may be prepared from carbodiimides and guanidine (eq 83).^{255,256}



Anilines react with carbodiimides to give the corresponding *N*-arylguanidines^{257,258} and (dimethylamino)-acetonitrile reacts to give α -cyano-*N,N*-dialkylformamidine, probably through an initial guanidine adduct (eq 84).²⁵⁹ Imidazole and its derivatives react with

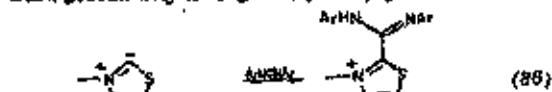


carbodiimides to the corresponding guanidine (eq 85).²⁶⁰ Polyguanidines have been prepared by the addition of biscarbodiimides with diamines.^{260a}



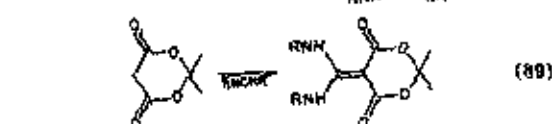
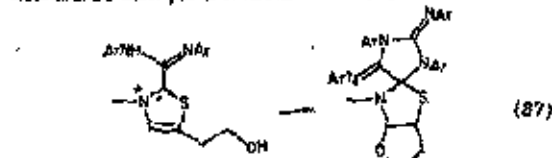
a. Carbon Nucleophiles

Carbon nucleophiles form C-C bonds with carbodiimides. Reaction with thiazolium salts yields a 1:1 adduct, presumably through the ylide (eq 86),²⁶¹ and a 1:2



adduct is obtained with concomitant saturation of the thiazoline ring (eq 87).

Similar addition reactions occur between indolizine, Meldrum's acids, and carbodiimides (eq 88 and 89).^{262,263}



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I. Introduction

The heterocumulenes form a large class of unsaturated compounds based on the allene structure (Table I). Some of the members of this class are very well-known whereas others are relatively unstable or have only been detected as transients. Carbodiimides, despite being relatively stable molecules, have only in the past 20 years become other than chemical curiosities. General use of these species was stimulated by Khorana's pioneering investigations¹ of their action in peptide and nucleotide syntheses. Even a decade and a half ago at the time of the second comprehensive review,² the only major use of carbodiimides was in peptide and nucleotide coupling reactions. Since that time the discovery of catalysts to convert isocyanate to carbodiimide with the loss of carbon dioxide has allowed the industrial scale production of carbodiimides and their availability for use in many manufacturing processes. The incorporation of carbodiimides into polymeric materials probably takes the bulk of world production. Other growing points in carbodiimide chemistry include the continued use of synthesis of nucleotides and peptides, heterocycle synthesis, oxidation with dimethyl sulfoxide, permease inhibition, biological modification, and cycloaddition reactions.

In this review we shall cover the literature comprehensively from 1965 until mid-1980 and will assume that the reader is cognizant of the material in the two earlier reviews.^{1,2} During the period under consideration several large fields have opened up, such as in permease inhibition where carbodiimides have been used extensively and where carbodiimide chemistry is not of

TABLE I. Some Heterocumulenes

$O=N=O$	$O=C=O$	$R_1C=C=O$
$O=S=O$	$S=C=S$	$R_1C=C=S$
$RN=S=NR$	$S=C=O$	$R_1C=S=O$
$RN=S=O$	$S=C=NR$	$R_1C=SO_2$
$RN=SO_2$	$O=C=NR$	$R_1C=C=NR$
$RN=PO_2$	$RN=C=NR$	$O=SO_2$
$RN=PO$	$O=P=O$	$RN=P=NR$
NR_2	O	NR_2
$R_1C=S=CR_2$	$RN=P=S$	$R_1C=N=O$
$R_1C=N=NR$	NR_2	R
$R-N=NR$	$R_1C=N=O$	$N=N=O$
O	$R_1C=N=NR$	$R-N=N=N$
$R-S=N=O$	NR_2	
	$R-N=N-R$	
	S	

primary importance; references not relevant to the chemistry of carbodiimides will therefore only be mentioned in passing.

Probably the most important feature of carbodiimides relating to their wide use in their relatively low uncatalyzed reactivity which allows easy storage. The driving force for most of the reactions is the very powerful saturating ability of the $C=N$ bond and in the case of dehydrations the very stable product. The carbodiimide fulfills most of the properties of a perfect reagent: it is unreactive until a catalyst is added but provides a powerful driving force for a reaction to proceed. A drawback to the use of carbodiimides is their powerful action as contact allergens (particularly the lipid-soluble reagents);³ this need only be obvious to the careless worker.

II. Synthesis and Formation of Carbodiimides

A. General

A useful review on carbodiimide synthesis has been published.⁴

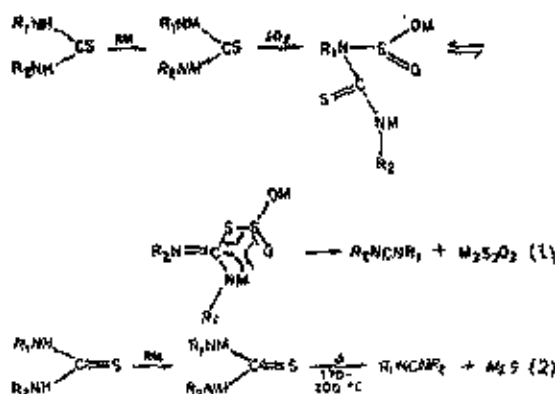
Carbodiimides may be constructed by three major processes, including a preformed $N-C-N$ skeleton, addition of N to $C=N$, and an $N + C + N$ scheme.

The classical process involves elimination of ligands from the $N-C-N$ skeleton; more recently electrophilic substitution into an existing carbodiimide has been employed. Addition of N to CN is the basis of the modern exchange and catalytic processes. The $N + C + N$ method involves preassociation of C and N followed by further addition of the N grouping.

B. Metal and Metal Oxide Preparations from Thioureas

Lead, silver, and mercury oxides have been used to abstract H_2S from thioureas⁵⁻¹¹ via classical method.¹² Active aluminum oxide has also been utilized with thioureas.¹³ A novel method has involved the formation of the amide salt from thioureas and Grignard reagent or butyllithium followed by attack of sulfur dioxide (eq 1).¹⁴

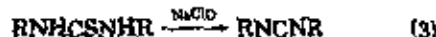
A further interesting method involving metals is the decomposition of the metal salt to yield metal sulfide and carbodiimide in 90-60% yield (eq 2).¹⁴ The reaction with lithium is accelerated by CS_2 probably via a mechanism similar to eq 1. A similar method involves trialkyltin oxide as the "metal salt".^{15,16} N-Saccha-



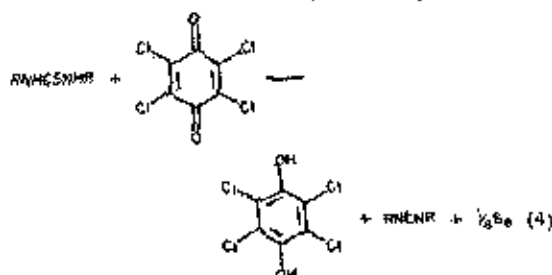
ryl-*N'*-phenylcarbodiimide has been prepared from the urea by heating with lithium carbonate.^{16b}

C. Oxidation of Thiouras

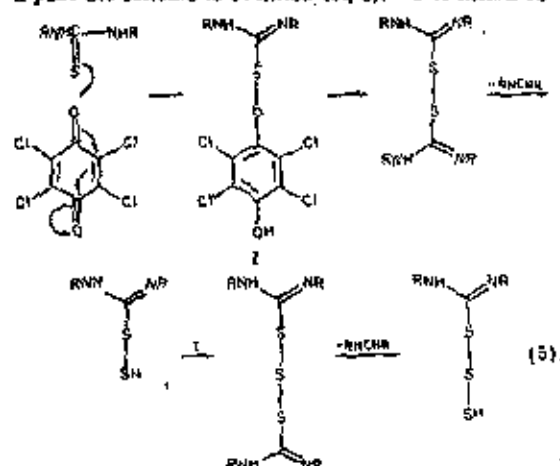
Sodium hypochlorite has continued to be a good oxidizing agent for production of carbodimides from thioureas (eq 3),¹⁷⁻²¹ and *N*-bromosuccinimide has been



used to good effect.²² Dehydrodesulfuration with a quinone has provided an interesting pathway to carbodiimides²³ with the formation of a quinol and elemental sulfur; the stoichiometric equation (eq 4) masks a



somewhat complicated mechanism. The mechanism involves a 2:1 adduct of thiourea with the quinone, and a possible scheme is outlined (eq 8). The initial re-



action of thiourea and quinone yields a sulfonate ester (3) which acts as a carrier. The final step in the reaction

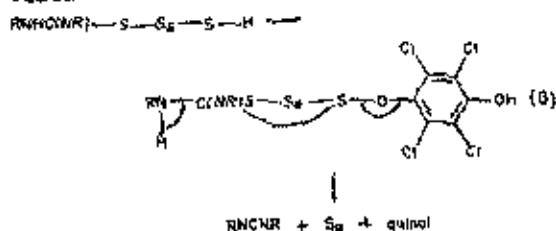


Andrew Williams was born in 1907 at Whiston, Middlesex, and obtained his B. Phil from Oxford under Dr. Gordon Lowe in 1934. He has been at Kent since 1938 and has studied at Northwestern under Myron Bender and at Brandeis under William Jenkins.

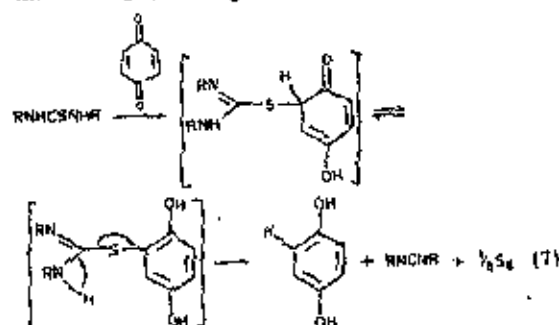


Abdullah Tashir Ibrahim was born in Iraq in 1952 and gained his B.Sc. from Baghdad University in 1974. He obtained his M.Sc. from Baghdad in 1976 under the supervision of Dr. M. Shamsel and his Ph.D. from Kent in 1980.

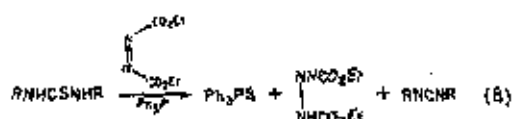
must involve quinone (eq 6) in a cyclization to split out sulfur.



Another method with *p*-quinol involves addition of the thiouras to the ring followed by elimination (eq 7).²²



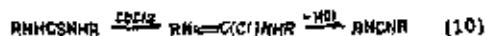
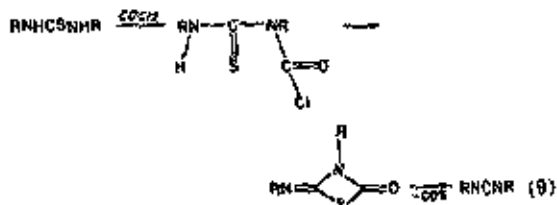
Diethyl azodicarboxylate reacts with thiourea in the presence of triphenylphosphine to yield carbodimide in good yield (eq 8).²⁻⁵ The sulfur is recovered as phosphine sulfide.



D. Reactions of Thioureas with Acid Halides

a. Phosgene

Reaction of thioureas with phosgene in the presence of base gives very good yields of carbodiimides.³⁷⁻³⁹ The mechanism of the reaction is not understood but could involve formation of a four-membered ring followed by expulsion of COS (eq 9) or go through a chloro imide intermediate (eq 10).

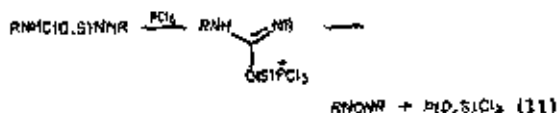


b. Sulfur Acid Halides

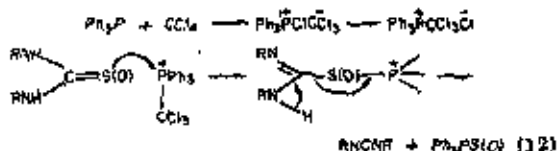
Carbodiimides may be obtained by reaction of thioureas with thionyl chloride, sulfonyl chloride, chlorosulfonic acid, SOCl_2 and SO_2Cl_2 followed by neutralization with base.^{35,36}

c. Phosphorus Halides

Ureas and thioureas may be dehydrated or dehydrothiofurfurated by phosphorus halides, which most likely provide a good leaving function (eq 11).³⁷⁻⁴⁰



An interesting variation of the above method involves the action of triphenylphosphine, carbon tetrachloride, and tertiary amines on ureas and thioureas (eq 12).⁴¹



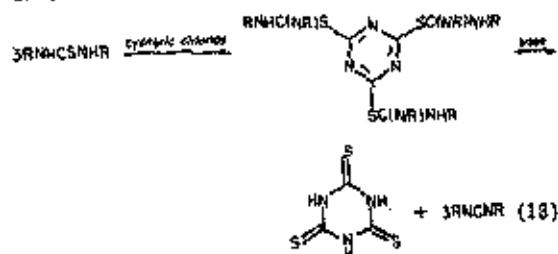
The stability of the PO and PS bonds provide the driving force for these reactions.

E. Synthesis from Ureas and Thioureas by Elimination

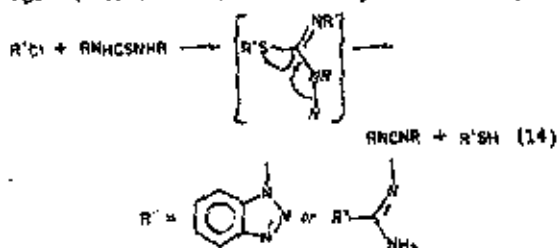
a. Heterocyclic Halides

Cyanuric chloride reacts with thioureas to yield an *S*-heteroarylisothiourea which may be split with base to eliminate a thiol; this procedure is the basis of a synthetic method (eq 13) giving yields of up to 80%⁴²⁻⁴⁵ (eq 13). Similar methods based on chloropyrimidines,⁴⁷

N-phenylbenzimidoyl chloride,⁴⁷ 2-chlorobenzothiazole,⁴⁸ and 2-chloropyridinium ion⁴⁹ give good yields of carbodiimide. 1-Chlorobenzothiazole⁵⁰ and *N*-

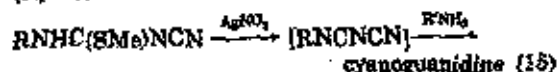


chloroimidines⁵¹ have been used essentially as oxidizing agents; a reasonable mechanism is postulated in eq 14.

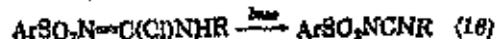


b. Simple Elimination Reactions

Elimination of thiol from *S*-alkyl- or -arylisothioureas has not been used preparatively except where these species are intermediates; carbodiimides are found as intermediates in the decomposition of these species (eq 15).⁵²



Direct elimination of HCl from chloroformamidines has been used to form sulfonylcarbodiimides (eq 16).^{53,54}

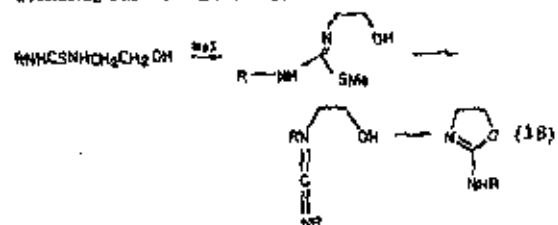


The dehydration of ureas with P_2O_5 and by azeotropic distillation has also been used to prepare carbodiimides.^{55,56}

The mechanism of thiol formation from isothiouronium salts in base has been shown to involve cyanamide in the case of the parent thiourea⁵⁷ and presumably a carbodiimide in the case of symmetrically di-substituted thioureas (eq 17).



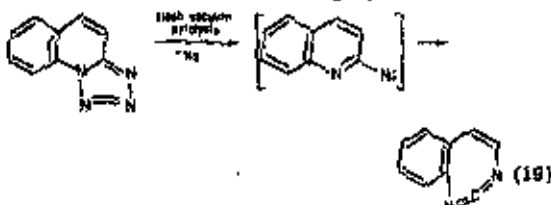
Carbodiimide is probably involved as an intermediate in the cyclization of 2-amino alcohols to give 2-amino-2-oxazepines (eq 18).⁵⁸ There is, however, no definitive evidence for this mechanism.



F. Fragmentation Reactions

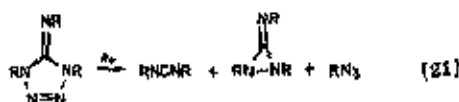
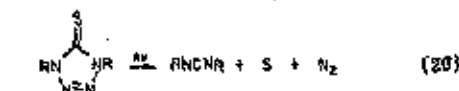
a. Five-, Six-, and Seven-Membered Rings

Fragmentations of heterocyclic species to yield carbodiimide and easily removed byproduct have been exploited extensively for synthesis. Tetrazoles have been used to synthesize a novel 7-membered endocyclic carbodiimide (eq 19) through a proposed nitrene.⁶⁰ A

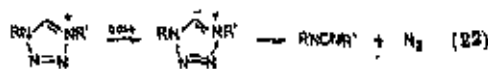


similar reaction involving carbodiimide formation is also thought to involve a nitrene intermediate.⁶⁰

Tetrazole species have also been used in the synthesis of carbodiimides; photolysis of 2-tetrazolines yields carbodiimides in reasonable yield (eq 20 and 21).⁶¹ The



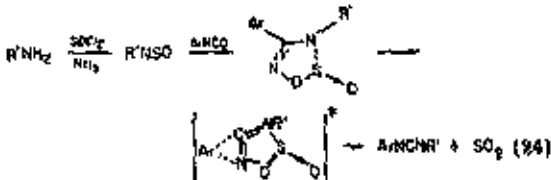
ylide from a tetrazolium ion also fragments to yield carbodiimide (eq 22).⁶²



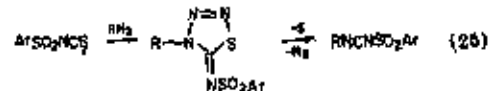
A limited synthesis related to eq 22 is of an acyl-carbodiimide from an oxadiazolium ion (eq 23).^{62,63}



The extrusion of SO₂ from 1,2,3,5-oxathiadiazole 2-oxides⁶⁴⁻⁶⁷ involves rearrangement, probably via a multicenter transition state (eq 24).⁶⁴

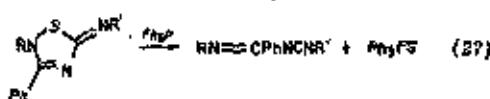


1,2,3,4-Thiadiazolines have been used to prepare carbodiimides where sulfur and nitrogen are fragmented (eq 25).⁶⁸

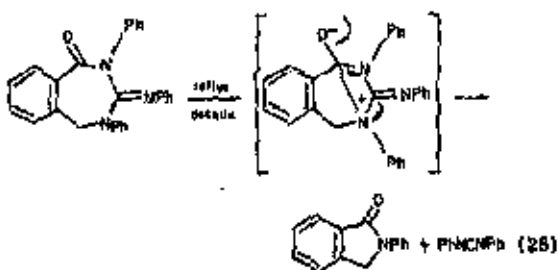


Elimination of CO₂ from 1,2,4-oxadiazolin-5-ones and their N-alkyl salts yields a carbodiimide in good yield (eq 26).⁶⁹

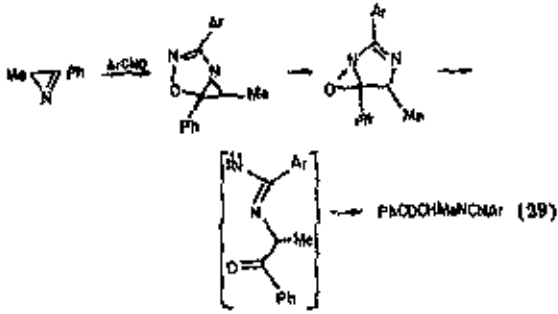
Triphenylphosphine abstracts sulfur from a thiadiazole (eq 27).⁷⁰



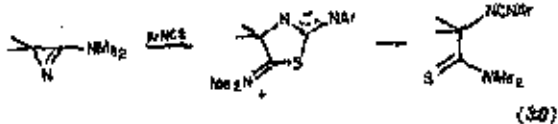
A novel degradation of a diazepine has been reported where the product is a carbodiimide; the mechanism is believed to involve a bicyclo derivative (eq 28).⁷¹



Cycloaddition of a hindered cyanate with a 2H-azirine yields an oxadiazoline which opens probably through a nitrene intermediate to give a carbodiimide (eq 29).⁷²

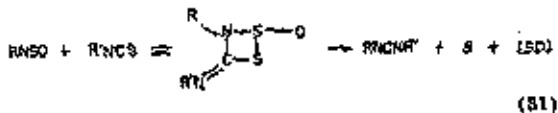


A similar cycloaddition reaction of an azirine with arylisothiocyanate yields a carbodiimide, probably through ring opening of a thiazolium intermediate (eq 30).⁷³

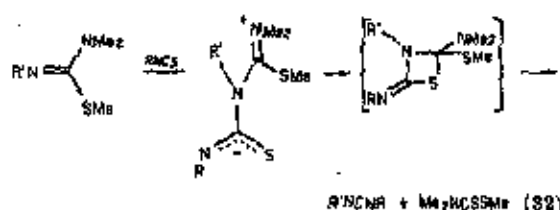


D. Four-Membered-Ring Heterocycles

This fragmentation reaction is essentially the reverse of a [2 + 2] cycloaddition which is considered later in this review. A simple reaction which, however, gives poor yields is the coupling of N-sulfinylamines with isothiocyanates to give a four-membered heterocycle which extrudes S and [SO] (eq 31).⁷⁴ Dithiocarbamates



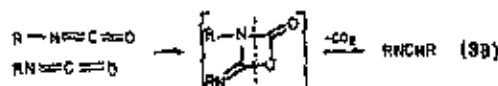
and carbodiimides are the products from the reaction of isothiocyanate derivatives and isothiocyanates (eq 32).⁷⁵



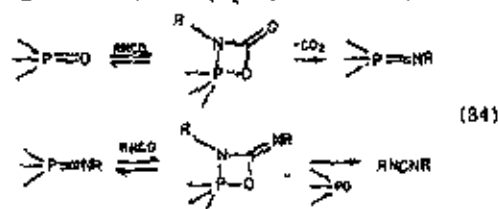
G. Catalytic Methods

a. Phosphorus Catalysts

The reaction of two molecules of isocyanate to yield one of carbodiimide with the extrusion of CO_2 is essentially a cyclization procedure (eq 38),^{18,77} and it



may be catalyzed by compounds with $P=X$ groups. This approach to synthesis has a major disadvantage in that only symmetrical carbodiimides may be prepared. There is now considerable evidence in favor of the original mechanism (eq 34).^{18,78} The reaction is



catalyzed by pentavalent phosphorus compounds which may be ring or linear and which may possess different ligands.⁸⁰⁻⁸² The formation of the $\pi-P=NR$ intermediate is confirmed by its synthesis and use with $R'NCO$ as a method for forming mixed carbodiimides (eq 35) in up to 70% yield.^{84,85} This method allows the for-

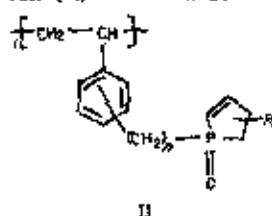


mation of unsymmetrical carbodiimides which are not available from the simpler catalytic procedure and has been reported earlier.⁸⁶ The mechanism of eq 34 is consistent with the observation that ^{18}O -enriched phosphine oxide catalysts yield CO_2 with considerable ^{18}O incorporation.⁸⁷

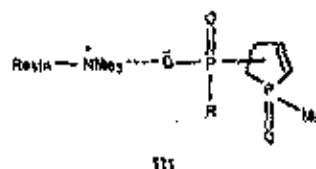
Arsines⁸⁸ and vanadium and tungsten oxides⁸⁹ have proved to be efficient catalysts of the decarboxylation of isocyanates.

b. Solid-Phase Catalysts Based on Phosphorus

Attachment of the phosphorus catalyst to a solid phase has been attempted, and an example of such a catalyst is given (II)^{100,101} in which the phosphorus



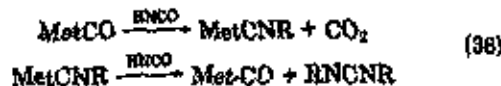
bicyclic is covalently attached to a styrene/divinylbenzene matrix. An alternative solid-phase catalyst involves binding an anionic species to an anion-exchange resin (III).^{102,103} Arsine oxides bound covalently



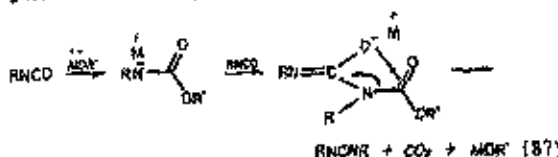
to polystyrene matrices have also been successfully used as carbodiimide forming catalysts.^{104,105}

c. Organometallic Catalysts

Iron pentacarbonyl and other metal carbonyls catalyze the decarboxylation of isocyanates. It is thought that a cycloaddition reaction occurs with the expulsion of carbon dioxide (eq 36).^{106,107} Metallic salts of alcohols

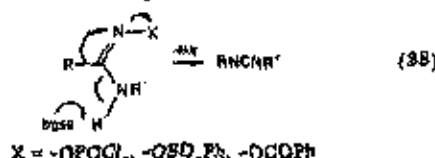


are also effective catalysts for the decarboxylation of isocyanates, and carbamate esters have been proposed as reactive intermediates (eq 37).^{108,109} up to 80% yields have been observed with these catalysts.

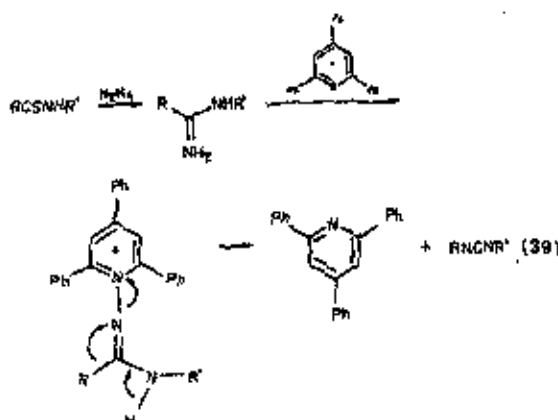


H. Tiamann Rearrangements

Several useful syntheses of carbodiimides utilize an electron-deficient rearrangement (eq 38). Amidoximes

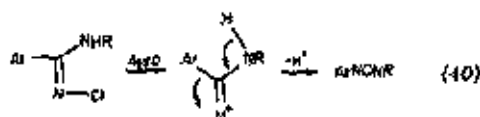


in the presence of phenyl halides^{110,111} and base give carbodiimides in up to 80% yield. O-Benzoylation of



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an amidoxime followed by base-catalyzed elimination¹¹² also gives a good yield of carbodiimide. Recently a versatile method of carbodiimide formation from amidrazones has been reported (eq 39);^{113,114} triphenylpyrylium ions form the corresponding pyridinium species which then eliminates with rearrangement to carbodiimide. Reaction of *N*-chloramidines with silver oxide yields carbodiimides, probably through a nitrenium ion (eq 40).¹¹⁶

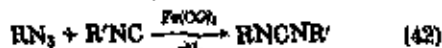


I. Syntheses through Combination of N + CN

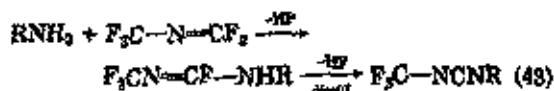
The synthetic method for carbodiimides involving decarboxylation of isocyanates through phosphorus catalysis is strictly an *N* + CN pathway but is best dealt with separately. The reaction of amines or their derivatives with isocyanides has been exploited as a useful synthesis. Palladium dichloride has been used as a catalyst for the reaction of primary amines with isocyanide in the presence of silver oxide;¹¹⁸ the reaction yielding up to 90% carbodiimide is thought to involve a complex species (eq 41). Azide and isocyanide in the



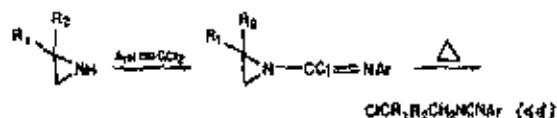
presence of iron pentacarbonyl catalyst give a 50–80% yield of carbodiimide (eq 42).¹¹⁷ Carbodiimides are



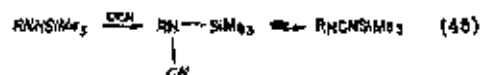
prepared in up to 80% yield by the interaction of amine and $\text{C}=\text{N}-$ groups (eq 43).¹¹⁸ Aliphatic amines require



a distillation step to expel the second HF molecule. Cleavage at a CN bond occurs when the amine is secondary (eq 44).¹¹⁹ Reaction of amidosilanes with



cyanogen halides yields silylcyanamide which tautomerizes to the carbodiimide (eq 45).^{120,121}

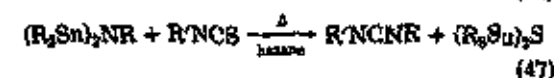
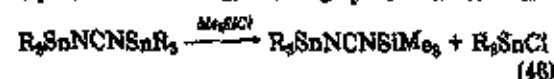


J. Exchange Reactions

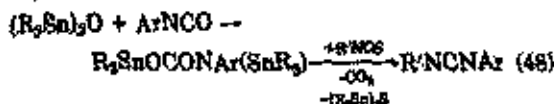
Simple exchange of a carbodiimide with halides have been utilized in preparations with up to 80% yield.^{122–124} Equation 46 exemplifies a typical process.¹²²

Stannylamines exchange with isothiocyanate to give

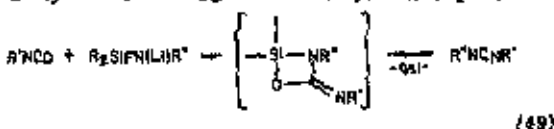
stannyl sulfides and carbodiimides in up to 90% yield (eq 47).¹²⁵ A similar exchange process involves iso-



cyanate or isothiocyanate and trialkylthiocarbamates (eq 48).¹²⁷

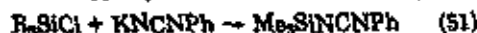
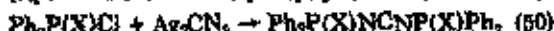


A novel method involves exchange of the nitrogen of a silylamine for oxygen of an isocyanate (eq 49).¹²⁸



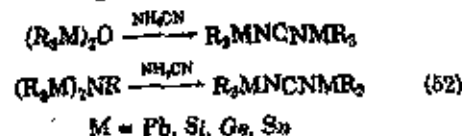
K. Synthesis from Cyanamide and Its Derivatives

The preparation of carbodiimides can be effected through electrophilic substitution on the preformed carbodiimide or cyanamide. Synthesis from metal cyanamides using reactive halides has been exploited (eq 50 and 51).^{129,130} for phenacyl ($\text{X} = \text{S}, \text{O}$) and silyl

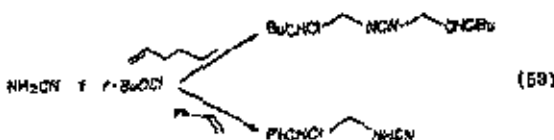


carbodiimides. Other examples use zinc or lead cyanamide^{131,132} and calcium or sodium cyanamide¹³³ to give moderate to good yields of carbodiimide from reactive halides. Action of halides on $\text{N}=\text{C}=\text{N}$ species in the presence of base has also given good yields of carbodiimide.^{13,134–138}

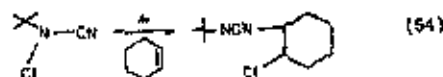
Oxides and amides of group 4 elements can act as electrophilic substitution agents for cyanamides to give carbodiimides in good yield (eq 52).^{77,137–140}



Carbodiimides may be prepared from cyanamide and olefins with *tert*-butyl hypochlorite, possibly through a free-radical process (eq 53).¹⁴¹ A further synthesis



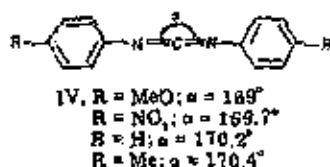
giving a 22% yield of carbodiimide is also thought to involve free radicals (eq 54).¹⁴²



III. Structure and Physical Properties

A. Structure

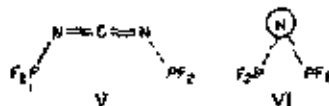
The allene-type structure of carbodimides was well established by the time of the last review.² Recent work was aimed at detailed structural analysis. The interesting feature of X-ray crystallographic studies is that the carbodimide bond itself is nonlinear, with NCN bond angles varying from 166 to about 170° for both aromatic and mixed-aliphatic-aromatic species (IV).¹⁴⁴⁻¹⁴⁶ The dihedral angle between the substituents



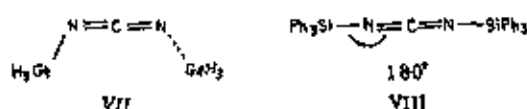
ranges near 90°, but the CNAr angle is larger than the expected 120°; values range from 123 to 163°. The anomalous NCN angle could be attributed to "packing" factors in the crystals, but the fact that all carbodimides that have been investigated possess the anomaly makes this explanation doubtful.¹⁴⁴ The bending of the NCN bond may be due to steric interactions between the two nitrogen substituents. The X-ray crystallographic structure of allene-1,3-dicarbonylate shows a similar buckling effect occurs in the central allene carbon, and a similar steric explanation is advanced for this.¹⁴⁷ Symmetrically substituted allenes (e.g., 1,1,3,3-tetraphenylpropadiene) have perfectly linear central allene bonds,¹⁴⁷ presumably because steric repulsion from one side is balanced by that on the other. The salt Li₂NCN has of course a linear structure because the NCN²⁻ is a symmetrical dianion.¹⁴⁸

It is interesting to note that other heterocumulenes have also been shown to have a slightly buckled three atom bond. Microwave and electron-diffraction studies of chlorocyanate (ClNC)^{149a} indicate an angle of approximately 171°. This angle has been reproduced by *ab initio* studies^{149b} and CNDO/2^{149c} calculations. Microwave studies^{149d} also indicate a bent structure ($\angle$ NNN $\sim 172^\circ$) for chlorine azide (ClN₃). *Ab initio* calculations¹⁵⁰ predict trans bent structures for HONCO ($\angle$ NCO $\sim 170^\circ$), HNCO ($\angle$ NCO $\approx 169.7^\circ$), MeNCO ($\angle$ NCO $\approx 169.6^\circ$), H₂BNCO ($\angle$ NCO $\approx 171.9^\circ$), and NC-NCO ($\angle$ NCO $\approx 169.7^\circ$). These data indicate that the buckled carbodimide group may result from an electronic effect such as steric or lone-pair repulsion rather than from crystal packing.

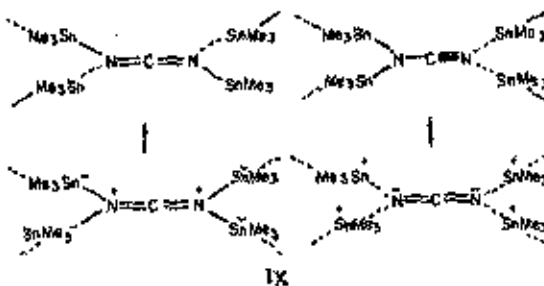
Electron-diffraction studies on bis(difluorophosphino)carbodimides indicate a dihedral angle of 55° (V and VI).¹⁵⁰ Both electron diffraction¹⁵⁰ and



X-ray crystallographic¹⁵¹ studies indicate a nonlinear and linear structure respectively for digermyl- (VII) and bis(triphenylsilyl)carbodimides (VIII); gas-phase electron-diffraction studies also indicate a linear SiNCNSi configuration for disilylcarbodimide.¹⁵² The crystalline



bis(trimethylstannyl)carbodimide has been shown by X-ray crystallography to possess a highly aggregated structure with an NCN group intermediate between cyanamide, carbodimide, and ionic NCN²⁻ (IX).¹⁵³



The structure consists of an infinite helical network of planar trimethyltin groups linked by NCN units; the dihedral angle between the Sn₂NC planes is 68°, and the SnNC angle is 117.8°. The CN bond length is 1.24 Å, close to that in CaN₂C, but the SnN bond is 0.38 Å longer than that in Me₃SnNCs.

B. Electronic Structure

Molecular orbital calculations have been carried out on a number of simple carbodimides. A geometry search using the INDO method¹⁵⁴ for dimethylcarbodimide¹⁵⁵ has revealed that the lowest energy singlet state has a dihedral angle of 90° and an angle for CH₃-N=C (CNC) of 90°; the latter value is 120° for difluorocarbodimide and parent carbodimide. Energy-optimized geometries were obtained by using the Gaussian 70 program¹⁵⁶ and STO-3G and 6-31G basis sets, and the dihedral angle of carbodimide was found to be 83° and that of HNC 111.4°. Molecular orbital calculations indicate a negative potential maximum in the region of the nitrogen lone pair;¹⁵⁵ the dihedral angle was assumed to be 90°, and energy minimization of the HNC angle gave a value of 115°. The cyanamide molecule was shown to be more stable than carbodimide and the equilibrium constant (eq 55) calculated



to be 10¹⁰ at 300 K in the gas phase. The physical parameters: ¹⁴N-quadrupole coupling constant, dipole moment, average diamagnetic susceptibility, molecular quadrupole moment, and diamagnetic shielding have been calculated from molecular orbital theory.¹⁵⁵

Molecular orbital drawings have been published for the parent carbodimide.¹⁵⁰ The two highest filled orbitals correspond to the n electrons and have vanishingly small coefficients on the central carbon. The lowest vacant orbital (6B) has a large coefficient on the central atom. There is a general similarity between the molecular orbitals of the heterocumulenes CO₂, CH₂CO, CH₂CCH₂, CH₂N₂, and carbodimide. Table II gives the detailed comparison, and the differences lie in the existence of degeneracy and the type of the highest occupied molecular orbital.

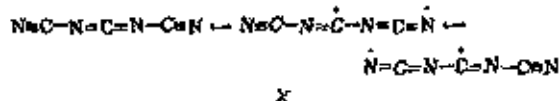
TABLE II. Molecular Orbitals of Species Isoelectronic with Carbodiimide

allene	ketene	diazomethane	CO ₂	carbodiimide
2B ₁ -π ⁺ CC	2B ₁ -π ⁺ CO	2B ₁ -π ⁺	5B ₁ -n	5B ₁ -n
1B ₁ -π ⁺ CH ₂	1B ₁ -π ⁺ CH ₂	2B ₁ -π ⁺ N ⁺ N	5A ₁ -n	5A ₁ -n
3B ₁ -π ⁺ CCCH ₂	1B ₁ -π ⁺ CH ₂	7A ₁ -π ⁺ CCN	1π _g -π ⁺	4B ₁ -n
4A ₁ -π ⁺ CH ₂ CC	7A ₁ -π ⁺ CC	1B ₁ -π ⁺ CH ₂	3σ _g -π ⁺	3B ₁ -π ⁺ N ⁺ NH
2B ₁ -π ⁺ CH ₂	5A ₁ -π ⁺ CCCH ₂	6A ₁ -π ⁺	4σ _g -π ⁺	4A ₁ -π ⁺ NH ⁺ NH
3A ₁ -π ⁺ CC	4A ₁ -π ⁺ CO	5A ₁ -π ⁺	2σ _g -π ⁺	2B ₁ -π ⁺ NH
		4A ₁ -π ⁺ NNCCN	3σ _g -π ⁺	3A ₁ -π ⁺ NH

C. Stereochemistry

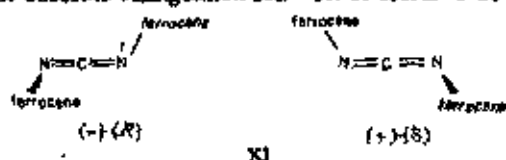
Molecular orbital theory has been applied to the problem of racemization of carbodiimides. Since carbodiimides are analogous to allenes, they should in principle be resolvable. An *ab initio* SCF LCAO MO study of nitrogen inversion in carbodiimide indicates a barrier to racemization of some 8.4 kcal/mol.¹⁶² An INDO study which also minimized geometry to give a dihedral angle of 94° calculated the energies of structures of carbodiimide on possible paths of racemization.¹⁶³ Two paths exist—the rotational and the inversion—both with very similar energies; Table III collects the energies for fluorocarbodiimide and carbodiimide.

It was concluded that the CNR valence angles opened out slightly in the planar (rotational) transition state. The lowest triplet state is 60 kcal/mol higher than ground, effectively ruling out such a mechanism for racemization. An interesting point is that the difluorocarbodiimide with energy for racemization of about 28 kcal/mol should be resolvable. The low energy for racemization of the parent of 8 kcal/mol is comparable with that for NH₃ inversion; the high energy of the FNCNF racemization parallels the high barrier for inversion at NF₃.¹⁶² Similar low barriers for racemization have been calculated for dimethylcarbodiimide (5 kcal/mol for inversion and 4.5 kcal/mol for rotation).¹⁶³ The dicyanocarbodiimide structure is flexible, with even less barrier for racemization than regular carbodiimides, and a linear resonance structure is proposed (X).¹⁶³



The diaminocarbodiimide has a (calculated) barrier to inversion of 18.5 and to rotation of 41.5 kcal/mol.¹⁶³ A semiempirical method confirms the low barrier to racemization in carbodiimides of <10 kcal/mol.¹⁶⁴

The problem of the configurational instability of carbodiimides has recently been reviewed.¹⁶⁵ Despite the low barriers to the optical isomerization calculated for regular carbodiimides, bisferrocenylcarbodiimide has been partially resolved;¹⁶⁶ application of Lowe's rule for allenes¹⁶⁷ indicates that the resolved components have the absolute configuration XI. There seems to be no



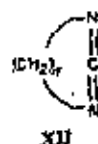
reason why the ferrocenyl derivative should be any different from the parent with regard to the racemiza-

TABLE III. Energies of Difluorocarbodiimide and Carbodiimide¹⁶³

	R = H		R = F	
	dihedral/ deg	E/(kcal mol ⁻¹)	dihedral/ deg	E/(kcal mol ⁻¹)
		18.8		51.4
	0	15.2	0	46.6
		8.1		22.4
	180	7.8	180	22.8
	94	0	93	0

tion process, and we suggest that the relatively small expected dihedral angle of about 90° allows an interaction stabilizing either of the ground-state forms to occur. Such an interaction has been already proposed as the cause of the $\angle \text{N}=\text{C}=\text{N}$ and $\angle \text{C}=\text{C}=\text{C}$ buckling. The species bis(methylphenyl)methylcarbodiimide has also been resolved by using partially acetylated cellulose.¹⁶⁸ Application of the Brewster model applied to chiral allenes¹⁶⁹ in conjunction with Lowe's rule¹⁶⁷ allows assignment of configuration.

Optically active *cyclohexyl* carbodiimides have been resolved on partially acetylated cellulose;¹⁶⁸ the homologue with $n = 7$ (XII) is resolvable, but that with $n =$



11 is not. The cause of the relatively high barrier to racemization is the restraint affected by the medium-sized ring ($n = 7$); as these restraints are lifted ($n = 11$), rotation or inversion become possible.

Measurements of the energy barrier of racemization have been made by using NMR techniques^{169,170} and found to be in the range 6–9 kcal/mol, in remarkable agreement with theory.

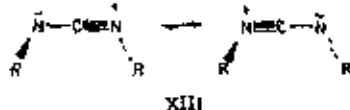
D. Nuclear Magnetic Resonance

The use of NMR techniques has been mainly aimed at the racemization problem as above, but structural problems have been attacked. ¹³C NMR chemical shift studies have shown that the resonance of the central carbon of carbodiimides occurs at an unusually high field ($\delta = 140$ ppm) whereas that of allenes is at about 310 ppm.¹⁷¹ *N,N'*-Dialkylcarbodiimide has a ¹³C resonance at 180 ppm¹⁷² and that of the ²⁹Si at -0.8 ppm.¹⁷³ Thus ¹⁵N resonances of carbodiimides occur (like those of ¹³C) at high fields due possibly to the contribution from polar resonance structures which increase the

TABLE IV. A Value of Groups Attached to Cyclohexane

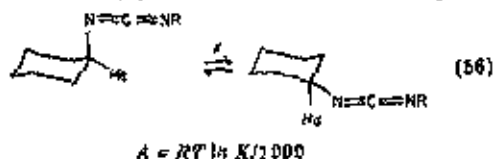
substituent	A
-NCNC ₂ H ₅	1.00
-NCO	0.51
-NCS	0.28
-N=C	0.21
-NO ₂	1.05
-CHCH ₃	1.35
-C≡CH	0.41

shielding of nitrogens and the central carbon of the carbodiimide (XIII).¹⁷⁴ Polar solvents have little effect

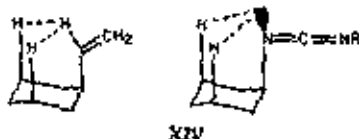


on the ¹³C chemical shift of the central carbon but significantly alter that of the ¹⁵N resonance.¹⁷⁴ This is probably related to the ability to solvate at the nitrogen and its lack at the carbon.

The A value of carbodiimide attached to a cyclohexane ring has been estimated by NMR techniques with CS₂ solvent (eq 66).¹⁷⁵ The value of A is compared



with that of other substituents (Table IV). The conformational requirement of the nonbonded lone pair on the nitrogen of the carbodiimide is not as severe as that of the hydrogen in the vinyl group (XIV).



The ¹⁵N resonance in carbodiimides is half way between that of CN and NR₂ in cyanamides.¹⁷⁶ NMR studies with N-ethyl-N'-[(dimethylamino)propyl]-carbodiimide indicate the presence of a cyclic species in solution,^{174,177} and we shall return to this problem later.

E. Infrared Spectroscopy

Low-temperature matrix isolation methods have been used to observe the infrared spectrum of carbodiimide and its deuterio analogue for the first time.¹⁷⁸ The 27 fundamental vibrations in dimethylcarbodiimide have been assigned by analyzing the infrared spectrum of vapor, liquid, and crystalline forms together with Raman spectroscopy.¹⁷⁹⁻¹⁸¹ The asymmetric vibrational frequency of carbodiimide with aryl substituents may be correlated with the appropriate Hammett σ or σ^+ values.^{182,183} The Hammett substituent constants have been determined for the NCNPh group on a phenyl ring making use of the relationship of eq 57¹⁸⁴ where A is

$$A = 0.0079A^{1/2} - 0.027 \quad (57)$$

the area under the peak for the ν_{18} ring band in mo-

nosubstituted benzene.¹⁸⁵

The vibronic spectrum of digermylcarbodiimide indicates that the structure is a carbodiimide and not a cyanamide (XV and XVI).¹⁸⁶ The selection rules are



consistent with a linear heavy atom skeleton. The spectrum is similar to that of bis(trimethylsilyl)carbodiimide.¹⁸⁶

The structure and lattice dynamics of bis(tri-phenylstannyl)carbodiimide have been studied by using Raman ¹¹⁹Sn Mössbauer correlational spectroscopy (Raman frequency $\omega = 26$ cm⁻¹).¹⁸⁸ The infrared spectrum of dicyclohexylcarbodiimide has been investigated.¹⁸⁹

F. Photoelectron Spectroscopy

He(I) photoelectron spectra of dialkylcarbodiimides have been studied.^{187,190} A distinct peak due to lone-pair character is separated from the rest of the ionization. Dimethylcarbodiimide shows bands at 9.5, 11.55, and 12.26 eV; the first maximum consists of two ionizations representing two orbitals on the NCN part with both π and n character. The 9.5-eV bands represent orbitals of B character and are probably assigned to the n orbitals described in Table II.¹⁹⁰

G. Ultraviolet Spectroscopy

The ultraviolet spectra of several alkyl- and arylcarbodiimides have been measured.¹⁸⁹⁻¹⁹¹ The absorption spectrum of dimethylcarbodiimide in the vapor phase has a maximum at 191 nm, a shoulder at 207-210 nm, and three maxima at 248.4, 252.5, and 258.4 nm; in heptane solution there is a strong band at 208.6 nm and three at 247.5, 254, and 280 nm due to the allowed $n \rightarrow \pi^*$ transitions polarized perpendicularly to the plane of the CNC angle.¹⁹¹ The near-UV absorption spectrum of N,N'-diphenylcarbodiimide is sensitive to substituent effects and varies systematically with σ .¹⁹²

H. Mass Spectroscopy

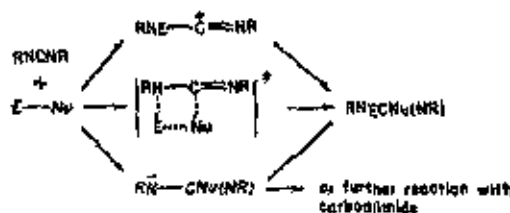
The mass spectra of both alkyl- and arylcarbodiimides have been investigated.¹⁹³ Diarylcarbodiimides have relatively stable molecular ions; there is a little fragmentation decomposition via the rearranged benzimidazole for 4- or 3-substituted phenyl groups. The dialkylcarbodiimides have weaker molecular ions which suffer N-alkyl cleavage and α -cleavage fragmentation.¹⁹⁴ The fragmentation pattern of bis(trimethylsilyl)- and -(trimethylgermyl)carbodiimides are similar.¹⁹⁴ Bis-(trifluoromethyl)carbodiimide fragments to yield C₂F₅N₂, C₂F₄N, C₂F₃N₂, C₂F₂N₂, C₂F₂N, C₂F₂N₂, CF₂, CFN, CN, and CF.¹⁹⁵

I. Miscellaneous Physical Properties

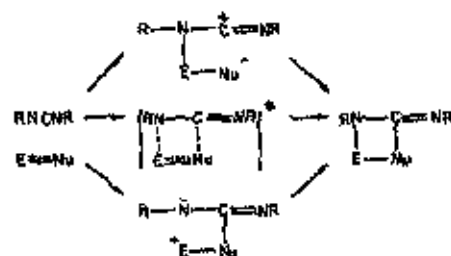
Physicochemical properties (viscosity, surface tension, refractive index, and ρ_{400}) have been measured for bis(trimethylstannyl)carbodiimide.¹⁹⁶ The Sn-N bond energy is of the order of 100 kcal/mol, as determined

TABLE V. Pathways for Reactions of Carbodiimides

Addition



Electrocyclic Addition



from heats of formation in the liquid and gaseous states and the heats of atomization for bis(tributylstannyl)-carbodiimide.¹⁰¹ The dipole moment of bis(triethylstannyl)carbodiimide is 2.79 D.¹⁰²

IV. Chemical Properties

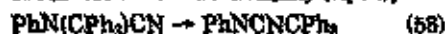
A. General Properties

The carbodiimide molecule has two centers of reactivity; the central carbon atom is electrophilic and the terminal nitrogens electron rich. By far the most important reactions involve nucleophilic attack of a reagent E-Nu which may add by stepwise or concerted paths (Table V). The reaction essentially occurs by interaction of the highest occupied molecular orbital of the reagent and the lowest vacant orbital on the carbodiimide which has a large coefficient on the central carbon.

Table VI illustrates a comparison between reactivity of a series of heterocumulenes and nucleophiles; as might be expected, the oxygen analogues, carbon dioxide and isocyanate, are much more reactive than carbodiimides.

B. Isomerization

The isomerization of *N*-phenyl-*N*-triethylcyanamide to carbodiimide has been studied kinetically (eq 58),^{103,100}



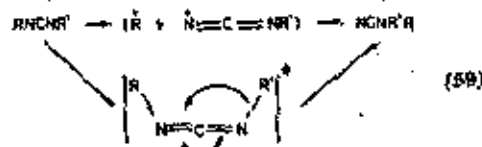
and an ionic mechanism was postulated to account for

TABLE VI. Reactivity of Some Heterocumulenes to Nucleophiles^a

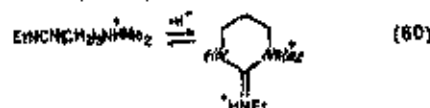
heterocumulene	k_N (M ⁻¹ s ⁻¹)	k_{OH} (M ⁻¹ s ⁻¹)	k_{H_2O} s ⁻¹	$k_{NH_3}/(M^{-1} s^{-1})$
HNCO	0.16	980	0.079	1200 ^b
n-PrNCPn	930	0.014	<10 ⁻⁴	0.015 ^c
O=C=O		4000 ^d	0.0145 ^e	9810 ^d
O=C=S		4.2 ^f		12000 ^d
S=C=S		1.1 × 10 ⁻³ ^f		1.7
n-BuN=C=S		0.0268		4.2 × 10 ⁻³ ^g

^a 25°C aqueous solution. ^b Methylamine. ^c Ethylamine. ^d M. E. Jensen, *Acta Chem. Scand.*, 13, 289 (1959). ^e B. R. W. Piment, L. Pearson, and F. J. W. Roughton, *Trans. Faraday Soc.*, 52, 1512 (1956). ^f B. Philipp and H. Dautzenberg, *Z. Phys. Chem. (Leipzig)*, 231, 279 (1956). ^g B. Philipp and H. Dautzenberg, *Faserforsch. Textiltech.*, 19, 23 (1958).

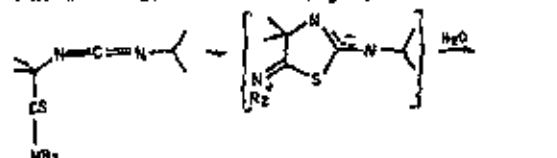
the accelerated rate constant in polar solvents. The formation of cyanamides from carbodiimides was also studied, but the mechanism is uncertain.¹⁰¹ Possibilities involve radicals reacting in cages or an intramolecular cyclic reorganization of σ or π electrons (eq 59).¹⁰¹



Ring-chain tautomerism has been demonstrated in the well-known water-soluble carbodiimide 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (eq 60).¹⁰² At

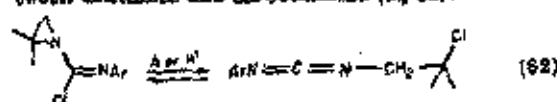


neutral pH the cyclic form contributes some 7% of the total material. A similar form of tautomerism is deduced from the unusual product of hydrolysis of a thiocarbonylcarbodiimide (eq 61)^{104,105} where intra-

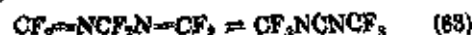


molecular rearrangement yields a thiazolidine which extrudes the secondary amine (NHR₂) to yield a thiohydantoin.

A novel form of tautomerism has been observed between aziridines and carbodiimides (eq 62).¹⁰⁶



Bis(trifluoromethyl)carbodiimide may be prepared by isomerization of perfluoro-2,4-diox-1,4-pentadiene (eq 63).¹⁰⁷

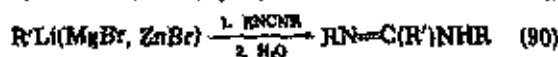


C. Addition of HX

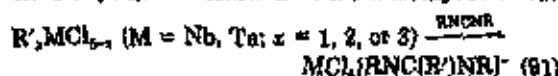
a. Water and Alcohols

The hydrolysis of carbodiimides is a relatively slow

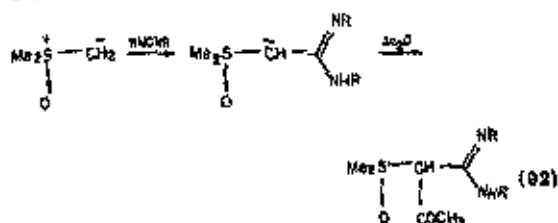
Grignard type reagents react with the central carbons of carbodiimides (eq 90).^{264,265} A similar reaction is



observed with alkylniobium(V) and tantalum(V) chlorides (eq 91).²⁶⁶ Reaction of the dimethyl sulfoxide

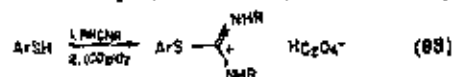


alkyl ylide yields a C-C bond with carbodiimides (eq 92).²⁶⁷

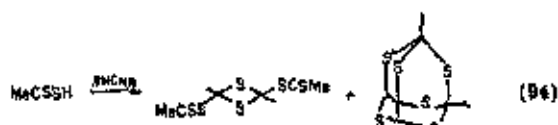


d. Sulfur Nucleophiles

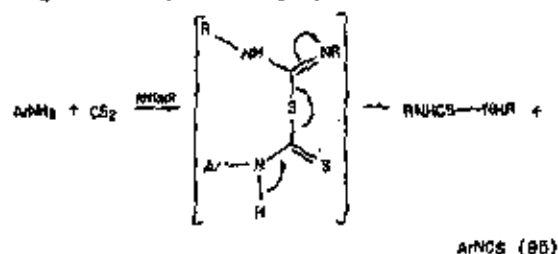
Thiophenols react directly with carbodiimides to yield S-arylisothioureas (eq 93)²⁶⁸ which may be conveniently



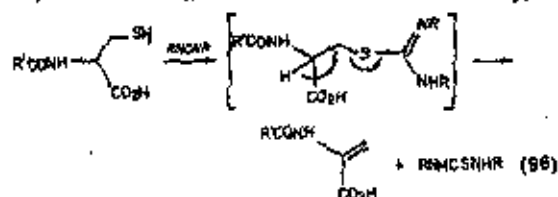
isolated as the oxalate salts. Reaction of monothiocarboxylic acids with carbodiimides yield the monothioamides,²⁶⁹ and dithioacetic acid yields iron-2,4-dimethyl-2,4-bis(thioacetylthio)-1,2-dithietane (eq 94).²⁷⁰



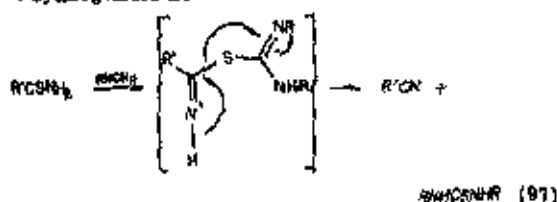
Dithiocarbamates from carbon disulfide and anilines undergo elimination of the elements of hydrogen sulfide to give isothiocyanates (eq 95).^{271,272} Direct attack of



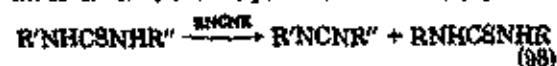
thiol on carbodiimide is followed by elimination of thiourea if a suitably acidic β hydrogen is available (eq 96).²⁷³ Thioureas react with carbodiimides to yield



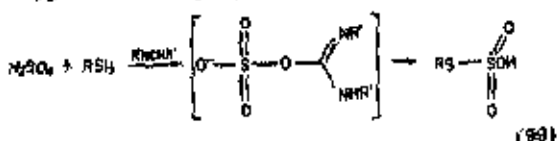
the nitrile (eq 97).^{274,275} Ammonium thiocyanate reacts with two molecules of carbodiimide to give thiourea and α -cyanoguanidines.²⁷⁶



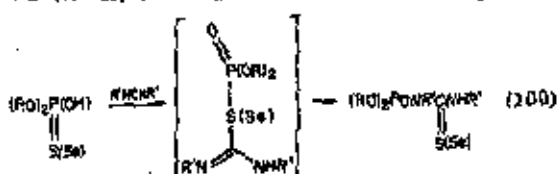
A further elimination reaction promoted by carbodiimides involves exchange with thiourea and provides a possible synthetic route to carbodiimides (limited by the favorability of the equilibrium constant) (eq 98).²⁷⁶



The reaction of thiols with sulfuric acid in the presence of dicyclohexylcarbodiimide probably involves oxygen attack (eq 99)²⁷⁷ rather than that of sulfur.



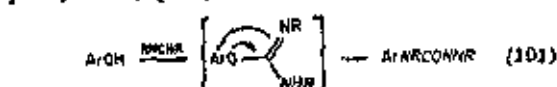
Phosphorothio(seleno)ic acid forms the N-phosphorothio(seleno)urea via an isourea intermediate (eq 100).²⁷⁸



which has been detected by using low-temperature FT ³¹P NMR spectroscopy. Adducts of phosphorodithioate and carbodiimides have been used as antioxidants.²⁷⁹

e. Phenols

Acidic phenols add to carbodiimides to give the N-phenylurea (eq 101).²⁸⁰⁻²⁸² Some acidic phenols yield

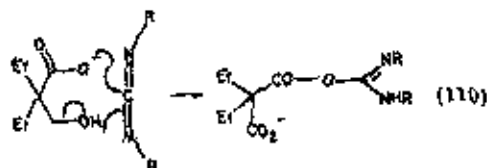


O-phenylisourea products,²⁸³⁻²⁸⁵ and well-defined crystalline O-arylisoureas are obtained from pentachloro-^{286,287} and 2,6-dichloronitrophenol.²⁸⁸ It has been suggested that the bulky *o*-chloro substituents are involved in preventing the usual O→N shift in the latter compounds.²⁸⁹ The O-arylisoureas from reaction of phenols with carbodiimide may be hydrogenolyzed over Pd/charcoal to yield the aromatic species (eq 102).²⁹⁰

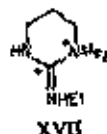


Acetyltyrosine ethyl ester reacts with 1-ethyl-3-(3-dimethylamino)propylcarbodiimide to yield the O-arylisourea rather than the N-arylisourea.²⁹¹ Picric acid yields N-arylisourea with carbodiimide, although the

observed in the reaction of dicarboxylic acids with carbodiimides (eq 110).²⁹⁸

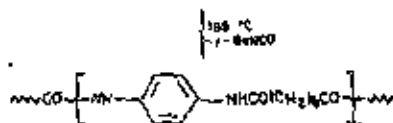
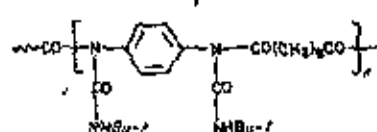
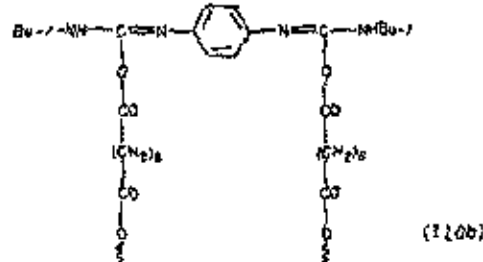
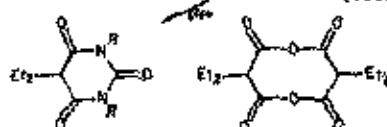
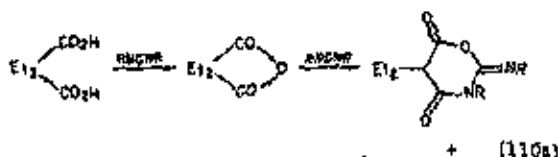


The water-soluble carbodiimide 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide has been shown to react with acetic acid through the cyclic tautomer XVII



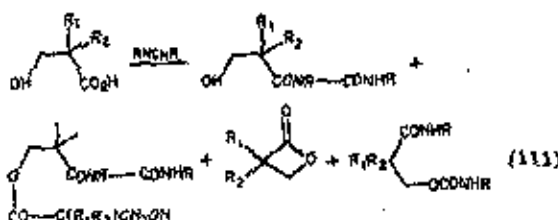
by comparison of the reactivity with that of the quaternary ammonium analogue 1-ethyl-3-(3-(trimethylammonio)propyl)carbodiimide.²⁹⁴ This reaction pathway has relevance to the mode of action of the tautomeric carbodiimide as a modification agent for biological polymers.

Diethylmalonic acid anhydride has been detected spectroscopically in the reaction of the acid with dicyclohexylcarbodiimide (eq 110a).^{297a}

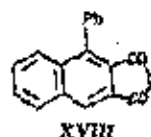


An interesting synthesis of a polymer is obtained from reacting a bis-carbodiimide with dicarboxylic acids; the synthesis exploits the O→N acyl shift reaction (eq 110b).^{297b}

Reaction of 2,2-disubstituted 3-hydroxypropionic acids with aliphatic carbodiimides in tetrahydrofuran yields a variety of rearranged products (eq 111).²⁹⁸

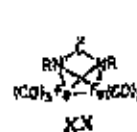
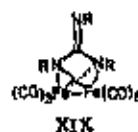


Phenylpropionic acid undergoes a novel cyclization reaction in the presence of carbodiimide to yield 1-phenylnaphthalene-2,3-dicarboxylic anhydride by a mechanism which is not yet understood (XVIII).²⁹⁹ The reaction is also initiated by acetic anhydride.³⁰⁰

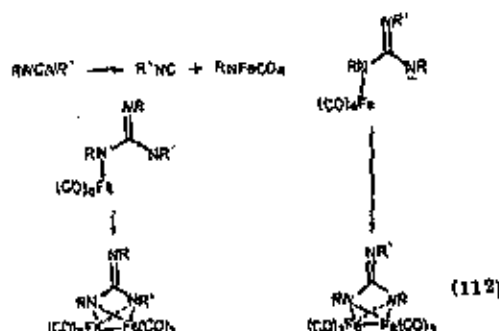


g. Reactions with Metals

There has been considerable work on the coordination of carbodiimides with iron pentacarbonyl to yield XIX.^{310,311} Experiments using unsymmetrical carbo-

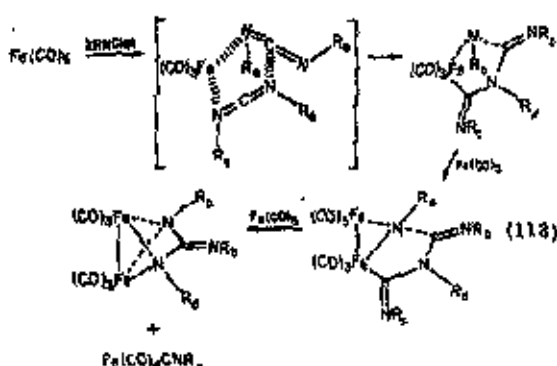


diimides³¹⁰ allow the exclusion of the symmetrical intermediate XX.³¹¹ The observation that some dehydroguanidine complexes have both coordinated nitrogen bearing the same substituent is not consistent with the above intermediates, and a mechanism (eq 112) involving

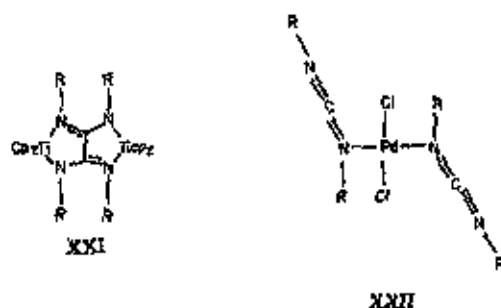


a metal-nitrene intermediate³¹⁰ is proposed. An alternative mechanism eliminates one-half of the carbodiimide unit as isocyanide in the form of a complex $(Fe(CO)_4(CNR))$ (eq 113).³¹²

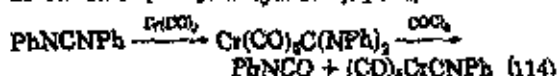
Carbodiimides may act as ligands to metals, and structures XXI³¹³ and XXII^{314,315} have been confirmed by X-ray crystallography.



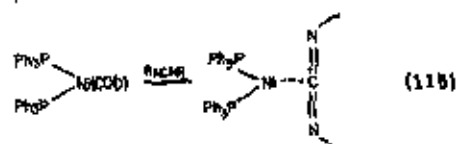
Reaction of chromium pentacarbonyl with di-phenylcarbodiimide yields a product which possibly



contains a metal-carbon bond.³¹⁸ Reaction of phosgene with the product yields an isocyanide complex with liberation of phenyl isocyanate (eq 114).

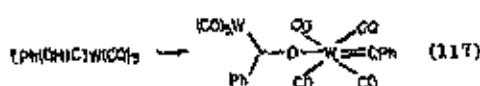


A further type of complex has been observed with a three-center bond (eq 115);³¹⁷ analogous complexes are



observed with isocyanates and ketenes.

Carbodiimides effect some interesting coupling reactions between metal complexes, in some cases attacking via the metal (eq 116³¹⁹ and 117³²⁰).



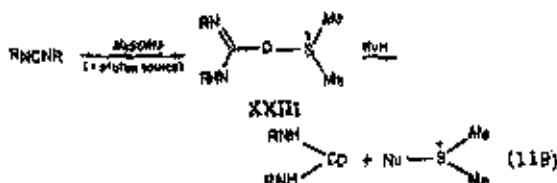
Simple displacement of ligands on group 4 carbodiimides has been observed (eq 118).^{321a}



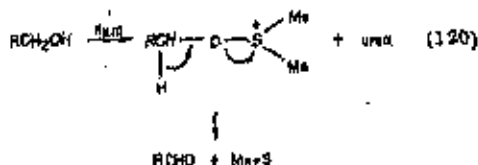
The formation of isocyanates from carbodiimides and CO_2 or CO has been claimed to be catalyzed by RhCl_3 and V_2O_5 .^{320b}

h. Reactions Involving Dimethyl Sulfoxide

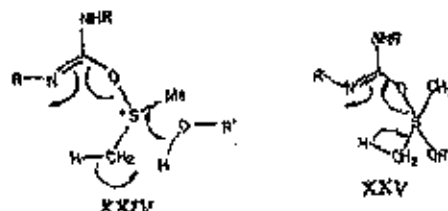
Dimethyl sulfoxide is thought to yield an electrophilic adduct with carbodiimide (XXIII, eq 119); this adduct



reacts with nucleophiles in a number of interesting and useful ways.^{322,323} Probably the most important reaction is with an alcohol to give an intermediate which subsequently eliminates dimethyl sulfide to give an aldehyde or a ketone (eq 120). The reaction is selective

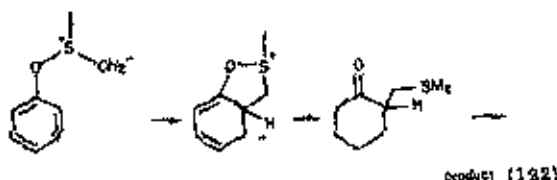
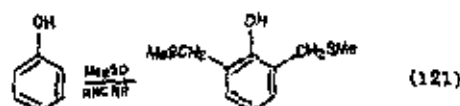


to yield the carbonyl derivative, and overoxidation does not occur.^{321,322} The oxidation of 5 α -lactost-3-en-3 β -ol to 5 α -lactost-3-ene-3-one does not involve allylic oxidation.³²³ The mechanism is similar to the Pummerer reaction which utilizes dimethyl sulfoxide and acetic anhydride; the function of the carbodiimide is solely to provide a good leaving group. The mechanism of the transfer of the sulfur atom from the carbodiimide adduct probably involves intramolecular hydrogen transfer from the methyl group (XXIV or XXV) be-



cause fully deuterated dimethyl sulfoxide transfers one deuterium to the product urea.^{324,325} A three-body mechanism postulated to account for the deuterium transfer³²⁶ is probably not valid.³²⁷

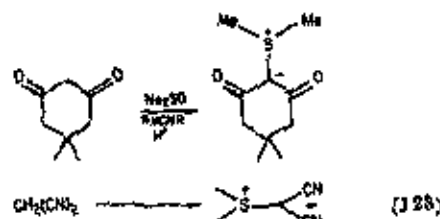
Aromatic substitution at phenols has been observed with the dimethyl sulfoxide/carbodiimide reagent (eq 121).³²⁸⁻³³² The mechanism probably involves intra-



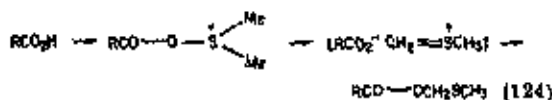
molecular attack via an ylide (eq 122) rather than action of the methylenemethylsulfonium ion ($\text{CH}_2=\text{SMe}^+$);

the latter sulfonium ion is thought to be involved in *para* substitution.³²⁸

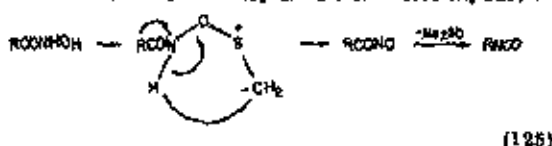
Stabilized carbon nucleophiles yield sulfonium ylides (eq 123).³²⁹ Carboxylic acids react with carbodiimide



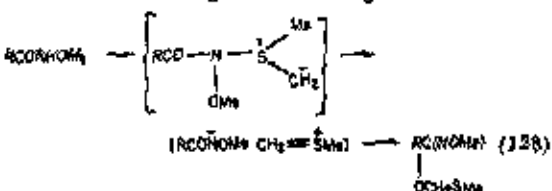
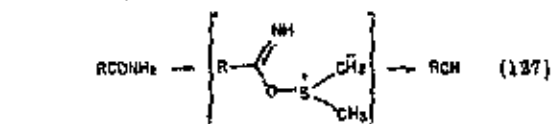
and dimethyl sulfoxide to give esters (eq 124).³³⁴ Hy-



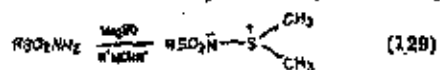
droxamic acids yield isocyanates and esters (eq 125).³³⁴



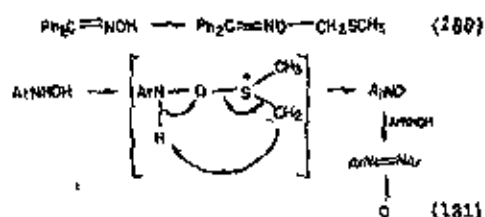
Amides yield nitriles (eq 127)³³⁴ and *O*-methylhydroxamic acids give imino esters (eq 128).³³⁴ Sulfonamides



react with Me_2SO /carbodiimide reagent to yield *S*-*N* ylides (eq 129).³³⁴ Ketoximes yield *O*-alkylketoximes (eq

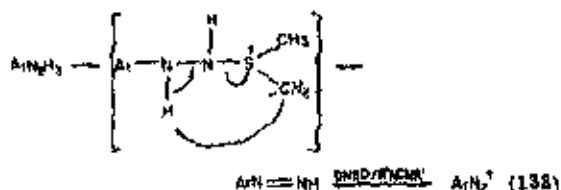
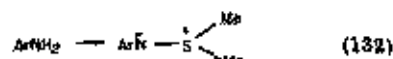


130) and arylhydroxylamines yield azoxy aromatic species (eq 131).³³⁵ Amines yield an *S*-*N* ylide with



Me_2SO /carbodiimide reagent (eq 132)³³⁶ and aromatic hydrazines undergo a complicated series of reactions (eq 133).³³⁶

The oxidation of carbohydrate derivatives is an ob-



vious extension of the use of the mild and selective Me_2SO /carbodiimide reagent and has been extensively reviewed.³³⁷⁻³⁴⁰

1. Solid-Phase Oxidations

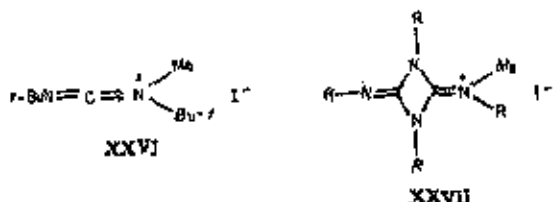
Polymers with pendant or chain-incorporated carbodiimide groups have been prepared for action as solid-phase reagents in the oxidation of alcohols with Me_2SO .³⁴¹⁻³⁴⁴ Hydroxyalkyl methacrylate gels have been treated with Me_2SO /carbodiimide to yield a polymer gel to act as a carrier for biologically active compounds (eq 134).³⁴⁵



D. Reactions of Carbodiimide Involving the Nitrogen as a Nucleophile

a. Alkylation

Di-*tert*-butylcarbodiimide may be methylated to give *N*-*tert*-butyl-*N'*-butyl-*N''*-methylcarbodiimidium iodide.³⁴⁶⁻³⁵⁰ Only the highly hindered carbodiimides yield the monomeric species XVI. Less hindered carbodi-



imides form the dimeric type of product (XXVII).^{351,352,353,357} Both products have been used as the basis for novel dehydrating reagents.

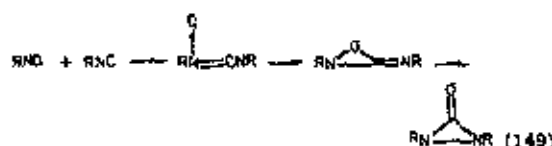
Group 4 element carbodiimides react with alkyl halides with the expulsion of the element already on the nitrogen as its halide (eq 135).^{184,353-355} This reaction



is the basis of the exchange method of carbodiimide synthesis (see earlier).

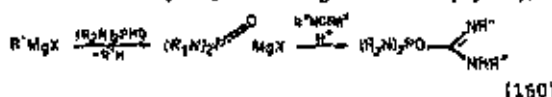
b. Acylation

Group 4 element carbodiimides react with "acidic" electrophiles such as halides or anhydrides to eliminate the group 4 element (eq 136).³⁵⁵⁻³⁶¹ Anthranil reacts with carbodiimide to yield a quinazoline by a novel reaction probably involving electrophilic attack on the carbodiimide nitrogen (eq 137).³⁶² Sulfonyl halides

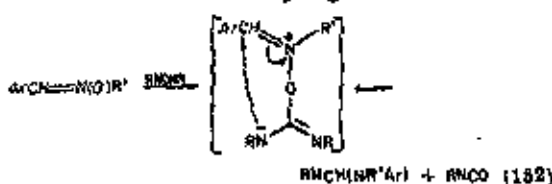
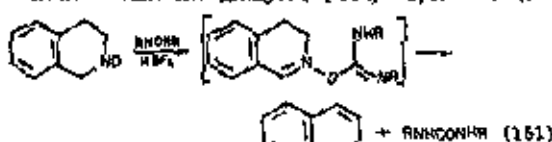


be oxidized with 3-chlorobenzoyl peroxide⁵⁷⁶ and hydrogen peroxide⁵⁷⁷ to yield diaziridinone. Oxidation may be effected with trifluoroacetyl peroxide.⁵⁷⁸

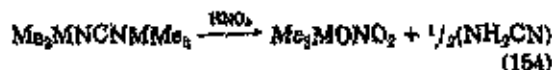
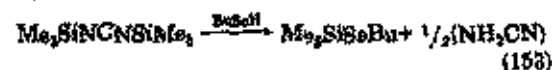
Reaction with phosphorus as a nucleophile has been effected with a phosphorus magnesium salt (eq 150).⁵⁷⁹



Nitrones react with carbodiimides in the presence of tetrafluoroboric acid catalyst (eq 151, 152; R = t-Bu).⁵⁸⁰



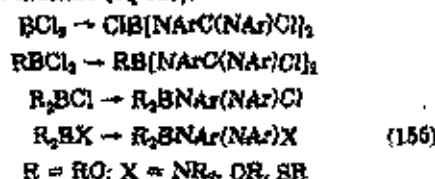
Protic reagents act on trimethyl silylcarbodiimides and germyl analogues to yield dicyanamide (presumably from the parent carbodiimide) (eq 153, 154; M = Ge, Si).⁵⁸¹⁻⁵⁸⁴



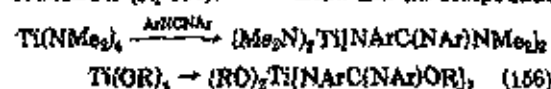
V. Metal Insertion Reactions

Organometallic insertion reactions at the carbodiimide conform to the general reaction type proposed in Table V; the electrophilic component "E" is usually a proton but can be other functions such as RCO-. In the present case a family of reactions is reviewed where E = metal or metalloid species. Reviews of metal insertion reactions at heterocumulene derivatives have appeared,⁵⁸⁵ and the carbodiimide reactivity is in general in the order carbodiimide > isocyanate > isothiocyanate.⁵⁸⁶

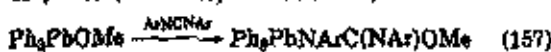
Insertion into boron compounds has been studied extensively and the following scheme elucidated for diarylcarbodiimides (eq 155).^{584,587}



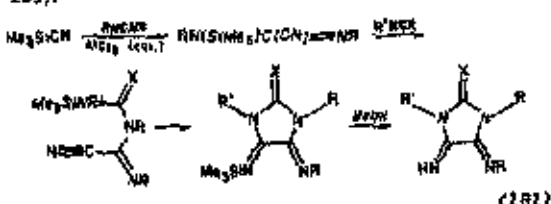
Titanium(IV) amides and alkoxides insert into carbodiimides (eq 156).^{588,589} Lead and tin compounds



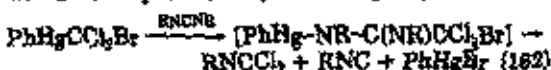
undergo insertion reactions with carbodiimides (eq 157, 158, 159, 160).^{590,591,592,593,594}



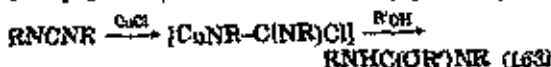
Trimethylsilyl cyanide reacts with carbodiimides in the presence of a catalytic amount of aluminum trichloride to give an insertion product which cyclizes (eq 161).^{595,596}



The second reaction is, in effect, a further insertion and is followed by a ring-forming insertion. N-Benzoyl-N'-tert-butylcarbodiimides have been shown to react with silyl and germyl compounds to yield the respective insertion products.⁵⁹⁷ Organomercury species react with carbodiimides to yield insertion products which decompose to isocyanides (eq 162).⁵⁹⁸



Carbodiimides have been shown to insert into cuprous chloride. The product reacts with alcohols to yield O-alkylisoureas; the reaction scheme (eq 163)⁵⁹⁹ prob-



ably accounts for the catalytic effect of copper salts on the reaction of alcohols with carbodiimides.

Other examples of "metal" insertion reactions with carbodiimides and Grignard reagents have been discussed earlier.

VI. Formation of Heterocycles

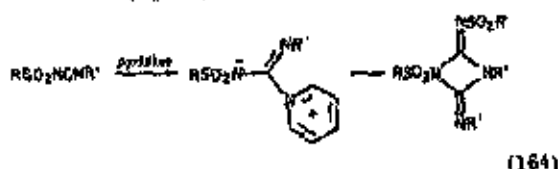
A. Cycloaddition Reactions

Cycloaddition reactions of carbodiimides are now very well documented and may occur to yield 1:1 or 2:1 adducts. The 1:1 cycloaddition may be concerted or stepwise (see Table V), and there is evidence for both pathways. Carbodiimides are involved in 1,2-, 1,3-, and 1,4-cycloaddition reactions.

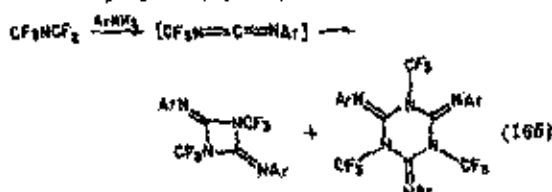
B. Condensation with C=N

Self-condensation leads to dimers and trimers. The dimerization of a sulfonylcarbodiimide is catalyzed by

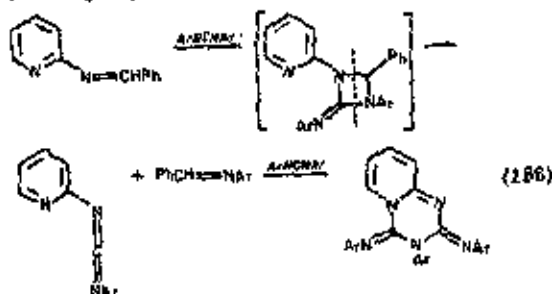
pyridine through an addition complex, probably a zwitterion (eq 164).⁴⁰⁰



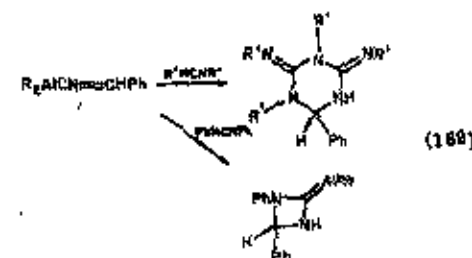
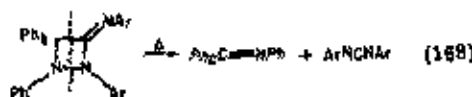
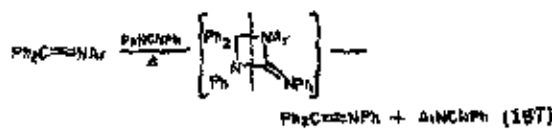
Recent work on the alkylation of carbodiimides has indicated^{401,402} that unless both the nitrogens in the carbodiimide possess very bulky groups such as tert-butyl the product is the diazetidinium ion rather than the linear alkylated species (see structures XXVI and XXVII and ref 281, 347, 348, and 350). Dimer and trimer are obtained in the synthesis of *N*-aryl-*N*-(trifluoromethyl)carbodiimides from aniline and perfluoroazapropene (eq 165);⁴⁰³ the carbodiimide is too



unstable to isolate. Azomethines undergo cycloaddition with carbodiimides with the expulsion of the transferred group (eq 166).⁴⁰⁴



Evidence has been provided for an imine-carbodiimide 1,2-cycloaddition adduct from the nature of the disproportionation products of the coupling in eq 167.⁴⁰⁵

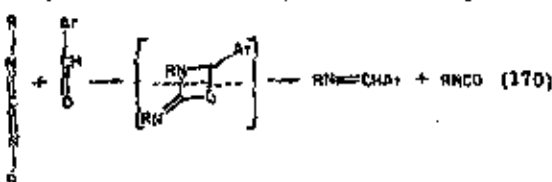


An interesting retro cycloaddition from a 1,2-diazetidinium imine is reported (eq 168).⁴⁰⁶

There is a report of the synthesis of the diphenylcarbodiimide using tri-*n*-butylphosphine catalyst⁴⁰⁷ and of the cycloaddition of carbodiimides to *N*-benzylidenaluminum amides (eq 169).⁴⁰⁷

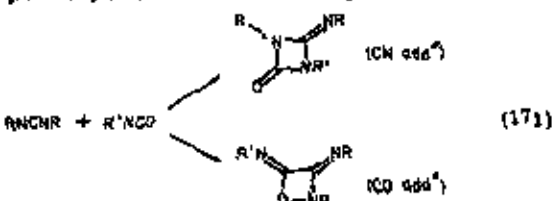
b. Condensation with C=O

Carbodiimides react with aromatic aldehydes to yield isocyanates and the corresponding imine (eq 170).⁴⁰⁸

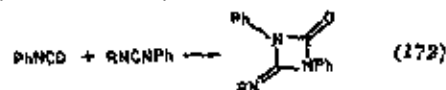


c. Condensation with Isocyanates

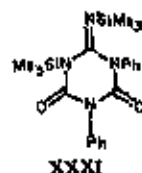
Condensation (1:1) with isocyanates involves a regioselectivity problem where CN or CO addition takes place (eq 171). The oxazetidine product has not been



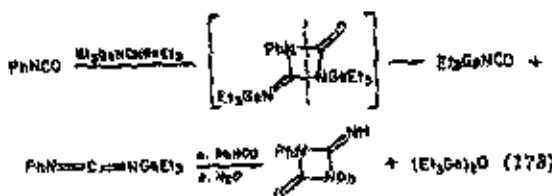
reported, and it is thought that the diazetidines (uretidinones) are the major products (eq 172).⁴⁰⁹



Phenyl isocyanate reacts with (trimethylsilyl)carbodiimides to yield the 2:1 cyanurate product (XXXI),⁴¹⁰

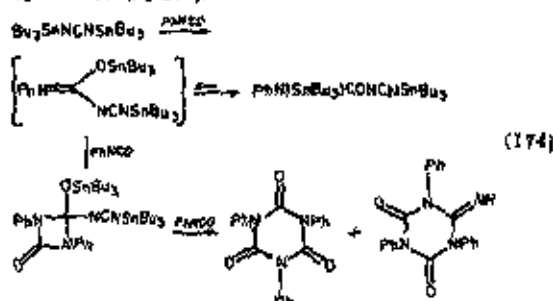


but with (triethylgermyl)carbodiimide exchange occurs, presumably through the uretidinone, and further cycloaddition and hydrolysis results in a 1,3-diphenyl-uretidinone (eq 173).⁴¹⁰



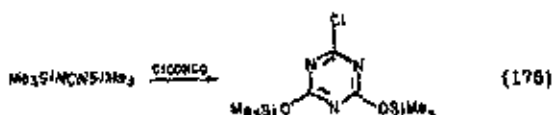
Phenyl isocyanate inserts into (tributylstannyl)carbodiimide and the CN product cycloadds to a further isocyanate molecule to yield a 2:1 uretidinone derivative

(eq 174).⁴¹¹ Yet further phenyl isocyanate gives the 3:1 cyanurate (eq 174).⁴¹²

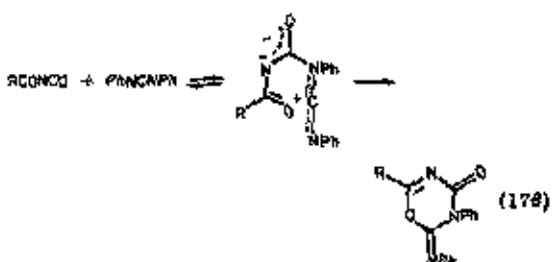


d. Condensation with Acyl Isocyanates

A 1,3 cycloaddition occurs between chloroformyl isocyanate and bis(trimethylsilyl)carbodiimide to yield the chlorotriazine (eq 175)⁴¹³ in 84% yield. Other acyl

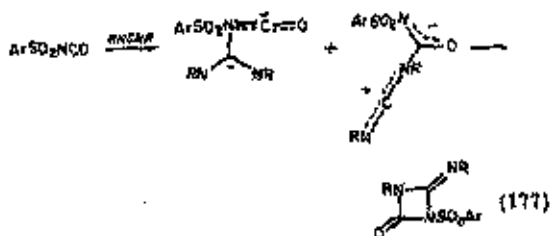


isocyanates react to give oxadiazinones presumably via a zwitterionic intermediate (eq 176).^{413,414}



e. Condensation with Sulfonyl Isocyanates

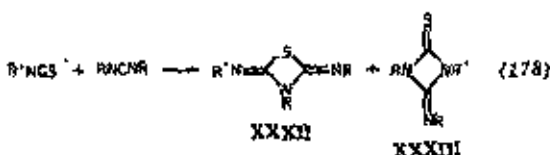
Evidence has been advanced for the stepwise addition of sulfonyl isocyanates to carbodiimides (eq 177).^{415,416}



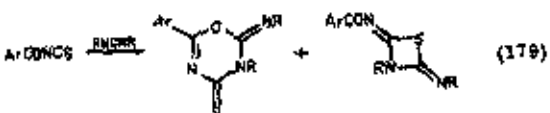
Infrared absorption peaks at 1869 and 1724 cm^{-1} appear on addition of carbodiimide to isocyanate,^{416,417} followed by their slow disappearance. Addition of tolyl isocyanate to *N*-*tert*-butyl-*N*'-methylcarbodiimide results in a shift in the *N*-methyl NMR signal from 2.9 to 3.32 ppm; this signal slowly decays and is replaced by new ones at 2.9 and 3.6 ppm. The acyclic intermediate consistent with these observations may be intercepted by a dipolarophile to yield a six-membered heterocycle, and this is the basis of the synthesis of several triazine derivatives.⁴¹⁷⁻⁴¹⁹

f. Condensation with Isothiocyanates

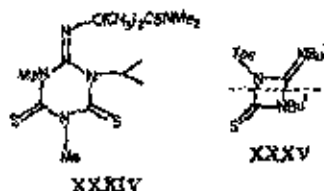
The regioselectivity in the addition of carbodiimides to isothiocyanates in the 1:1 stoichiometry results in thiazetidine formation (XXXII)⁴²⁰⁻⁴²² as well as the diazetidinethione (XXXIII)^{423,424} (eq 178). Benzoyl



Isothiocyanates add to carbodiimides to yield thiazetidine and 1,3,5-oxadiazine (eq 179)⁴²⁵ in a 1,2- and



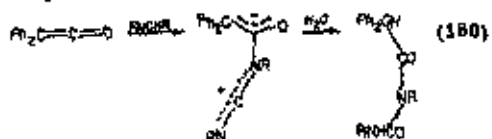
1,4-cycloaddition, respectively. The cycloaddition of methyl isothiocyanate to *N*-isopropyl-*N*'-(*N,N*-dimethylthiocarbamoyl)dimethylmethylcarbodiimide yields a triazine (XXXIV) derivative which is shown



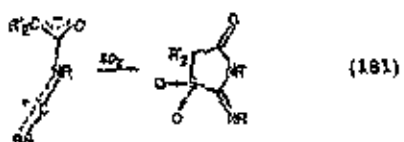
to have a boat conformation.⁴²⁷ *tert*-Butylcarbodiimide and tosyl isothiocyanate interact to yield *tert*-butyl isothiocyanate and tosyl-*tert*-butylcarbodiimide, presumably through the diazetidinethione XXXV.⁴²⁸

g. Condensation with C=C

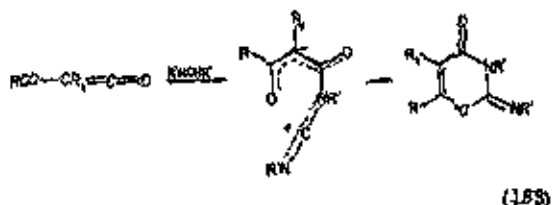
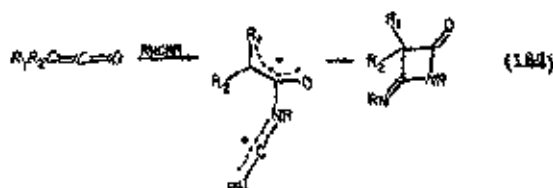
Ketenes react with carbodiimides to yield a variety of products. The evidence that there is an acyclic intermediate in the reaction with diphenylketene is that quenching the reaction with water yields an acyclic amide (eq 180).⁴²⁹ In sulfur dioxide as solvent the



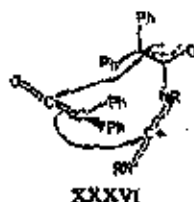
reaction is diverted to a thiazolidinone S,S-dioxide (eq 181).⁴³⁰⁻⁴³² In the absence of dipolarophiles the cor-



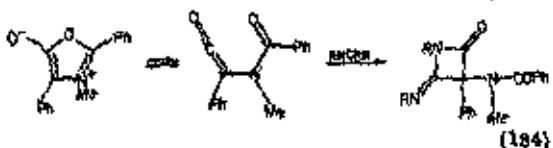
responding azetidinone is formed (eq 182).⁴³³⁻⁴³⁷ Regioselectivity to yield the oxazetidine is not observed. Reaction of acylketenes with carbodiimides has been shown to yield the amineoxazinone, presumably by intramolecular trapping of an intermediate zwitterion (eq 183).⁴⁴⁰



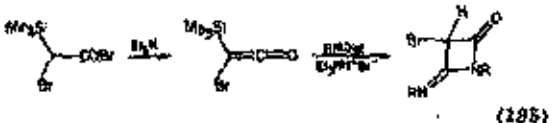
Addition of diphenylketene with carbodiimides in a 2:1 ratio has not been observed,⁴⁴¹ probably due to steric inhibition of the bulky adduct to a bulky dipolarophile (XXXVI).



The reactivity of mesoionic 6-oxazolones with carbodiimides is probably due to the small equilibrium percentage of ketene (eq 184).⁴⁴² Carbodiimide traps the

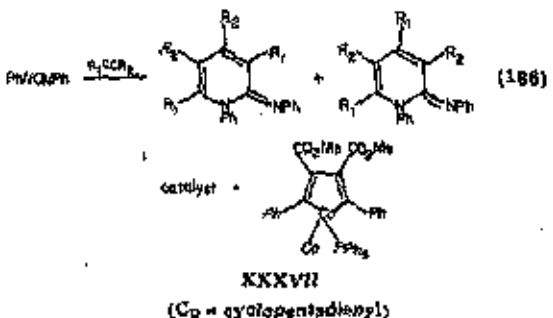


ketene from the interaction of base with (trimethylsilyl)bromoaacetyl bromide (eq 185)⁴⁴³ and that from the

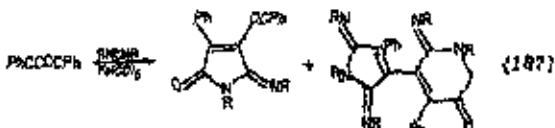


interaction with chloroacetyl chlorides.⁴⁴⁴

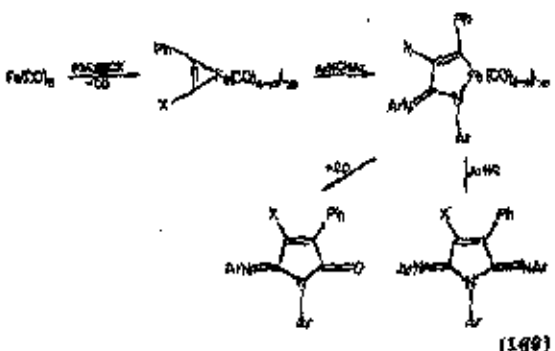
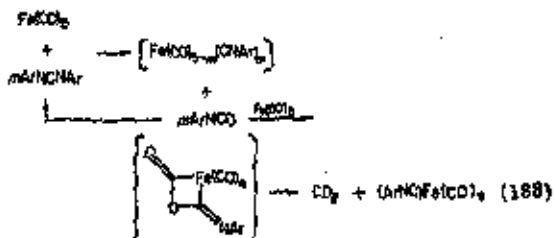
Cycloaddition of acetylenes with carbodiimides to yield pyridine derivatives is catalyzed by cobalt complexes (XXXVII) (eq 186).^{444,445} The reaction is also catalyzed by nickel(0) complexes such as $(Ph_3P)_2NiC_2H_4$.⁴⁴⁴



Iron pentacarbonyl catalyzes the addition of carbodiimide across diphenylbutadiyne to give iminopyrrolidin-2-ones and 1,5-bisaryliminopyrrolines (eq 187).⁴⁴⁶ The complex $RCN-Fe(CO)_5$ is also obtained,

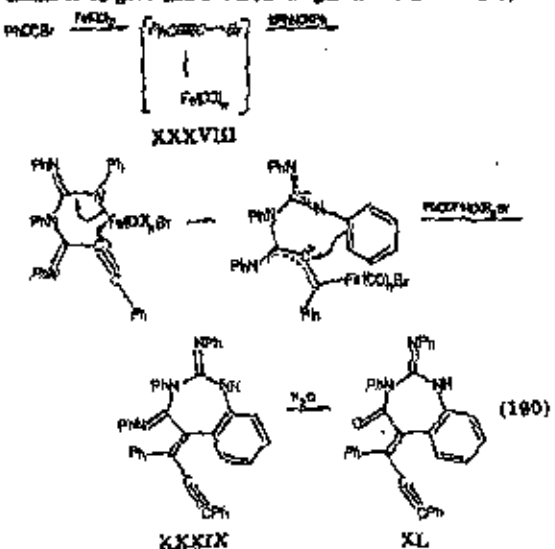


but in small yield, and the mechanism is thought to be as in eq 188 and 189.^{445,446} Reaction of X (as $-C=O$)



O-Ph) in eq 189 with further $ArNCNAr$ and $Fe(CO)_5$ gives the bis(pyrroline).

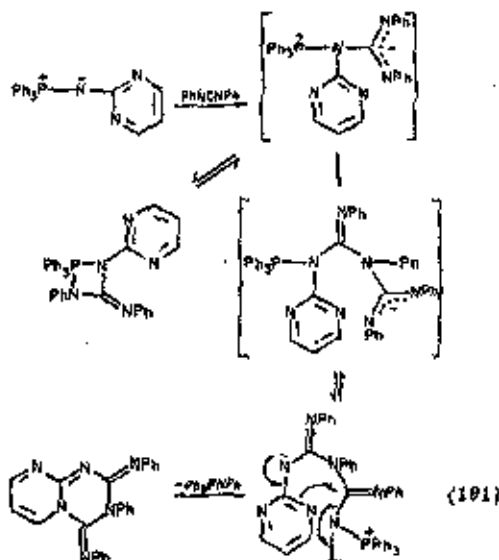
Phenylacetylene bromide with diphenylcarbodiimide in the presence of iron pentacarbonyl yields benzodiazepinones (eq 190).⁴⁴⁷ The diyne is produced via the acetylene adduct (XXXVIII) which reacts with carbodiimide to give the benzodiazepinimine (XXXIX); the



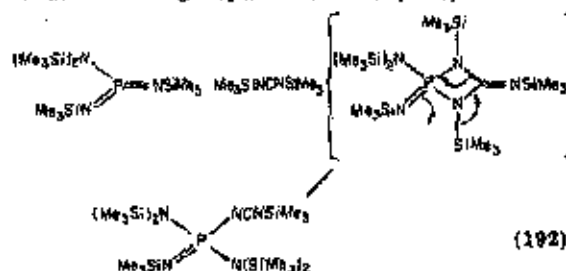
(after undergoing hydrolysis on work up with water to yield the benzodiazepinone (XI)).⁴⁴⁷

h. Condensation with PN and PC

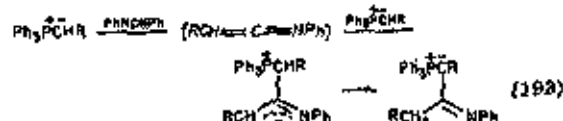
The ylide $\text{Ph}_3\text{P}=\text{NR}$ adds to diphenylcarbodimide (eq 191)^{448,449} via zwitterionic intermediates. Tetrakis(tri-



methylsilyl)aminodiphenylphosphorane reacts with bis-(trimethylsilyl)carbodimides to yield phosphorcarbodimides through cycloaddition (eq 192).⁴⁵⁰ The

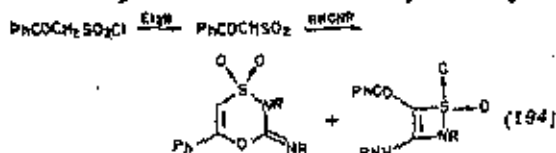


"Wittig" reagent ($\text{Ph}_3\text{P}=\text{CHR}$) acts on diphenylcarbodimide to yield an iminophosphorane after a cycloaddition reaction to form a ketenimine (eq 193).⁴⁵¹

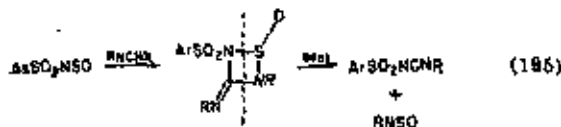


i. Miscellaneous Cycloaddition Reactions

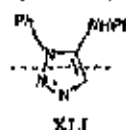
Sulfones produced by the action of tertiary amine base on sulfonyl chlorides are trapped by carbodimides to give four- and six-membered heterocycles (eq 194).⁴⁵² Nonactivated sulfones do not undergo cycloaddition with dialkylcarbodimides. *N*-Sulfinylamines yield



thiadiazetidine *S*-oxides which may be split by heating to yield the transferred carbodimide (eq 195).^{453,455}



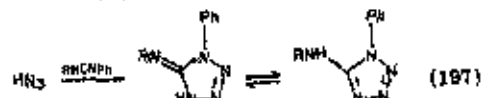
Reaction of carbodimides with diazoalkanes can involve 1,3-addition to yield a 1,2,3-triazole (XLI)⁴⁵⁴ or



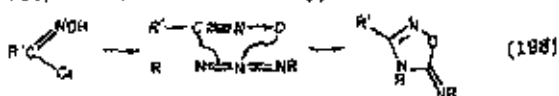
nitrogen may be eliminated in the diazoester case to give an iminoxazoline (eq 196).⁴⁵⁵⁻⁴⁵⁷ the reaction is



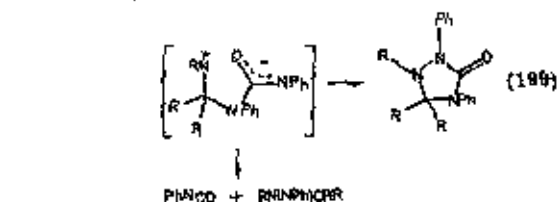
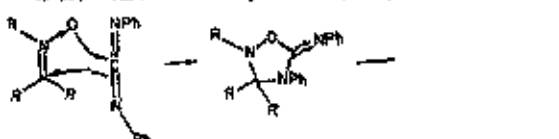
catalyzed by copper triflate and may involve a carbene. Aminotetrazoles are formed from hydrazoic acid and carbodimides (eq 197).⁴⁵⁸⁻⁴⁶⁰



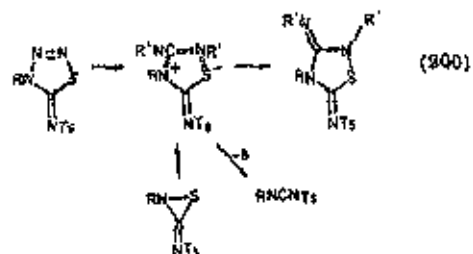
The addition of the C-N-O unit to carbodimides yields isoxazoles; hydroxamoylchloride reacts to give the nitrile oxide which then adds to the carbodimide (eq 198).⁴⁶¹ Nitrones act similarly, but the oxadiazolidine



product rearranges to a triazolidinone (eq 199).^{462a} 1,2,3,4-Thiadiazoline yields a 1,3-dipole which reacts

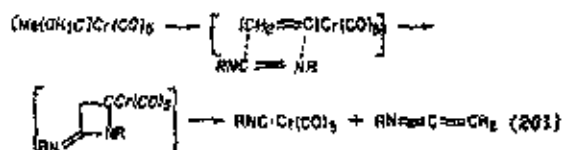


with carbodimide to give an iminodithiazolidine (eq 200).^{462b-465} In the absence of carbodimide sulfur is



also extruded to yield a carbodiimide.^{64,65} Trapping experiments are not conclusive for the thiaziridinimine intermediate.

Pentacarbonyl(hydroxymethylcarbene)chromium(0) reacts with dicyclohexylcarbodiimide, possibly through the dehydrated species (eq 201), to yield the isonitrile complex and ketenimine.⁶⁶

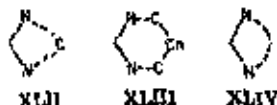


B. Incorporation of Carbodiimides into Heterocycles

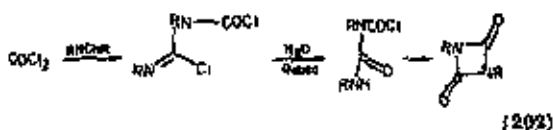
In this section we review the synthesis of heterocycles where carbodiimide is incorporated in the ring. The carbodiimide nucleus has been found to incorporate all three atoms, two, or only one in the ring, and the chapter is divided accordingly. We shall not deal with those syntheses yielding four-membered heterocycles where these result from cycloaddition reactions as these are covered in the previous section; there is of necessity a little overlap between the sections.

a. Full Incorporation

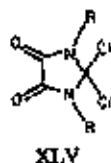
Heterocyclic syntheses involving full incorporation have been noted for systems such as XLII and XLIII.



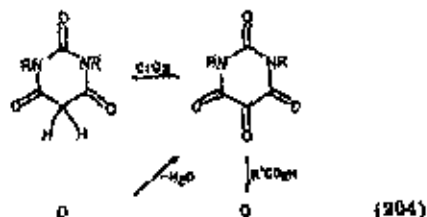
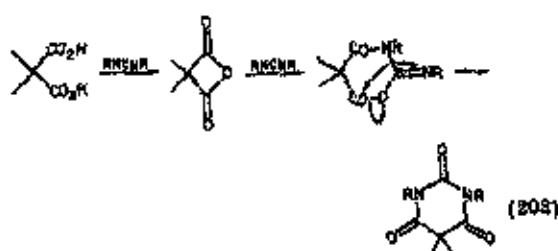
An example of XLII involves the interaction of phosgene with carbodiimide in acetone to yield a chloroformamidate which cyclizes in the presence of diazabicyclooctane (Dabco) to give a 1,3-dialkylazetidinone (eq 202).⁶⁷



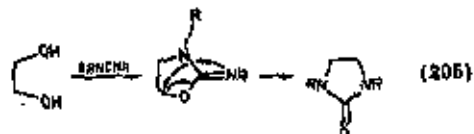
Oxalyl chloride yields 2,2-dichloroimidazoline-4,5-diones with carbodiimides (XLV).^{68,69}



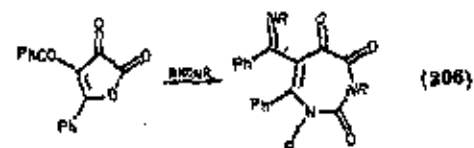
Malonic acids react through the scheme represented by XLII ($n = 1$) to yield alloxans.^{420,471} It is thought that the carbodiimide first dehydrates the malonic acid;⁴⁷¹ the anhydride then acylates the carbodiimide in the usual way and the acyclic intermediate presumably is further dehydrated by extra carbodiimide (eq 203). The alloxan product has been utilized as a coupling agent for ester formation (eq 204).⁴⁷¹



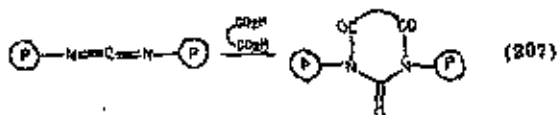
Dials yield iminoxazolidines with carbodiimides in the presence of CuCl catalyst. The products rearrange to give imidazolidinones (eq 205).^{472,473} Tetrahydro-



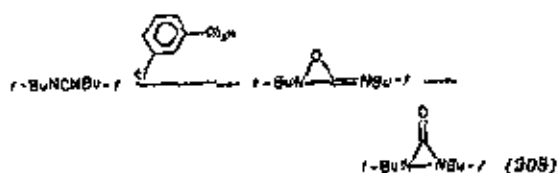
diazepotrienes may be prepared through interaction of carbodiimides with furandiones (eq 206).⁴⁷⁴ Poly-

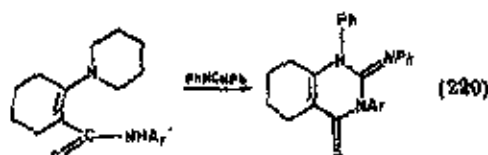


ureides have been prepared from polycarbodiimides through reaction with dicarboxylic acids at 100-180 °C (eq 207).⁴⁷⁵ Diaziridinones (XLIV) are prepared by

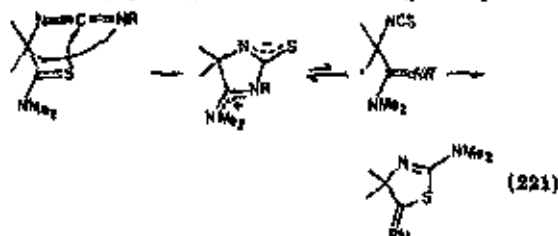


peracid oxidation of carbodiimides possibly through an oxaziridine imine (eq 208).⁴⁷⁶

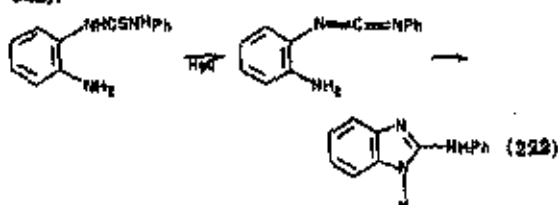




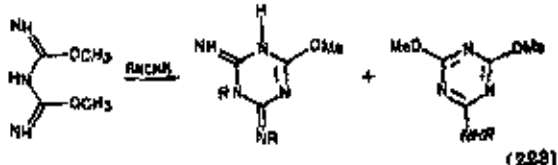
solidines and oxazolidines has been carried out through XLVIII (eq 221);⁴²⁹ reaction is thought to proceed



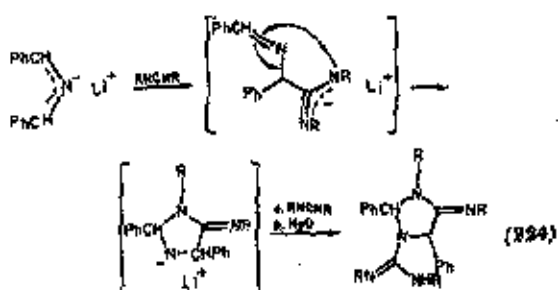
through the isothiocyanate. Benzimidazoles have been synthesized from thiourea through carbodiimide (eq 222).⁴³⁰



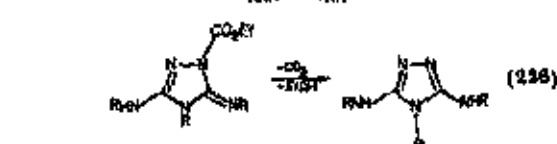
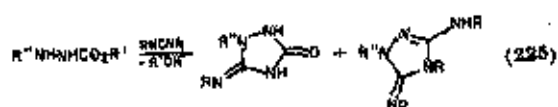
Thiazines may be synthesized through XLIX from dimethyl iminobiscarbimide (eq 223).⁴³¹



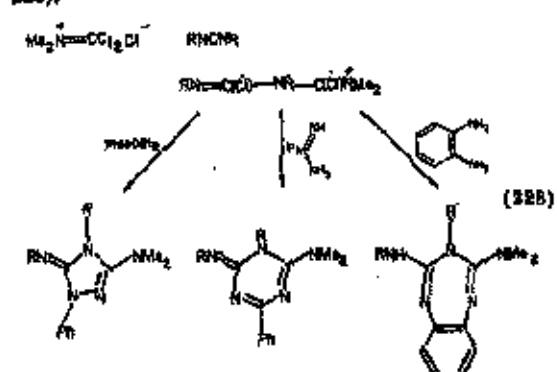
L has been reported for the synthesis of an imidazoline species (eq 224)⁴³² from carbodiimides and (1,3-diphenyl-2-allyl)lithium.



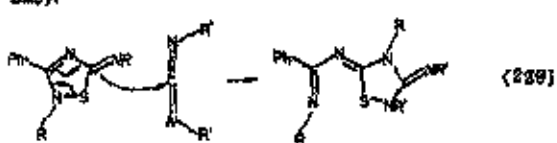
There has been considerable activity in heterocyclic syntheses through L. The NNC moiety in these syntheses is a hydrazide grouping, and the reactions are illustrated below; 1,2,4-triazolidines result (eq 225,⁴³³ 226,⁴³⁴ and 227⁴³⁵⁻⁴³⁷).



Examples of LII-LIV have been reported.⁴³⁸ The carbon element comes from phosgeniminium salts (eq 228).



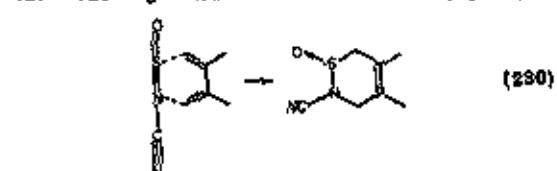
Reaction of 5-imino-Δ²-1,2,4-thiadiazolines with carbodiimide is an example of a synthesis using LV (eq 229).⁴³⁹



c. Incorporation of One Element

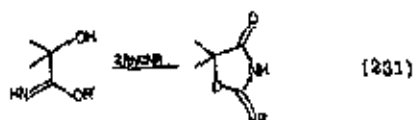
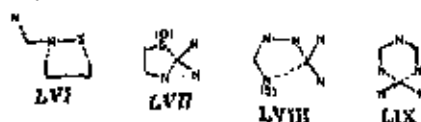
The schemes of Table VIII have been observed for incorporation of one element from the carbodiimide skeleton. The atom involved is usually C but can be N.

LVI is observed in the explosive decomposition of a mixture of thionyl cyanamide with 2,3-dimethylbutadiene to give a six-membered adduct (eq 230).⁴⁴⁰

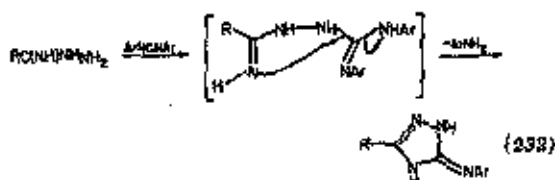


LVII is involved in the synthesis of iminopoxazolidinones (eq 231)⁴⁴¹ catalyzed by Cu₂Cl₂. The reaction path probably involves an O-alkylisourea as an intermediate since the reaction is copper catalyzed. Reaction of am-

TABLE VIII. Schemes for Incorporation into Heterocycles One Element from the Carbodiimide Skeleton

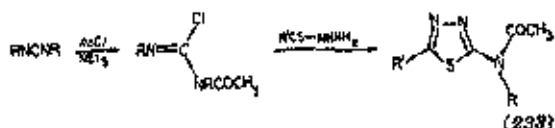


Hydrazone with carbodiimide follows LVIII to yield 3-substituted 5-(arylamino)-1,2,4-triazoles (eq 232).^{502,503}



Dimethyl iminobiscarbimide reacts with diarylcarbodiimides via LIX to yield triazines (eq 233).⁴⁹¹

1,3,4-Thiadiazoles may be prepared by the interaction of acetylated carbodiimides with thioacylhydrazides (LVIII, eq 233).⁵⁰⁴

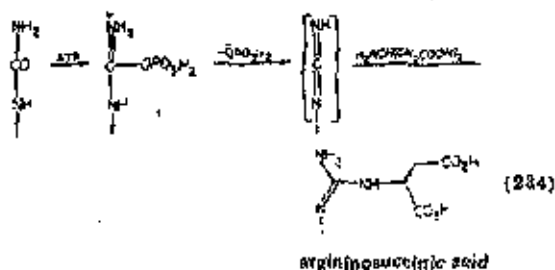


VII. Carbodiimides in Biological Chemistry

A. General

The synthetic usefulness of carbodiimides was first recognized because of their application to peptide and nucleotide chemistry; other biological properties were not very well-known at the time of the previous comprehensive review,² and only five references were recorded of work directly related to physiology. It has since been recognized that carbodiimides may play a role as effectors in biology other than that of synthetic tools, for example, as protein-modifying agents or as site-directed modifiers.

The carbodiimide moiety has never been postulated as an intermediate in biological transformations; however, it is probable, in view of previous work on E1cB mechanisms,⁵⁰⁵ that carbodiimides play a role in the urea cycle reactions. The synthesis of arginine from citrulline ATP and argininosuccinate synthetase is

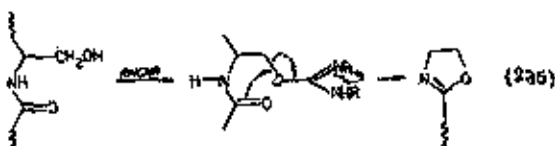


likely to involve a carbodiimide (eq 234).

It is, however, unlikely that the carbodiimide would enjoy a free existence but would most probably be bound in an enzyme complex.

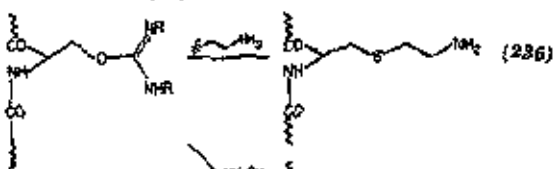
B. Modification and Inactivation of Proteins and Enzymes

Proteins carry a normal complement of reactive groups and therefore will react with carbodiimides largely in the same fashion as with simple nucleophiles (see earlier). α -Chymotrypsin has been inactivated with a water-soluble carbodiimide which reacts with the active-site serine (residue 195) (eq 235).⁵⁰⁶ The O-

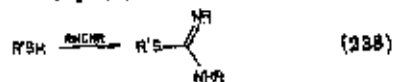


Ser-195

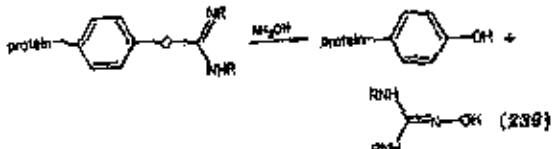
acylsourea also reacts with cysteamine (eq 236) and hydroxylamine (eq 237); the inhibition is analogous to that caused by cyanate and isocyanate.⁵⁰⁷



Protein thiol groups react with water-soluble carbodiimides,⁵⁰⁸⁻⁵¹⁰ papain is modified at residue cysteine-25,⁵⁰⁸ and the free thiol group of buckwheat α -glucosidase is protected (eq 238).⁵⁰⁸



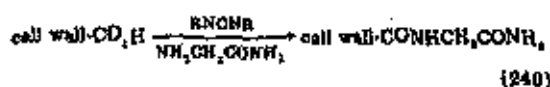
Tryptamine residues may be modified by carbodiimides,^{509,511} and the inactivation of yeast hexokinase is reversed by hydroxylamine which presumably forms the *N*-hydroxyguanidine (eq 239).⁵¹¹



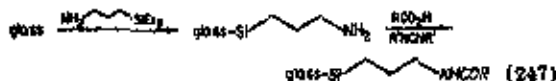
For the possibility of other pendant groups reacting with carbodiimides (e.g., imidazoles, amines), see the section on chemical properties.

C. Modification of Carboxyl Groups in Proteins

Carboxyl groups may be modified by using carbodiimide and a nucleophile such as an amine. Glycanamide has been attached to the carboxyl groups of cell walls to remove the negative charge (eq 240).⁵¹² Radioactive



imides,⁶³² and the carbodiimide method of binding chymotrypsin to carboxymethylcellulose has been evaluated.⁶³³ The pH optimum for coupling collagen to acrylic acid polymers is 4.4, and only accessible carboxyl groups are active.^{634,635} Carbodiimides have been employed to couple ovalbumin to mouse spleen cells⁶³⁶ and melibionate to serum albumin.⁶³⁷ Immunologically active species may be joined to glass through 3-(tristhialyl)propylamine (eq 247).⁶³⁸ Car-



bodilimide has also been employed to coat glass beads or modified polyacrylamide beads with polyamines.^{639,640}

b. Carbodiimide as a "Fixing Agent"

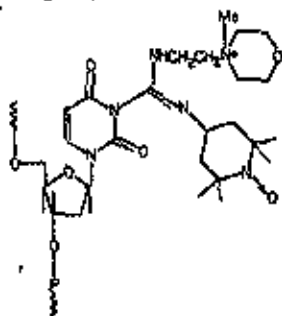
Carbodiimides have been used as fixatives for immunohistochemistry; intestinal glucagon has been preserved and localized by a water-soluble carbodiimide.⁶⁴¹ "Fixation" by carbodiimides is useful as an ultrastructure preservative for electron microscopy,⁶⁴² and the quality of the result is similar to that from the action of glutaraldehyde a conventional fixative.⁶⁴³ The action of the carbodiimide in these processes is probably to effect cross-linking between carboxyl and amino groups.

c. Cross-Linking of Proteins

Lysozyme and α -chymotrypsin when treated with water-soluble carbodiimide undergo intermolecular cross-linking to yield thermostable proteins.⁶⁴⁴ A similar stability has been induced in hemoglobin used in transfusions by cross-linking with water-soluble carbodiimides.⁶⁴⁵ Intermolecular cross-linking caused by carbodiimides leads to an increase in viscosity of collagen fibers.^{646,647} Carbodiimides have been utilized to cross-link wool,⁶⁴⁸ hair (in a permanent wave composition),⁶⁴⁹ and bovine luteotropin.^{649,650}

d. Spin-Labeling with Carbodiimides

We have already discussed an example of spin-labeling in the problem of carbodiimide binding proteins of ATPases.⁶⁵¹⁻⁶⁵³ Water-soluble spin-labeled carbodiimides have been synthesized and reacted with nucleosides;⁶⁴⁹⁻⁶⁵² poly(uridylic acid) is modified on the pyrimidine nitrogen (LXIII).⁶⁴³

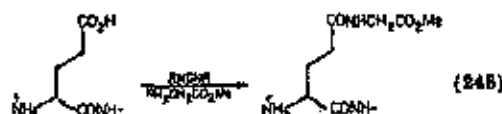


LXIII

e. Peptide Sequence Determination

N-Terminal glutamic acid or aspartic acid may be

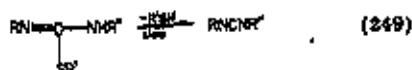
modified with carbodiimide and methylglycinate to yield a residue which may be distinguished readily from glutamine or asparagine in the Edman method (eq 248).⁶⁴³



f. Carbodiimides as Biological Effectors

Carbodiimides have been shown to act as herbicides,⁶⁴⁴ involvement of ATPase activity with initiation of germination has been inhibited by carbodiimides.⁶⁴⁵ Antifoliant,⁶⁴⁶ fungicide,⁶⁴⁷ and antitumor⁶⁴⁸ activities are all observed with carbodiimides. Carbodiimides may be used in pesticide formulations of thiophosphates to prevent hydrolytic decomposition.⁶⁴⁹ Insecticidal and acaricidal^{650,651} and ectoparasitocidal^{652,653} activities have also been observed with carbodiimides.

Mitocidal and lepidopterocidal activities are observed with isothiourea species;⁶⁵⁴ this may be due to the operation of a controlled-release mechanism producing carbodiimides (eq 249).



g. Other Membrane Activities of Carbodiimides

Low concentrations of carbodiimides modify the effector portion of the β -adrenergic receptor of the adenylyl cyclase system in frog erythrocytes.⁶⁵⁵ Dicyclohexylcarbodiimide blocks the catecholamine activation of adenylyl cyclase in turkey erythrocytes.⁶⁵⁶ Carbodiimide modifies neuromuscular transmission in the frog⁶⁵⁷ and has been examined as a possible affinity label for the acetylcholine receptor at the frog neuromuscular junction.⁶⁵⁸ Dicyclohexylcarbodiimide has been shown to affect the photoinduced changes in electric potential differences and resistance in plasma membranes of Nitella cells.⁶⁵⁹

h. Action on Nucleotides and Nucleosides

Water-soluble carbodiimides have been shown to inhibit transcription of supercoiled PM2 DNA with *E. coli* B RNA polymerase.^{660,661} Reaction of carbodiimides with cytidine 2'(3')-phosphate yields an adduct which leads to cyclic 2',3'-phosphate, hydrolysis product, and N'-amidyl product similar to LXIII.⁶⁶² Uridine reacts to give an N-substituted product (LXIII).^{663-665,666} Polynucleotides react with positively charged water-soluble carbodiimides much faster than do the monomers owing to the electrostatic effect.^{661,66}

VIII. Carbodiimides and Polymer Chemistry

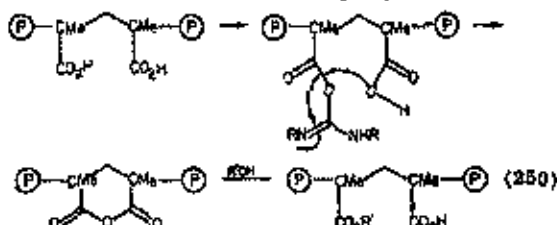
A. General

Since the discovery of catalytic methods for the preparation of carbodiimides from the readily available isocyanates, carbodiimides have been increasingly studied as precursors for polymer materials. At the same time the use of carbodiimides as reagents in polymer chemistry has been increasing, and we have

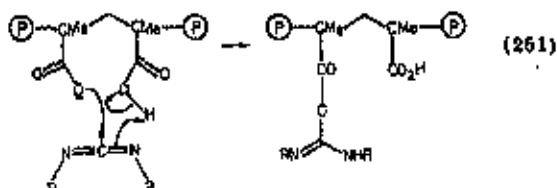
already dealt with this aspect for biological polymers. Carbodiimides may participate in polymer structures as part of the backbone (chain or cross-link) or as a pendant group. Incorporation in polymers by polymerization of carbodiimides is dealt with elsewhere in the review with regard to dimers and trimers; polymerization by condensation with an appropriate reactive group such as diamine is discussed under chemical properties.

B. Modification of Polymers

Syndiotactic poly(methacrylic acid) is esterified by alcohols in the presence of carbodiimides to give alternate ester links.²⁵²⁻²⁵⁴ Strong acid catalysts yield random esterification; the explanation is believed to involve anhydride formation from the isomer, yielding one ester for every two carboxyl groups (eq 250). The



simple explanation (eq 250) can only be partially correct, as it requires the formation of alternating isocure groups. This condition can arise through concerted acid catalysis, as discovered recently (eq 110),²⁵⁵ and we propose the initial reaction to be as in eq 251.



Water-soluble carbodiimides have been used to couple glycine ethyl ester with poly(acrylic acid); it is thought that the reaction proceeds through the carboxylic anhydride.²⁵⁶

Carboxyl group site-site interactions have recently been shown to occur in functionalized cross-linked polystyrene resins. Dicyclohexylcarbodiimide treatment of the carboxyl resin was followed by infrared spectroscopy, and the appearance of a band at 1785 cm⁻¹ indicates a lower limit for anhydride formation.²⁵⁶ A band at 1660 cm⁻¹ was proposed to be due to the N-acylurea group. Previous to this work²⁵⁶ there was no definitive evidence, and it was generally assumed that there was little or no interaction between groups in cross-linked polymers.

Hardening of amino/carboxyl emulsion polymers has been affected with dicyclohexylcarbodiimide to yield films.²⁵⁷ Butadiene/acrylonitrile copolymers with 0.09% carboxyl group content have been cross-linked with a bi-functional carbodiimide (LXIV).²⁵⁸ Water-soluble



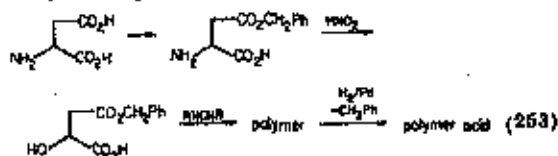
carbodiimides suitable for polymer modification have been synthesized from basic carbodiimides and sulfones (eq 252).²⁵⁹



Hemin has been derivatized as amide and ester by using water-soluble carbodiimides.²⁶⁰ Hydroxyl polymers may be modified to yield more hydrophobic species by using dicyclohexylcarbodiimide with tetrafluoroboric acid through O-alkylisocure formation²⁷¹ and to contain guanidine groups.²⁷² The latter species with *M*_n 400-2000 are useful in the preparation of polyurethanes.²⁷³ Fluoroaliphatic carbodiimides have been used to impart oil- and water-repellent finishes to nylon and polyester fabric²⁷⁴ and also to leather.^{275,276}

C. Polymerization Catalysts and Reagents

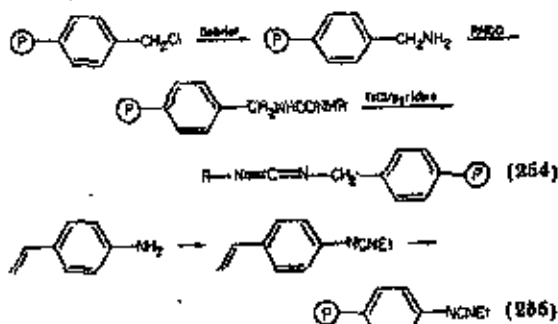
Carbodiimides may be used to polymerize malic acid to yield a possible protease inhibitor (eq 253).²⁷⁷



Protamine sulfate may be polymerized by carbodiimides;²⁷⁸ dicyclohexylcarbodiimide induces the formation of a tacky fire-resistant polyphosphoramidate from diamines and inorganic phosphate.²⁷⁹ Carbodiimides catalyze the polymerization of lactones;²⁸⁰ the reaction requires a catalytic amount of sodium.

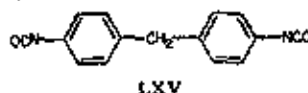
D. Polymers with Functional Carbodiimides

Polymers with pendant carbodiimides have been prepared and used as dehydrating agents (eq 254²⁸¹ and 255²⁸²).



E. Insulators and Heat-Resistant Plastics

Cross-linked organosilicon carbodiimide polymers have been prepared and found to be useful for electrical insulating coatings and high-temperature paints.²⁸³ Cross-linked carbodiimide polymers with electrical insulating properties may be prepared by using bis(isocyanatophenyl)methane (LXV) and a catalyst.²⁸⁴ Lac-

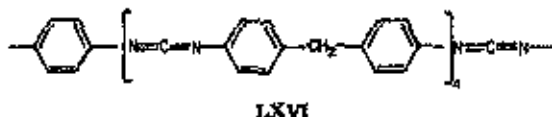


cyanurate foams²⁸⁵ and other plastics containing poly-carbodiimides are useful as heat-stable materials.²⁸⁶⁻²⁸⁸

The fire resistance of carbodiimide foams based on polyols from trichlorobutene oxide or epichlorohydrin has been reviewed.⁶⁹⁰

F. Reinforcements

Poly(4,4'-diphenylmethanecarbodiimide) (LXVI) at 1% in nylon increases the relative melt strength and viscosity.⁶⁹¹ Polycarbodiimides have been used as fiber



reinforcements^{692,693} and in strengthening glass-fiber compositions.^{694,695} The strengthening effect probably comes from the rigid nature of the polymer carbodiimide which has relatively few degrees of rotational freedom.

G. Adhesives and Microcapsules

Polycarbodiimides have been used as adhesive primers.⁶⁹⁶⁻⁶⁹⁸ Film forming carbodiimide homo- or copolymers have been used in microcapsulation techniques for pressure-sensitive copy paper.⁶⁹⁹⁻⁷⁰¹

H. Foams and Microcellular Elastomers

Catalytic formation of polycarbodiimides from bis-isocyanate monomers results in carbon dioxide liberation (eq 256); use is made of this phenomenon in the



production of rigid cellular foams for mouldings, sealing compounds, reinforcements, and other useful purposes.⁷⁰²⁻⁷⁰³

I. Stabilization of Polymers with Carbodiimides

The instability of cross-linked polyesters is due to the hydrolysis of the ester link which is accelerated as the carboxyl groups are formed.⁷²⁴⁻⁷²⁷ Scavenging the carboxyl end groups with carbodiimide has been shown to prevent hydrolysis.⁷²⁴ Monomeric carbodiimides⁷²⁸⁻⁷³⁰ and poly(carbodiimides)⁷⁴⁰⁻⁷⁴⁵ have been suggested as stabilizing additives for polyesters. The blocking function may be due to formation of *N*-acylurea or to formation of ester links with adjacent hydroxyl groups. The stabilizing effect is felt in both aqueous emulsions⁷³¹ or solutions⁷³² of polyester as well as in the bulk polymer.

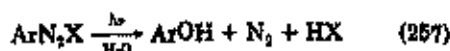
The storage life of liquid poly(isocyanates) is improved by the addition of carbodiimides which presumably scavenge water.⁷⁴⁶⁻⁷⁵¹

IX. Photography and Related Subjects

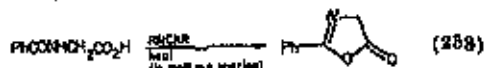
Carbodiimides have been used extensively as gelatin hardeners;⁷⁵²⁻⁷⁵⁹ the action of the carbodiimide is to link carboxyl and amino groups on the gelatin chains, effectively cross-linking the polymer.⁷⁵⁶ Carbodiimides also have application as "antifoggants".^{757,758}

Applications for carbodiimides have been found in

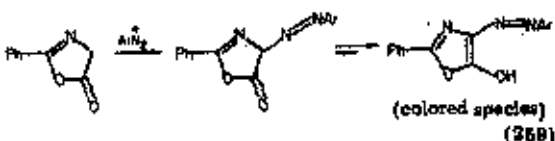
the generation of azo-dye images from light-sensitive heat-developable diazotype compositions. These compositions comprise a light-sensitive diazonium compound, a normally solid carbodiimide, and a normally solid diazo-coupler precursor. The latter is converted to a reactive coupler by dehydration with the carbodiimide (effected by melting). The light process converts diazo species to a phenol (eq 257), and the re-



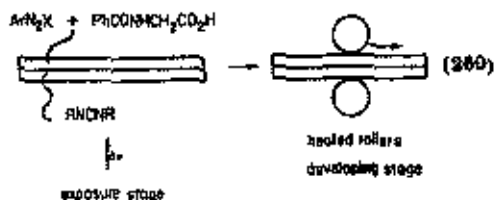
maining diazo compound couples with the oxazalone (eq 258, 259) in the developing process effected by heat.



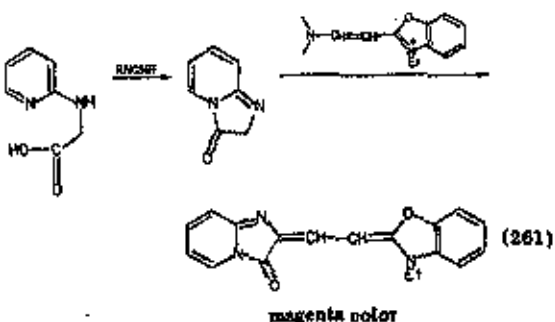
Diazo coupling:



The process may be envisaged as in eq 260; the light-exposed areas are colorless.⁷⁶⁰

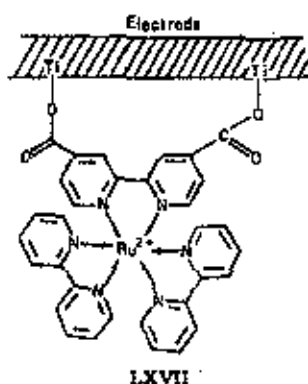


A thermographic process involves printing by infrared radiation; the heat warms and mixes solid carbodiimide with the dye precursor which cyclizes to give the dye (eq 261).⁷⁷⁰



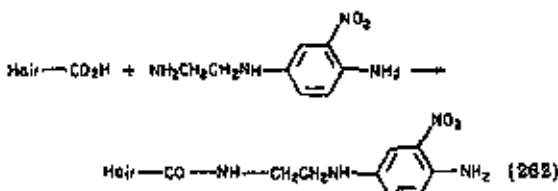
Carbodiimides have been used as stabilizing agents for a photosensitive polymer composed of cinnamate attached to a polyether chain through ester links. The carbodiimide presumably acts as a water scavenger.⁷⁷¹ Adhesion of the gelatinous photographic material to polyethylene terephthalate supports has been improved through the addition of carbodiimides; the mechanism probably involves the formation of ester linkages.⁷⁷²

Titanium(IV) oxide electrodes may be dye sensitized by coupling with a bipyridylruthenium complex; ester links are formed from the TiOH group and carboxyl groups through the action of carbodiimide (LXVII).⁷⁷³

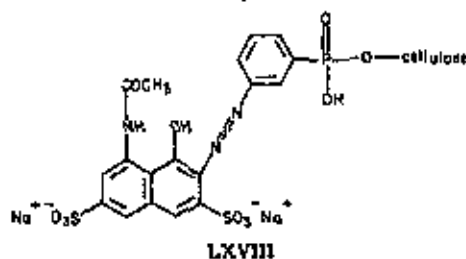


X. Dyeing and Related Subjects

Most of the applications of carbodimides to dyeing refer to improving the wash-fastness of the dye. Wool^{774,775} and hair⁷⁷⁶ dyeing is improved by treatment with carbodimides. 1-Ethyl-3-[3-(trimethylammonio)propyl]carbodiimide fixes the red dye [2-nitro-4-[(8-aminooethyl)amino]aniline] to hair, probably via an amide link (eq 262).⁷⁷⁶ Neutral or acid condi-



tions may be used to couple a phosphorus dyestuff with a cellulosic material by using carbodiimide (LXVIII).⁷⁷⁷

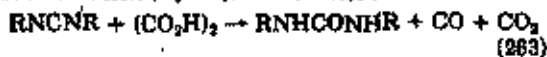


The cosmetic qualities of bleached human hair may be improved, presumably by some form of internal cross-linking, by treatment with 1-cyclohexyl-3-(N-methylmorpholino)carbodiimide.⁷⁷⁸

XI. Analysis

A. Assays for Carbodiimide

The estimation of carbodimides has been relatively unsatisfactory in that no reliable, sensitive, color assay has been available. Despite increasing use of carbodimides at low concentrations as biological effectors, the only assays available until the present involved the estimation of carbon monoxide from oxalic acid under anhydrous conditions or of excess oxalic acid by back-titration (eq 263).² The latter method was used



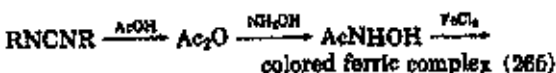
to determine carbodiimide in polymer supports⁷⁷⁹ and in other analyses.^{780,781} GLPC analysis⁷⁸¹ and infrared absorption spectroscopy⁷⁸² have been used as assays for carbodimides. An interesting technique for polymer-supported carbodimides involved reaction with acetic acid to give an equivalent amount of acetic anhydride which was then analyzed by GLPC.⁷⁸³ Paper or thin-layer chromatograms of free dicyclohexylcarbodiimide were exposed to iodine vapor; colored spots formed at the carbodiimide which disappeared in the free atmosphere.⁷⁸⁴

Recently a sensitive method for estimation of carbodimides has been reported to involve a color development (400 nm) when the water-soluble carbodiimide is added to a pyridine buffer at pH 7 containing ethylenediamine.⁷⁸⁵ The cause of the color is not apparent, but concentrations in the assay mixture down to 50 μM of carbodiimide may be estimated.

Two methods of assay based on the known chemistry of carbodimides have been developed.⁷⁸⁶ The first method involves guanidine formation by reaction of the carbodiimide with 1 M anilinium hydrochloride followed by quenching in 1 M HCl and reading the absorption at 230 nm (eq 264). The phenylguanidine



spectrum has a very large absorbance at 236 nm, and the large extinction coefficient at 230 nm (ϵ 1×10^4) allows concentrations to be measured down to 0.2 μM . The second technique⁷⁸⁶ relies on the formation of an amount of acetic anhydride equivalent to the carbodiimide by addition of acetic acid. The acetic anhydride is quenched in alkaline hydroxylamine and the color developed (at 540 nm) with ferric chloride solution (eq 265).⁷⁸⁶ The sensitivity of this method is close to that



claimed for the pyridine/ethylenediamine technique.⁷⁸⁵

B. Determination of Carboxylic Acids

Carboxylic acids have been assayed by using carbodiimide to promote ester formation followed by GLPC analysis.⁷⁸⁷ A colorimetric method utilizes carbodiimide as a coupling agent to yield hydroxamic acid with hydroxylamine; color is developed with ferric chloride,⁷⁸⁸⁻⁷⁹⁰ and the chemical basis of the method is as described in eq 266. The assay of carboxylic acids in biological polymers is dealt with earlier.

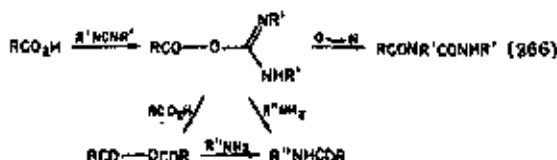
C. Carbodiimide in Biological Assays

Carbodiimides have been used as coupling agents to form conjugates between steroids and chemiluminescent species; these act as the basis for an assay of plasma progesterone through antibody-enhanced chemiluminescence.⁷⁹¹ Conjugate formation through carbodimides is the basis of the immunoassay of secretin and IBQ.^{792,793} Antibodies have been coupled to carboxymethylcellulose through carbodiimide to form the basis of an immunoassay.⁷⁹⁴ The preparation of tritium-labeled dicyclohexylcarbodiimide for the assay of biological species has been described.⁷⁹⁵

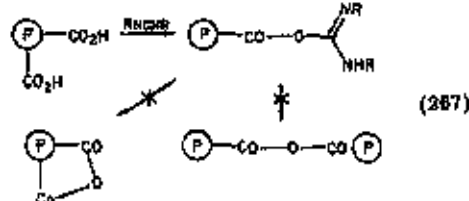
XII. Uses of Carbodiimide in Synthesis

A. Peptide Synthesis

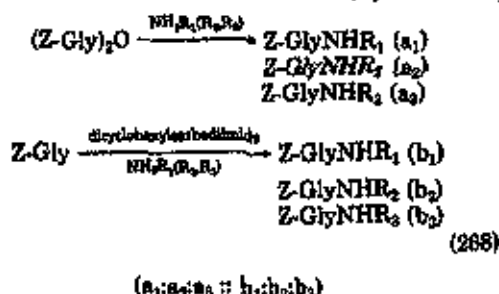
Peptide synthesis continues to utilize the carbodiimide "method" and its major coupling procedure.⁶⁰⁻⁶² The mechanism of peptide coupling involves the overall scheme given in eq 266 (see also eq 103). There are two



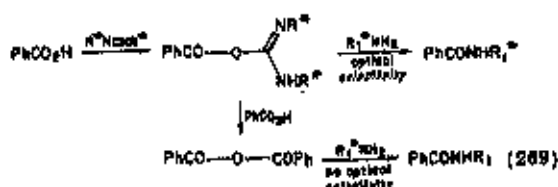
main side reactions, namely, the O→N acyl shift to give N-acylurea and racemization. The anhydride and O-acylurea pathways to peptide remain as protagonists. Reaction of dicyclohexylcarbodiimide couples monomer amines to a cross-linked polymer containing pendant carboxyl groups; it is unlikely that anhydride formation could occur between polymer acids even in an intrapolymer reaction (eq 267).⁶³ However linear poly-



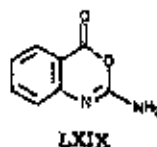
(acrylic acids) appear to form anhydrides readily,⁶⁴ and even some carboxyl functionalized polystyrenes form intramolecular anhydrides.⁶⁵ The product distribution in the reaction of a mixture of three amino acid amines with benzyloxycarbonylglycine anhydride ((Z-Gly)₂O) and benzyloxycarbonylglycine (Z-Gly) with carbodiimide is different under identical conditions; this indicates that the O-acylurea path predominates for the carbodiimide method in solution (eq 268).^{61,62} A



similar method involves the use of an optically active carbodiimide coupling on optically inactive acid (PhCO₂H) with an optically active amine. The anhydride pathway should involve no optical selectivity because the anhydride is symmetrical. The O-acylurea, however, is an asymmetric molecule, and the observation of optical selectivity in the synthesis indicates that the O-acylurea pathway is being followed (eq 269).⁶¹ Carbodiimides with only one optically active substituent have been found to be weakly selective in the coupling of cyclohexylamine with racemic carboxylic acids.⁶² The presence of excess acid in the coupling



reaction leads to anhydride being the major path; when acid is present in equimolar amount with respect to carbodiimide, the O-acylurea pathway predominates.⁶¹ The isolation of the O-acylurea has been claimed during a peptide synthesis in solution.⁶² The anhydride path is not a necessary requirement as the benzoxazine analogue of the O-acylurea (LXIX) does

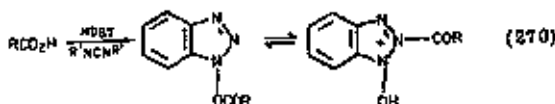


LXIX

not require the action of a carboxyl group in order to acylate amines.⁶⁰⁻⁶² Under the conditions of solid-phase peptide synthesis using a resin-bound amino acid as the amino group the mechanism which predominates is the anhydride.⁶¹ The solution studies indicate that neither mechanism is necessarily predominant but depends on the conditions employed. The relatively slower reactions with solid-phase amine will presumably allow the O-acylurea to react with the usually less nucleophilic carboxyl group to yield the anhydride which then becomes the major acylator. The latter conditions may also be reached by increasing the carboxylic acid concentration.⁶¹ The evidence for the two pathways has been reviewed.^{61,62}

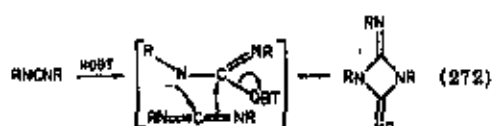
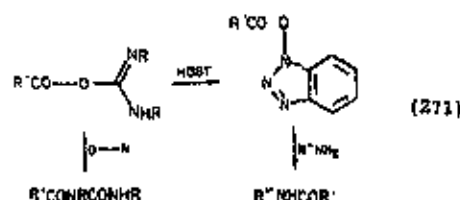
The overall reaction of leucylleucine synthesis in aqueous solution effected by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide involves a maximal yield at 0.1 M HCl;⁶¹ the reason for this result is not clear.

The racemization problem is acute in carbodiimide-mediated coupling. Racemization decreases according to carbodiimide structure in the order C₆H₁₁NCNC₆H₁₁ > PhCH₂NCNEt > 4-CH₃C₆H₄NCNEt > PhNCNEt.⁶² Coupling with carbodiimides is accelerated by catalysts such as N-hydroxybenzotriazole and N-hydroxysuccinimide which also tend to suppress racemization.^{61,62} The action of these catalysts is probably as a transfer agent (eq 270), but it is not certain which group in, for

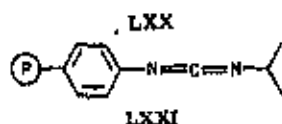
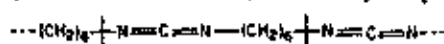


example, hydroxybenzotriazole (HOBT) is acylated (eq 270).

The problem of N-acylurea formation arises especially when long reaction times are involved,⁶³⁻⁶⁵ as in solid-phase methods. This problem can be resolved if a reactive nucleophile such as HOBT is added to react with the O-acylurea to yield a secondary reacting species (eq 271). N-Hydroxybenzotriazole catalyzes the formation of a further byproduct, namely, the diazotidine (eq 272), in a peptide synthesis⁶⁶ probably by a stepwise cycloaddition reaction involving the acyl hydroxybenzotriazole.

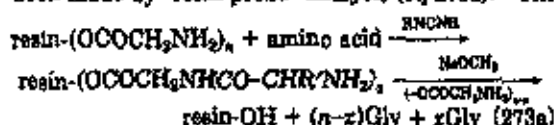


Solid-phase carbodiimides have been utilized as dehydrating agents in peptide coupling; both long-chain polymers⁵⁴⁰ and pendant side chains⁵⁴⁰⁻⁵⁴³ have been used (LXX⁵⁴⁰ and LXXI⁵⁴⁰). The cyclic peptide



gramicidin S has been synthesized by using a resin-bound carbodiimide with HOBT additive.⁵⁴³

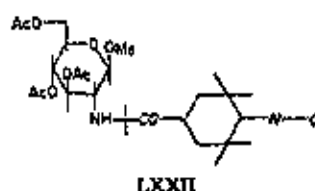
Solid-phase peptide synthesis has utilized carbodiimides for coupling; reaction with radioactive dicyclohexylcarbodiimide has shown that less than 0.2% of the polymer-bound amine reacts directly with the reagent.⁵⁴² Studies have been made of the availability of carbodiimide-activated N-protected amino acids in solid-phase synthesis.^{544,545} Carbodiimide has been shown to be superior to the mixed anhydride or Woodward method of peptide coupling in solid-phase synthesis.⁵⁴⁶ The evaluation of carbodiimide stoichiometry in the reaction of glycine with amino acid has been made by "resin probe" analysis (eq 273a). The



glycyl-resin is reacted with amino acid derivative in the presence of dicyclohexylcarbodiimide and the product cleaved from the resin; the ratio of free glycine to glycyl peptide as determined by amino acid analysis gives a measure of the stoichiometry of the reaction. The method of course suffers from the grave disadvantage that some of the glycine esters will be protected from reaction by the polymer architecture. A pentapeptide fragment of substance P has been synthesized by using Sephadex LH-20 as the polymer support.⁵⁴⁵

B. Amide Synthesis

Dicyclohexylcarbodiimide has been used to couple nitroxide spin-labeled species with monosaccharides (LXXII).⁵⁴⁷ Carbodiimide has been used as a reagent (albeit an expensive one) for coupling amine and acid groups to synthesize potential local anesthetics from benzocaine,⁵⁴⁸ analgesic and antiinflammation drugs from 2-aminobenzothiazoles,⁵⁴⁹ and ureas direct from carbon dioxide and amines.⁵⁵⁰

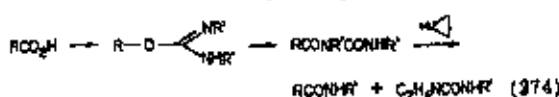


Kinetic studies on N-arylamide formation indicate that anhydride production is the rate-limiting step.⁵⁵¹

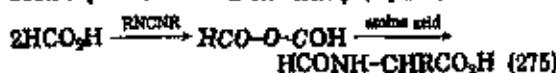
A complicating feature in amide synthesis is a side reaction, presumably caused by the attack of amine on the N-acylurea. In the dicyclohexylcarbodiimide coupling of an aziridine with a fatty acid some 22% of the product is N-cyclohexylamide and N-cyclohexyl-N'-aziridinylurea (eq 273b and 274).⁵⁵²



R' = cyclohexyl

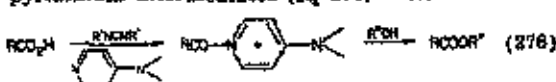


The very high nucleophilicity ("supernucleophile") of the aziridine moiety⁵⁵³ probably accounts for the cleavage of the N-acylurea; we would therefore not regard this problem as generally very troublesome, as most amines are not "supernucleophiles". A new technique for formulating sensitive amino acids has been reported to work efficiently (eq 275).⁵⁵⁴

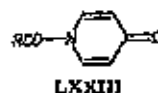


C. Ester and Anhydride Formation

Carbodiimide continues to provide a useful route to ester; the preparation of thiol esters has been exemplified⁵⁵⁵ and the difficulty experienced with simple alcohols may be relieved by the use of pyridine catalysts⁵⁵⁶⁻⁵⁶⁰ which probably act by formation of acylpyridinium intermediates (eq 276). An alternative



pyridine derivative is the 4-hydroxy species; acylation still occurs at nitrogen to give the N-acyl-4-pyridine species (LXXIII).⁵⁶¹⁻⁵⁶³



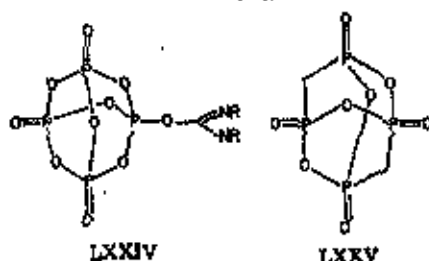
Toluenesulfonic acid has been employed as a catalyst for ester formation using carbodiimides;⁵⁶⁴ the esterification method is generally used for exotic esters on account of the cost of the reagent.^{565,566}

Carbodiimides have been used as reagents for the synthesis of rare symmetric¹ anhydrides⁵⁶⁷⁻⁵⁶⁹ and formic anhydride.⁵⁶⁸

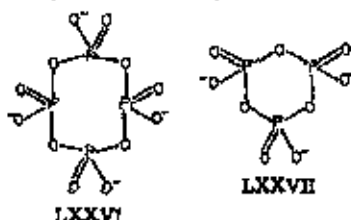
D. Phosphorus Esters

Reaction of dicyclohexylcarbodiimide with phospho-

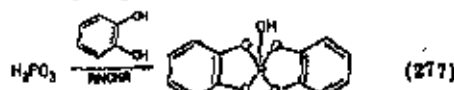
phoric acid leads to an anhydride complex analogous to phosphorus pentoxide (P_2O_5 , LXXIV).^{870,871} Ms.



thylenebisphosphonic acid ($H_2O_2PCH_2PO_2H_2$) yields the methylene analogue of P_4O_{10} (LXXVI).⁸⁷⁰ The esterification of phosphonic acid mediated by carbodiimides involves phosphonic acid anhydrides (LXXVII); in the



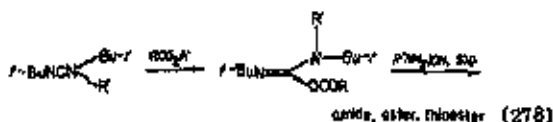
presence of tertiary amine the trimer LXXVII is the major intermediate.⁸⁷² The stepwise esterification of phosphate competes with condensation to form polymeric phosphoric acids and their esters. Esterification is promoted by increased acidity, smaller size, and increased concentration of the alcohol.⁸⁷³ Pyridinephosphonic acids have been esterified by the use of carbodiimide⁸⁷⁴ and the pentacoordinate phosphorane (eq 277) from phosphorous acid.⁸⁷⁵ Carbodiimides



continue to be used in nucleotide synthesis,⁸⁷⁶⁻⁸⁸³ and several reports have indicated phosphonic anhydride intermediates.⁸⁷⁸⁻⁸⁷⁹

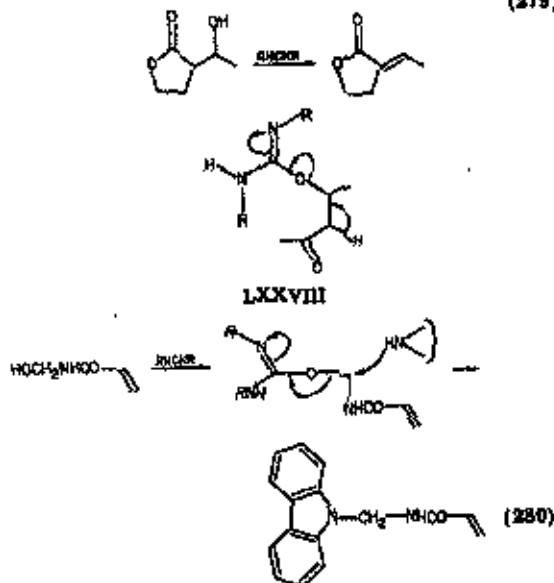
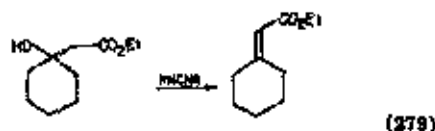
E. Miscellaneous Dehydration Reactions

Toluenesulfonic esters have been synthesized from toluenesulfonic acids and alcohols.⁸⁸⁴ A very powerful agent for a number of dehydration reactions involves the linear N-alkylated di-*tert*-butylcarbodiimide (XXVI) or the dimeric analogue (XXVII)^{881,882,885} (eq 278).



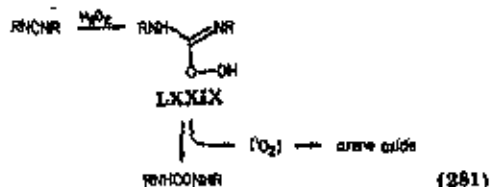
Carbodiimides effect the dehydration of β -hydroxycarbonyl moieties (eq 279),⁸⁸⁴ presumably through the intermediate LXXVIII.

An intermediate similar to LXXVIII is probably involved in the formation of a tertiary amine from carbazole and *N*-(2-hydroxymethyl)acrylamide in the presence of toluenesulfonic acid (eq 280).



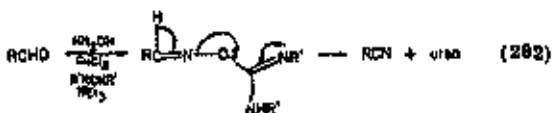
F. Use in Oxidation

We dealt with the considerable literature on the dimethyl sulfoxide-carbodiimide method for oxidizing alcohols to carbonyl moieties earlier in this review. Hydrogen peroxide with carbodiimide has been shown to react with polycyclic aromatic hydrocarbons to form arene oxides which are possible intermediates responsible for the carcinogenicity and mutagenicity of polycyclic aromatic hydrocarbons.^{886,887} The mechanism is shown to involve an intermediate (LXXIX) which degrades to urea and oxidation products (eq 281). The



oxidation is supposed to involve singlet oxygen.⁸⁸⁸

Aldehydes may be oxidized to the acid level oxidation state by a process involving dehydration of an oxime (eq 282).^{888,889} *o*-Hydroxy substituents block the oxidation.⁸⁸⁹



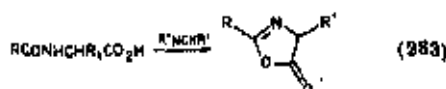
G. Diazoketone Synthesis

The synthesis of diazoketones from acid chlorides with diazomethane is not always possible due to the

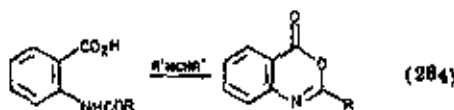
sensitivity of the acid acylamino acid chlorides give the oxazolinones. Interaction of diazoalkane with a mixture of acid and carbodiimide effects the synthesis.^{861,862} The reaction probably involves the anhydride as an intermediate in the case of simple acids.⁸⁶²

H. Heterocycle Formation through Dehydration

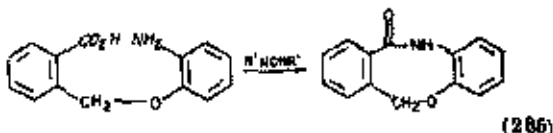
Oxazolinones are well-known as troublesome intermediates in peptide syntheses through the N→C terminal strategy and have been prepared from N-acylamino acids by interaction with carbodiimides (eq 283).⁸⁶⁰⁻⁸⁶³ Carbodiimides have also been used in



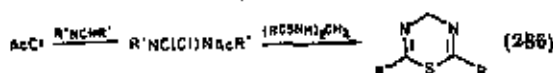
benzoxazinone synthesis (eq 284).^{869,860} The synthesis



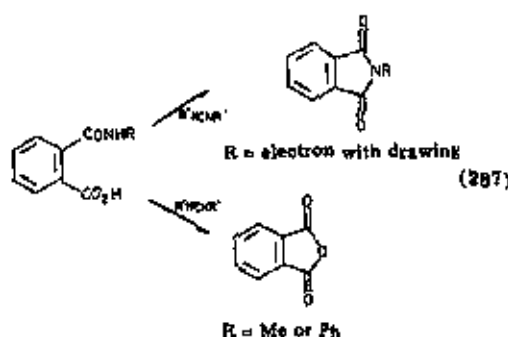
of dibenzoxazocines has been accomplished for 2-carboxybenzyl 2-aminophenyl ether (eq 285)⁸⁶¹ using carbodiimide. Intramolecular elimination of hydrogen



sulfide has been effected from bis(thionacylamido-methane) using an acetylated carbodiimide (eq 286).⁸⁶²

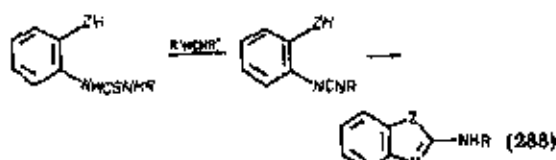


The dehydration of phthalamic acids yields the isophthalimide if the nitrogen substituent is methyl or phenyl and the imide when the substituent is electron withdrawing (eq 287).⁸⁶³ Bentimidazoles, benz-

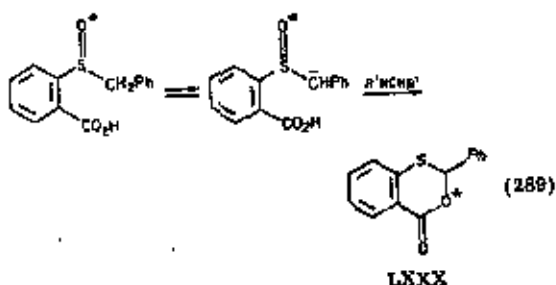


thiazoles, and benzoxazoles have been obtained by desulfurization of thionamides.⁸⁶⁴ The reaction probably involves the formation of a carbodiimide intermediate (eq 288; see, e.g., eq 141⁸⁶⁵).

Dicyclohexylcarbodiimide effects an intramolecular Pummerer reaction in a sulfone to yield the 1,3-benzothioxan-4-one LXXX. Oxygen-18 transfer takes place (eq 289).⁸⁶⁶

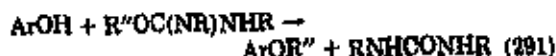
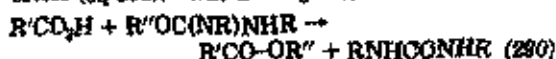


Z = O, NH, or S

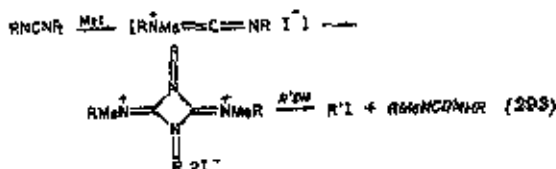


I. Alkylation Reactions

Carbodiimides have been employed as precursors of O-alkylisoureas which are proving to be valuable alkylating agents.⁸⁶⁷⁻⁸⁷⁰ A recent review⁸⁶⁸ indicates that O-alkylisoureas may be used in the formation of esters (eq 290), phenyl esters (eq 291), and phosphate esters (eq 292). The driving force of these reactions



is the thermodynamic stability of the urea; sulfur, nitrogen, and carbon may also be alkylated. N-Alkylated carbodiimides (which are probably dimers) may be used as alkylating agents (eq 293).⁸⁴⁶



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