THE CHEMISTRY OF CARBODIIMIDES

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CONTENTS

I. INTRODUCTION

Carbodiimides (I) are a class of easily accessible compounds which do not appear to be generally known. Although some aromatic carbodiimides were

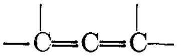
$$RN{=}C{=}NR'$$

$$\text{I: } R, R' = \text{alkyl or aryl}$$

prepared over seventy years ago, interest in the chemistry of these substances has recently been revived and a large number have been prepared and studied. These factors have prompted the preparation of this review.

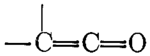
Structurally, the carbodiimides can be considered to be derived from the parent substance $HN{=}C{=}NH$ (43), which probably exists mainly as the tautomeric form, cyanamide, $H_2NC{\equiv}N$ (6, 20, 25, 28, 68, 72, 87). The disubstituted derivatives include, in addition to the carbodiimides, the dialkylcyanamides, R_2NCN (6, 14, 18, 28). The two classes differ markedly in their reactions.

The carbodiimides are one of the several classes of unsaturated compounds with twinned double bonds:



$-\overset{|}{C}=C=\overset{|}{C}-$

Allenes



$-\overset{|}{C}=C=O$

Ketenes

$R{-}N=C=O$

Isocyanates

$R_2C=C=N{-}R$

Ketenimines

The chemistry of the first three classes is well known (1, 23, 45, 56, 73), whereas only a few ketenimines have been prepared (74, 75) and are being studied. It is interesting to compare the properties of these classes of compounds with those of carbodiimides. Reference is made to this aspect later.

II. Preparation of Carbodiimides

A. FROM THIOUREAS

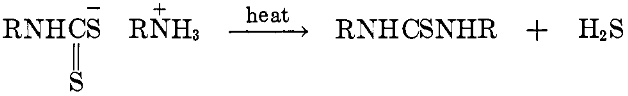
The most general method for the preparation of carbodiimides consists in the removal of the elements of hydrogen sulfide from a disubstituted thiourea (II).

$$\underset{\text{II}}{RNHCSNHR'} \xrightarrow{-H_2S} RN=C=NR'$$

R and R′ = alkyl or aryl.

1. *Preparation of thioureas*

The symmetrical thioureas (II: R = R′ = alkyl or aryl) are conveniently prepared from the corresponding amines and carbon disulfide. An aliphatic amine forms first a salt of a substituted dithiocarbamic acid, which on continued refluxing in solvents (e.g., ethanol) loses hydrogen sulfide to form a thiourea.



$$RNH\underset{\underset{S}{\|}}{C}\overset{-}{S}\quad R\overset{+}{N}H_3 \xrightarrow{heat} RNHCSNHR + H_2S$$

An arylamine yields a thiourea directly on being refluxed, usually with an excess, of carbon disulfide in an organic solvent (e.g., benzene) (17, 21, 99). Generally, the above reactions proceed in excellent yield.

The unsymmetrical thioureas (II) are prepared readily by the reaction of alkyl- or arylamines with alkyl or aryl isothiocyanates (mustard oils) (64, 66, 67, 94, 99).

$$RNCS + R'NH_2 \rightarrow \underset{\text{II}}{RNHCSNHR'}$$

R, R′ = alkyl or aryl.

2. *Conversion of thioureas to carbodiimides*

Yellow mercuric oxide was first used for the formation of aromatic carbodiimides from the corresponding thioureas (83, 84, 85) and has remained the most general reagent.

$$\underset{s\text{-Diphenylthiourea}}{C_6H_5NHCSNHC_6H_5} + HgO \rightarrow \underset{\text{Diphenylcarbodiimide}}{C_6H_5N=C=NC_6H_5} + HgS + H_2O$$

The cheaper lead oxide has also been successfully employed in some cases, but it does not appear to be as effective as mercuric oxide (see below). Instances are also known where it was not possible to prepare carbodiimides by the use of lead oxide (94). The ease of "desulfurization" of thioureas depends on the nature of the substituents.

A large number of carbodiimides have been prepared satisfactorily through the use of metallic oxides. More recently, detailed study has been made of the "desulfurization" reaction for the improved preparation of aromatic carbodiimides by Zetzsche and collaborators (99) and of aliphatic carbodiimides by Schmidt and coworkers (62, 65). These studies have been mainly concerned with the influence of the solvent, the temperature, and the amount and the physical state of the metallic oxide on the rate of reaction in order to minimize the side reactions. Of the latter, the most serious is the reaction of the water produced with the carbodiimide to form a urea. (The formation of some amounts of a urea has been

$$RN{=}C{=}NR + H_2O \rightarrow RNHCONHR$$

observed by most workers.) Other side reactions are (*1*) the formation of traces of isothiocyanates and guanidines and (*2*) polymerization, especially of aromatic carbodiimides.

A number of solvents can be used to dissolve the aliphatic thioureas (62). Often the reaction proceeds smoothly at room temperature in an ethereal solution of the thiourea. If the reaction is sluggish, ether can be replaced by benzene or carbon disulfide; the use of the latter, however, gives rise to certain sulfur-containing byproducts which might not be easily removed by distillation (62). The diarylthioureas are rather insoluble substances, and the above solvents are often not suitable. Boiling acetone has been recommended as a general solvent for the purpose, even though the thiourea might not completely dissolve at first (99). Higher-boiling solvents, e.g., toluene, cause polymerization of aromatic carbodiimides. Also other byproducts, e.g., guanidines, begin to be formed in increasing amounts (52).

In the heterogeneous reaction of dissolved or suspended thioureas with metallic oxides, the actual form of the latter is important. Precipitated yellow mercuric oxide (62) and some very finely divided commercial preparations of lead oxide ("Tegoglaette" (98, 99)) have been found to be very active. Generally an excess of the metallic oxide is employed. Excellent yields of a large number of aliphatic carbodiimides have been obtained by using 2.5 times the theoretical amount of the oxide (62). However, in the preparation of aromatic carbodiimides, the use of a large excess of the reagent has been claimed to be harmful, because it accelerates the formation of ureas from carbodiimides; a 50 per cent excess has been recommended (99). Sometimes in the more difficult cases, the addition of the metallic oxide is carried out in portions and elevated temperatures are employed (98).

The time of the reaction varies in different cases. Very often a few hours are sufficient for the completion[1] of the reaction. The influence of the solvent on the

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[1] This can be tested by shaking an aliquot of the clear filtrate from the reaction mixture with ammoniacal silver nitrate; no darkening should be observed.

speed of the reaction has already been mentioned. In boiling acetone half an hour was usually found to be sufficient, but in some cases much longer times and higher temperatures have been necessary (99).

With the hope of eliminating the formation of urea, dehydrating agents such as calcium chloride (54) and sodium sulfate (62, 64) were added to the reaction mixture to remove the water formed. The azeotropic removal of water from the reaction mixture has also been tried (98), but these devices apparently are without appreciable effect. Obviously, increased rate of the desulfurization reaction means shorter contact of the carbodiimide with water. In fact, the use of an aqueous suspension of freshly precipitated mercuric oxide gave highly satisfactory results (65). It is not known whether this modification can be applied to the preparation of aromatic carbodiimides.

Some interesting observations have been made on the effect of adding sulfur to the reaction mixture (finely divided lead oxide was employed in these experiments) (99). Very small amounts have a pronounced catalytic effect on the desulfurization reaction; much larger amounts appear to retard simultaneously the side reactions, e.g., urea formation and polymerization (p. 472 of reference 99). As a result of these detailed studies, highly satisfactory procedures have been described for the preparation of several aromatic carbodiimides (99).

Finally, a welcome modification for the large-scale oxidation of some dialkylthioureas involving the use of the easily prepared alkaline solution of sodium hypochlorite has recently been described (63). The products are, however, contaminated and purification is sometimes troublesome. Some urea is certainly formed, but because of the cheapness of the materials used throughout, the method makes these compounds available in quantity.

$$\mathrm{RNHCSNHR' + 4NaOCl + 2NaOH \rightarrow RN{=}C{=}NR' + 4NaCl + Na_2SO_4 + H_2O}$$

The compounds which have been prepared by the desulfurization of thioureas are listed in table 1.

B. MISCELLANEOUS METHODS

Diethylcarbodiimide was first prepared by the novel reaction of ethyl isocyanate with triethylphosphine-ethylimine (III), which in turn was obtained from triethylphosphine and ethyl azide (74).

$$\underset{\text{Triethylphosphine}}{\mathrm{(C_2H_5)_3P}} + \underset{\text{Ethyl azide}}{\mathrm{C_2H_5N_3}} \rightarrow \underset{\text{III}}{\mathrm{(C_2H_5)_3P{=}NC_2H_5}} + \mathrm{N_2}$$

$$\underset{\text{III}}{\mathrm{(C_2H_5)_3P{=}NC_2H_5}} + \mathrm{C_2H_5N{=}C{=}O \rightarrow (C_2H_5)_3PO + C_2H_5N{=}C{=}N{-}C_2H_5}$$

The reaction of carbon dioxide with triethylphosphine-ethylimine (III) also furnished the carbodiimide, ethyl isocyanate being the intermediate.

$$\underset{\text{III}}{\mathrm{(C_2H_5)_3P{=}NC_2H_5}} + \mathrm{CO_2 \rightarrow (C_2H_5)_3PO + C_2H_5N{=}C{=}O}$$

TABLE 1

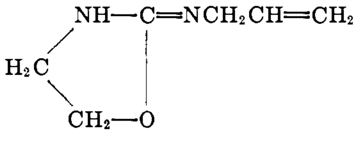
Carbodiimides prepared by the desulfurization of thioureas

CARBODIIMIDE	YIELD	REFERENCES
Symmetrical aliphatic carbodiimides		
Diallyl		(36, 61)
Dibenzyl	76	(94)
Dibornyl	84	(94)
Dibutyl	90	(35, 62)
Di-*tert*-butyl	93.5	(66)
Dicyclohexyl	86	(35, 62, 63)
Diethyl		(35, 62)
Diisobutyl	87	(62)
Diisopropyl	91	(35, 65)
Di-*l*-menthyl	82	(94)
Dimethyl		(36, 61)
Dioctyl		(55)
Dipropyl	93	(14, 62, 65)
Symmetrical aromatic carbodiimides		
Di-*p*-bromophenyl	50–65	(51, 52, 98)
Di-*o*-bromophenyl		(51)
Di-*p*-carbethoxyphenyl	85	(52)
Di-2,4-dibromophenyl		(51)
Di-2,5-dibromophenyl		(51)
Di-*p*-diethylaminophenyl	90	(99)
Di-*p*-dimethylaminophenyl	95	(98, 99)
Di-*p*-(*p'*-ethoxybenzeneazo)phenyl		(81)
Di-*p*-iodophenyl	60–85	(98)
Di-*p*-isobutylphenyl		(47)
Di-α-naphthyl	30	(24, 54)
Di-β-naphthyl	25	(24, 54)
Diphenyl		(35, 55, 84, 85, 98, 99)
Di-*p*-propylphenyl		(19)
Di-α-pyridyl	40–60	(98)
Di-*o*-tolyl		(16)
Di-*m*-tolyl		(51)
Di-*p*-tolyl	90	(98, 99)
Unsymmetrical carbodiimides		
Allylcyclohexyl	83	(62)
Allyl-2-hydroxyethyl* (2-allyliminoöxazolidine)	84	(62, 65)
Allyl-2-hydroxypropyl* (2-allyliminotetrahydro-1,3-oxazine)	72	(65)
Allylphenyl		(16, 99)
Allylpropyl	81	(62)
Allyltrityl	78	(6)
(*p*-Benzeneazophenyl)phenyl	58	(99)
Benzyltrityl		(6)
Bornyl(*p*-dimethylaminophenyl)		(94)

TABLE 1—*Concluded*

CARBODIIMIDE	YIELD	REFERENCES
Unsymmetrical carbodiimides—*Continued*		
(β-Bromoallyl)cyclohexyl	90	(66)
β-Bromoallyl(γ-dimethylaminopropyl)	86	(66)
(β-Bromoallyl)isopropyl	90	(66)
(β-Bromoallyl)propyl	93	(66)
β-Bromoallyl-*tert*-butyl	91	(66)
Cyclohexyl-*tert*-butyl	96.5	(66)
tert-Butyl(γ-dimethylaminopropyl)	91	(66)
tert-Butylisopropyl	92	(66)
tert-Butylmethyl	92	(66)
tert-Butylpropyl	89	(66)
Carboxyethylmethyl		(55)
p-Chlorophenylisopropyl		(35)
Crotylcyclohexyl	85	(62)
Cyclohexyl(*p*-dimethylaminophenyl)	70	(94)
Cyclohexyl(ethoxymethyl)	89	(64)
Cyclohexylisopropyl	95	(65)
Cyclohexyl(methoxymethyl)	88	(64)
Cyclohexylphenyl		(30, 59)
Cyclohexylpropyl	92	(65)
(*p*-Dimethylaminophenyl)-*l*-menthyl	67	(94)
(γ-Dimethylaminopropyl)isopropyl	89	(65)
(Dimethylaminopropyl)methoxymethyl	86	(65)
(γ-Dimethylaminopropyl)propyl	85	(65)
Dodecylisopropyl	87	(65)
(Ethoxymethyl)methyl	57	(64)
(Ethoxymethyl)isopropyl	85	(64)
Ethyl-2-methoxyethyl		(55)
Ethylphenyl		(86)
Ethylpropyl		(55)
Isohexyl(methoxymethyl)	87	(64)
Isopropyl(methoxymethyl)	84	(64)
Isopropylpropyl	90	(65)
(*p*-Methoxyphenyl)propyl		(35)
(Methoxymethyl)methyl	52	(64)
(Methoxymethyl)propyl	88	(64)
(Methoxypropyl)naphthyl		(35)
Methylphenyl		(55)
Methylpropyl	81	(66)
Phenyl-*o*-tolyl	65	(24)
Phenyl-*p*-tolyl	50	(24)
Phenyltrityl	35	(6)

* These compounds appear to exist as the cyclic isomers



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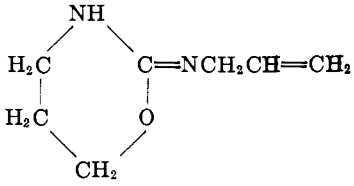
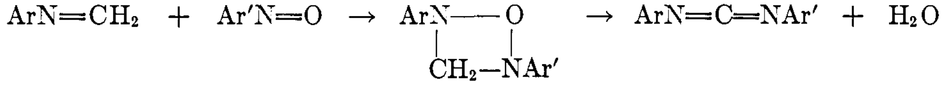


respectively, with basic properties.

Diphenylcarbodiimide was formed on heating phenyl isocyanate in a sealed tube at 180°C. for 24 hr. (78). Although interesting, the reaction obviously is of no preparative value.

$$2C_6H_5NCO \xrightarrow{\text{heat}} C_6H_5N{=}C{=}NC_6H_5 + CO_2$$

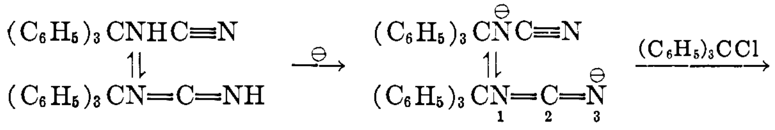
Several symmetrical and unsymmetrical aromatic carbodiimides were encountered as the main decomposition products of the four-membered ring compounds of the type shown in formula VI (26). These compounds arose readily from the additive reaction of azomethines (IV) and nitroso compounds (V).



$$\mathrm{ArN{=}CH_2 + Ar'N{=}O \rightarrow \begin{array}{cc} ArN & \text{---}O \\ | & | \\ CH_2 & \text{—}NAr' \end{array} \rightarrow ArN{=}C{=}NAr' + H_2O}$$

IV V VI

The preparation of ditritylcarbodiimide from the monotrityl compound (VII) is the only example of the formation of a carbodiimide by direct alkylation (6). It is well known that the monoalkyl derivatives of cyanamide give on treatment of their sodio derivatives with alkyl halides the dialkyl cyanamides, which are quite distinct from the dialkylcarbodiimides. The formation of ditritylcarbodiimide is obviously due to steric hindrance on nitrogen atom 1 of the anion (VIII).



$$\begin{array}{c}(C_6H_5)_3CNHC{\equiv}N\\ \rightleftharpoons\\ (C_6H_5)_3CN{=}C{=}NH\end{array} \xrightarrow{\ominus} \begin{array}{c}(C_6H_5)_3C\overset{\ominus}{N}C{\equiv}N\\ \rightleftharpoons\\ (C_6H_5)_3C\underset{1}{N}{=}\underset{2}{C}{=}\underset{3}{\overset{\ominus}{N}}\end{array} \xrightarrow{(C_6H_5)_3CCl}$$

VII VIII

Tritylcarbodiimide

$$(C_6H_5)_3CN{=}C{=}NC(C_6H_5)_3 + Cl^-$$

Ditritylcarbodiimide

III. Properties of Carbodiimides

A. PHYSICAL PROPERTIES

1. *Stability and polymerization*

The aliphatic carbodiimides are colorless distillable liquids which have a neutral reaction when freshly prepared. Some aromatic carbodiimides are liquids and can be distilled; a large number are crystalline solids which on heating or distilling decompose or polymerize. Decomposition and polymerization also occur often on prolonged standing. The stability of the carbodiimides in both the aliphatic and the aromatic series is a function of the substituting groups. The study of a large number of aliphatic carbodiimides has shown that (*1*) increase in the chain length of the alkyl substituents has some, but not very marked, stabilising effect (66), (*2*) the stability increases markedly with the branching of the alkyl substituents on the two nitrogen atoms in the following order: $RCH_2 <$

$R_2CH < R_3C$. Thus, diethylcarbodiimide polymerizes in a few days (66, 74), while diisopropyl- and dicyclohexylcarbodiimides are stable over a period of months (66). Further, unsaturation in the substituting groups decreases the stability of the carbodiimides. Thus, diallyl-, β-bromoallyl-, and *tert*-butylcarbodiimides are rather unstable (43).

The aromatic carbodiimides also vary considerably in stability. Di-*p*-iodophenylcarbodiimide polymerizes very readily; the parent diphenylcarbodiimide, a mobile liquid when freshly distilled, sets to a solid paste on standing for some days (96). Di-*p*-tolylcarbodiimide, when obtained pure in crystalline form, is stable for several months. Di-*p*-dimethylaminophenylcarbodiimide was found to be stable over a period of three years (97, 98). When in solution, particularly in alcohol (96, 98), the aromatic carbodiimides are much more sensitive to heat than are their aliphatic analogs.

The decomposition and polymerization products[2] of aliphatic carbodiimides have a basic reaction and are undistillable (62, 67), but they have not been examined further. The dimeric and trimeric forms of diphenyl- and di-*p*-tolylcarbodiimides have long been known (a dimeric form of dibenzylcarbodiimide has also been characterized) (94). The controversy about these "modifications" being stereoisomers (57, 60) was settled long ago (13, 40, 42) in favor of the polymeric structures, which are given later (page 162).

2. *Infrared spectra*

The infrared absorption spectra of dicyclohexyl-, di-*p*-tolyl-, and di-*p*-dimethylaminophenylcarbodiimides (32) show a strong absorption band at 4.75–4.77 μ, which appears to be characteristic of —N=C=N— stretching. The allenes (C=C=C) show characteristic absorption at 5–5.16 μ (4, 89) and the ketenimines (>C=C=N—) at 5 μ (75).

3. *Stereochemistry*

A clear discussion of the theoretical expectation of optical isomerism in carbodiimides has been given by Baker and Taylor (72) and by Rolls and Adams (52). It has, however, not been possible so far to achieve optical resolution experimentally (52). The very large dipole moments of diphenyl- and di-*p*-tolylcarbodiimides (4) nevertheless show dissymmetry in these molecules, contrary to the views of Vorländer (81).

B. CHEMICAL PROPERTIES

The carbodiimides are characterized by their unsaturation and therefore show addition reactions.

1. *Reaction with acids*

(*a*) *Reaction with weak acids:* The addition reactions of diphenylcarbodiimide with weak acids, e.g., hydrogen sulfide (24, 84), hydrogen selenide (100), thiophenol (11), and hydrogen cyanide (34, 41, 69), have been known for a long time.

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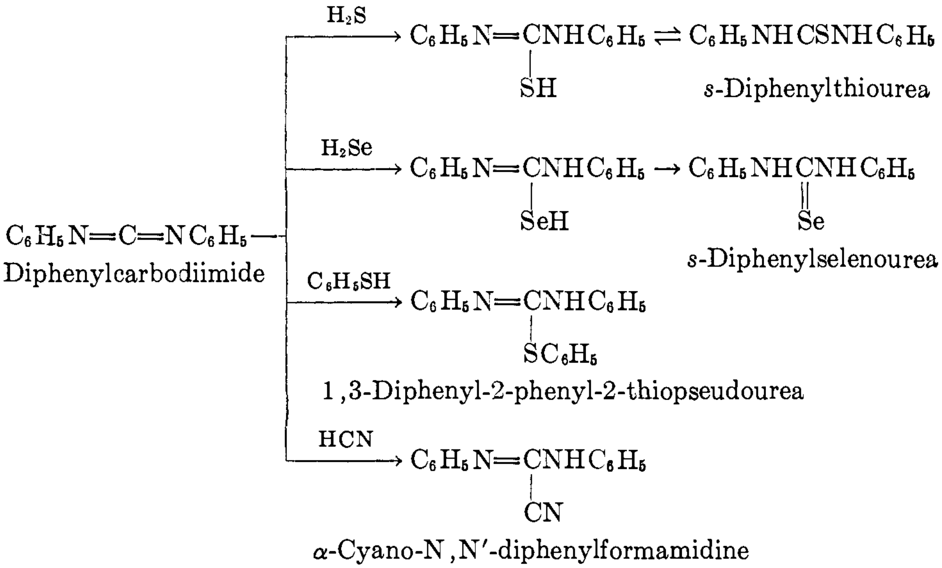
[2] Added sodium catalyzes the polymerization of the carbodiimides. It was observed that the resistance of the carbodiimides towards sodium paralleled their stability on prolonged standing (65).



$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{H_2S} C_6H_5N{=}\underset{\displaystyle SH}{\underset{|}{C}}NHC_6H_5 \rightleftharpoons C_6H_5NHCSNHC_6H_5$$

s-Diphenylthiourea

$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{H_2Se} C_6H_5N{=}\underset{\displaystyle SeH}{\underset{|}{C}}NHC_6H_5 \rightarrow C_6H_5NH\underset{\displaystyle Se}{\underset{\|}{C}}NHC_6H_5$$

s-Diphenylselenourea

$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{C_6H_5SH} C_6H_5N{=}\underset{\displaystyle SC_6H_5}{\underset{|}{C}}NHC_6H_5$$

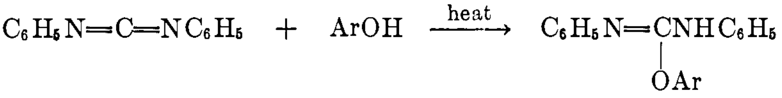
1,3-Diphenyl-2-phenyl-2-thiopseudourea

$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{HCN} C_6H_5N{=}\underset{\displaystyle CN}{\underset{|}{C}}NHC_6H_5$$

α-Cyano-N,N′-diphenylformamidine

Diphenylcarbodiimide

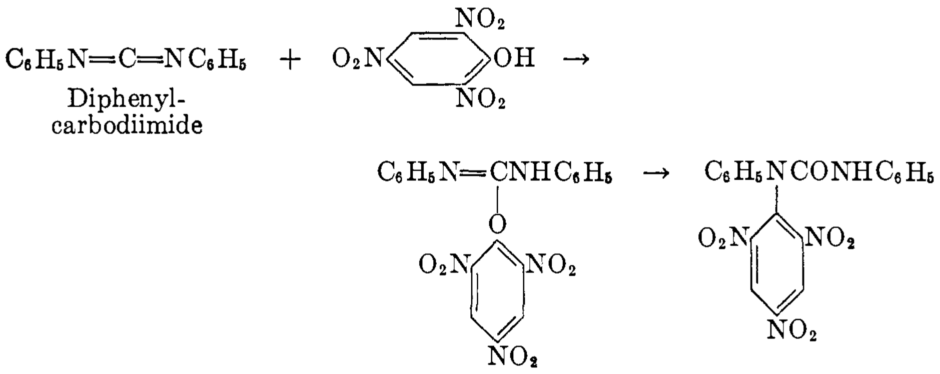
(b) *Reaction with phenols:* The very weakly acidic phenols react only at high temperatures (11) to form crystalline ethers (IX) of pseudourea. With picric acid, which is strongly acidic, the reaction resembles that of aromatic carbodiimides with carboxylic acids (see below) in that migration from oxygen to nitrogen occurs, as indicated below:



$$C_6H_5N{=}C{=}NC_6H_5 + ArOH \xrightarrow{heat} C_6H_5N{=}\underset{\displaystyle OAr}{\underset{|}{C}}NHC_6H_5$$

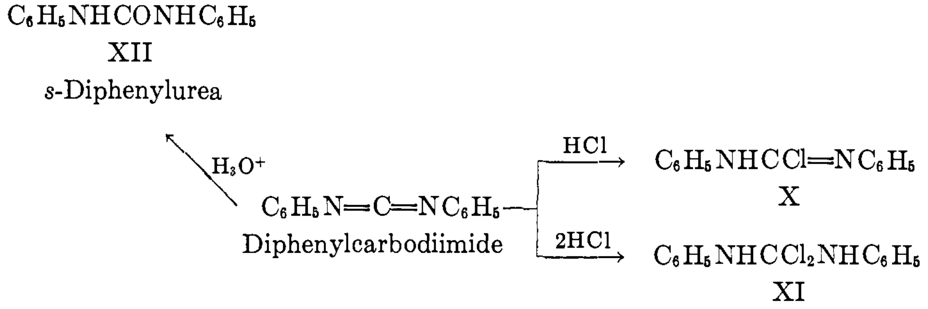
IX

Ar = aryl.

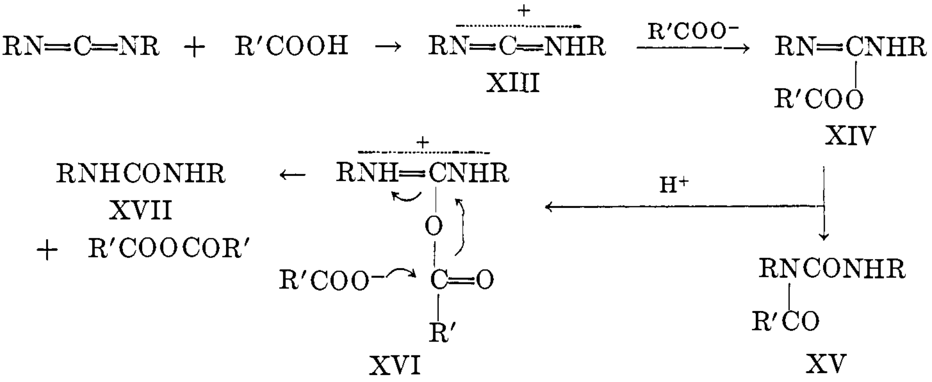


(c) *Reaction with inorganic acids:* The exothermic instantaneous reaction of dry hydrogen chloride with diphenylcarbodiimide leads to the dichloro compound (XI) (38, 84), but under carefully controlled conditions the monochloro compound

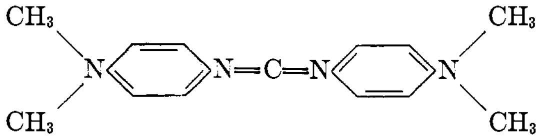
(X) has been prepared (38, 39, 40, 71). Aqueous mineral acids catalyze the hydration of carbodiimides to the corresponding ureas, e.g., XII.



(*d*) *Reaction with carboxylic acids:* The reactions of carbodiimides with carboxylic acids are particularly interesting and have been studied extensively in recent years. The following two general reactions have been found to occur. The first is the attachment of a proton (XIII), followed by the attack of the acid anion to form XIV. This can rearrange to form an acylurea (XV). Alternatively, the attachment of a second proton can overtake the oxygen-to-nitrogen migration and the cation XVI results; the subsequent attack of the acid anion forms a urea (XVII) and the acid anhydride. The products of the reaction depend on the nature of the carbodiimide, the acid, the solvent, and the temperature.



With aromatic carbodiimides reaction proceeds in most cases readily to form the acylureas (59, 92, 93, 96, 97, 101, 102, 103, 104). A number of solvents can be employed for this reaction: e.g., ether, benzene, dioxane, pyridine, etc. (Alcohols are not completely satisfactory because of some polymerizing effect on the carbodiimides (96, 98).) As the reaction conditions are very mild and the acylureas, which are formed usually in excellent yield, are highly crystalline substances, carbodiimides have been recommended as reagents for the characterization of carboxylic acids (90, and subsequent papers). From a study of a large number of carbodiimides di-*p*-dimethylaminophenylcarbodiimide (XVIII) has been suggested as the most suitable reagent for the purpose (97).



XVIII

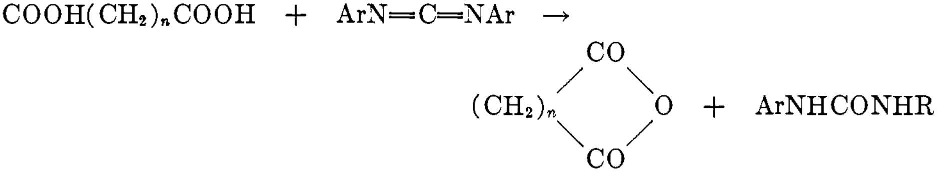
To extend the scope of the reagents of this class, the preparation of water-soluble methiodides and methosulfates of the basic carbodiimide (XVIII) was carried out (90), but the expected acylureas could not be obtained because of the rapid hydration of the carbodiimides by water. In view of the obvious advantage which they would confer, some optically active carbodiimides (94) were also prepared, but here the competing reaction, the formation of the urea (XVII), became predominant.

In extended investigations adducts of the basic carbodiimide (XVIII) with different types of carboxylic acids were prepared. α,β-Unsaturated (101), α-halogen-substituted (103), and mono- and polynuclear substituted aromatic carboxylic acids (102, 105) formed in general colored products; those from β,γ-unsaturated and β-halogen-substituted carboxylic acids were colorless. The preparation of these derivatives was thus suggested as a means of identification of the former classes of acids. (For details, and in particular the influence of substituents on the color, the original papers should be consulted.)

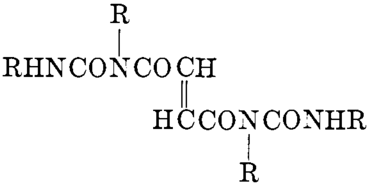
The products of the reaction of dicarboxylic acids, $COOH(CH_2)_nCOOH$, depend on the length of the alkyl chain and often on the solvent (95); under all conditions oxalic acid forms quantitatively the disubstituted urea and a mixture of carbon monoxide and carbon dioxide. This provides a method of estimation

$$RN{=}C{=}NR + (COOH)_2 \rightarrow RNHCONHR + CO + CO_2$$

of carbodiimides (91). Malonic, succinic, and glutaric acids form either exclusively or predominantly the disubstituted urea and the cyclic anhydrides. It is obvious that in these cases after the first 1,2-addition, the ease of cyclization is the predominating factor. Similarly, phthalic and maleic acids also form exclusively the cyclic anhydrides, whereas fumaric acid gives, as expected, the normal adduct (XIX).



n = 1, 2, 3.



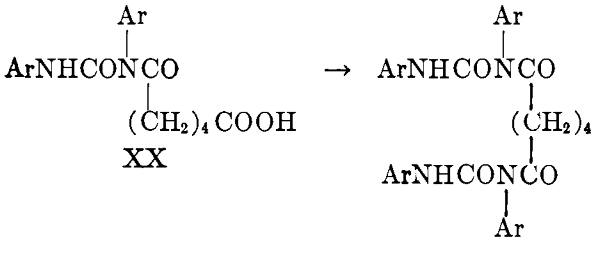
$$RHNCO\underset{R}{N}COCH{=}HCCO\underset{R}{N}CONHR$$

XIX

Adipic acid forms both monoacyl-(XX) and diacylureas (XXI). The higher members in the series form normal derivatives, each carboxylic group reacting independently (95).

$COOH(CH_2)_4COOH + ArN{=}C{=}NAr \rightarrow$

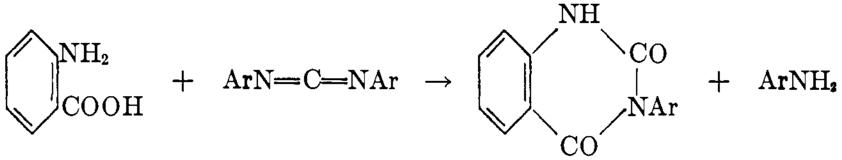
Adipic acid



$ArNHCON(Ar)CO(CH_2)_4COOH \rightarrow ArNHCON(Ar)CO(CH_2)_4CON(Ar)CONHAr$

XX XXI

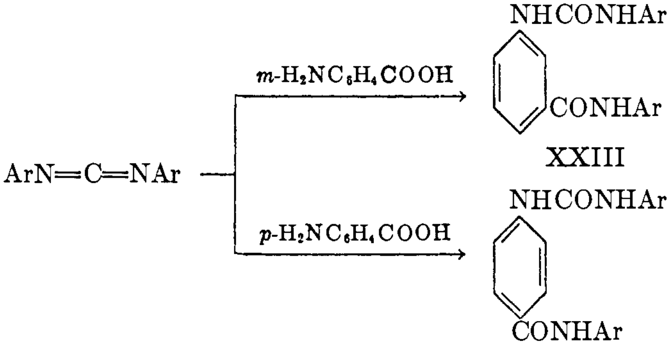
The reaction of anthranilic acid with diphenyl- and di-*p*-tolylcarbodiimides gives XXII (11, 105):



Anthranilic acid XXII

Ar = phenyl or *p*-tolyl.

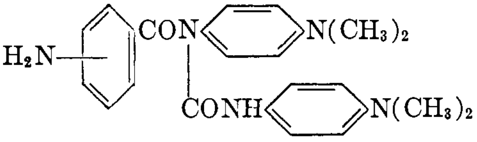
m-Amino- and *p*-aminobenzoic acids give, respectively, XXIII and XXIV.



XXIII

XXIV

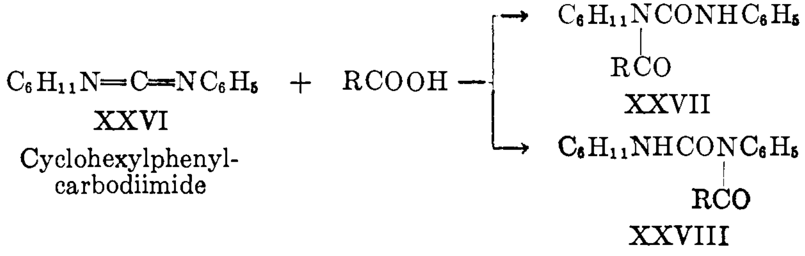
These amino acids form the normal acylureas (XXV) (105) with Zetzsche's basic carbodiimide (XVIII).



XXV

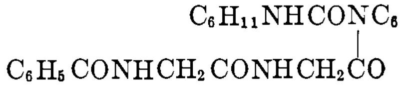
The reaction of aliphatic carbodiimides with carboxylic acids usually proceeds to the second stage (XVI, XVII) to form the disubstituted urea and the acid anhydride (92, 94). However, by employing reaction conditions which accelerate the oxygen-to-nitrogen migration (XIV → XV) and perhaps hinder the attachment of the second proton (XVI), the formation of the "acylurea" (XV) can be made the main reaction. Thus, by carrying out the reaction in hot pyridine and adding the carboxylic acid in portions to dicyclohexylcarbodiimide, satisfactory yields of some acylureas were prepared (93).

The reaction of unsymmetrical carbodiimides (e.g., cyclohexylphenyl (XXVI)) with carboxylic acids can theoretically yield two acylureas (XXVII and XXVIII).



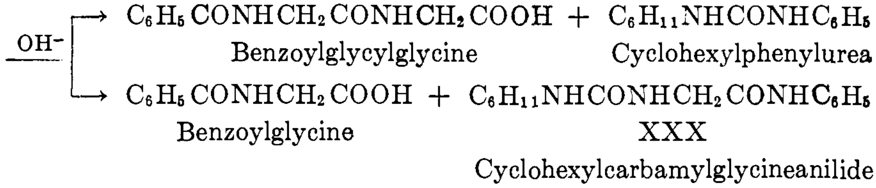
$$\underset{\substack{\text{XXVI}\\ \text{Cyclohexylphenyl-}\\ \text{carbodiimide}}}{C_6H_{11}N{=}C{=}NC_6H_5} + RCOOH \rightarrow \begin{cases} \underset{\text{XXVII}}{C_6H_{11}\underset{RCO}{\underset{|}{N}}CONHC_6H_5} \\ \underset{\text{XXVIII}}{C_6H_{11}NHCO\underset{RCO}{\underset{|}{N}}C_6H_5} \end{cases}$$

Actually only one appears to be formed (30, 94). It would be expected that the initial attachment of the proton (XIII) would preferably occur to the nitrogen atom with higher electron density (e.g., to the nitrogen carrying the cyclohexyl residue in XXVI) and that consequently in the final product, the acyl group would be found attached to the less basic nitrogen (formation of XXVIII). In at least one case it was proved that this is so and it seems reasonable to generalize the conclusion from this example (30). The mild alkaline treatment of the adduct (XXIX) of benzoylglycylglycine with cyclohexylphenylcarbodiimide (XXVI) degraded the molecule as shown below:



$$C_6H_5CONHCH_2CONHCH_2\overset{\overset{C_6H_{11}NHCONC_6H_5}{|}}{CO}$$

XXIX

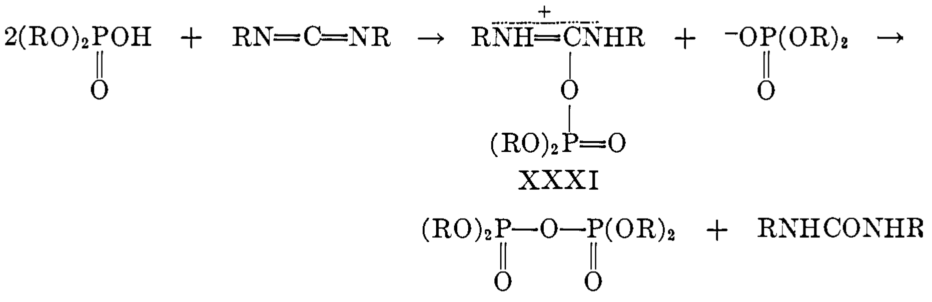


$$\xrightarrow{OH^-} \begin{cases} \underset{\text{Benzoylglycylglycine}}{C_6H_5CONHCH_2CONHCH_2COOH} + \underset{\text{Cyclohexylphenylurea}}{C_6H_{11}NHCONHC_6H_5} \\ \underset{\text{Benzoylglycine}}{C_6H_5CONHCH_2COOH} + \underset{\substack{\text{XXX}\\ \text{Cyclohexylcarbamylglycineanilide}}}{C_6H_{11}NHCONHCH_2CONHC_6H_5} \end{cases}$$

The structure of XXX, which confirms the formulation (XXIX) of the original adduct, was proved by synthesis (30).

(*e*) *Reaction with phosphoric esters and with sulfonic acids:* The reaction of aliphatic and aromatic carbodiimides with monobasic and dibasic esters of phosphoric acid has recently been investigated (33). The reaction with these strong acids is, as expected, instantaneous and exothermic in concentrated solutions.

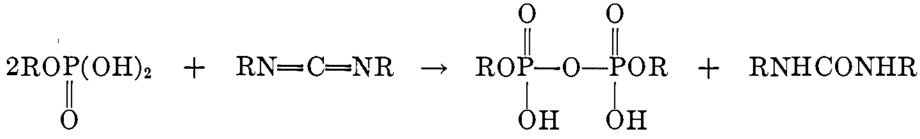
Monobasic esters yield quantitatively the symmetrical tetrasubstituted esters of pyrophosphoric acid (XXXII), cations of the type of XXXI being the probable intermediates.



$$2(RO)_2\underset{\underset{O}{\parallel}}{P}OH + RN{=}C{=}NR \rightarrow \overset{+}{RNH{=}CNHR}\text{ with }-O-P(=O)(RO)_2\ (\text{XXXI}) + {}^{-}O\underset{\underset{O}{\parallel}}{P}(OR)_2 \rightarrow (RO)_2\underset{\underset{O}{\parallel}}{P}-O-\underset{\underset{O}{\parallel}}{P}(OR)_2 + RNHCONHR$$

XXXII

Dibasic esters also form predominantly symmetrical diesters of pyrophosphoric acid (XXXIII), isolated after treatment with water when presumably the un stable polymeric products break down to the stable ones (XXXIII).

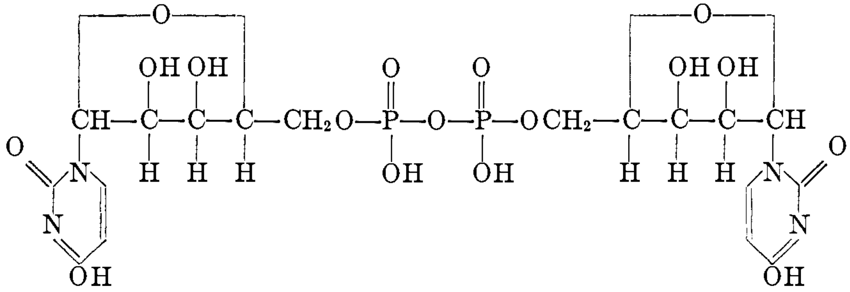


$$2RO\underset{\underset{O}{\parallel}}{P}(OH)_2 + RN{=}C{=}NR \rightarrow RO\overset{\overset{O}{\parallel}}{\underset{\underset{OH}{|}}{P}}-O-\overset{\overset{O}{\parallel}}{\underset{\underset{OH}{|}}{P}}OR + RNHCONHR$$

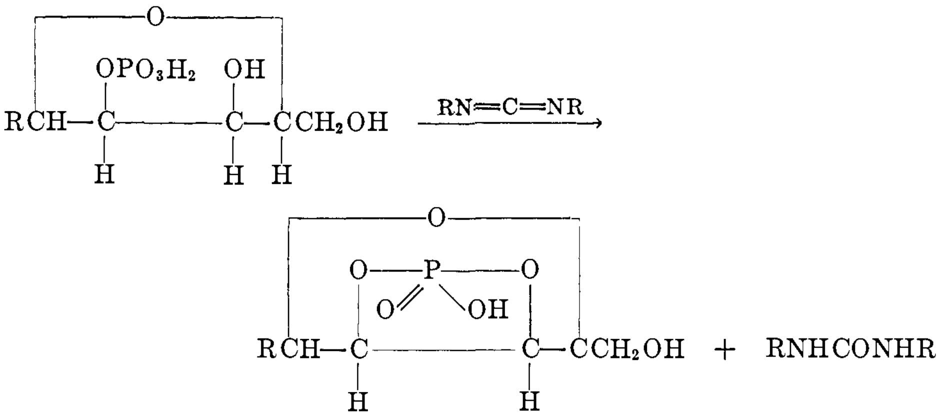
XXXIII

This reaction has applications in synthesis in the general field of the nucleotides (15). It obviates the need for the protection of the free acidic groups and the intermediate preparation of chlorophosphonates; the disubstituted pyrophosphates can in principle be prepared directly at room temperature.

The synthesis of di(uridine-5′)-pyrophosphate (XXXIV) from uridine-5′-phosphate has actually been achieved (29). The action of dicyclohexylcarbodiimide on 2′- or 3′-nucleoside phosphate appears to form the cyclic 2,3-phosphate (XXXV) (8). This reaction is analogous to that of trifluoroacetic anhydride on these substances (9).



XXXIV



XXXV

R = uracil, etc.

Similarly, alkyl- and arylsulfonic acids react exothermally with aliphatic and aromatic carbodiimides to form the sulfonic anhydrides (XXXVI) (31) in excellent yield.

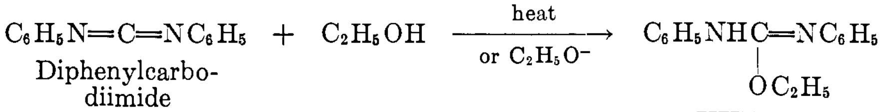
$$2RSO_2OH + RN{=}C{=}NR \rightarrow \underset{\text{XXXVI}}{RSO_2OSO_2R} + RNHCONHR$$

The separation in all these cases of the anhydride from the accompanying ureas can usually be achieved without difficulty because of the relative insolubility of, especially, the disubstituted aromatic ureas.

It is interesting to observe that the "anhydride" formation is not susceptible to the presence of small amounts of water in the reaction medium (30). This follows from the reaction mechanism (see above) in which the cations, e.g., XXXI, and the anions of the strong acids are the reaction entities and the relatively weakly nucleophilic water molecules are much less effective than acid anions during attack on XXXI.

2. Base-catalyzed addition reactions

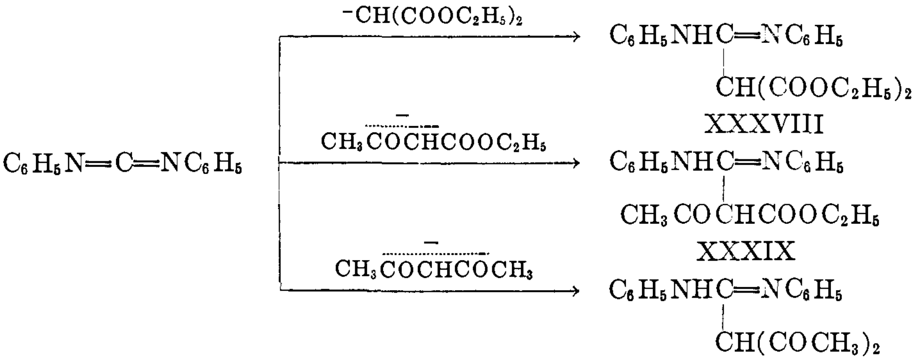
(*a*) *Reaction with alcohols:* Alcohols are quite inert towards carbodiimides at ordinary temperature. However, when heated in alcoholic solution in a sealed tube, diphenylcarbodiimide was converted quantitatively to the ether of the pseudourea (XXXVII) (37). The same addition occurs readily and exothermally in the presence of some sodium ethoxide, and the products can be isolated in excellent yield after treatment with water (16, 76).



$$\underset{\text{Diphenylcarbodiimide}}{C_6H_5N{=}C{=}NC_6H_5} + C_2H_5OH \xrightarrow[\text{or } C_2H_5O^-]{\text{heat}} \underset{OC_2H_5}{\underset{|}{C_6H_5NHC{=}NC_6H_5}}$$

XXXVII

(*b*) *Reaction with compounds containing active hydrogen:* Malonic ester, acetoacetic ester, and acetylacetone form, in the presence of catalytic amounts of their sodio derivatives, the corresponding substituted amidines (XXXVIII–XL) (79, 80).



$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{^{-}CH(COOC_2H_5)_2} C_6H_5NH\underset{\substack{|\\ CH(COOC_2H_5)_2}}{C}{=}NC_6H_5$$

XXXVIII

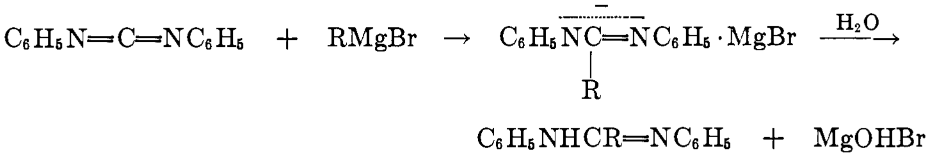
$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{CH_3CO\overset{-}{C}HCOOC_2H_5} C_6H_5NH\underset{\substack{|\\ CH_3CO\overset{}{C}HCOOC_2H_5}}{C}{=}NC_6H_5$$

XXXIX

$$C_6H_5N{=}C{=}NC_6H_5 \xrightarrow{CH_3CO\overset{-}{C}HCOCH_3} C_6H_5NH\underset{\substack{|\\ CH(COCH_3)_2}}{C}{=}NC_6H_5$$

XL

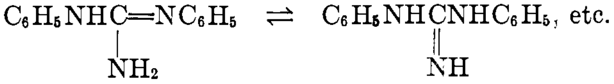
(*c*) *Reaction with Grignard reagents:* This is also simple 1,2-addition to form alkylamidines (12).



$$C_6H_5N{=}C{=}NC_6H_5 + RMgBr \rightarrow C_6H_5N\overset{-}{\underset{\substack{|\\ R}}{C}}{=}NC_6H_5\cdot MgBr \xrightarrow{H_2O}$$

$$C_6H_5NHCR{=}NC_6H_5 + MgOHBr$$

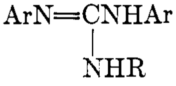
(*d*) *Other addition reactions:* Ammonia reacts with diphenylcarbodiimide to form diphenylguanidine (XLI) (84);



$$C_6H_5NH\underset{\substack{|\\ NH_2}}{C}{=}NC_6H_5 \rightleftharpoons C_6H_5NH\underset{\substack{\|\\ NH}}{C}NHC_6H_5,\ \text{etc.}$$

XLI

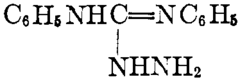
with amines, trisubstituted guanidines are formed (24, 83, 84, 85) (XLII).



$$ArN{=}\underset{\substack{|\\ NHR}}{C}NHAr$$

XLII

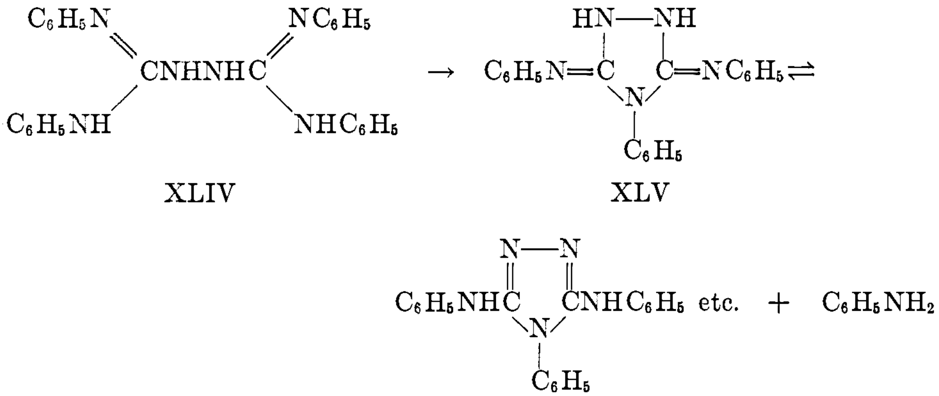
Hydrazine reacts to give both XLIII and XLIV (13). The latter on heating



$$C_6H_5NH\underset{\substack{|\\ NHNH_2}}{C}{=}NC_6H_5$$

XLIII

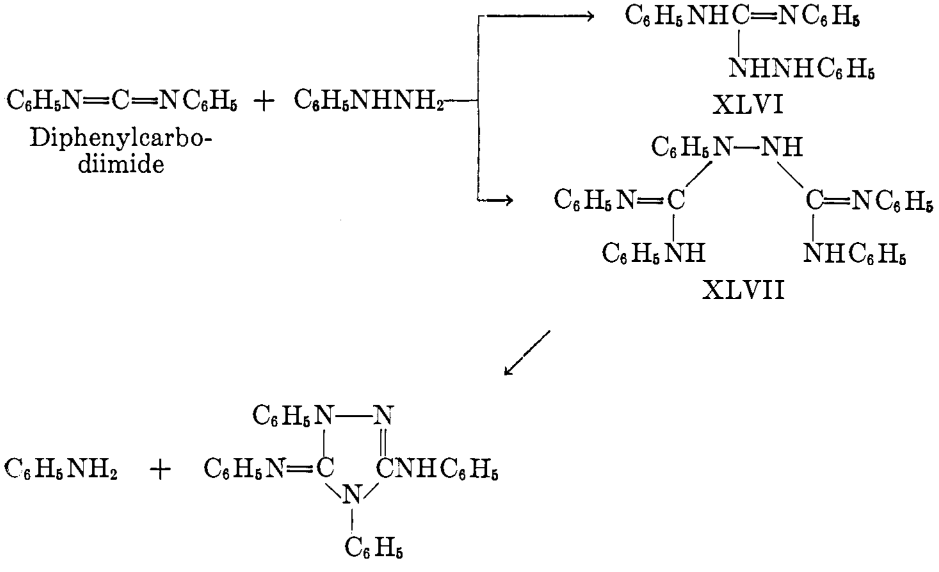
undergoes intramolecular cyclization with elimination of aniline to form XLV.



XLIV

XLV

Phenylhydrazine forms under mild conditions with diphenylcarbodiimide "anil guanidine" (XLVI) (10, 51). The structure XLVIII has been assigned (13, 58) to the compound obtained by Wessel (82) from phenylhydrazine and diphenylcarbodiimide under vigorous conditions; the adduct (XLVII) is thought to be the intermediate (13).



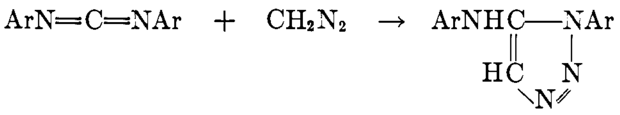
Diphenylcarbodiimide

XLVI

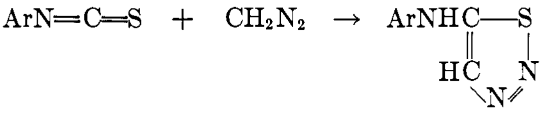
XLVII

XLVIII

Diazomethane has been found to give triazole derivatives (XLIX) with aromatic carbodiimides (53, 54). A similar reaction occurs between phenyl isothiocyanate and diazomethane to form L (48).

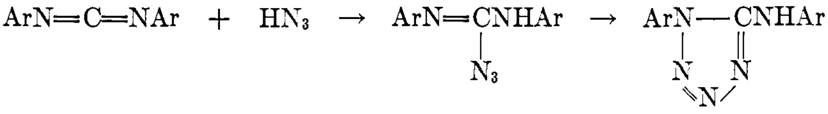


XLIX



L

The reaction of hydrazoic acid with aromatic carbodiimides is a 1,2-addition, analogous to the reactions of acids discussed earlier, followed by cyclization (46, 77) to form a tetrazole (LI).

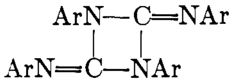


LI

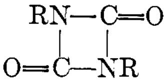
C. COMPARISON OF CARBODIIMIDES WITH SIMILAR SYSTEMS

There are some broad similarities in the fundamental behavior of the unsaturated systems with twinned double bonds, i.e., the isocyanates, the ketenes, and the carbodiimides (the limited information available on ketenimines (75) indicates that they are similar in their reactions to the compounds discussed here). Recent detailed reviews of the chemistry of isocyanates (49, 50, 56, 70) and ketenes (1, 22, 23, 45) are available.

The dimerization of ketenes, isocyanates, and carbodiimides is essentially similar. Dimers of only a few carbodiimides have been characterized; these are formulated as shown in structure LII.



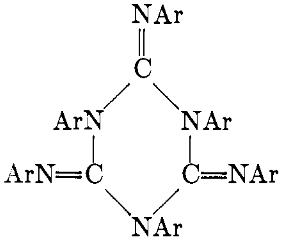
LII



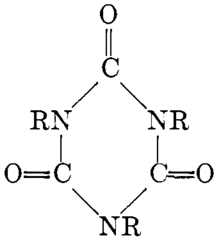
LIII

The dimers of many isocyanates have been well characterized and assigned analogous structures (LIII). The four-membered ring dimers of ketenes have been variously formulated, depending on the nature of the substituents on the carbon atom (1, 23, 27, 45, 88).

The trimers of diphenyl- and di-*p*-tolylcarbodiimides (11, 57) and phenyl isocyanate (56) have structures LIX and LX, respectively, analogous to that of cyanuric acid. It is possible that the formation of higher polymers is similar but this has not been studied.

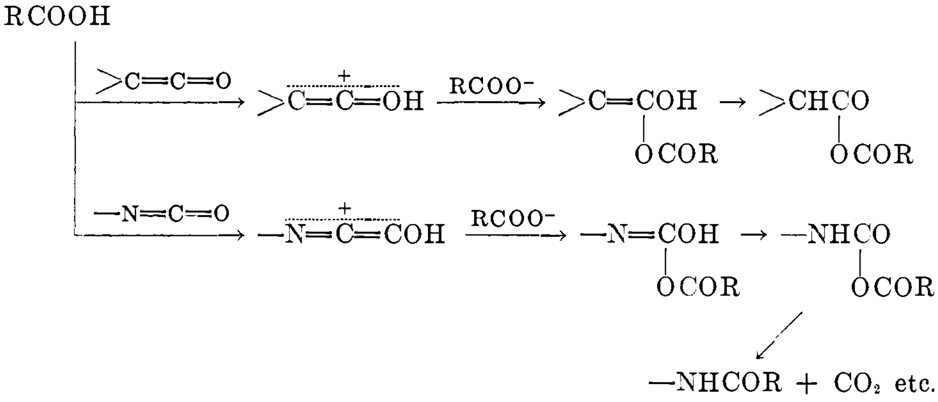


LIV



LV

There is similarity in the addition reactions of these classes of compounds but, as expected, there are great differences in reactivity towards different functional groups and in the nature of the final products. The primary 1,2-addition occurs to one of the two twinned double bonds. In symmetrical carbodiimides, the two double bonds are of course identical; among the unsymmetrical carbodiimides only the reaction with carboxylic acids has been examined so far (see above). In many reactions of ketenes addition occurs first to the carbonyl group (1, 74). Recent studies of the reactions of aryl isocyanates (2, 3) indicated a similar mechanism. The carbodiimides are much less reactive under ordinary conditions towards water, alcohols, and possibly amines than are ketenes and isocyanates. The reactions of carboxylic acids with ketenes (1, 73), isocyanates (44), and carbodiimides are also 1,2-additions followed by secondary reactions.

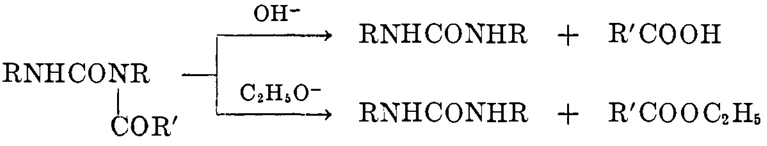


Furthermore, the reactions with Grignard reagents and the base-catalyzed addition of compounds with active hydrogen to aryl isocyanates (56) and carbodiimides (see above) are similar.

IV. Uses of Carbodiimides

1. The use of aromatic carbodiimides for the characterization of carboxylic acids has been discussed above. Di-*p*-dimethylaminophenylcarbodiimide (XVIII) has also been employed for the separation of fatty acids from large amounts of neutral oils and fats (7, 92).

The acids can be recovered from the derivatives by very mild hydrolysis with aqueous alcoholic alkali (30, 97); alternatively, sodium ethoxide reacts readily to form the corresponding esters (30).

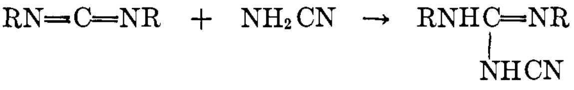


$$\underset{\displaystyle \mathrm{COR'}}{\mathrm{RNHCONR}} \begin{cases} \xrightarrow{\mathrm{OH^-}} \mathrm{RNHCONHR} + \mathrm{R'COOH} \\ \xrightarrow{\mathrm{C_2H_5O^-}} \mathrm{RNHCONHR} + \mathrm{R'COOC_2H_5} \end{cases}$$

2. The formation of acylureas from peptides with free end carboxyl groups has been used in a method for the identification of end amino acids in peptides (30). The end amino acid is cleaved under mild alkaline conditions, as in compounds of the type of XXX (page 157).

3. The application of carbodiimides in the synthesis of nucleotides and sulfonic anhydrides has been pointed out.

4. A recent patent covers the use of carbodiimides in the fixation of size in textiles (55). Another patent (35) describes the preparation of 1,2-disubstituted-3-cyanoguanidines (LVI) by treating the appropriately disubstituted carbodiimide with cyanamide; the products are used in synthetic resins and as textile and dyestuff assistants.



$$\mathrm{RN{=}C{=}NR} + \mathrm{NH_2CN} \rightarrow \underset{\displaystyle \mathrm{NHCN}}{\mathrm{RNHC{=}NR}}$$

LVI

The author wishes to thank Dr. C. L. Stevens of Wayne University for communicating his results (75) in advance of publication.

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