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ADVANCES IN THE CHEMISTRY OF CARBODIIMIDES

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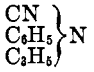
I. INTRODUCTION

During recent years, carbodiimides have attracted increasing attention, because of both their intrinsic interest and their great importance as versatile reagents in organic synthesis. Their use as condensing agents in the preparation of peptides and nucleotides is of particular significance.

Although much of the fundamental work in this field is of comparatively early date, a more systematic study of carbodiimides and their consequent wide application in organic synthesis is of recent origin. The first review on carbodiimides was provided by Khorana (333) only 13 years ago. By drawing attention to this class of highly reactive compounds, this paper no doubt contributed significantly to the increasing interest in this field. Since then shorter general articles have appeared (67, 520, 608), as well as a special summary dealing with the synthesis of carbodiimides from isocyanates (509). Khorana has recently surveyed the use of carbodiimides in phosphorylation reactions, in a chapter of his book on phosphate esters (328).

The present account attempts to describe the existing state of our knowledge of carbodiimide chemistry. Special emphasis is placed on the more recent work, earlier contributions being dealt with only insofar as they furnish the necessary background to the discussion; however, all the older work has been noticed in the form of references. The literature is covered, through *Chemical Abstracts*, to the end of 1964, and numerous later references are included. It must be emphasized that during most recent years the use of carbodiimides as condensing reagents has become so general that examples are often no longer indexed specifically under this heading in the abstract literature.

Although first correctly formulated and characterized by Weith (816) in 1873, carbodiimides were undoubtedly obtained by earlier workers. As early as 1852, Hinterberger (255) reported the isolation of a compound, $C_6H_{10}N_2$, from the reaction of N-allyl-N′-ethylthiourea with hydrated lead oxide. Zinin (870) (1852) and Biziro (61–63) (1861) also described a compound, $C_{10}H_{10}N_2$, obtained by the action of hydrated lead oxide on N-allyl-N′-phenylthiourea; the latter worker formulated it, under the name "cyanallylphenylamine," as



$$\left.\begin{matrix}CN\\C_6H_5\\C_3H_5\end{matrix}\right\}N$$

There is little doubt that the compounds concerned were in fact the appropriate carbodiimides $C_2H_5N{=}C{=}NC_3H_5$ and $C_3H_5N{=}C{=}NC_6H_5$, respectively.

II. SYNTHESIS OF CARBODIIMIDES

A. FROM THIOUREAS

1. *Removal of the Elements of Hydrogen Sulfide*

a. By Metal Oxides

The desulfurization of N,N′-disubstituted thioureas by yellow mercuric oxide, reported as early as 1873 by Weith (816), remains one of the best methods for the preparation of carbodiimides (40, 75, 144, 196, 336, 383, 394, 395, 397, 449, 558, 593, 594, 628, 638, 639, 681, 683, 688, 689, 795, 817, 818, 858, 861).

$$\underset{\text{I}}{\text{RNHCSNHR}} + \text{HgO} \rightarrow \underset{\text{II}}{\text{RN}{=}\text{C}{=}\text{NR}} + \text{HgS} + \text{H}_2\text{O}$$

The reaction proceeds in a variety of solvents; ether, benzene, and acetone are preferred, but toluene, xylene, and carbon disulfide have been used, though to a lesser extent. The last has the disadvantage of giving rise to sulfur-containing by-products which are not easily removed by direct distillation (628); a recent patent claims the removal of such sulfurous impurities from crude carbodiimides by distillation over alkali metal hydroxide (195). Toluene and other high-boiling solvents cause polymerization and favor the formation of by-products (558) such as aniline, isothiocyanates, and guanidines.

The water eliminated during this reaction may add to the carbodiimide to form the urea. This side reaction is inhibited by the presence, in the reaction mixture, of suitable dehydrating agents [*e.g.*, $CaCl_2$ (593, 594), Na_2SO_4 (394, 628, 638), $MgSO_4$, $MgCO_3$ (449), "Anhidrite" (383), etc.], or by the azeotropic removal of water (861). However, the presence of water is often not detrimental, particularly in the case of aliphatic examples. Thus, Sheehan and Hlavka (689) have obtained carbodiimide in excellent yields in the absence of dehydrating agents, and Schmidt and Striewsky (639) have indeed prepared aliphatic carbodiimides in aqueous suspensions of freshly precipitated mercuric oxide.

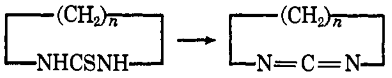
Mercuric oxide is by far the most effective desulfurizing agent in this reaction; lead oxide has also been used (181, 253, 532, 640, 819) but has occasionally failed (858). The quantity, physical state, and source of the oxide all influence the yields of products (285, 383, 628, 863). The use of 1.5 to 2.5 molar excess of finely divided oxide gives optimum results. The presence of a little sulfur (or selenium) not only catalyzes the desulfurization but also retards the side reactions (863).

The following oxides and salts of other elements have been used to a lesser extent: As_2O_3 (253), ZnO, $ZnCl_2$, $ZnSO_4$ (132, 133), $PbCO_3$, $Pb(NO_3)_2$, and $PbCl_2$ (682).

In the preparation of aromatic carbodiimides, the presence of substituents in the benzene ring affects the yields of the product and the isothiocyanate formed in side reactions (285).

Cyclic carbodiimides (III) have been prepared by this method (41); they exist from the eight-membered ring upward [*i.e.*, $n = 5$; compare cyclic allenes, where $n = 4$ (160, 184), and acetylenic systems, where $n = 5$ (65, 161)].

Recently, the synthesis of a number of (1,3,4,6-tetra-O-acetyl-β-D-glucose-2-yl)carbodiimides (in 62–93% yield) (305) and N-carbethoxy-N′-substituted carbodiimides (IV) (in 37–45% yield) (505) employing this procedure have been reported.



III

$RN{=}C{=}NCOOEt$

IV

b. By Mercuric Complexes

The desulfurization has been performed using mercuric complexes in the presence of an inorganic base (133). An aqueous solution of potassium iodide, mercuric chloride, and potassium hydroxide is reported to be effective in providing high yields of the carbodiimides. The procedure is, of course, limited to carbodiimides that are sufficiently inert toward water in the presence of catalytic quantities of alkalis.

$$4KI + HgCl_2 \rightarrow 4K^+ + [HgI_4]^{2-} + 2Cl^-$$

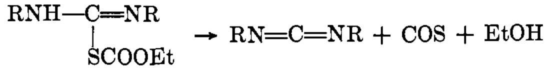
$$RNHCSNHR + [HgI_4]^{2-} + 2OH^- \rightarrow RN{=}C{=}NR + HgS + 2H_2O + 4I^-$$

$$R = C_6H_{11} \text{ or } (CH_3)_2CH$$

c. By Alkyl Chloroformates

Treatment of a suspension of N,N'-disubstituted thioureas in chloroform at −5 to −10° with lower alkyl chloroformates in the presence of a tertiary amine (*e.g.*, triethylamine) results in the formation of low yields of carbodiimides (133).

$$RNHCSNHR + ClCOOEt + R'_3N \xrightarrow{-R'_3NHCl}$$



$$\underset{\displaystyle SCOOEt}{RNH{-}\overset{}{C}{=}NR} \rightarrow RN{=}C{=}NR + COS + EtOH$$

$$R = C_6H_{11} \text{ or } (CH_3)_2CH$$

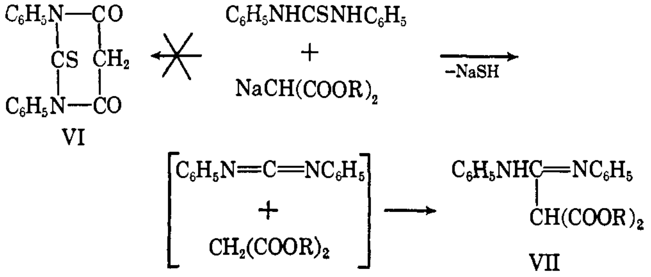
d. By Arylsulfonyl Chlorides

Sheehan has recently reported the suitability of benzenesulfonyl chloride and aqueous potassium carbonate as desulfurizing agents in this reaction and has described the preparation of a number of soluble 1-alkyl-3-(aminoalkyl)carbodiimides of type V by this method (682). This desulfurization thus resembles the conversion of N-arylthioureas into arylcyanamides by the same reagents (374).

$$RNHCSNH(CH_2)_nNR'_2 \rightarrow \underset{\text{V}}{RN{=}C{=}N(CH_2)_nNR'_2}$$

2. Interaction of N,N'-Disubstituted Thioureas with Certain Sodium Salts

The interaction of *s*-diphenylthiourea and sodium malonic esters does not yield the expected diphenylthiobarbituric acid (VI) but affords the amidine (VII), probably by way of the intermediate carbodiimide (768).



VI

VII

Using sodio derivatives of volatile compounds, such as sodamide, sodium alkoxide, or sodium hydride, Schlack and Keil (183, 625) converted *s*-dialkylthioureas into carbodiimides. While sodamide and sodium alkoxides usually provide only very poor yields of carbodiimide, with large quantities of by-products, sodium hydride (2 moles) in dioxane affords good yields (45–75%) of the desired products.

$$RNHCSNHR + NaX \rightarrow RN{=}C{=}NR + NaSH + HX$$

$$X = NH_2, OR', H \text{ (R'OH = alcohol of low boiling point)}$$

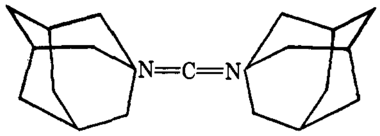
3. Oxidation of Thioureas

N,N'-Dialkylthioureas are readily oxidized to the corresponding carbodiimides by alkaline hypochlorites below 0° in excellent yields (174, 635, 637). The use of an excess of the oxidizing agent ensures the oxidative removal of sulfur (arising by double decomposition of the thiourea and hypochlorite) as sulfate. An advantage of the process is its applicability to the large scale (634) and cheapness of the reagents. The main side reaction is the formation of urea.

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

$$R, R' = \text{alkyl}$$

The reaction is of fairly general applicability; a particularly interesting example is Stetter and Wulff's recent preparation of N,N'-di(adamantyl-1)carbodiimide (VIII) by this procedure (738).



VIII

Schmidt and his co-workers (633, 641, 642) have reported the successful use of alkali chlorites (*e.g.*, $NaClO_2$) in the presence of cuprous salts (*e.g.*, Cu_2Cl_2) in the above oxidation.

It is recalled that the oxidation of monosubstituted thioureas ($RNHCSNH_2$) (641, 642) or dithiocarbamic acids (RNHCSSH) (627, 629, 633) affords the corresponding cyanamide or isothiocyanate, respectively. The general course of this oxidation may therefore be represented as

$$RNHCSXH + O \rightarrow RN{=}C{=}X + H_2O + S$$

$$X = S, NH, NR$$

B. FROM S-ALKYLISOTHIOUREAS

The pyrolysis of isothiourea ethers into mercaptan and cyanamide (and thence into cyanoguanidine) has long been known (50, 821). The analogous fission of S-alkyl-N,N'-diphenylisothioureas (IX, R = R' = Ph) into mercaptan and diphenylcarbodiimide was observed by Will (832, 833) in 1881, and by Werner (821) in 1890.

$$NH_2C(SCH_3){=}NH \rightarrow CH_3SH + NH_2CN\ (\rightarrow NH_2C({=}NH)NHCN)$$

$$\underset{\text{IX}}{RNHC(SR''){=}NR'} \rightarrow R''SH + RN{=}C{=}NR'$$

These reactions have recently been adapted to preparative purposes. Schlack and Keil (625) prepared a number of dicycloalkyl- and biscarbodiimides (RN=C=N—X—N=C=NR') from the corresponding S-methylisothioureas at 125–240° and 1–760 mm, the yields (40–90%) depending on the nature of the substituents (R, R′).

Ferris and Schutz (185) removed the elements of mercaptan from both aliphatic and aromatic isothioureas (IX) by means of silver nitrate or mercuric chloride in organic solvents (*e.g.*, dimethylformamide) in the presence of an acid acceptor (*e.g.*, triethylamine). The metal mercaptan is precipitated from the solution.

$$\underset{\text{IX}}{\text{RNHC(SR}'')\text{=NR}'} + \text{AgNO}_3 + \text{Et}_3\text{N} \rightarrow \text{RN=C=NR}' + \text{AgSR}'' + \text{Et}_3\text{N}\cdot\text{HNO}_3$$

$$\text{IX} + \text{HgCl}_2 + \text{Et}_3\text{N} \rightarrow \text{RN=C=NR}' + \text{HgCl}\cdot\text{SR}'' + \text{Et}_3\text{N}\cdot\text{HCl}$$

C. FROM UREAS

In the absence of rearrangement, dehydration of an N,N′-disubstituted urea yields the corresponding carbodiimide. Thus, toluene-*p*-sulfonyl chloride in pyridine (which acts both as a solvent and a base) dehydrates N,N′-dicyclohexylurea to the carbodiimide in 82% yield (12). The reaction resembles the analogous conversion of arylureas to sulfonylcyanamides (373) and of primary amides to nitriles by aromatic sulfonyl chloride in pyridine (737). The method is particularly useful for preparing dicyclohexylcarbodiimide, which is the most widely used condensing agent in the synthesis of peptides and nucleotides (see section V. I).

$$(\text{C}_6\text{H}_{11}\text{NH})_2\text{CO} + \text{RSO}_2\text{Cl} + 2\text{C}_5\text{H}_5\text{N} \rightarrow \text{C}_6\text{H}_{11}\text{N=C=NC}_6\text{H}_{11} + \text{RSO}_2\text{OH}\cdot\text{C}_5\text{H}_5\text{N} + \text{C}_5\text{H}_5\text{N}\cdot\text{HCl}$$

By a modification of this procedure, Sheehan and his co-workers (683) have prepared a number of new acid- and water-soluble carbodiimides (X) from commercially available starting materials. The basic urea is dehydrated in methylene chloride in the presence of triethylamine, so that the use of a large volume of pyridine is avoided. The analogous action of sulfonyl chlorides on thioureas is described in section IIA1d.

$$\underset{\text{X}}{\text{RN=C=NCH}_2\text{CH}_2\text{CH}_2\text{N(CH}_3)_2} \quad \text{R} = \text{C}_2\text{H}_5, (\text{CH}_3)_2\text{CH}, \text{C}_6\text{H}_{11}$$

For comparison purposes, Sheehan, *et al.* (683), prepared the same carbodiimides by desulfurizing the appropriate thioureas; in spite of the higher yields obtained, they do not prefer the thiourea procedure because of the large quantities of mercuric oxide, the long reaction times required, and the likely contamination of the products with sulfurous impurities.

Phosphorus oxychloride has been used instead of the sulfonyl chloride (806).

D. FROM ISOCYANATES

Next to N,N′-disubstituted thioureas (see section IIA), isocyanate esters are probably the most useful and versatile starting materials in the production of carbodiimides. In the presence of suitable catalysts, particularly certain phosphorus compounds, the conversion of isocyanates into carbodiimides proceeds smoothly and in excellent yields and has been developed into a reaction of considerable preparative value. Its scope, significance, and technical potentialities have been discussed and summarized by Neumann and Fischer (509).

1. *Catalytic Conversion of Isocyanates into Carbodiimides*

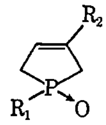
Hofmann (261) first isolated carbodiimides by heating isocyanate esters in the absence of catalysts, but he does not appear to have realized the nature of the products.

$$2\text{RNCO} \rightarrow \text{RN=C=NR} + \text{CO}_2$$

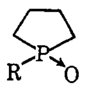
Stolle (741) performed this reaction by heating phenyl isocyanate to 180° in a sealed tube. Campbell, *et al.* (108), have recently reported that phenyl isocyanate was recovered (97%) after prolonged refluxing (46.5 hr); however, carbodiimide was formed in fair yield when a slow stream of nitrogen was passed through the boiling isocyanate. In the presence of suitable catalysts (see below), aromatic carbodiimides are obtained in high yield under much milder conditions (36, 106–109, 164, 478–480, 509, 512, 708, 781). The catalyzed reaction is generally carried out at room temperature or slightly above, with or without solvents, employing 0.1 to 4% by weight of the catalyst. Aliphatic isocyanates react more slowly; greatly improved yields are attainable in high-boiling solvents (108), but carbodiimides so obtained may be contaminated (509) by isocyanuric acid derivatives and more complex products, probably polymeric carbodiimides. Diphenylmethyl isocyanate (Ph_2CHNCO) failed to yield the desired carbodiimide but gave the isocyanuric acid derivative instead, possibly because of steric effects (509).

a. Types of Catalysts

The most active catalysts so far reported appear to be the oxides and sulfides of phospholenes (XI) and phospholanes (XII) (426, 427). In contrast, tertiary phosphines polymerize the isocyanates to dimers and trimers (37, 64, 260, 563, 706, 723).



XI



XII

Monagle and his co-workers (108) consider 3-methyl-1-ethyl-3-phospholene 1-oxide (XI, $\text{R}_1 = \text{C}_2\text{H}_5$; $\text{R}_2 = \text{CH}_3$) the most efficient catalyst; the 1-phenyl analog (XI, $\text{R}_1 = \text{C}_6\text{H}_5$; $\text{R}_2 = \text{CH}_3$), though more easily accessible, is somewhat less active. Full details for the preparation of the catalyst (XI, $R_1 = C_6H_5$; $R_2 = CH_3$) have been provided (427), together with a typical example of its use (106).

Simple phosphine oxides (*e.g.*, triphenyl-, tributyl-, tribenzyl-, phenyldibutylphosphine oxides) are also effective, though less so (509, 512). Dyer and Reed (164) examined aluminum isopropoxide and the naphthenates of Mn, Fe, Co, Cu, and Pb as catalysts; they are less active than the phosphorus compounds but are advantageous in being more readily accessible.

In a more systematic study Monagle (478) has shown that certain oxides and sulfides of elements of groups Vb and VIb are effective catalysts. Other compounds, such as sodium phenoxide, tertiary amines (203), $Ba[Bu_2B(OBu)_2]_2$ (708), metallic (*e.g.*, Be, Al, Zn, Cr) derivatives of acetylacetone (251), and others (480) have also been used.

b. Effect of Substituents in the Isocyanate

The nature of the isocyanate has a marked influence on the ease of carbodiimide formation in this reaction. The presence of electron-releasing groups in the aromatic ring tends to inhibit the reaction; this is particularly noticeable with *ortho* isomers, indicating a pronounced steric effect. On the other hand, electron-withdrawing groups increase the rate roughly in proportion to their electron-withdrawing power. Thus, for example, the catalyzed conversion of *p*-nitrophenyl isocyanate into the carbodiimide is almost explosive (107); again, the reaction of the *o*-chloro compound is about seven times as fast as that of the *o*-methyl analog, although their mesomeric and steric effects should be similar (479). Thus, the higher the inductive effect ($CH_3 > H > Cl$), the lower is the rate of the reaction.

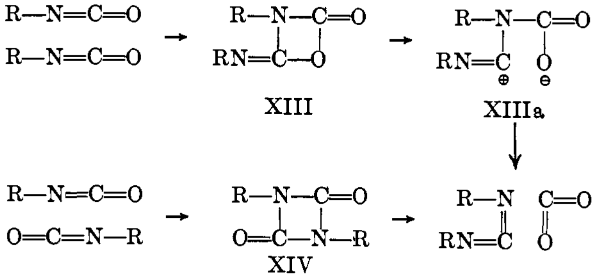
c. Effect of Solvents

Kinetic studies employing solvents of widely different structures and polarity have revealed that their effect on the rate of carbodiimide formation is small. The exceptions are solvents of high dielectric constant (*e.g.*, nitrobenzene, dimethylformamide, etc.).

d. Mechanism

The noncatalyzed formation of carbodiimides from isocyanate esters is thought (108) to proceed by a mechanism involving the initial dimerization of the reactant to the unsymmetrical intermediate (XIII). The carbodiimide arises therefrom by a cyclic electronic displacement (*e.g.*, to XIIIa), with elimination of carbon dioxide.

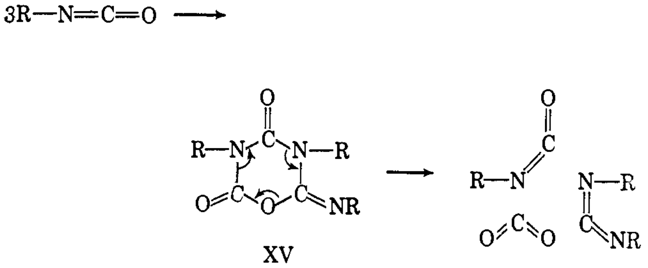
Gaylord and Snyder (203) and Neumann and Fischer (509) also favor the unsymmetrical structure (XIII) for the intermediate dimer because it accounts for the formation of carbodiimides more readily than does the symmetrical uretidinedione structure (XIV) proposed by Staudinger (550, 734).


XIII

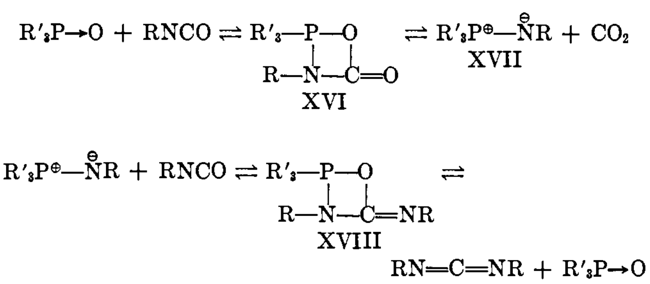
XIIIa

XIV

Dyer and Reed (164) considered the initial formation of the isocyanate trimer (XV), which is capable of decomposing into carbodiimide and isocyanate, probably by a cyclic displacement. A point in favor of this mechanism is Kogon's (364) observation that trimeric isocyanates are formed in excellent yields from the monomers in the presence of metal naphthenates at room temperature.


XV

Monagle, *et al.* (479), have concluded from their kinetic studies that the catalyzed reaction is of the first order with respect to isocyanate and catalyst over 95% of the reaction in an "open" system. They have put forward the following mechanism.



$$R'_3P{\rightarrow}O + RNCO \rightleftharpoons \underset{\text{XVI}}{\begin{array}{c}R'_3\text{—P—O}\\ \text{R—N—C=O}\end{array}} \rightleftharpoons \underset{\text{XVII}}{R'_3P^{\oplus}\text{—}\overset{\ominus}{N}R} + CO_2$$

$$R'_3P^{\oplus}\text{—}\overset{\ominus}{N}R + RNCO \rightleftharpoons \underset{\text{XVIII}}{\begin{array}{c}R'_3\text{—P—O}\\ \text{R—N—C=NR}\end{array}} \rightleftharpoons RN{=}C{=}NR + R'_3P{\rightarrow}O$$

The cyclic transition complex XVI arises by nucleophilic attack of the polarized oxygen of the phosphine oxide and decomposes in a rate-determining stage, with elimination of carbon dioxide, to the phosphinimide (XVII). Once formed, the phosphinimide reacts very rapidly with another mole of the isocyanate to yield the intermediate (XVIII) which decomposes into carbodiimide and phosphine oxide. The following points support the suggested mechanism.

(i) The reaction is reversible and is catalyzed by phosphine oxide. Passage of carbon dioxide through a solution of di-*p*-tolylcarbodiimide in the presence of the catalyst in benzene produces some *p*-tolyl isocyanate (as shown by the infrared spectrum of the liquid, and by the isolation of N-*t*-butyl-N′-*p*-tolylurea after treatment of the benzene solution with *t*-butylamine).

(ii) Phosphinimides are known to react with isocyanates to yield carbodiimide and phosphine oxide (479, 735).

(iii) The high negative value for the entropy of activation ($\Delta S = -37.9 \pm 3.9$ eu for phenyl isocyanate) indicates a marked order in the transition state.

e. The Effectiveness of Other Catalysts

According to the preceding mechanism, the chief requirement for catalytic activity appears to be the dative covalent bond between the phosphorus and the oxygen atoms; other compounds incorporating such bonding should therefore also possess catalytic activity.

Monagle (478) has examined the efficiency as catalysts of various organic compounds incorporating oxides and sulfides of elements of groups Vb and VIb. Trimethylamine oxide shows no catalytic activity (since formation of the transition state would require a pentavalent nitrogen), but the oxides of triethylphosphine and triphenylated phosphine, arsine, and stibine are all active. These effects decrease in the order As > P > Sb, apparently parallel with the dipole moments (triphenylarsine oxide 5.50 D., triphenylphosphine oxide 4.3 D., and triphenylstibine oxide ~2.0 D.). The catalytic effects of the phosphorus derivatives tested were in the order of the nucleophilicity (and polarity) of the phosphoryl groups (247): phosphine oxide > phosphinate > phosphonate > phosphate. This provides yet further evidence in favor of the proposed mechanism, since phosphine oxide is much more easily polarized than phosphate.

2. Synthesis from Isocyanate and Phosphinimines

Phosphinimines (XIX), arising in the interaction of trisubstituted phosphines and azides with loss of nitrogen, react with iso(thio)cyanates to form carbodiimide and the phosphine oxide (or sulfide) (275, 735).

$$R'N_3 + PR_3 \rightarrow R'N{=}PR_3 + N_2$$

$$\underset{\text{XIX}}{R'N{=}PR_3} + R''NCX \rightarrow R'N{=}C{=}NR'' + R_3PX$$

$$X = O \text{ or } S$$

$$\text{XIX} + CO_2 \rightarrow R'N{=}C{=}O + R_3PO$$

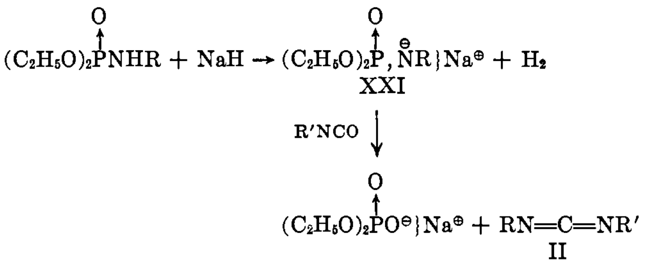
With carbon dioxide (or disulfide), the phosphinimines (XIX) yield iso(thio)cyanates; these react in turn with a further molecule of phosphinimine to yield, as before, symmetrical carbodiimides.

Messmer, *et al.* (457), have prepared several bis(acetylglucosyl)carbodiimides (*e.g.*, 2,3,4,6-tetra-O-acetyl-β-D-glucosyl-2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-D-cellobiosylcarbodiimide) by this method.

3. Synthesis from Isocyanates and Phosphoramidates

Phosphoramidate anions (XXI) react with carbonyl compounds (799, 800) as do phosphinimides (XIX) (735) and phosphorimidates (XX) (313). Thus, phenyl isocyanate and XXI ($R = C_6H_{11}$) (prepared by the action of sodium hydride on the phosphoramidate in dimethoxyethane) give 60% yields of N-phenyl-N′-cyclohexylcarbodiimide (II, $R' = C_6H_5$; $R = C_6H_{11}$) (336), identified by its infrared spectrum (ν 2150 cm^{-1}) and by conversion into the corresponding urea (705) by dilute hydrochloric acid.

$$\underset{\text{XIX}}{R_3P{=}NR} \qquad \underset{\text{XX}}{(RO)_3P{=}NR}$$



$$(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}NHR + NaH \rightarrow \underset{\text{XXI}}{(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P},\overset{\ominus}{N}R\}Na^{\oplus}} + H_2$$

$$\downarrow R'NCO$$

$$(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}O^{\ominus}\}Na^{\oplus} + \underset{\text{II}}{RN{=}C{=}NR'}$$

The procedure is limited by the tendency of many isocyanates, particularly straight-chained aliphatic ones, to polymerize in the basic medium (674).

E. FROM ISOTHIOCYANATES

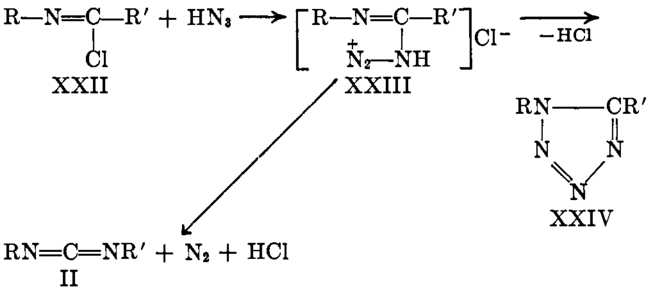
Campbell and his co-workers (108) found that prolonged heating of phenyl isothiocyanate with 4% of 3-methyl-1-ethyl-3-phospholene 1-oxide (XI, $R_1 = C_2H_5$; $R_2 = CH_3$) gave a small fraction of diphenylcarbodiimide contaminated with isocyanate and isothiocyanate. Their proposed mechanism resembles that involving isocyanates.

$$\begin{tikzcd}
R'_3P{\rightarrow}O + RNCS \arrow[r, shift left, harpoon] & R'_3\overset{+}{P}{-}\overset{-}{N}R + COS \arrow[l, shift left, harpoon] \arrow[d, shift right, harpoon, "R'NCS"'] \\
& R'_3PS + R'N{=}C{=}NR \arrow[u, shift right, harpoon]
\end{tikzcd}$$

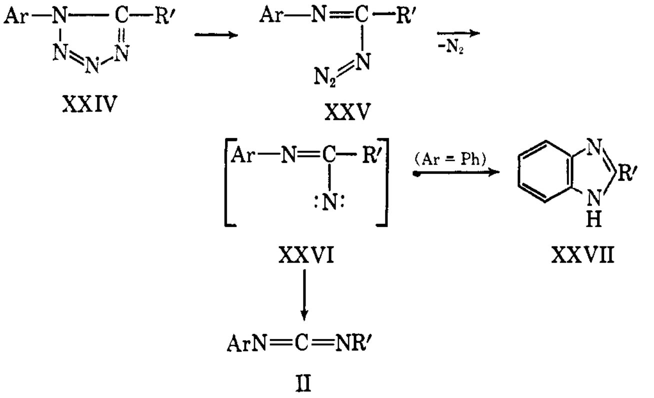
On the basis of this mechanism, phospholene sulfides should also be good catalysts, and this is indeed found to be the case.

F. FROM TETRAZOLES

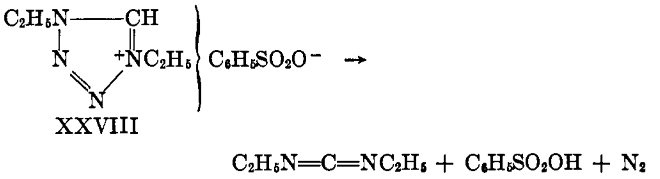
In an attempt to prepare 1-phenyl-5-(1′-phenanthryl)tetrazole (XXIV) from the imidyl chloride (XXII) and hydrazoic acid by von Braun and Rudolf's method (79) at temperatures above 200°, Smith (718) isolated N-phenyl-N′-(1-phenanthryl)carbodiimide (II, R = Ph; R′ = 1-phenanthryl). The pyrolysis of suitable tetrazoles to carbodiimides was subsequently shown to be a general reaction (28, 718, 719, 785); 1,5-disubstituted tetrazoles with identical substituents afford a single carbodiimide in high yield (*e.g.*, II, $R = R' = C_6H_5$, 70%). From tetrazoles bearing unlike substituents, the primary unsymmetrical carbodiimide disproportionates into the two symmetrical ones; a mixture of three carbodiimides is thus formed. When one of the substituents is phenyl, appreciable amounts of 2-arylbenzimidazoles (XXVII) arise in the pyrolysis.



Mechanism.—In the initial step of the reaction, the tetrazole is believed to undergo ring opening to the isomeric imidyl azide (XXV) which, in common with azides, decomposes at the pyrolysis temperature to the intermediate (XXVI); this may cyclize to the 2-arylbenzimidazole (XXVII) or isomerize to the carbodiimide by a type of Beckmann rearrangement. The second alternative (*i.e.*, the migration of the grouping R′ (in XXVI) from C to N) may be regarded as the azide analog of the Tiemann rearrangement (767) of amidoximes, $RC(=NOH)NH_2$, which is known to produce cyanamides as primary products (533).



The last stage of this reaction thus involves a competition between (i) the migration of a grouping from carbon to nitrogen and (ii) a direct cyclization. As in the formally comparable Beckmann rearrangement (118), the nature of the substituent in the aryl group (R′ in XXVI) determines its relative ease of migration. Just as a *p*-chloro substituent retards the migration of a phenyl group from C to N in the Beckmann rearrangement, it inhibits carbodiimide formation in the present reaction; conversely, a *p*-methoxy group (in R′, XXVI) has the expected opposite effect (785).

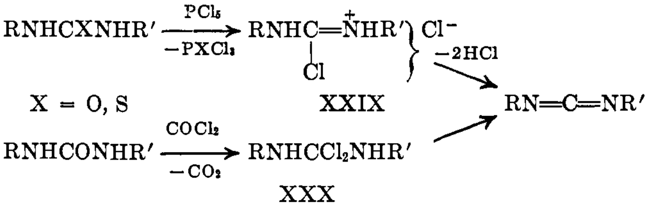


Olefson, *et al.* (524), have recently found that the tetrazolium salt (XXVIII) is cleaved quantitatively to carbodiimide under basic conditions.

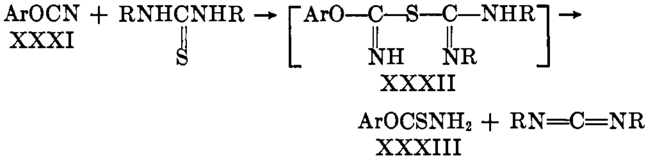
G. MISCELLANEOUS SYNTHESES

1. *From Ureas and Thioureas*

N,N′-Disubstituted imino chlorides (XXIX) (170, 670), obtained by halogenation of the corresponding ureas or thioureas, are dehydrohalogenated to carbodiimides by suitable bases, *e.g.*, potassium hydroxide and triethylamine (170, 670, 782). Pyrolysis of amidino dichlorides (XXX), produced by the halogenation of the corresponding urea by phosgene, also yields carbodiimides (508).

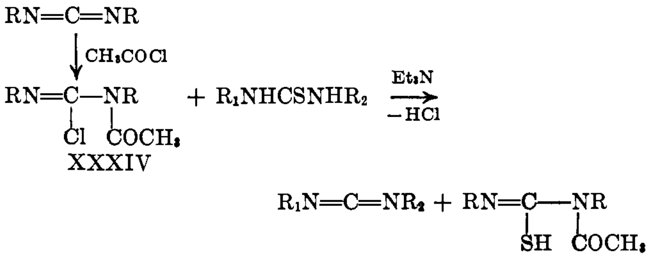


Grigat and Putter (233) have recently reported that N,N′-diphenylthiourea reacts with 2,4-dimethylphenyl cyanate (XXXI, Ar = $2,4\text{-}Me_2C_6H_3$) to give very high yields of diphenylcarbodiimide and O-(2,4-dimethylphenyl)thiocarbamate (XXXIII, Ar = $2,4\text{-}Me_2C_6H_3$) probably by way of the unstable amidino monosulfide (XXXII). Under these conditions, monosubstituted thioureas give the corresponding cyanamide.



2. *From N-Acyl-N,N′-dialkylamidino Chlorides*

Aliphatic N-acylimino chlorides of type XXXIV (244) react with many thioamides in the presence of triethylamine under very mild conditions, with loss of the elements of hydrogen sulfide (245). Extended to N,N′-disubstituted thioureas, the reaction is a suitable route to carbodiimides and has furnished these products in excellent yield (>70%).



R = $(CH_3)_2CH$; $R_1 = R_2$ = alkyl or aryl

3. From Cyanamides

Alkylation of monotritylcyanamide with trityl chloride gave di(trityl)carbodiimide (81) instead of the expected di(trityl)cyanamide. This exceptional carbodiimide formation is probably due to steric hindrance exerted by the trityl group present in the cyanamide.

$$Ph_3CNHC{\equiv}N \rightarrow Ph_3C\bar{N}C{\equiv}N \rightarrow Ph_3CN{=}C{=}\bar{N} \xrightarrow{Ph_3CCl} Ph_3CN{=}C{=}NCPh_3 + Cl^-$$

4. Isocyanate–Carbodiimide Exchange

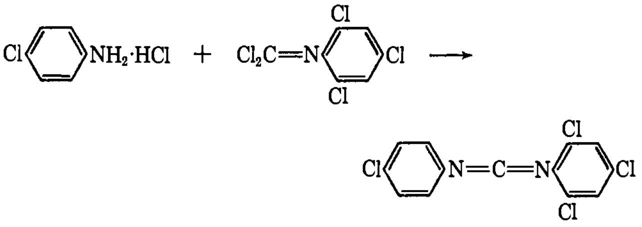
Isocyanates react with carbodiimides to form labile adducts which on pyrolysis give a pair of carbodiimide and isocyanate different from the starting materials. An example prepared by this method is 1-naphthyl-3-cyclohexylcarbodiimide (509).

$$R'NCO + RN{=}C{=}NR \rightarrow \text{adduct} \rightarrow R'N{=}C{=}NR + RNCO$$

The reaction has been reviewed by Neumann and Fischer (509), who have also discussed its application to the production of polycarbodiimides.

5. From Isocyanide Dichloride and Amines

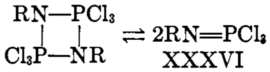
Prolonged heating of an isocyanide dichloride with a primary amine hydrochloride in an inert solvent at 180° under nitrogen results in the formation of the appropriate carbodiimide (182).



6. From Isocyanate and Phosphazene

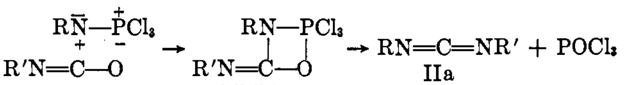
N-Substituted trichlorophosphazenes (XXXV) react with phenyl isocyanate in boiling *o*-dichlorobenzene producing N-substituted N′-phenylcarbodiimides (IIa) and phosphorus oxychloride (778, 781, 783). Yields are moderate to good (*e.g.*, IIa, $R' = C_6H_5$; $R = CH_3$, 51%; $R = C_6H_5$, 34%). The reaction is believed to involve the initial scission of the phosphazene (XXXV) into phosphorus alkyl(aryl)iminochloride (XXXVI); interaction of the latter with isocyanate may yield the final products by way of the four-membered ring compound (XXXVII).

Similarly, phenyl phosphazoanilide $(C_6H_5N{=}PC_6H_5)_2$ reacts with two molecules of phenyl isocyanate, forming diphenylcarbodiimide in 41% yield.



$$\begin{matrix} RN{-}PCl_3 \\ | \quad\ | \\ Cl_3P{-}NR \end{matrix} \rightleftharpoons 2RN{=}PCl_3$$

XXXV XXXVI

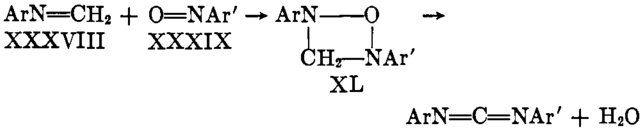


$$\begin{matrix} R\bar{N}{-}\overset{+}{P}Cl_3 \\ R'N{=}\overset{+}{C}{-}\bar{O} \end{matrix} \rightarrow \begin{matrix} RN{-}PCl_3 \\ | \quad\ | \\ R'N{=}C{-}O \end{matrix} \rightarrow RN{=}C{=}NR' + POCl_3$$

XXXVII IIa

7. From Other Four-Membered Ring Systems

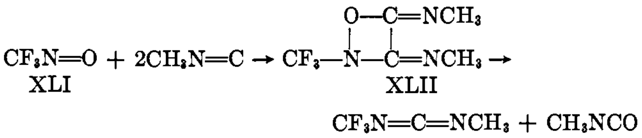
The thermal decomposition of the four-membered 1,2,4-oxadiazetidines (XL), obtained readily by the reaction of azomethines (XXXVIII) with aromatic nitroso compounds (XXXIX), yields carbodiimides as the main product (293). Side reactions give rise to urea, amines, and isonitriles.



$$ArN{=}CH_2 + O{=}NAr' \rightarrow \begin{matrix} ArN{-}O \\ | \quad\ | \\ CH_2{-}NAr' \end{matrix} \rightarrow ArN{=}C{=}NAr' + H_2O$$

XXXVIII XXXIX XL

Russian workers (437) have recently shown that trifluoronitrosomethane (XLI) reacts vigorously with methyl isocyanide at 25°; the resulting 1,2-oxazetidine (XLII) is pyrolyzed *in vacuo* at 400° to methyl isocyanate and N-methyl-N′-trifluoromethylcarbodiimide.

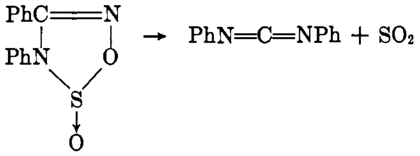


$$CF_3N{=}O + 2CH_3N{=}C \rightarrow \begin{matrix} O{-}C{=}NCH_3 \\ | \quad\ | \\ CF_3{-}N{-}C{=}NCH_3 \end{matrix} \rightarrow CF_3N{=}C{=}NCH_3 + CH_3NCO$$

XLI XLII

8. From 1,2,3,5-Thiaoxadiazoles

Pyrolysis of 4,5-diphenyl-1,2,3,5-thiaoxadiazole 1-oxide (XLIII) at 100° gives diphenylcarbodiimide and sulfur dioxide (564).



$$\rightarrow PhN{=}C{=}NPh + SO_2$$

XLIII

III. PHYSICAL PROPERTIES

At room temperature, aliphatic and aromatic carbodiimides are liquid (*e.g.*, diisopropyl- or diphenylcarbodiimides) or solid (*e.g.*, dicyclohexyl- or di-*p*-tolylcarbodiimides). They are normally sufficiently stable to be purified by vacuum distillation; in some cases, they have been crystallized from nonpolar solvents such as *n*-heptane at −70° (201), ether–light petroleum (305), benzene–ethanol (311), etc.

Stability.—Freshly prepared aliphatic carbodiimides are neutral (394, 640), but polymerize on storage to basic products. In general, the stability of substituted carbodiimides increases in the following order: $RCH_2 < R_2CH < R_3C$ (640) thus, 1-methyl-3-*n*-propyl- and 1,3-di-*n*-propylcarbodiimides (117) are considerably less stable than the 1-methyl-3-*t*-butyl and 1,3-diisopropyl homologs. However, the reactivity of the carbodiimides decreases with increased stability (484). Ascent of the homologous alkyl series has only a slight effect on the stability, but introduction of unsaturation into the substituent groups decreases it

(640). Diallylcarbodiimide, for example, is unstable. Alicyclic carbodiimides, notably the cyclohexyl derivative, are very stable.

In the aromatic series, the storage stability varies considerably. The liquid carbodiimides polymerize quite readily (285, 860), but most solid carbodiimides when pure are stable over long periods (*e.g.*, di-*p*-dimethylaminophenylcarbodiimide, 3 years). The presence of substituents in the aromatic nucleus affects the stability; thus, the introduction of an electron-attracting group tends to increase the polymerization tendencies and alkali sensitivity of the resulting carbodiimide.

Little is known about the nature of carbodiimide polymers, but the dimers and trimers of a few carbodiimides have been characterized (97, 616, 800, 858). The alleged stereoisomers of diarylcarbodiimides reported by Schall (612, 615, 616) have proved to be polymeric forms (466, 614).

IV. STRUCTURE OF CARBODIIMIDE AND N,N′-DISUBSTITUTED CARBODIIMIDES

A. CARBODIIMIDE

Carbodiimide, $HN{=}C{=}NH$, is isomeric with cyanamide, $NH_2C{\equiv}N$. The former may be regarded as the symmetrical, and the latter as the unsymmetrical anhydride of urea. The possibility of the real individual existence of the two tautomers (particularly XLV) has been considered by many workers (38, 147, 287, 314, 333, 648, 752, 845). In attempts to study this question more closely, the molecular structure of cyanamide has been examined by a number of physical methods, under various conditions.

$$\underset{\text{XLIV}}{H_2N{-}C{\equiv}N} \rightleftarrows \underset{\text{XLV}}{HN{=}C{=}NH}$$

On the basis of a study of Raman spectra, Kahovec and Kohlrausch (314) favored the cyanamide structure. Imanishi and Tachi (292), on the other hand, interpreted the ultraviolet spectra of gaseous cyanamide in terms of contributions by the diimino structure (XLV). On the basis of analytical tests, Otagiri (527) considered the structures $H_2NC{\equiv}N$ and $H_2N\text{-}NC$ in dilute and concentrated solution, respectively; it is questionable if the isonitrile structure is acceptable.

Schneider (648) has determined the dipole moments of cyanamide (4.52 D.), diisopropyl cyanamide (4.76 D.), and diisopropyl carbodiimide (2.08 D.). The closeness of the values for cyanamide and its diisopropyl derivative was taken to indicate the analogy of their structure; the small difference (0.24 D.), which might possibly result from cyanamide–carbodiimide tautomerism, was attributed to the effect of the more negative isopropyl group causing a small additional polarization in the molecule. Schneider (648), in discounting this tautomerism, attributed the high dipole moment of cyanamide to the resonance of the cyano group: $-C^+{=}N^-$.

Further evidence against the existence of free carbodiimide is provided by Sukhornkov and Finkelstein's (752) study of the infrared spectra of cyanamide, deuteriocyanamide, cyanamide dihydrochloride, and the cyanamide salts of Ca, Zn, Pb, and Ag. The spectra of crystalline cyanamide and deuteriocyanamide are both indicative of structure XLIV. Calculations based on the frequencies derived from the infrared spectra gave structural parameters which indicate that crystalline cyanamide should be represented as $H_2N^+{=}C{=}N^-$ (*cf.* Schneider's (648) conclusion, immediately above).

The salts of cyanamide appear to contain the symmetrical anion $^-N{=}C{=}N^-$. The interatomic distances of C–N, calculated from spectroscopic data (752), are close to those obtained by X-ray techniques (845) (1.255 and 1.25 A, respectively), thus favoring a symmetrical structure.

The infrared spectra of cyanamide dihydrochloride and its deuterated form show that the compounds are ionic; in salt formation the protons of the acid are therefore transferred totally (or almost so) to the nitrogen. In cyanamide hydrochloride, the intense band due to H–Cl in the region 2500 to 2700 cm^{-1} was in fact absent, while two bands, due to the antisymmetric and symmetric vibrations of the NH_2 group, appear at 3205 and 2985 cm^{-1}. Cyanamide dihydrochloride should thus be represented as

$$[H_2\overset{+}{N}{=}C{=}\overset{+}{N}H_2]Cl_2{}^{2-}$$

On the basis of their spectral data, Sukhornkov and Finkelstein (752) calculated the force constants of the anion and cation of cyanamide and thence computed the theoretical spectrum of carbodiimide, $HN{=}C{=}NH$, assuming the value of the force constant in this molecule to have the intermediate values characteristic of the ions $N^-{=}C{=}N^-$ and $H_2N^+{=}C{=}N^+H_2$. The skeleton vibrations in the carbodiimide form were thus calculated to be ν_{as} 1858 cm^{-1} and ν_s 1165 cm^{-1}, and the interatomic distance to be 1.288 A.

The monosubstituted cyanamides, like the parent compound, do not exhibit tautomerism.

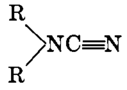
$$RNH{-}C{\equiv}N \;\not\rightleftarrows\; RN{=}C{=}NH$$

B. N,N′-DISUBSTITUTED CARBODIIMIDES

N,N′-Disubstituted carbodiimides (II) are of course distinct from the corresponding disubstituted cyanamides (XLVI). The structure assigned to the carbodiimides (II) is fully supported by both their physical and chemical properties.

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

II



$$R_2NC{\equiv}N$$

XLVI

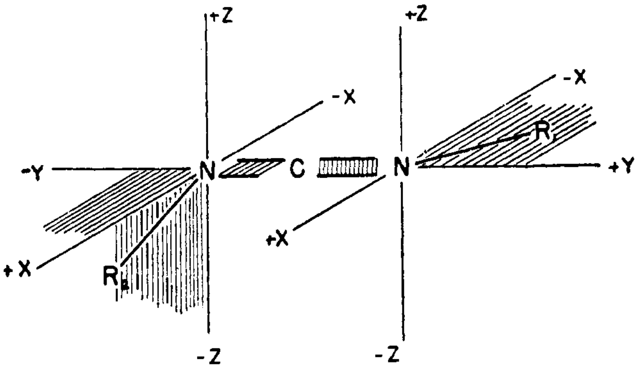
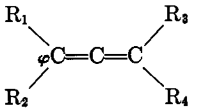


Figure 1.—Reproduced from Schneider's paper (648), by permission of the publishers of the *Journal of the American Chemical Society.*

Schall and Paschkowestzky (616) and Sidgwick (699) have pointed out many years ago that the spatial arrangement of the C and N bonds in an N,N′-disubstituted carbodiimide with unlike substituents ($R_1N{=}C{=}NR_2$) should permit the existence of optically active isomers (Figure 1). Thus, if the N–R$_2$ bond is situated in the $(-Y, -Z)$ plane, then for one enantiomorph the N–R$_1$ bond lies in the $(-X, +Y)$ plane and for the other in the $(+X, +Y)$ plane. However, all attempts to resolve N,N′-disubstituted carbodiimide into its two isomers have so far been unsuccessful (*e.g.*, 588).

Bergmann and Schutz (48) found that diphenylcarbodiimide has a finite dipole moment (1.89 D.); they attribute this to the N═C═N moiety and prefer a linear structure for carbodiimides. Schneider (648), in discussing this result, has pointed out that the result does not conflict with a three-dimensional asymmetrical structure of diphenylcarbodiimide. He found that *p,p′*-dichlorodiphenylcarbodiimide has zero dipole moment; this is thought to be due to the exact balancing of the opposite moments due to the C–N and the C–Cl bonds, and *not* due to a symmetrical structure of the carbodiimide.

More recently, Freichtmayr and Wurstlin (201) measured the dipole moment of five carbodiimides in different solvents and obtained slightly different results from those of their predecessors (48, 648). Recalling the existence of enantiomorphic forms of the allenes (XLVII) (365, 435) bearing substituents R$_1$, R$_2$ and R$_3$, R$_4$ in planes at right angles to one another (47), ($<\varphi$ being 119 to 120°), they confirmed that carbodiimide should exist in two mirror images with the planes containing R$_1$ and R$_2$ (Figure 1) at right angles to one another.



XLVII

If the two nitrogen atoms exhibit pure sp^2 hybridization, the valency angle C—N═C should be exactly 120°. Unfortunately, neither dipole measurements nor N^{14} nuclear resonance measurements (571) have provided information concerning this question.

1. *Molecular Refraction*

Schmidt and his co-workers (633) have computed the molecular refraction of carbodiimides from the individual atomic refractions, taking the value of 10.62 for the group –N═C═N–, the atomic refraction of nitrogen and carbon in the grouping C—N═C being 4.10 (24) and 2.42 (590), respectively. The calculated and experimental values are found to be in reasonable agreement (see Table I).

TABLE I
MOLECULAR REFRACTION OF CARBODIIMIDES, RN═C═NR′

		MR$_D$	
R	R′	Calcd	Found
3-Dimethylaminopropyl	*t*-Butyl	67.577	67.239
4-Dimethylaminocyclohexyl	*t*-Butyl	69.975	69.555
n-Hexadecyl	*t*-Butyl	105.200	105.198
9-Octadecenyl	*t*-Butyl	113.969	113.950
1-Diethylaminopropyl	*t*-Butyl	76.813	76.537
2-N-Morpholylethyl	*t*-Butyl	62.402	62.040

2. *Ultraviolet Absorption Spectra*

Behringer and Meier (41) have mapped ultraviolet spectra of a number of N,N′-disubstituted carbodiimides. Both aliphatic and alicyclic members have a characteristic band at 212–213 mμ, while the corresponding thioureas mostly have bands at 245–250 mμ.

3. *Infrared Spectra*

Khorana (333) first reported that disubstituted carbodiimides have infrared absorption bands near 2150 cm^{-1}. In a more extensive investigation, Meakin and Moss (449) confirmed the range of the characteristic peak between 2150 and 2100 cm^{-1} and assigned it to probable –N═C═N– stretching. A number of compounds of type X ═ C ═ Y (incorporating a carbon atom bearing two substituents attached by double bonds) and their infrared absorption frequencies are listed in Table II.

TABLE II
INFRARED SPECTRA OF COMPOUNDS INCORPORATING CUMULATIVE DOUBLE BONDS

Compound	Absorption frequency, ν, cm^{-1}	Ref
HN═C═O	2289, 2260	148, 252
PhN═C═O	2274, 2263	148
$CH_3N{=}C{=}O$	2230	148
O═C═O	2349	252
HN═C═S	1963	252
>C═C═C<	1938–2000	48, 837
>C═C═N-	~2000	739

It is apparent that the 2150–2100-cm^{-1} range may reasonably be assigned to the –N=C=N– stretching frequency as carbodiimide is structurally related to the allenes, iso(thio)cyanate esters, ketenes, and ketenimines.

Aliphatic carbodiimides give rise to a single peak in the 2140–2125-cm^{-1} range, owing to the antisymmetric stretching of the –N=C=N– system [compare Sukhornkov and Finkelstein's (752) calculated ν_{as} 1858 cm^{-1} for HN=C=NH, which is low compared with its disubstituted derivatives]. Aromatic carbodiimides exhibit two bands (Table III). This may be due to the following: (i) the bands arise by the resonance coupling between the –N=C=N– fundamental and one of the aromatic overtones present in this region, the coupling enhancing the intensity of the normally weak aromatic band; (ii) conjugation of the diimide system may be partly responsible for these bands. In the absence of data on relevant conjugated aliphatic compounds, no final choice between these can be made, and, indeed, other possible explanations can be given (449).

TABLE III

INFRARED ABSORPTION BANDS OF SOME CARBODIIMIDES

Aliphatic	ν_{max}, cm^{-1}	Ref
Carbodiimide (calcd)	[1858]	752
Dibenzyl-	2140	449
Di-*sec*-butyl-	2128	449
Diethyl-	2138	449
Diisopropyl-	2128	449
Di-*n*-butyl-	2138	449
Dicyclohexyl-	2130	449
Aromatic		
Di-*p*-methoxyphenyl-	2148, 2120	449
Di-*p*-tolyl-	2145, 2120	449
Di-*p*-naphthyl-	2152, 2100	449

4. Nuclear Magnetic Resonance Spectrum

Ray, Piette, and Hollis (571) have studied the N^{14} resonance of dicyclohexylcarbodiimide and observed a single signal which is in accordance with expectation from a symmetrical structure (II). An unsymmetrical structure (*i.e.*, N,N-dicyclohexylcyanamide) would show a doublet as was shown to be the case with ethylcyanamide (571).

So far, no information appears to be available concerning the structural evaluation of cyanamide and disubstituted carbodiimides by means of microwave spectra and electron or X-ray diffraction.

V. CHEMICAL PROPERTIES

A. HYDRATION OF CARBODIIMIDES

Like cyanamides (254), carbodiimides react additively with water to form ureas. The reaction is catalyzed both by acids (286, 311, 394, 816) and alkalis (286, 394, 395). Alkali-sensitive carbodiimides, *e.g.*, di-*m*-nitro- (or cyano-) diphenylcarbodiimide, however, undergo polymerization preferentially.

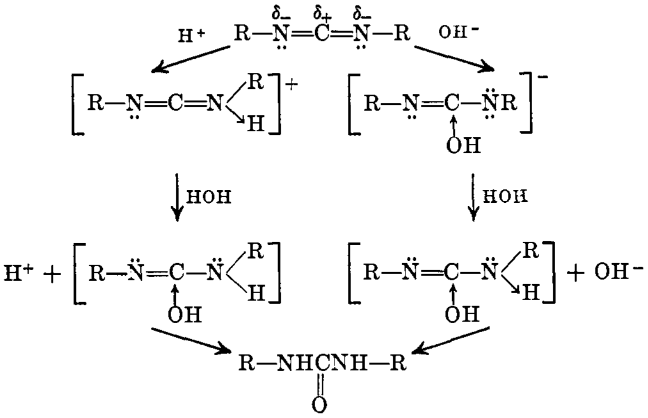
$$RN{=}C{=}NR + H_2O \rightarrow RNHCONHR$$

$$NH_2C{\equiv}N + H_2O \rightarrow NH_2CONH_2$$

Hunig, Lehmann, and Grimmer (285, 286) have studied the kinetics of the hydration of aromatic carbodiimides bearing various substituents on the benzene ring. The reaction is pseudo-monomolecular; *para* and *meta* substituents, which decrease the basicity of the imido nitrogen, increase its rate in alkaline solution and decrease the rate in acid media. The effect of the substituents on the rate of hydration in alkaline medium is in the following order: m-I < m-Br < m-Cl < m-CH$_3$CO < p-I < p-Cl < p-F < m-CH$_3$O < m-CH$_3$ < H < p-CH$_3$ < p-CH$_3$O < m-(CH$_3$)$_2$N < p-(CH$_3$)$_2$N (< denotes increase in the rate).

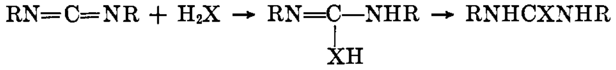
In acid media, this order is reversed, as expected. Further, if this addition is regarded as an aromatic side-chain reaction, the observed effects of the substituents obey Hammett's rule (242, 659) in both acid and alkaline media.

The acid- or base-catalyzed hydration may be interpreted in terms of the following mechanism (286).



B. REACTIONS WITH HYDROGEN SULFIDE, HYDROGEN SELENIDE, HYDROGEN CYANIDE, AND PHOSPHINE

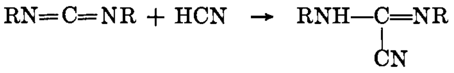
Hydrogen sulfide (283, 816, 819) or hydrogen selenide (864) add to carbodiimide to form the corresponding thio- or selenourea, respectively.



$$RN{=}C{=}NR + H_2X \rightarrow RN{=}\underset{\textstyle XH}{\underset{|}{C}}{-}NHR \rightarrow RNHCXNHR$$

X = S, Se

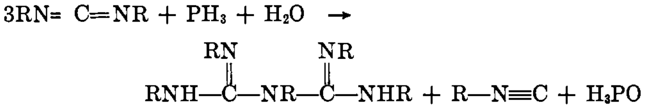
The addition reaction between carbodiimides and hydrogen cyanide yields α-cyano-N,N′-disubstituted formamidines (XLVIII) (210, 238, 285, 391, 465, 657). It is recalled that the diphenyl compound (XLVIII, R = C$_6$H$_5$) is an intermediate in Sandmeyer's indigo synthesis (238).



$$\mathrm{RN{=}C{=}NR + HCN \rightarrow RNH{-}\underset{\displaystyle CN}{\underset{|}{C}}{=}NR}$$

XLVIII

Phosphine reacts with diphenylcarbodiimide to form pentaphenylbiguanide (XLIX, R = C_6H_5) and phenylisonitrile (L) (275, 276).



$$\mathrm{3RN{=}C{=}NR + PH_3 + H_2O \rightarrow RNH{-}\overset{\displaystyle RN}{\overset{\|}{C}}{-}NR{-}\overset{\displaystyle NR}{\overset{\|}{C}}{-}NHR + R{-}N{\equiv}C + H_3PO}$$

XLIX L

C. REACTIONS WITH ALCOHOLS, THIOALCOHOLS, AND RELATED COMPOUNDS

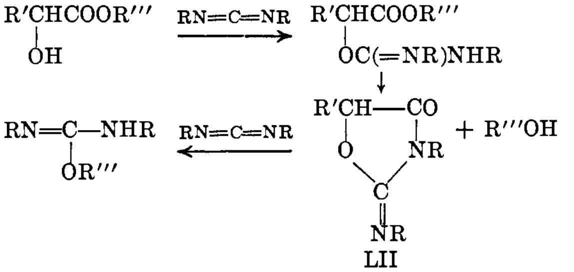
In the absence of catalysts, alcohols are fairly inert toward carbodiimides at room temperature. Under drastic conditions, diphenylcarbodiimide reacts additively with ethanol forming O-ethyl-N,N′-diphenylisourea (LI) (400).

$$C_6H_5N{=}C{=}NC_6H_5 + C_2H_5OH \rightarrow C_6H_5NHC({=}NC_6H_5)OC_2H_5$$

LI

The addition occurs readily and exothermically under the influence of certain catalysts. Thus, pseudoureas have been prepared successfully using sodium ethoxide in this procedure (144, 330, 331). Tertiary bases (*e.g.*, triethylamine, pyridine) and trimethyl phosphate are not suitable as catalysts (330, 626), but certain copper salts [*e.g.*, Cu_2Cl_2 (630), $CuCl_2$ (626, 631)] are effective, particularly in the case of aliphatic carbodiimides. Copper sulfate exhibits only slight catalytic activity, and nickel and cobalt salts (*e.g.*, $NiCl_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$) show none. The reaction time varies from 4 hr to 28 days (*e.g.*, for tertiary alcohols). Thus borneol and diisopropylcarbodiimide in the presence of cupric chloride yield the pseudourea in 82% yield (626). The procedure has occasionally failed (*e.g.*, di-*t*-butylcarbodiimide with methanol or cyclohexanol, and diisopropylcarbodiimide with β-chloroethanol (630)).

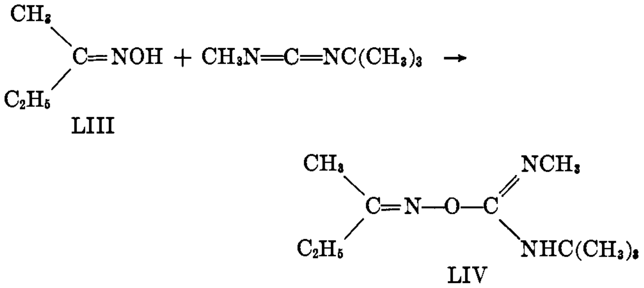
α-Hydroxycarboxylic esters, on being treated with 2 moles of aliphatic carbodiimides in the presence of cupric chloride, yield the 2-alkylimino-3,5-dialkyl-4-oxazolidone (LII), together with the O-alkylisourea, both in excellent yield (626).



LII

R′′′ = alkyl

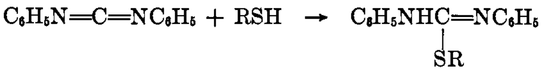
Aliphatic ketoximes (LIII) add to carbodiimides in the presence of powdered sodium hydroxide as catalyst to form adducts (626) (*e.g.*, LIV).



LIII

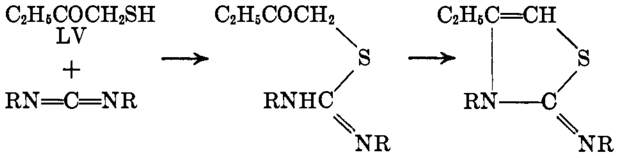
LIV

Thioalcohols react additively to form the expected S-substituted isothioureas (97, 625). These isothioureas are in fact obtained more simply by S-alkylation of thioureas and are useful in the preparation of carbodiimides by the reverse reaction (see section IIB).



$$\mathrm{C_6H_5N{=}C{=}NC_6H_5 + RSH \rightarrow C_6H_5NH\underset{\displaystyle SR}{\underset{|}{C}}{=}NC_6H_5}$$

α-Mercaptocarbonyl compounds (*e.g.*, LV) react with carbodiimides to form thiazole derivatives (440) (*e.g.*, LVI, R = C_6H_5) by successive addition and cyclization.



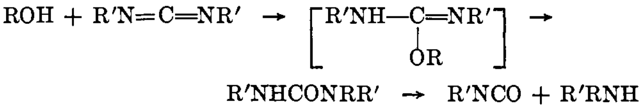
LV

LVI

D. REACTION WITH PHENOLS

According to Busch and his co-workers (97), diphenylcarbodiimide reacts with weakly acidic phenols at high temperatures (*ca.* 160°) to form O,N,N′-triarylisoureas, but with strongly acidic phenols (*e.g.*, picric acid) to yield the N,N,N′-triarylureas (97, 394). Using dicyclohexylcarbodiimide, Vowinkel (798) confirmed the production of O-phenylisoureas from weak phenols. Copper salts (particularly $CuCl_2$) catalyze the addition which may then be carried out at room temperature (631), but the use of solvents generally lowers yields. The O-arylisoureas thus obtained decompose once again into phenols and dicyclohexylcarbodiimide at 100–110° under reduced pressure.

In contrast, nitrophenols give N,N′-disubstituted N-arylureas (8, 97, 798) which decompose above their melting point into cyclohexyl isocyanate and the appropriate secondary amine.



$$\mathrm{ROH + R'N{=}C{=}NR' \rightarrow \left[R'NH{-}\underset{\displaystyle OR}{\underset{|}{C}}{=}NR'\right] \rightarrow R'NHCONRR' \rightarrow R'NCO + R'RNH}$$

$R' = C_6H_{11}$

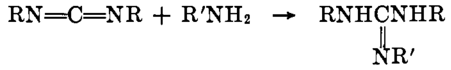
Unidentified products were obtained when dicyclohexylcarbodiimide was treated with substituted o-hydroxybenzaldehydes (8).

The addition of carbodiimides to thiophenols yields the expected N,N′-disubstituted S-arylisothioureas (97).

E. REACTION WITH AMINO COMPOUNDS

1. *Ammonia and Amines*

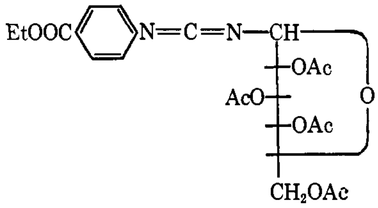
Ammonia and amines react additively with carbodiimide to form the expected di- (LVII, R′ = H) (289, 290, 311, 432, 703, 818) and trisubstituted guanidines (LVII) (11, 181, 283, 288–290, 311, 333, 380, 432, 440, 441, 461, 532, 622, 626, 703, 816–819), respectively (compare cyanamides (173)).



$$RN{=}C{=}NR + R'NH_2 \rightarrow RNH\underset{\underset{NR'}{\|}}{C}NHR$$

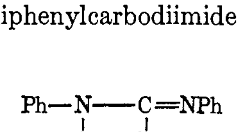
LVII

The procedure has been particularly useful in providing a number of glucosylguanidines from N-(2,3,4,6-tetra-O-acetylglucosyl)-N′-(p-carbethoxyphenyl)carbodiimide (LVIII), which could not be prepared by the aminolysis of the corresponding S-alkylisothiourea (461). In some cases, the method has been known to fail (305, 377, 755).

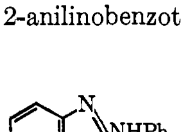


LVIII

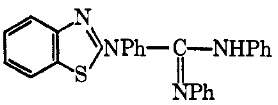
The oxidation product of N,N′-diphenylthiourea (281), originally formulated as 3,5-diphenylimino-2,4-diphenyl-1,2,4-thiadiazolidine (LIX) (281), has been proved to be in fact N-2-benzthiazolyl-N,N′,N″-triphenylguanidine (LXI) (753) by its synthesis (789) from diphenylcarbodiimide and 2-anilinobenzothiazole (LX).



LIX

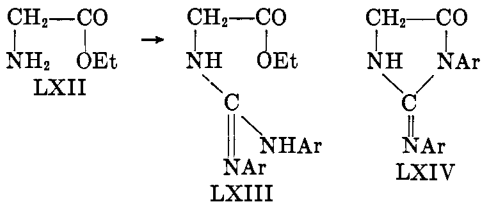


LX

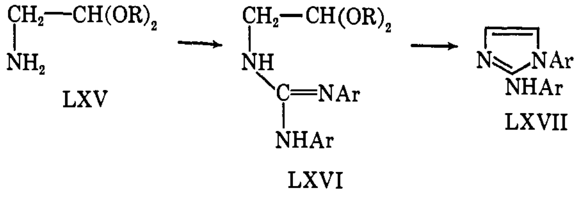


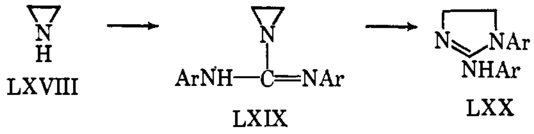
LXI

The reaction of diarylcarbodiimides with ethyl glycinate (LXII) yields imidazolidones (LXIV) as the final products (1).



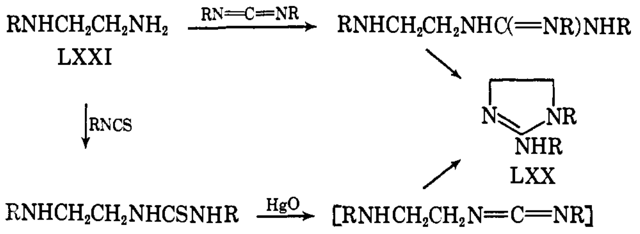
The postulated intermediate of type LXVI was isolated when β-diethoxyethylamine (LXV, R = C_2H_5) was employed; on acid hydrolysis it gave the imidazole LXVII (464).





Adcock and Lawson (2) have extended this general reaction to the synthesis of imidazolines: thus aziridine (LXVIII) and diarylcarbodiimides yield 1-(N,N′-diarylamidino)aziridines (LXIX) which rearrange to 1-aryl-2-arylamino-2-imidazoline (LXX) on prolonged boiling with potassium iodide in acetone.

The same imidazolines have also been prepared from β-anilinoethylamine (LXXI) and carbodiimide or isothiocyanate, followed by cyclization of the respective intermediates.

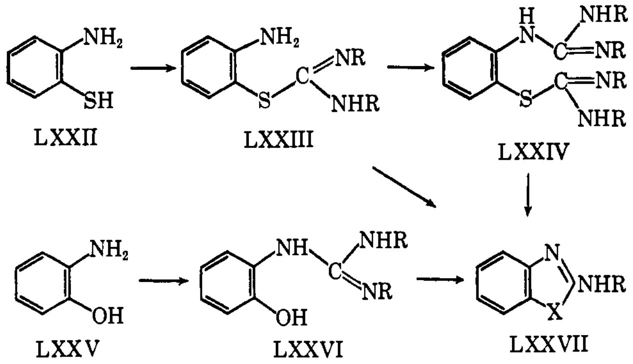


The addition of carbodiimides to amines, which incorporate functional groups that are themselves capable of interacting with these reagents, has provided a number of interesting reactions, usually culminating in cyclizations.

a. o-Aminothiophenol

Thus, o-aminothiophenol (LXXII) yields successively S-o-aminophenyl-N,N′-diarylisothioureas (LXXIII) and N,N′-diaryl-S-o-[(N,N′-diarylguanidino)phenyl]-isothioureas (LXXIV). Both these isothioureas are readily cyclized to 2-arylaminobenzothiazoles (LXXVII, X = S) (381).

With o-aminophenol (LXXV), exclusive monoaddition results in N-o-hydroxyphenyl-N′,N″-diarylguani-

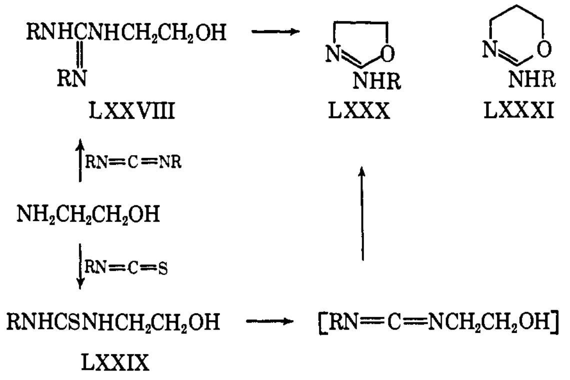


dine (LXXVI) (382). Like its S-analog, this guanidine derivative is cyclized to 2-arylaminobenzoxazole (LXXVII, X = O) (97, 382). These observations suggest that aromatic substituents exhibit decreasing reactivity toward carbodiimides in the order SH > NH_2 > OH.

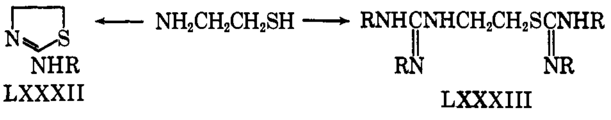
b. Amino Alcohols and Thioalcohols

Substituted 2-amino-2-oxazolines (LXXX), of special interest because of their vascular activity (234), are accessible by the addition of carbodiimides to ethanolamine and cyclization of the primary adducts (LXXVIII) (3). The same oxazolines result in the desulfurization of N-substituted N′-(2-hydroxyethyl)-thioureas (LXXIX) by mercuric oxide (1, 95, 628, 724).

From 3-aminopropanol, substituted 2-amino-5,6-dihydro-1,3-oxazines (LXXXI) are obtained analogously (1, 464, 639).



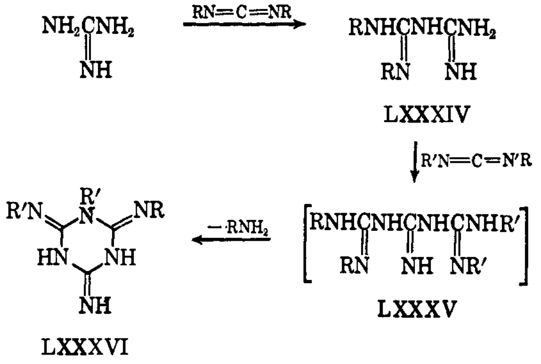
2-Mercaptoethylamine undergoes diaddition with diarylcarbodiimide in acetonitrile (to LXXXIII) in the cold; cyclization to 2-arylamino-2-thiazoline (LXXXII) occurs in dimethylformamide at 100° (1).



2. Guanidines and Biguanides

Guanidines react with equimolar quantities of carbodiimide to form disubstituted biguanides (LXXXIV) (379, 440).

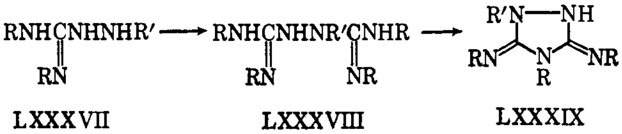
The interaction of biguanides (LXXXIV) and carbodiimides in dimethylformamide at 100° affords substituted melamines in good yields (379). Thus, the parent base (LXXXIV, R = H) and 1-mono- and 1,2-disubstituted biguanides give respectively mono-, 1,2-di-, and 1,2,6-trisubstituted melamines (LXXXVI). The reaction probably involves the formation of the triguanides (LXXXV), which, like the analogous seven-membered linear carbon–nitrogen system (467, 720), are unstable and cyclize spontaneously with elimination of amine.



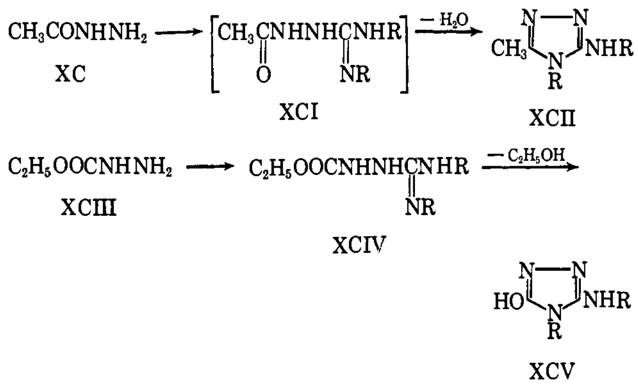
3. Hydrazine and Its Derivatives

As expected, hydrazine reacts with 1 or 2 moles of carbodiimide to give either mono- (LXXXVII, R′ = H) or diaddition products (LXXXVIII, R′ = H), the latter cyclizing readily to the substituted 1,2,4-triazole (LXXXIX, R′ = H) (99).

Phenylhydrazine similarly reacts with 1 mole of diphenylcarbodiimide to form 1,3,4-triphenylaminoguanidine (LXXXVII, R = R′ = C_6H_5) (95, 562). Under more drastic conditions, continued reaction and cyclization finally results in 1,4-diphenyl-3,5-di-(phenylimino)-1,2,4-triazolidine (LXXXIX, R = R′ = C_6H_5) and aniline (99, 613, 822).



Acetylhydrazine (XC) yields 3-methyl-4-substituted 5-(aralkylamino)-1,2,4-triazoles (XCII), prob-

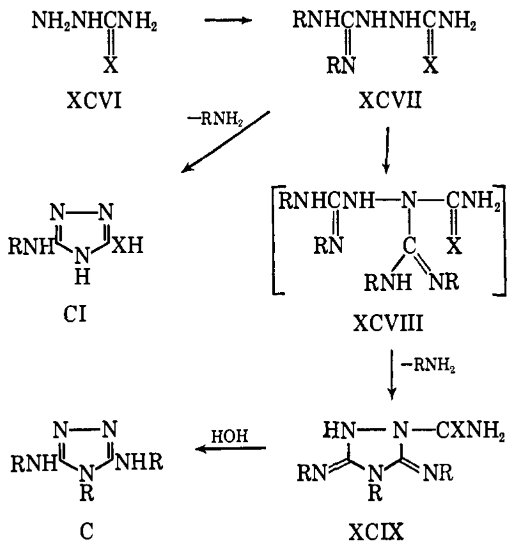


ably by way of the substituted guanidine (XCI) (1). The adducts (XCIV) arising from equimolar quantities of carbethoxyhydrazine (XCIII) and diarylcarbodiimides are readily isolated. They are stable toward acids but are rapidly cyclized, with loss of ethanol, by alkalis, or on pyrolysis, to 4-aryl-3-arylamino-5-hydroxy-1,2,4-triazoles (XCV) in excellent yields (378).

4. Aminoguanidine, Thiosemicarbazide, and Semicarbazide

In the interaction of carbodiimides with aminoguanidine and thiosemicarbazide, addition involves their hydrazino groups preferentially (223) but may be made to occur elsewhere if the hydrazino group is suitably blocked (375).

Diphenylcarbodiimide and aminoguanidine (XCVI, X = =NH) in dimethylformamide yield 1,2-diphenylbiguanidine (XCVII, X = =NH; R = C_6H_5) and 1-amidino-4-phenyl-3,5-di(phenylimino)-1,2,4-triazolidine (XCIX, X = =NH; R = C_6H_5) as main products (223). As shown in the reaction scheme, these are thought to arise by successive addition of 2 moles of the carbodiimide to aminoguanidine, one to each of the nitrogen atoms of the hydrazino group, followed by elimination of aniline.



The interaction of diphenylcarbodiimide with excess thiosemicarbazide (XCVI, X = S) gives the monoaddition product, 1-(N,N′-diphenylamidino)thiosemicarbazide (XCVII, X = S; R = C_6H_5) in high yield together with small quantities of 3-anilino-5-mercapto-(CI, X = S; R = C_6H_5) and 3,5-dianilino-4-phenyl-1,2,4-triazole (C, R = C_6H_5); the latter is thought to result from the addition of the carbodiimide to the thiosemicarbazide as shown (XCVII → XCVIII → XCIX) (223). Semicarbazide similarly gives the monoaddition product (XCVII, X = O)(223).

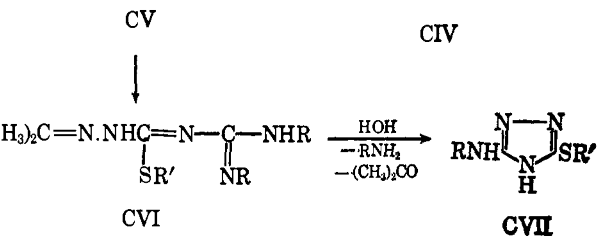
Monoaddition products of this general structure (XCVII, X = =NH, S, O) are useful intermediates, being cyclized to 1,2,4-triazoles and 1,3,4-thiadiazoles under appropriate conditions (223); they also react with a further mole of carbodiimide to give 3,5-diarylamino-4-aryl-1,2,4-triazole (C) in each case (223).

The reaction between diphenylcarbodiimide and 4-phenyl-3-thiosemicarbazide did not result in the expected simple addition but gave 3,5-dianilino-4-phenyl- and 3-anilino-5-mercapto-4-phenyl-1,2,4-triazole directly (96).

Aminoguanidine, like semicarbazide and its thio analog, readily yields derivatives with aldehydes and ketones; as expected, these also react with carbodiimides to afford adducts that are useful intermediates in the synthesis of 1,2,4-triazoles.

Thus, the product (CII, X = NH) formed from aminoguanidine and acetone reacts with diarylcarbodiimides to yield 1-(N,N′-diarylamidino)-3-isopropylideneguanidines (CIII, X = NH). These are cyclized, with loss of arylamine, to 3-amino-5-arylamino-1,2,4-triazoles (CIV) in acid media (375). By the same sequence of reactions, 1-amino-3-phenylguanidine yields 3,5-di(arylamino)-1,2,4-triazoles (375).

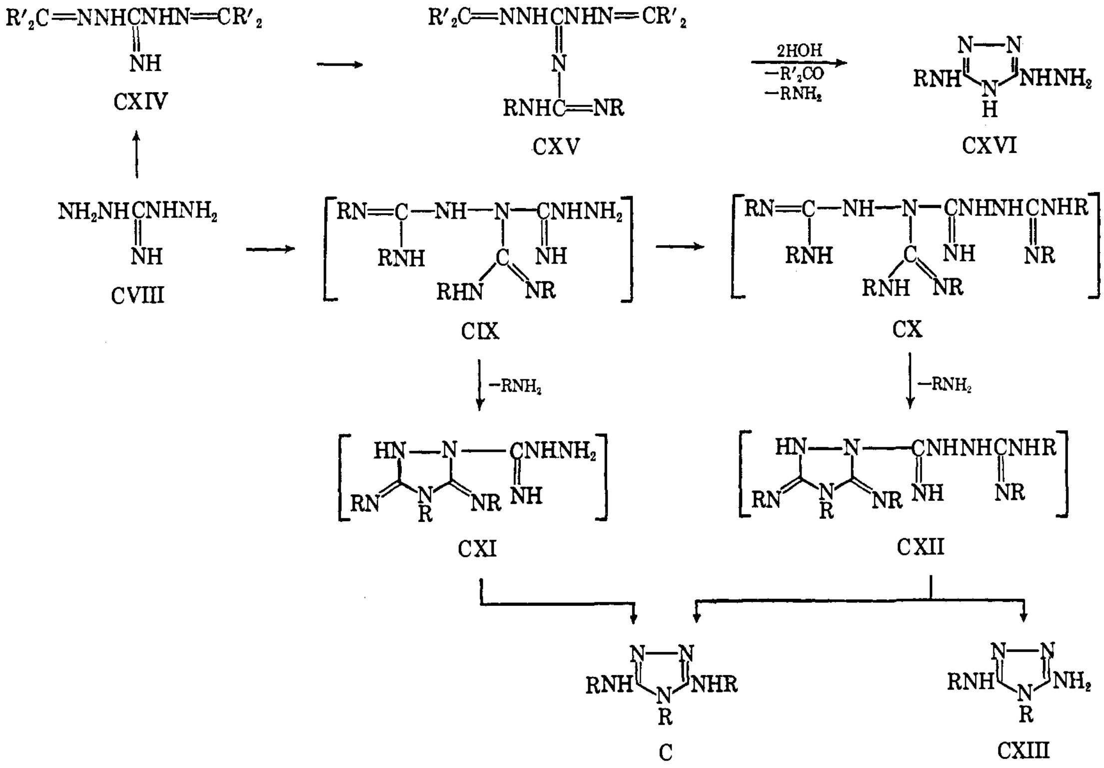
Acetone thiosemicarbazone (CII, X = S) fails to react with diarylcarbodiimides, its thioamido grouping being apparently not sufficiently basic to participate in the addition. However, the thiosemicarbazone does undergo the addition readily after being S-alkylated; the resulting acetone 4-(N,N′-diarylamidino)-S-benzylisothiosemicarbazones (CVI) are ring-closed by mineral acids to 3-arylamino-5-benzylthio-1,2,4-triazoles (CVII) (375).



R′=alkyl

5. Diaminoguanidine

As in the case of aminoguanidine (*cf.* preceding section), the course of the addition of carbodiimides to N,N′-diaminoguanidine differs when the hydrazino groups are blocked or unsubstituted (376). Diaminoguanidine (CVIII), lacking protecting groups, SCHEME I



reacts with an excess of carbodiimide in dimethylformamide yielding 4-aryl-3,5-di(arylamino)- (C) and 3-amino-4-aryl-5-arylamino-1,2,4-triazoles (CXIII) directly as main products. Primary addition compounds are not isolated, but the formation of the triazoles is accounted for by a mechanism involving the successive addition of carbodiimide molecules to the hydrazino groups of diaminoguanidine, involving intermediates of types CIX–CXII, followed by cyclization (376). See Scheme I.

The addition of carbodiimides to N,N′-diaminoguanidine having its hydrazino groups blocked occurs exclusively at the central imino group of the latter (376). Thus, equimolar proportions of N,N′-di(isopropylideneamino)guanidine (CXIV, R = CH_3) and diarylcarbodiimides in acetone or dimethylformamide give 3-(N,N′-diarylamidino)-1,2-di(isopropylideneamino)guanidines (CXV) rapidly and in good yields. These adducts are a useful source of 3-arylamino-5-hydrazino-1,2,4-triazoles (CXVI), which are formed from them by cyclization under the influence of mineral acids. Certain of the chemical properties of these hydrazinotriazoles have been examined (376).

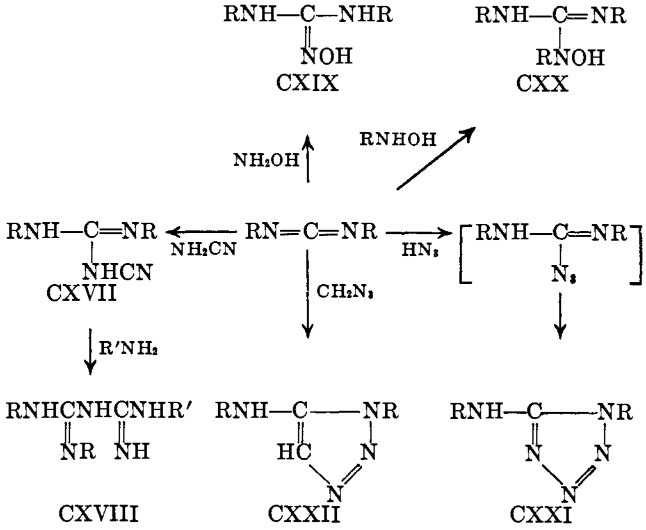
6. *Cyanamide*

Carbodiimides and cyanamide react additively to yield the expected 1,2-disubstituted 3-cyanoguanidines (CXVII) (10, 11, 396, 397), convertible into diguanides (CXVIII) by aminolysis (11).

7. *Hydroxylamine, Hydrazoic Acid, and Diazomethane*

Stolle and Laske (743) showed that hydroxylamine was convertible by diphenylcarbodiimide into the N-hydroxyguanidine (CXIX). Phenylhydroxylamine yields N-hydroxy-s-triphenylguanidine (CXX) (97).

The reaction of hydrazoic acid with aromatic carbodiimides results in the formation of 1-aryl-5-arylaminotetrazoles (CXXI) (525, 742). Diazomethane reacts additively to yield 1-aryl-5-arylamino-1,2,3-triazoles (CXXII, R = Ar) (593, 594).

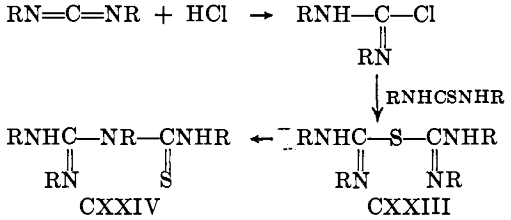


8. *Thiourea*

Weith (820) reported as early as 1876 that diphenylcarbodiimide reacts with *s*-diphenylthiourea to give N,N′,N″-triphenylguanidine and phenyl isothiocyanate.

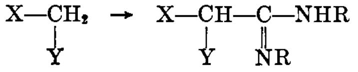
RNHCSNHR + RN=C=NR → RNHC(=NR)NHR + RNCS

In the presence of hydrogen chloride and under restrained conditions, 1-(N,N′-diphenylamidino)-1,3-diphenylthiourea (CXXIV) (312) is obtained, possibly by way of the formamidine monosulfide of type CXXIII.



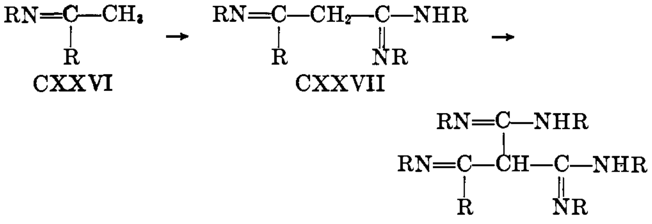
F. REACTIONS WITH OTHER COMPOUNDS CONTAINING ACTIVE HYDROGEN

Compounds containing active hydrogen react in the form of their sodio derivatives with carbodiimides to yield the corresponding amidino compounds. Thus, acetoacetic ester (772), acetylacetone (772), or malonic ester (768, 772) afford amidines of type CXXV.



CXXV

X = $COOC_2H_5$, Y = $COOC_2H_5$
$COCH_3$ $COOC_2H_5$
$COOCH_3$ $COCH_3$



Acetophenone anil (CXXVI, R = C_6H_5) at about 150–160° similarly gives rise to mono- (CXXVII) and di- (CXXVIII) adducts (488, 491) [compare with isocyanates and isothiocyanate, which cause exclusive di- and monoaddition, respectively (489, 490)].

G. REACTION WITH CARBOXYLIC ACIDS

1. *Monocarboxylic Acids*

Carboxylic acids react with carbodiimides to form N-acylureas, or acid anhydrides and the appropriate ureas, the relative yields depending on the nature of the reagents and conditions (715).

R′COOH + RN=C=NR → R(R′CO)NCONHR
2R′COOH + RN=C=NR → R′COOCOR′ + RNHCONHR

With aromatic carbodiimides, the N-acylurea greatly predominates (613, 668, 715, 856, 857, 860, 861, 865–867). In the presence of a tertiary base (*e.g.*, tri-*n*-butylamine), the reaction is slower, but anhydride formation is inhibited (715).

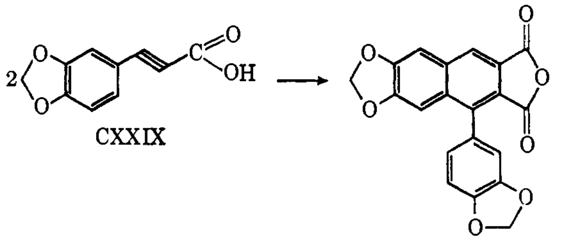
Since the reaction conditions are very mild and the acylureas are well-defined crystalline compounds, Zetzsche (854) has suggested carbodiimides as reagents for characterizing carboxylic acids and recommended di(*p*-dimethylaminophenyl)carbodiimide [p-$(CH_3)_2NC_6H_4N{=}C{=}NC_6H_4N(CH_3)_2$-$p$] as the compound most suitable for this purpose (861, 862). This reagent, sometimes referred to as "Zetzsche's carbodiimide," has been extensively used to characterize a variety of organic acids (82, 129–131, 145, 235, 774, 856), including lipoic (235), oleic (145), and C_4–C_{10} and C_{12}–C_{20} acids (774). The acid may be regenerated from the N-acylurea by mild alkaline hydrolysis. The water-soluble methiodide and methosulfate of Zetzsche's carbodiimide do not yield the expected N-acylurea, because of the rapid hydration of the carbodiimides to the urea (854).

Zetzsche and his co-workers (865–867, 869) have shown, and subsequent workers have confirmed, that di(*p*-dimethylaminophenyl)carbodiimide reacts with α,β-unsaturated acids to give deeply colored N-acylureas, but β,γ-unsaturated acids afford colorless ureides (865). α-Halogeno (867) and mono- and polynuclear substituted aromatic carboxylic acids (866, 869) also form, in general, colored acylureas, while β-halogenocarboxylic acids give colorless adducts. These color differences provide a convenient distinction between the acids concerned.

Aliphatic carbodiimides and carboxylic acids normally yield disubstituted ureas together with acid anhydrides (5, 495, 856, 858) but afford exclusively N-acylureas if organic bases (*e.g.*, pyridine or triethylamine) are present (308, 495, 857). Thus, gradual addition of carboxylic acids to dicyclohexylcarbodiimide (628) in hot pyridine (which is claimed to accelerate the oxygen-to-nitrogen migration, CXXXII → CXXXIII) (see mechanism, below), affords the acylurea as the main product (857). Muramatsu, *et al.* (497), recorded similar observations when ϵ-carbobenzoxyaminocaproic acid was used.

Brown and Stevenson (88) have recently reported a simultaneous cyclization in the anhydride formation of certain α-acetylenic acids. Thus, treatment of piperonylpropiolic acid (CXXIX) with dicyclohexylcarbodiimide in dimethoxyethane below 0° gave 6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic anhydride (CXXX).

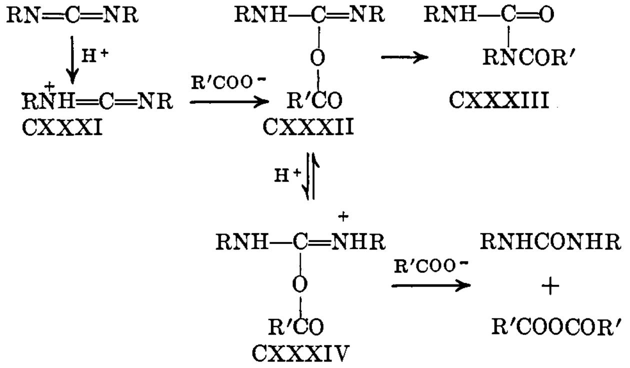
In the general addition reaction employing unsymmetrical carbodiimides (*e.g.*, $C_6H_{11}N{=}C{=}NC_6H_5$),



CXXIX CXXX

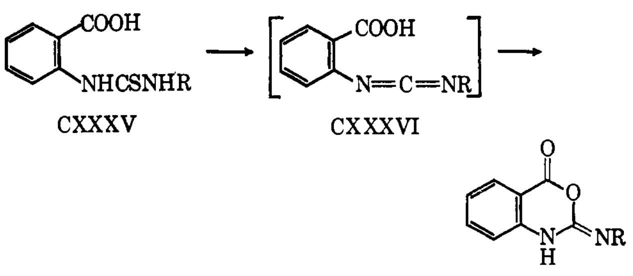
two acylureas should theoretically be expected; in fact, only one isomer appears to be formed (336), the acyl group attaching itself on the less basic nitrogen (*i.e.*, the one of lower electron density).

Mechanism.—The reaction is believed to be initiated by the protonation of the carbodiimide (to CXXXI), the cation being next attacked by the acid anion to form the O-acylisourea (CXXXII) (328, 336, 715). The latter may (i) either rearrange, by way of a cyclic electronic displacement, to the stable N-acylurea (CXXXIII), or may (ii) be protonated to the cation (CXXXIV), which is subsequently converted by attack of a second anion into the N,N′-disubstituted urea and the acid anhydride. A similar mechanism probably operates in the formation of esters and amides.



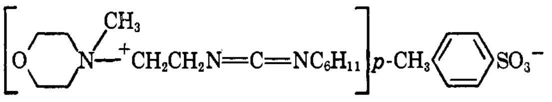
CXXXI CXXXII CXXXIII CXXXIV

Support for the above mechanism has been provided by Doleschall and Lempert (159), who isolated a cyclic O-acylisourea of type CXXXVII. Thus, desulfurization of N-*o*-carboxyphenyl-N′-phenylthiourea (CXXXV) with mercuric oxide in acetone produces 2-(1H)-phenylimino-4H-3,1-benzoxazin-4-one (CXXXVII) by the intramolecular cyclization of the intermediate carbodiimide (CXXXVI). This cyclic O-acylisourea is unaffected by water or methanol but is hydrated to the urea in the presence of mineral acid.

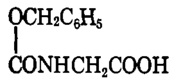


CXXXV CXXXVI CXXXVII

Knorre and Shubina (353) studied the kinetics of the reaction of N-cyclohexyl-N′-β-(N-methylmorpholinium)ethylcarbodiimide *p*-toluenesulfonate (CXXXVIII) with carbobenzoxyglycine (CXXXIX); the energy of activation of the acid-catalytic hydration of this carbodiimide was 1.07 kcal/mole.



CXXXVIII



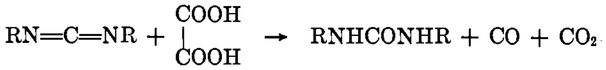
$$\underset{\text{CONHCH}_2\text{COOH}}{\overset{\text{OCH}_2\text{C}_6\text{H}_5}{|}}$$

CXXXIX

2. *Dicarboxylic Acids*

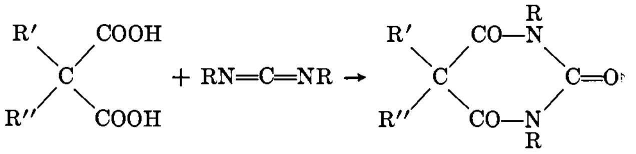
The length of the alkyl chain of dicarboxylic acids and the solvent employed influence the course of their interaction with carbodiimides and the nature of the resulting products (859).

Oxalic acid forms the disubstituted urea together with carbon monoxide and dioxide quantitatively under all conditions; the reaction has therefore been used to estimate carbodiimides (855) (see section XI).



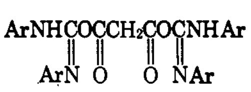
$$\text{RN=C=NR} + \begin{matrix}\text{COOH}\\|\\\text{COOH}\end{matrix} \rightarrow \text{RNHCONHR} + \text{CO} + \text{CO}_2$$

Malonic acid (CXL, R′ = R″ = H) and its homologs (CXL) react with aliphatic carbodiimides (II, R = C_6H_{11}, Me_2CH) exothermically in tetrahydrofuran to form substituted barbituric acids (CXLI) (76).

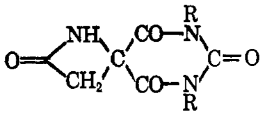


CXL CXLI

In the case of aromatic carbodiimides, the nature of the products varies; thus, the parent acid (CXL, R′ = R″ = H) and di(*p*-dimethylaminophenyl)-carbodiimide in pyridine give the diacylurea (859), while di-*p*-tolylcarbodiimide in tetrahydrofuran affords the O,O′-diamidino derivative (CXLII) (76) together with the urea (76, 859).



CXLII

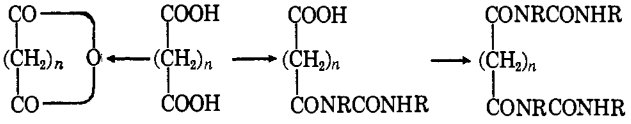


CXLIII

Ethylmalonic acid (CXL, R′ = H, R″ = Et) resembles its parent compound in its reaction with di-*p*-tolylcarbodiimide, but diethylmalonic acid yields the barbiturate (CXLI, R′ = R″ = Et; R = *p*-CH_3-C_6H_4) (76).

The usefulness of this novel barbiturate synthesis is demonstrated by the production of substituted spirobarbiturates (*e.g.*, CXLIII), which were previously inaccessible by the usual synthetic routes (76).

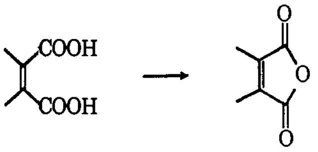
Succinic and glutaric acids form the cyclic anhydrides (CXLIV) together with the disubstituted urea, while adipic acid and the higher members yield the mono- (CXLV) and diacylureas (CXLVI), each carboxylic group reacting independently (859).



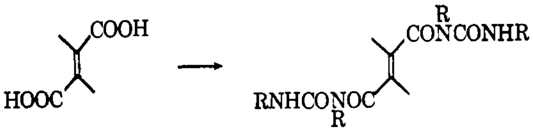
CXLIV CXLV CXLVI

$n = 2, 3$

Maleic and phthalic acids yield the cyclic anhydrides (CXLVII) while fumaric acid gives the normal adduct (CXLVIII) (97).

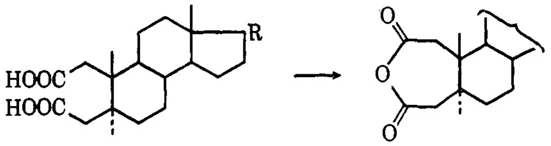


CXLVII



CXLVIII

An interesting application of this reaction is the dehydration, in 84% yield, of 2,3-seco-5α-cholestane-2,3-dioic acid (CXLIX) to the corresponding anhydride (CL) (162).



CXLIX CL

3. *Anhydrides of Carboxylic Acids*

N-Acyl-N,N′-disubstituted ureas are formed when carbodiimides react with acid anhydrides in boiling dimethylformamide. The appropriate O,N-diacylurea (CLI) is probably the primary intermediate (144, 656). At room temperature the reaction does not occur to an appreciable extent, and carbodiimide has been claimed to be useful for the removal of traces of acid from its anhydride (801).

$$C_6H_{11}N{=}C{=}NC_6H_{11} + RCOOCOR \rightarrow$$

$$\underset{\text{CLI}}{C_6H_{11}N{=}C(OCOR)N(COR)C_6H_{11}} \rightarrow$$

$$\underset{\text{CLII}}{C_6H_{11}NHCON(COR)C_6H_{11}} + RCOOH$$

4. *Formation of Diacyl Peroxides*

Of the several syntheses of diacyl peroxides (146, 156, 249, 804), the most common procedure is the treatment of an acyl chloride with aqueous alkaline hydrogen peroxide. In 1963, Greene and Kazan (231) reported that organic acids react with hydrogen peroxide in the presence of dicyclohexylcarbodiimide in inert solvents at 0° to form dicyclohexylurea and diacyl peroxide (CLIII) of high purity in excellent yields. The use of the appropriate peracids provides unsymmetrical diacyl peroxides (CLIV).

$$2RCOOH + H_2O_2 + 2C_6H_{11}N{=}C{=}NC_6H_{11} \rightarrow$$

$$\underset{\text{CLIII}}{RCOOOCOR} + 2C_6H_{11}NHCONHC_6H_{11}$$

$$RCOOH + R'COOOH + C_6H_{11}N{=}C{=}NC_6H_{11} \rightarrow$$

$$\underset{\text{CLIV}}{RCOOOCOR'} + C_6H_{11}NHCONHC_6H_{11}$$

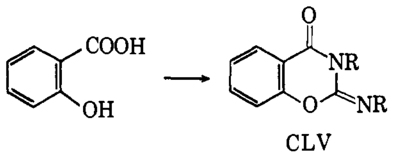
Certain cyclic anhydrides (*e.g.*, phthalic anhydride) similarly yield cyclic diacyl peroxides (phthaloyl peroxide). The mechanism of the reaction has been discussed (231).

At higher temperatures, diacyl peroxides continue to react with dicyclohexylcarbodiimide to form a variety of compounds, depending on the nature of the solvents (151). Benzoyl peroxide and dicyclohexylcarbodiimide in isopropyl alcohol yield N-benzoyl-N,N′-dicyclohexylurea, dicyclohexylurea, benzene, acetone, and carbon dioxide. In carbon tetrachloride, the products are N-cyclohexylbenzamide, chlorobenzene, cyclohexyl isocyanate, and carbon dioxide. The reactions are believed to proceed by a free-radical mechanism (151).

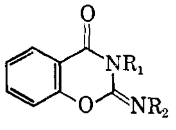
5. *Acids Containing Additional Functional Groups*

a. Hydroxy Group

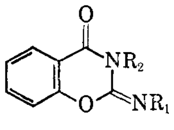
The products obtained from salicylic acid also depend on the nature of the carbodiimide. Diisopropyl- and dicyclohexylcarbodiimides yield benzoxazine derivatives (CLV, R = Me_2CH, C_6H_{11}) together with the corresponding dialkylurea (422, 459). Di-*t*-butyl-carbodiimide failed to react, probably owing to steric effects of the bulky *t*-butyl group. N-Methyl-N′-*t*-butyl-



CLV



CLVI

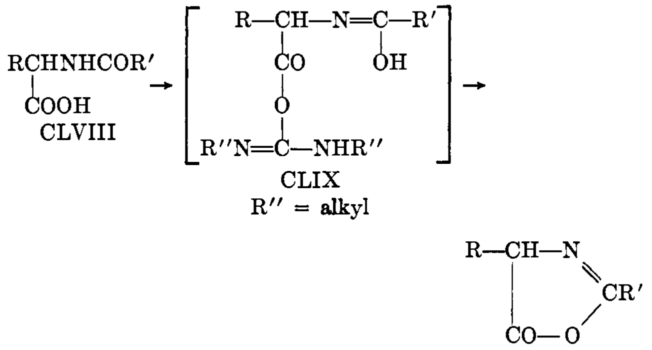


CLVII

carbodiimide reacts only at high temperature to give a mixture of imino- and oxobenzoxazine. N-Phenyl-N′-*t*-butylcarbodiimide, again at high temperature, gives only salicylanilide (459). Although an unsymmetrical carbodiimide may form two isomeric benzoxazines (CLVI, CLVII), only *one* (having the acyl group attached to the less basic nitrogen) is in fact obtained (compare section VG1).

With favorably situated hydroxy groups, lactone formation is possible (307, 308, 835, 836, 843). Thus, isoreserpic acid hydrochloride and dicyclohexylcarbodiimide in pyridine form isoreserpic acid lactone, which provided a step in Woodward's total synthesis of reserpine (835, 836).

Participation of Potential Hydroxy Groups.—Similarly, the products of the interaction of N-acyl-α-amino acids (CLVIII) and dicyclohexylcarbodiimide in chloroform or ethyl acetate are azlactones (CLX) (77, 445, 701, 702, 748). α-Benzoylamino-β-chloroacrylic acid (CLVIII, R = ClCH=), for example, gives 2-phenyl-4-(chloromethylene)oxazolin-5-one (CLX, R = ClCH=; R′ = C_6H_5) (748) in this reaction. The fact that no N-acyl-N,N′-dicyclohexylurea is formed suggests that the cyclization of the intermediate (CLIX) is much faster than its rearrangement to the acylurea.


CLVIII

CLIX

R″ = alkyl

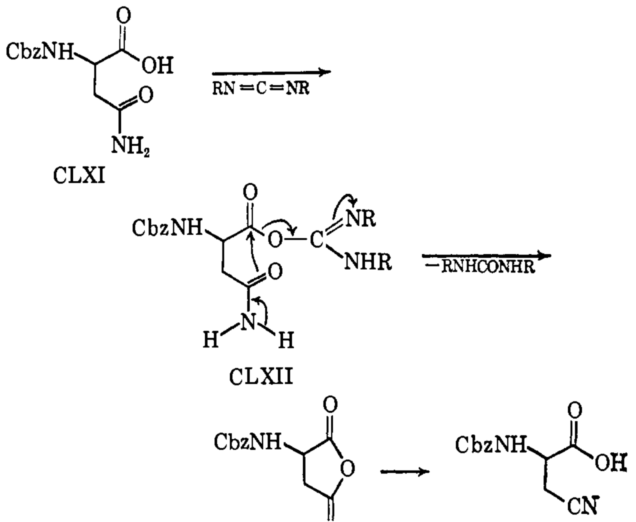
CLX

Ressler and Ratzkin (580) have found that dicyclohexylcarbodiimide dehydrated carbobenzoxy-L-asparagine (CLXI) and carbobenzoxy-L-glutamine in pyridine to the corresponding cyano compounds (*e.g.*, CLXIV).

Using O^{18}-carbobenzoxy-L-asparagine (CLXI) in this reaction, Paul and Kende (537, 538) have shown that the O^{18} is equally distributed between the product (CLXIV) and the dicyclohexylurea. They have accordingly proposed the mechanism shown in Scheme II which involves the internal acylation of the amide oxygen by the amidino-activated carboxyl group. The results of a mass spectrometric study of this reaction are in agreement with the mechanism in Scheme II and are fully discussed by Ressler and Kashelkar (579).

N-Substituted maleamic acids (*e.g.*, CLXV) are dehydrated to N-substituted isomaleimides (*e.g.*, CLXVI), which isomerize to the maleimide (*e.g.*, CLXVII) in the presence of sodium acetate (406, 537). The mechanism originally proposed for this reaction by Cotter, Sauers, and Whelan (134) (path A) has been disproved by Paul and Kende (537). Thus, N-butylmaleamic acid-1,1-O^{18} (CLXV) afforded the urea and N-butylisomaleimide (CLXVI) each carrying half the O^{18} of the starting material; the alternative mechanism (path B) accounts more satisfactorily for these observations.

SCHEME II

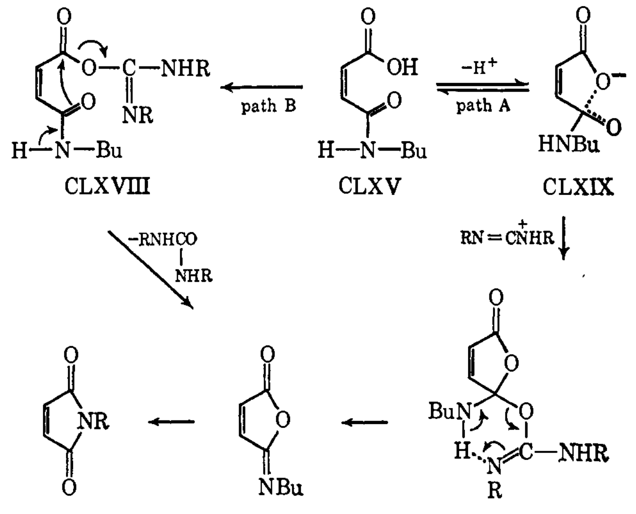


CLXI

CLXII

CLXIII

CLXIV



CLXVIII

CLXV

CLXIX

CLXVII

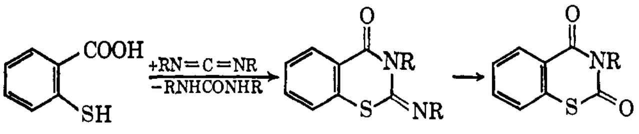
CLXVI

CLXX

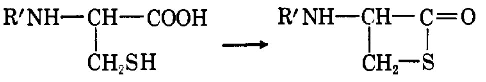
b. Mercapto Group

Carbodiimides react with thiosalicyclic acid exothermically in the absence of solvent to form 2-imino-1,3-benzthiazin-4-ones (CLXXI) (401, 459); these are in turn convertible into benzothiazin-2,4-diones (CLXXII) hydrolytically.

α-Acylamino-β-thiopropionic acids (CLXXIII) are dehydrated by aliphatic carbodiimides to α-acylamino-β-propiothiolactones (CLXXIV) (142, 143).



CLXXI CLXXII

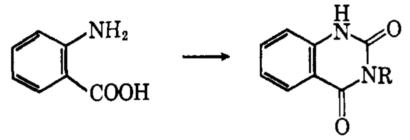


CLXXIII CLXXIV

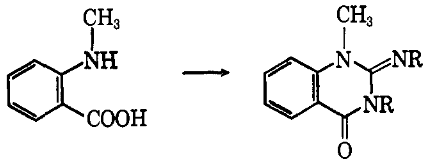
$R' = p\text{-}CH_3C_6H_4SO_2$ or $C_6H_5CH_2OCO$

c. Amino Group

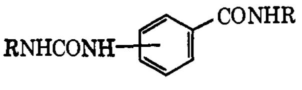
Anthranilic acid reacts with aromatic carbodiimides to form 3-substituted 1,3-quinazolin-2,4-diones (CLXXV) (97, 869). N-Methylanthranilic acid forms the 2-imino-1,3-quinazolin-4-one (CLXXVI) (459), but *m*- and *p*-aminobenzoic acid gives merely N-[*m*- (or *p*-) anilinoformyl]phenyl-N′-arylureas (CLXXVII) (869); *m*- and *p*-aminobenzoic acids react with Zetzsche's carbodiimide to give N-acylureas (CLXXVIII) (869).



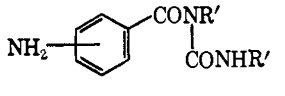
CLXXV



CLXXVI



CLXXVII



CLXXVIII

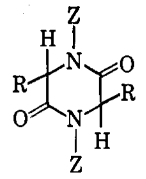
R = Ar; $R' = p\text{-}(CH_3)_2NC_6H_4$

ε-Aminocaproic acid reacts with dicyclohexylcarbodiimide in dioxane to form 1-cyclohexyl-3-[5-(cyclohexylcarbamoyl)pentyl]urea (CLXXIX) (497, see also 496).

$$NH_2(CH_2)_5COOH + C_6H_{11}N{=}C{=}NC_6H_{11} \rightarrow C_6H_{11}NHCONH(CH_2)_5CONHC_6H_{11}$$

CLXXIX

N-Protected amino acids react with dicyclohexylcarbodiimide to form the acylurea (*e.g.*, 214, 493, 496, 850), the acid anhydride (*e.g.*, 493, 495, 850), the diketopiperazine (CLXXX) (758), and the urea (758, 850), the relative proportions of which depend on the amount of carbodiimide used.

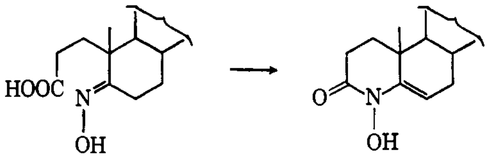


CLXXX

$Z = C_6H_5CH_2OCO$

d. Oxime Group

A dehydration involving carboxyl and oxime groups has been reported in the sterol field: 3,5-seco-4-norcholestan-5-on-3-oic acid 5-oxime (CLXXXI) yields 4-hydroxy-4-aza-5-cholestan-3-one (CLXXXII) by the usual technique (162).



CLXXXI CLXXXII

H. REACTION WITH SULFONIC AND SULFINIC ACIDS

Sulfonic acids are dehydrated exothermically by carbodiimides in benzene to the anhydrides in high yields (85–92%) (329, 602). Di-*p*-tolylcarbodiimide is preferred to the dicyclohexyl analog because the di-*p*-tolylurea is more easily removed from the reaction mixture. Field's general method (186) for the preparation of sulfonic anhydrides which involves the fusion of the acids with phosphorus pentoxide seldom gives yields greater than 50%. Sulfinic acids similarly yield the anhydrides (389) by this method.

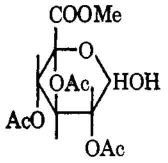
I. OTHER DEHYDRATING REACTIONS

Several dehydrating reactions of carbodiimides form the subject of separate sections (*e.g.*, sections G, H, above) or are described elsewhere in this review. The present section deals with the remaining reactions, in which carbodiimides act predominatingly as dehydrating agents. It includes the important application of these reagents in the synthesis of peptides and nucleotides.

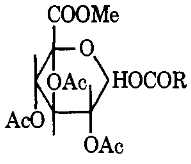
1. *Esterification of Carboxylic Acids*

Carboxylic esters are obtainable in excellent yield by the condensation of equimolar proportions of a carboxylic acid and an alcohol in the presence of a carbodiimide (102, 149, 175, 360, 361, 543, 557, 636, 671, 747) at room temperature. Examples include methyl phenoxyacetate ($PhOCH_2COOMe$, 94%) (175, 636), β-chloroethyl chloroacetate ($ClCH_2COOCH_2CH_2Cl$, 83–98%) (175), glycosyl N-carbobenzoxyalanine (60%) (360), and others.

A number of glucuronic esters have been prepared by this method (153, 494, 557). Thus, for example, the hemiacetal hydroxyl group of methyl 2,3,4-tri-O-acetyl-D-glucopyranuronate (CLXXXIII) is easily esterified with aliphatic, aromatic, and heterocyclic acids to methyl 2,3,4-tri-O-acetyl-1-O-acyl-D-glucopyranuronates (CLXXXIV) in high yields (557). Small quantities of N-acylurea appear as by-products.



CLXXXIII



CLXXXIV

2. *Phenolic Esters*

Phenolic esters are similarly accessible in 40–90% yield (68, 70, 71, 103, 171, 554). The presence of nitro groups in the aromatic nucleus, particularly in the *para* position, and the use of pyridine as solvent promote the formation of the esters.

Since phenolic esters of this type are readily purified crystalline solids, Buzas, Egnell, and Freon (103) have recommended this esterification procedure for characterizing phenols (using monochloroacetic acid) and organic acids (using *p*-nitrophenol).

2,4,5-Trichlorophenyl- (43), pentachlorophenyl- (369, 370), *p*-nitrophenyl- (32, 54, 68, 70–72, 171, 172, 220, 262, 264, 296, 298, 393, 515, 526, 536, 554, 587, 591, 830, 852), and thiophenyl esters (592) of N-acylamino acids, prepared conveniently in excellent yield by this method, have been used successfully in the stepwise lengthening of peptides.

$$\underset{(GlyOEt)}{NH_2CH_2COOEt} + CbzLeu\text{-}OC_6H_4NO_2 \longrightarrow$$

$$CbzLeu\text{-}GlyOEt \xrightarrow{HBr\text{-}AcOH} Leu\text{-}GlyOEt$$

$$Leu\text{-}GlyOEt + CbzPro\text{-}OC_6H_4NO_2 \longrightarrow$$

$$CbzPro\text{-}Leu\text{-}GlyOEt \xrightarrow{HBr\text{-}AcOH} \text{etc.}$$

du Vigneaud, *et al.* (68), have, in fact, synthesized lysine vasopressin from the nonapeptide S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-ε-tosyl-L-lysylglycinamide, which they had prepared stepwise by this nitrophenyl ester method.

3. *Amide Formation*

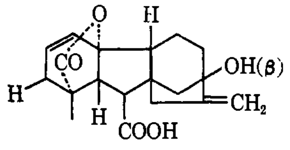
a. Simple Amides

In 1955, Sheehan and Hess (687) and Khorana (332) showed independently that suitably blocked amino acids may be joined through an amide linkage under the influence of carbodiimides (see also Peptides, below). Buzas, Egnell, and Freon (100, 101) produced a variety of simple amides by this procedure; the temperature and the nature of the amine and solvent influence the yield of amide, but that of the acid has little effect. Acylurea is formed as by-product.

$$2R'CH_2COOH + C_6H_5NH_2 + 2RN{=}C{=}NR \rightarrow$$

$$RCH_2CONHC_6H_5 + RNHCONHR + RNHCON(COCH_2R')R$$

Amides of D-glucosamine have been successfully prepared by this method (52, 74, 154, 310, 362, 444, 553). Amides of aromatic acids (543), gibberellic acid (CLXXXV) (321), and other acids (80, 496, 599, 725) have also been obtained. A useful application of this procedure in penicillin chemistry has been patented by Patchett, *et al.* (535).



CLXXXV

b. The Application of Carbodiimide in Peptide Synthesis

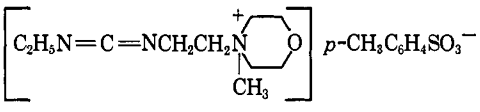
Peptides (52, 74, 100, 318, 321, 362, 543) arise by the elimination of water between two suitably protected amino acids, one containing a free carboxyl and the other a free amino group.

$$NH_2{-}X{-}COOR + R'NH{-}Y{-}COOH \rightarrow$$

$$R'NH{-}Y{-}CONH{-}X{-}COOR + H_2O$$

In 1955 Sheehan and Hess (687) reported that this condensation is effected advantageously by means of dicyclohexylcarbodiimide. This useful novel procedure does not require anhydrous conditions and can therefore be carried out in aqueous media (see also Nucleotides, section V.I5, below).

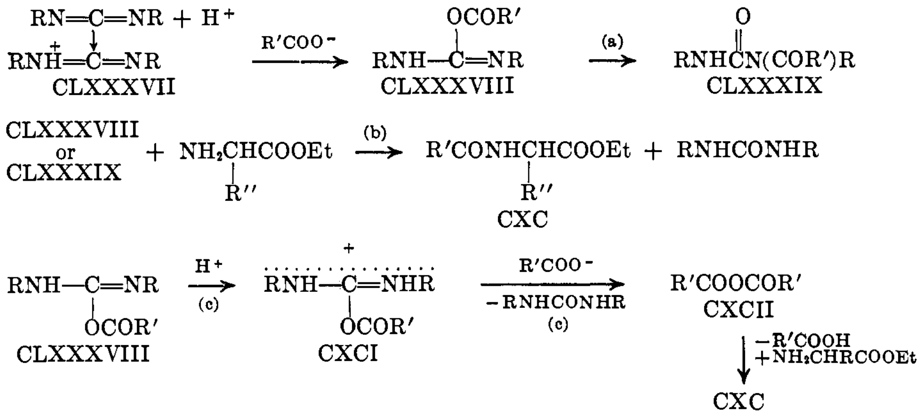
Although dicyclohexylcarbodiimide was first used for this purpose, other carbodiimides have been widely used with success. They include N-(3-dimethylaminopropyl)-N′-*t*-butyl-, N-ethyl-N′-(2-morpholinylethyl)-, and "soluble" carbodiimides, *e.g.*, N-ethyl-N′-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate (CLXXXVI) (78, 141, 352, 354, 355, 366–368, 392, 681).



CLXXXVI

Because of its low solubility, the N,N′-dicyclohexylurea formed is normally easily removed. In solvents such as dioxane and tetrahydrofuran, appreciable quantities of N-acyl-N,N′-dicyclohexylureas may be produced (*e.g.*, 332, 392, 684, 685). This side reaction, which is of course well known (see section VG1),

SCHEME III



is occasionally a drawback of this peptide synthesis, as is the formation of the anhydro derivatives of the compounds concerned (70, 222, 320, 406, 578, 580, 732, 858).

Mechanism.—The mechanism of amide formation under the influence of carbodiimide has been discussed by Khorana (332) and others (80, 850). Initial protonation of the carbodiimide is considered to yield the intermediate (CLXXXVII), which is attacked by a carboxylate anion to produce the O-acylurea (CLXXXVIII). This, in turn, can (a) form the N-acylurea (CLXXXIX) by intramolecular rearrangement, (b) react with the amino acid ester to form the peptide (CXC), or (c) react with another carboxyl group to yield the urea and the acid anhydride (CXCII). The latter participates in further peptide formation. (see Scheme III).

Steric Course of the Reaction.—Although a number of optically active peptides have been synthesized by the carbodiimide procedure (see, *e.g.*, 250, 408, 523, 690), the condensation may be attended by racemization (see, *e.g.*, 18, 265, 462, 658, 707, 846), the extent of which depends on the nature of the solvent and temperature (18). In the course of the synthesis of peptides containing up to four amino acid residues from optically active amino acids, Schwarz and Bumpus (658) obtained mixtures of optically active isomers. Thus, the condensation of carbobenzoxy-L-valyl-L-tyrosine and L-isoleucine methyl ester by means of dicyclohexylcarbodiimide afforded both diastereoisomers, *viz.*, carbobenzoxy-L-valyl-L- (and D-) tyrosyl-L-isoleucine methyl esters (658).

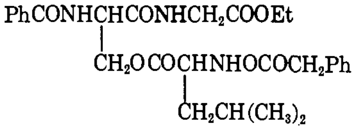
More recently, Liberek and Michalik (408) have studied the extent of racemization in the synthesis of carbobenzoxydipeptide esters; they observed no racemization in the condensation of carbobenzoxy-β-cyano-L-alanine with glycine methyl ester by the usual procedure. Shankman and Schvo (673) prepared optically active peptides by this method and observed that no significant racemization occurred in any of the condensations (as indicated by microbiological assay). Another example of retention of configuration is the synthesis of the optically active peptide O-benzyl-N-carbobenzoxy-L-seryl-L-tyrosine methyl ester (523).

Scope of the Method.—The new procedure has been of exceptional importance in the production of a wide variety of peptides. The technique has become universally established, so much so that the use of dicyclohexylcarbodiimide and its analogs in this connection is at present often no longer indexed under this heading in the abstract literature. An effort has therefore been made to document the existing knowledge by scrutinizing recent volumes of *Chemical Abstracts* directly, as well as some of the more important relevant journals. However, because of the large number of papers involved, examples cannot be dealt with individually in the present review, and the information is recorded in the form of references only (see Table IV). The carbodiimide procedure has also received increased attention in the patent literature and has been the subject of specifications in Belgium (126, 127, 211, 259, 403, 603, 771), France (207), Germany (419, 660), Great Britain (124, 125, 179, 772), Holland (606), Hungary (92, 204–206), Japan (501), and the United States (664, 681).

TABLE IV
USE OF CARBODIIMIDE IN PEPTIDE SYNTHESIS.
LIST OF REFERENCES

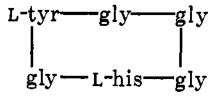
6, 7, 13– 19, 21, 31, 33, 42, 43, 49, 51,
55, 56, 69, 85, 91, 93, 110, 119–121, 128, 141,
157, 158, 194, 197–199, 208, 209, 215, 221, 224, 226,
227, 229, 236, 237, 241, 243, 248, 250, 262, 266–268,
280, 294, 295, 297, 303, 304, 316, 317, 319, 345–351,
356, 357, 371, 372, 390, 404, 405, 407, 412–418, 423,
424, 438, 439, 446, 448, 451–455, 462, 476, 477, 482,
483, 485, 506, 507, 516, 517, 528, 529, 531, 581, 583,
598, 600, 601, 607, 644–655, 661–663, 665, 666, 669,
672, 673, 679, 680, 689, 691, 692, 695–697, 700, 702,
733, 736, 740, 750, 751, 763, 764, 773, 791–794, 803,
805, 807, 823, 824, 829, 830, 839–842, 844, 846–849,
853.

In order to give a very small cross section of the variety of peptides, both simple and complex, that have been synthesized by this method, the following may be listed: carbobenzoxy-L-asparaginyl-S-benzylcysteine methyl ester (222), O-carbobenzoxyleucyl-N-benzoylserylglycine ethyl ester (CXCIII) (678), N^6-polypeptide derivatives of 3-β-D-glucopyranosylcytosine (CXCIV) (672), actinomycin C$_3$ (84–86), glycopeptides (152, 155, 363, 463), sarcolysine-containing peptides (221), and bradykinin (424). Among cyclic peptides may be mentioned cyclo-L-tyrosyltriglycyl-L-histidylglycine (CXCV) (367, 368, 828) and gramicidin S (667, 668), but the procedure has been reported to fail in certain cases (749).

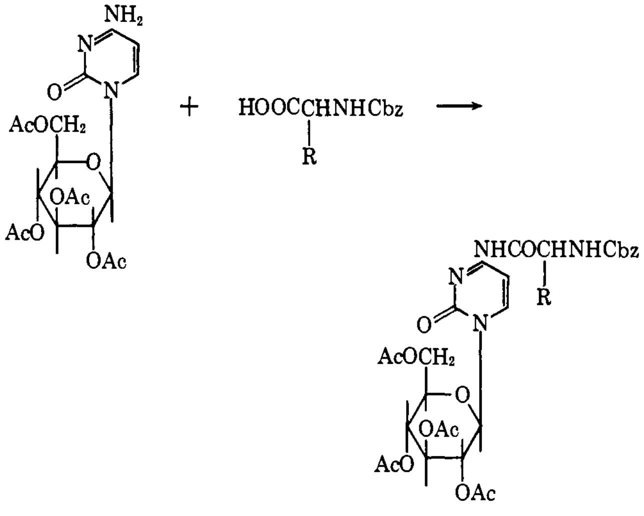


$$\begin{array}{l} PhCONHCHCONHCH_2COOEt \\ \quad\;| \\ \quad CH_2OCOCHNHOCOCH_2Ph \\ \qquad\qquad\;| \\ \qquad\quad CH_2CH(CH_3)_2 \end{array}$$

CXCIII



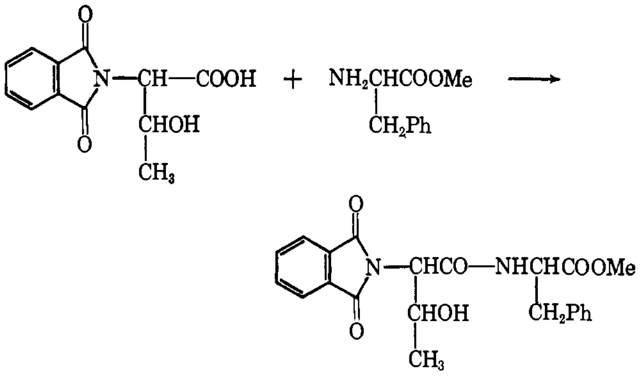
CXCV



CXCIV

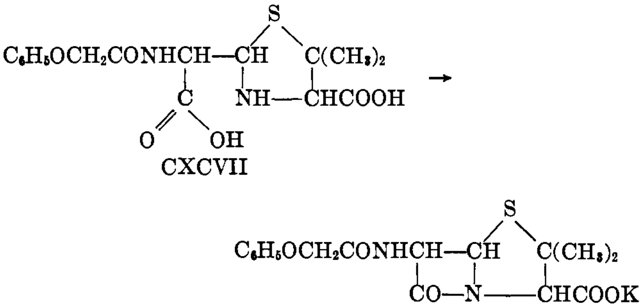
Further, hydroxy-containing peptides are accessible by this method from hydroxyamino acids, the hydroxy groups of which need not be protected by substitution. Such peptides (see, *e.g.*, 277, 831) have previously been synthesized only with difficulty by the multistep "azide method" (*e.g.*, 202, 263). Neither primary nor secondary hydroxyl groups interfere in this procedure (684, 685), which is thus applicable to both types of structures (*e.g.*, phthaloyl-L-threonyl-L-phenylalanine methyl ester, CXCVI).

Syntheses in the Penicillin Field.—Sheehan and Henry-Logan (686) achieved the total synthesis of penicilloic acid corresponding to penicillin V (phenoxymethylpenicillin) (CXCVIII) using dicyclohexylcarbodiimide as the condensing reagent in the final cyclization of the synthetically prepared monopotassium salt of D-α-phenoxymethylpenicilloic acid (CXCVII). The same results were obtained using CXCVII derived from natural penicillin V.



CXCVI

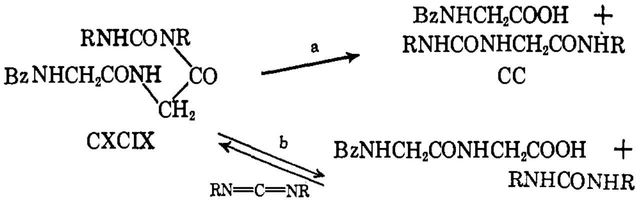
Sheehan's technique has provided new active synthetic penicillins, some of which contain the sulfonic or carboxylic acid function in their side chain (169). Additional examples have been given by Hobbs and English (258).



CXCVII

CXCVIII

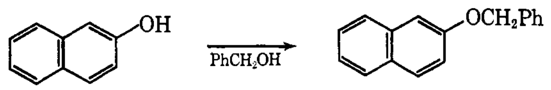
Degradation of Peptides.—Peptides can be degraded from the end bearing the free carboxyl group using carbodiimide (336). The amino group of the peptide is blocked (*e.g.*, by benzoylation) and the carboxyl group made to react with the carbodiimide to form the corresponding N-acylurea (CXCIX); this, on mild alkaline hydrolysis (path a), gives among other products the lower peptide (CC). The scope of the method is somewhat limited, as the degraded peptides tend to be contaminated with the starting materials regenerated from the acylureas by simple hydrolysis (path b).



Other Applications.—Gelatin, obtained by the hydrolysis of collagen and regarded as a partially degraded protein, gelates rapidly (586, 688) on treatment with soluble carbodiimides (*e.g.*, N-ethyl-N′-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate (CLXXXVI)). Wool which has been treated with dicyclohexylcarbodiimide shows an increased resistance toward alkali and trypsin (433). Both these phenomena are attributed to amide bond formation brought about by the carbodiimides.

4. Etherification

Phenols react with primary alcohols in the presence of dicyclohexylcarbodiimide in inert solvents at room temperature very slowly (30 days) to form alkyl aryl ethers [*e.g.*, CCI (38%)] (797). The presence of substituents in the phenols affects the yields markedly. Thus, electron-releasing groups (which depress the dissociation of the phenols) decrease the yield while electron-attracting groups increase it (see Table V). Steric hindrance tends to inhibit the reaction. This may be exerted by *ortho* substituents (*e.g.*, *o*-nitro) in the phenols or by the alcohols; isopropyl and *t*-butyl alcohols, for example, do not react with phenols at all (Table V).



CCI

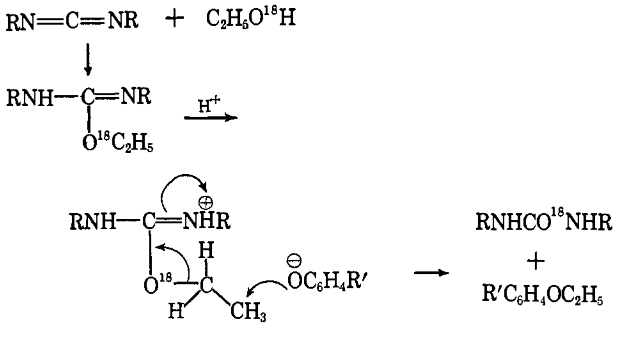
TABLE V

YIELDS OF ALKYL ARYL ETHERS (%)

	Benzyl alcohol	Allyl alcohol	Methanol	Isopropyl alcohol	*t*-Butyl alcohol
Phenol	26	12	16	0	0
p-Nitrophenol	53	32	27		
p-Cresol	20	10	11		
m-Nitrophenol	63	45	40		
m-Cresol	19	9	11		
o-Nitrophenol	9	6	6		
o-Cresol	3	1	1		

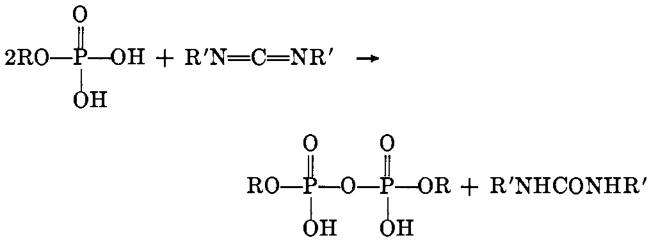
Excellent yields of alkyl aryl ethers (84–91%) are obtained when the phenol and alcohol are heated with dicyclohexylcarbodiimide in the absence of solvent at 100–110° for 1–4 days. The ethers are isolated in a state of high purity by chromatographing the reaction mixture on alumina and eluting with *n*-pentane–methylene chloride (796).

Using O^{18}-ethanol, Bach (29) has provided evidence for a mechanism involving the S_N2 attack by a phenate ion on an intermediate 2-alkylisourea. An alternative mechanism originally proposed by Vowinkel (797) is thereby disproved.

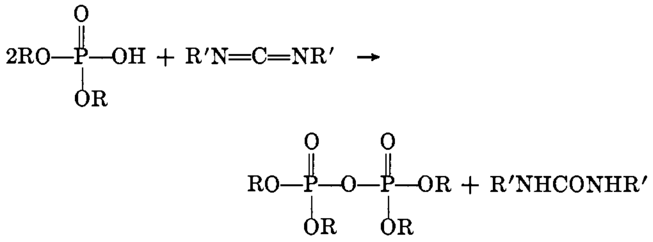


5. Reaction of Carbodiimides with Phosphoric Esters and Related Phosphorus Compounds (Nucleotide Synthesis)

In 1953, Khorana and Todd (333, 341) demonstrated the power of carbodiimides to condense mono- and diesters of phosphoric acid to the corresponding di- and tetraesters of pyrophosphoric acid.



$$2RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH + R'N{=}C{=}NR' \rightarrow RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OR + R'NHCONHR'$$



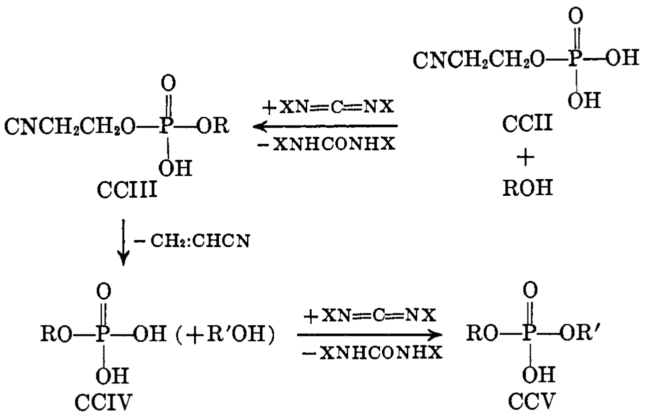
$$2RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{P}}-OH + R'N{=}C{=}NR' \rightarrow RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{P}}-OR + R'NHCONHR'$$

Since this time, carbodiimides (particularly the dicyclohexyl compound (637)) have been widely employed, notably by Khorana and his co-workers, in the synthesis of ortho- and pyrophosphate esters (112, 274, 282, 325, 331, 341, 420, 447, 458, 471, 694, 713, 726, 757, 759, 760, 777, 786, 787), nucleotides (114, 469, 545), cyclic phosphates (44, 150, 200, 340, 530, 711, 712, 726, 761, 838), oligoribonucleotides (327, 338, 722), polynucleotides (25, 113, 115, 122, 123, 135, 140, 187, 188, 217–219, 232, 300, 301, 338, 342–344, 387, 388, 398, 411, 565–574, 618–620, 716, 717, 727, 728, 775, 812–814), nucleoside-5′-phosphoramidates (113, 116, 474, 475, 589, 776), and mixed anhydrides (45, 46, 386, 428, 450, 575, 582, 757, 871).

This technique has contributed greatly to progress in the nucleotide field in recent years. A discussion of the scope and significance of this group of syntheses to compounds of biochemical importance has been given by Khorana in 1961 (328).

a. Esters of Phosphoric Acid

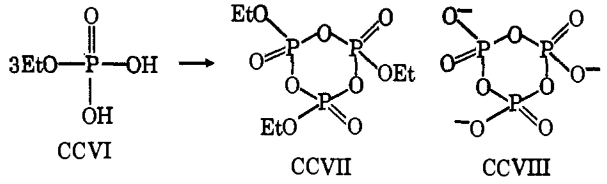
Esters of phosphoric acid react with alcohols (and phenols) under the influence of carbodiimides to give the diesters (CCV) quantitatively (114, 315, 335, 468, 521, 675, 676, 771). The monoesters of phosphoric acid (CCIII) required as starting material are themselves accessible by the action of β-cyanoethylphosphate (CCII) on a hydroxylic compound in the presence of dicyclohexylcarbodiimide; the cyano ester (CCIII) first formed readily loses its β-cyanoethyl group by mild alkaline hydrolysis (90, 94, 139, 358, 359, 402, 469, 548, 555, 573, 760, 765, 766, 777).



X = cyclo-C_6H_{11}

An excess of phosphoric acid (or its trialkylammonium or pyridinium salts) instead of β-cyanoethyl ester first yields the monoester which then reacts further to form the diester (715).

Under the influence of excess of dicyclohexylcarbodiimide in dry dioxane, ethylphosphoric acid (CCVI) is condensed to ethyl trimetaphosphate (CCVII) (813), which had previously been prepared from silver trimetaphosphate and ethyl iodide (30).



The interaction of monobenzylphosphoric acid (or its pyridinium salt) with dicyclohexylcarbodiimide, followed by treatment with sodium iodide, results in the formation of "inorganic" trimetaphosphate (CCVIII); the general procedure is thus also useful for preparing salts of metaphosphoric acid.

Mono- and diesters of phosphoric acid react with dicyclohexylcarbodiimide to form pyrophosphates (112, 341, 602, 715). The reaction, which is influenced by the nature of the carbodiimide, solvent, acidity, and temperature, can be carried out in partially aqueous media. In the absence of strong tertiary bases, the monoesters react with the carbodiimide more slowly, and the diesters are inert toward this reagent (715). A mixture of two unlike phospho monoesters yields the unsymmetrical pyrophosphate in preference to the two symmetrical pyrophosphate esters (30, 114, 335).

A number of nucleoside phosphites (*e.g.*, uridine 5'-phosphite) have been synthesized by this procedure (272). Alkyl derivatives of phosphinic acids under similar conditions form the anhydrides (240, 389).

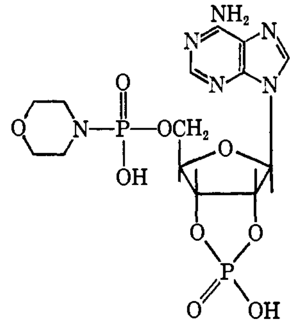
$$2R_2POOH + ArN{=}C{=}NAr \rightarrow (R_2PO)_2O + ArNH{-}CO{-}NHAr$$

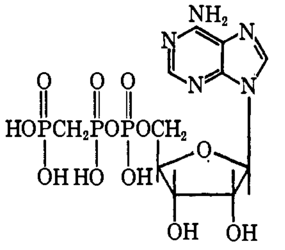
$$Ar = p\text{-}CH_3C_6H_4$$

b. Nucleoside Polyphosphates. Nucleotide Coenzymes

Nucleoside 5'-phosphates, such as adenosine (334) and uridine (122, 279), react with dicyclohexylcarbodiimide to form *sym*-dinucleoside pyrophosphates in high yield. In the presence of an excess of orthophosphoric acid, however, the main products of this reaction are nucleoside 5'-di- and triphosphate, together with some inorganic polyphosphates (53, 73, 239, 273, 279, 324, 334, 339, 539, 556, 694, 710, 745).

Dicyclohexylcarbodiimide has been employed as the condensing agent in the preparation of adenosine 2',3'-cyclic phosphate 5'-phosphoromorpholidate (CCIX) which was used by Khorana and Moffatt (473, 475) in their total synthesis of coenzyme A (410). A number of phosphonic acid analogs of nucleoside polyphosphate (*e.g.*, 5'-adenylyl methylenediphosphate (CCX) have also been synthesized by this procedure (498–500).


CCIX

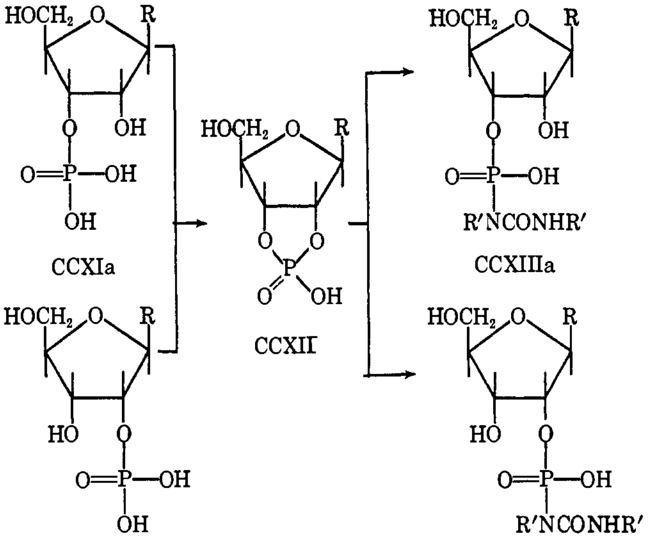

CCX

The use of carbodiimides as condensing agents in this field suffers from two main disadvantages: (a) the site at which condensation is effected cannot be directly controlled, and (b) intramolecular cyclization involving *one* component may occur instead of the desired condensation to pyrophosphate (see section 5c, below). Nevertheless, a number of polyphosphates such as ribo-, or deoxyribonucleoside 5'-triphosphate (282, 710), cytidine diphosphate glycerol (30), cytidine diphosphate choline, and deoxycytidine diphosphate choline have been successfully synthesized using dicyclohexyl- (25, 111, 112, 282, 322, 323, 398) or di-*p*-tolylcarbodiimide (278).

A considerable number of P^{32}-labeled nucleotides have also been conveniently prepared by this method (73, 420, 421, 539, 744, 759, 788, 815).

c. Cyclic Phosphates

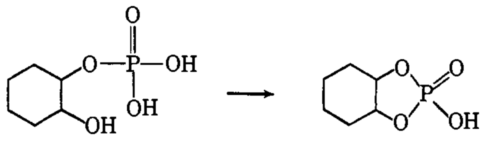
Monoesters of phosphoric acid bearing a suitably placed hydroxyl group (*e.g.*, ribonucleoside 2'- (or 3'-) phosphate, CCXIa,b) react with carbodiimide to yield five-, six-, or seven-membered cyclic diesters (73, 87, 150, 165, 279, 328, 340, 409, 443, 469, 552, 712, 715, 746, 754, 761, 762). When dicyclohexylcarbodiimide is used and strong bases are absent, the labile five-membered cyclic phosphate (CCXII) is first formed and reacts further with the carbodiimide to yield N-phosphorylureas (CCXIIIa,b). This urea formation is not observed with the six- and seven-membered cyclic phosphate, or when di-*p*-tolylcarbodiimide is used.



CCXIa CCXII CCXIIIa

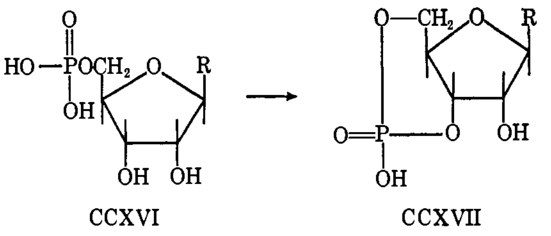
CCXIb CCXIIIb

A simpler example of this type of reaction is the intramolecular dehydration of *cis-* (or *trans-*) 2-hydroxycyclohexyl phosphate (CCXIV) to CCXV (87).



CCXIV CCXV

When the participating hydroxyl group is less favorably situated for intramolecular reaction, pyrophosphate formation (from two molecules of monoester) will also take place. Thus, 4-hydroxybutyl phosphate yields both the cyclic butane-1,4-phosphate and the symmetrical P^1,P^2-bis(4-hydroxybutyl) pyrophosphate side by side (340). Pyrophosphate formation was also encountered in the reaction of dicyclohexylcarbodiimide with nucleoside 5′-phosphates (CCXVI), but at high dilution the sterically unfavored ribonucleoside 3′,5′-cyclic phosphates (CCXVII) were obtained in excellent yield (409, 552, 762).

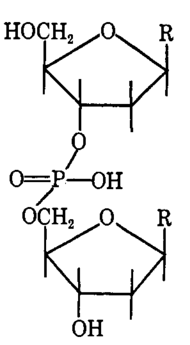


CCXVI CCXVII

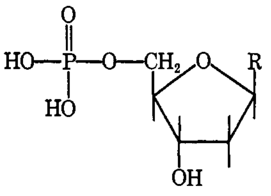
R=purine, pyrimidine

d. Polynucleotides

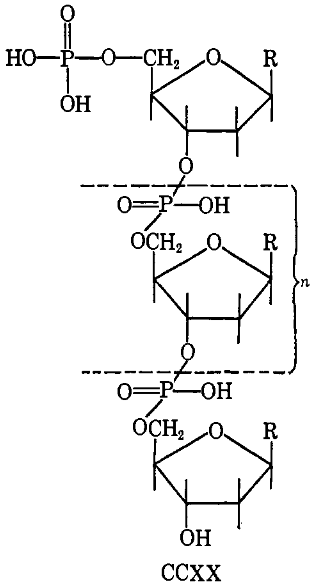
Many procedures have been described in the literature for the synthesis of polynucleotides (see, for example, 327, 460). The use of carbodiimides, notably dicyclohexylcarbodiimide, for effecting this synthesis has recently been shown (218, 338) to provide an elegant and highly effective procedure that is widely applicable (115, 135, 140, 187, 188, 216–219, 232, 300, 301, 327, 337, 338, 342–344, 387, 388, 411, 481, 565–574, 617–621, 714, 716, 717, 727, 728, 775, 812–814). The types of compounds that have thus become accessible include dinucleotides (*e.g.*, thymidylyl(3′→5′)thymidine (CCXVIII, where R = thymine), deoxycytidylyl(5′→3′)thymidine, deoxyadenylyl(5′→3′)thymidine (328), thymidylyl(5′→3′)deoxycytidine (334), uridylyl(3′→5′)uridine (714), uridylyl(3′→5′)adenosine (717)), dinucleotides bearing a phospho monoester group at one end (*e.g.*, thymidylyl(3′→5′)thymidylic-3′ acid (123, 239), uridyl(3′→5′)uridinylic-3′ acid (140)), trinucleotides (*e.g.*, thymidylyl(3′→5′)thymidylyl(3′→5′)thymidine), and tetranucleotides (334, 713). The number of examples of this general type is too large to be listed exhaustively.



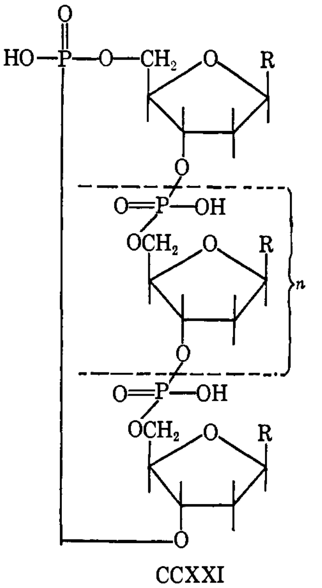
CCXVIII



CCXIX



CCXX



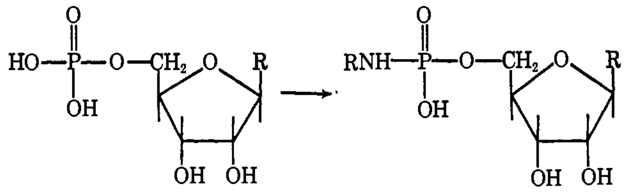
CCXXI

Linear polynucleotides (CCXX) and cyclic oligonucleotides (CCXXI) are the main products of the interaction of mononucleotides bearing a free hydroxyl group (CCXIX) and carbodiimides in anhydrous media (137, 138, 216, 291, 302, 343, 344, 472, 502, 503, 522, 716, 721, 762, 775). Dicyclohexylcarbodiimide favors the production of higher polymers than does diisopropylcarbodiimide (344). The mechanism of this condensation is still unknown, although attempts have been made to account for it (769–771, 813). Similarly, the polymerization of ribonucleotides with dicyclohexylcarbodiimide results in polynucleotides containing random C(2′)–C(5′) and C(3′)–C(5′) internucleotide bonds (715).

Oligonucleotides derived from thymidine 5′-phosphate and dicyclohexylcarbodiimide, on being further condensed with cellulose in the presence of this carbodiimide, form complex celluloses which have been used for the separation of polynucleotides (216, 217).

e. Nucleoside 5′-Phosphoramidates

Nucleoside 5′-phosphoramidates (CCXXIII) of adenosine, cytidine, guanosine, and uridine have been successfully synthesized by condensing nucleoside 5′-phosphate (CCXXII) with ammonia or amines in the presence of dicyclohexylcarbodiimide (113, 116, 474, 475, 589, 596, 693, 776, 811). The products (CCXXIII) are probably formed by the nucleophilic attack of the amine on the phosphorus atom of the intermediate. N,N′-Disubstituted guanidine is formed as a by-product.

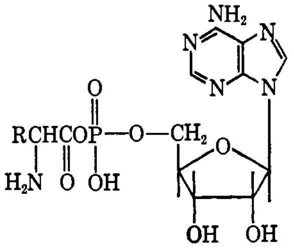

CCXXII CCXXIII

Nucleoside phosphorimidates have similarly been synthesized by this method (596).

f. Mixed Anhydrides

Mixed anhydrides (CCXXIV) of amino acids and adenylic acids have been shown to be the "activated" forms through which amino acids are incorporated into proteins (257, 487, 827). A number of such anhydrides (*e.g.*, luciferyl adenate (582) and L-methionyl adenate (CCXXIV, R = $CH_3SCH_2CH_2$) (45, 46)) have been synthesized from the appropriate acids using dicyclohexylcarbodiimide as the condensing agent (45, 386, 428, 450, 468, 519, 575, 582, 597, 871).

Mixed anhydrides other than those of amino acids, such as butyryl adenate (757), adenosine 5-phosphosulfate (575), and *p*-nitrophenylthymidine 5′-phosphate (468) have also been prepared.


CCXXIV

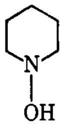
J. MISCELLANEOUS REACTIONS

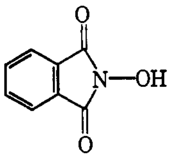
1. *Reactions with N-Hydroxy Compounds*

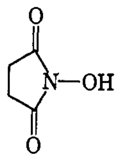
The condensation of hydroxylamine with carboxylic acids in the presence of dicyclohexylcarbodiimide gives hydroxamic acids (540, 541).

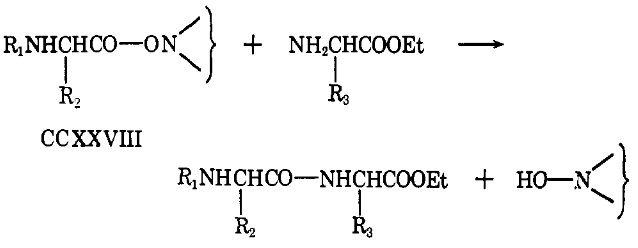
$$R'COOH + NH_2OH + RN{=}C{=}NR \rightarrow R'CONHOH + RNHCONHR$$

Esters of type CCXXVIII have been synthesized by the carbodiimide procedure (20, 262, 264, 504) from N-acylamino acids and N-hydroxy compounds, such as 1-hydroxypiperidine (CCXXV), N-hydroxyphthalimide (CCXXVI), and N-hydroxysuccinimide (CCXXVII). On being condensed with an amino acid ester, these esters (CCXXVIII) form amide linkages (20, 504).


CCXXV

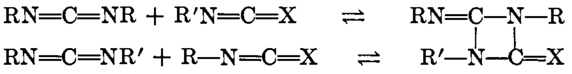

CCXXVI


CCXXVII


CCXXVIII

2. *Reaction with Isothiocyanate*

Adducts (1:1) are formed in the exothermic reaction of carbodiimide with monoisocyanates (176, 269, 509). Diisocyanates require two molecules of the carbodiimide. The product (of possible structure CCXXIX (X = O)) may be used as a source of carbodiimide or isocyanate (190, 509).



$$RN{=}C{=}NR + R'N{=}C{=}X \rightleftharpoons \begin{array}{c} RN{=}C{-}N{-}R \\ |\quad\;\; | \\ R'{-}N{-}C{=}X \end{array}$$
$$RN{=}C{=}NR' + R{-}N{=}C{=}X \rightleftharpoons$$

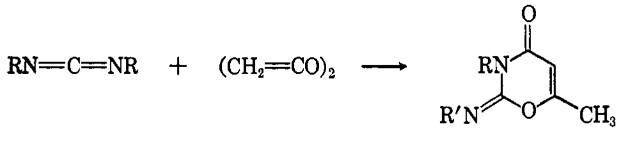
CCXXIX

The analogous addition of isothiocyanates to carbodiimides to give 2-imino-4-thioxo-1,3-diazetidines

(CCXXIX, X = S) has recently been reported by Ulrich and Sayigh (780).

3. *Reaction with Ketenes and Diketenes*

Diketenes and carbodiimides react additively, yielding substituted 2,3-dihydro-2-imino-4-oxo-1,3-oxazines (CCXXX) (177, 270, 385, 459). These had previously been prepared by Lacey from diketene and N,N′-disubstituted S-methylisothiourea, with simultaneous elimination of methylthiol (384).



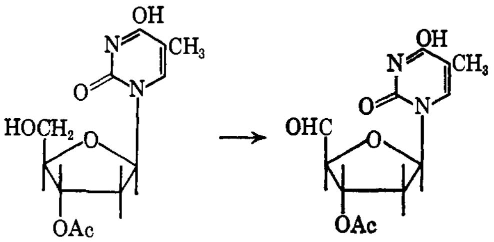
CCXXX

The slower reaction involving diarylcarbodiimides is catalyzed by cuprous chloride. The oxazines derived from N-alkyl-N′-arylcarbodiimides incorporate the aromatic residue in the imino group. Ketenes similarly give 1:1 adducts, but of yet undecided structure (177, 270).

4. *Oxidation or Alkylation*

This section concerns the use of carbodiimides in conjunction with dimethyl sulfoxide. Under suitable conditions, a combination of dimethyl sulfoxide and carbodiimides oxidizes primary alcohols to aldehydes or alkylates phenols.

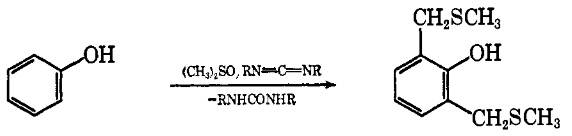
Nucleoside-5′-aldehydes have thus been obtained by the dehydrogenation of the corresponding alcohols (546, 547). 3′-O-Acetylthymidine (CCXXXI) in anhydrous dimethyl sulfoxide, orthophosphoric acid, and dicyclohexylcarbodiimide gives 3′-O-acetylthymidine-5′-aldehyde (CCXXXII) (90%) (546). 2′,3′-O-Isopropylideneuridine similarly gives the uridine-5′-aldehyde in high yields. Unlike other oxidative methods in the nucleoside field, which lead inevitably to the carboxylic acid (309, 486, 790), the present oxidation is a unique and useful procedure terminating at the aldehyde stage.



CCXXXI CCXXXII

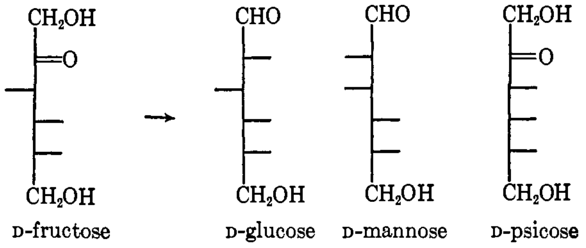
The procedure is equally useful for the conversion of secondary alcohols into ketones. It has been successfully applied to certain sugars (34, 35, 547) and has been effective in producing labeled benzophenone from benzhydrol-O^{18} (4).

Under the usual conditions, phenols are alkylated in the *ortho* position (or in the *para* position, if the former is blocked). The reaction is more complex in the case of more acidic phenols (*e.g.*, nitro derivatives), when several products result (4).



5. *Epimerization*

The epimerization of reducing sugars under acidic or basic conditions is well known (729). Passeron and Recondo (534) have recently performed this epimerization in neutral solution using dicyclohexylcarbodiimide. Thus, fructose heated with this reagent in anhydrous methanol did not yield a glucoside but gave a mixture of glucose, mannose, and psicose.

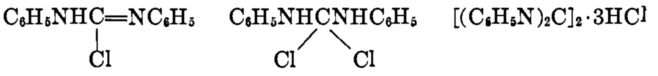


6. *Reaction with Halogen Compounds*

Carbodiimides add halides (of general type Y–X, where X = halogen) to yield halogenoformamidine derivatives (CCXXXIII).

RN=C=NR + Y—X → RNY—CX=NR
CCXXXIII

Thus, hydrogen chloride reacts instantaneously and exothermically to yield the dichloro derivative (CCXXXV) (399, 819). Under carefully controlled conditions, the monochloride (CCXXXIV) (196, 399, 429, 430, 698, 816) and a sesqui derivative (CCXXXVI) (399) can be isolated.



$C_6H_5NHC(Cl){=}NC_6H_5$ $C_6H_5NHC(Cl)_2NHC_6H_5$ $[(C_6H_5N)_2C]_2\cdot 3HCl$

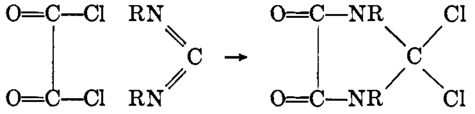
CCXXXIV CCXXXV CCXXXVI

Acyl chlorides derived from acids of carbon, phosphorus, and sulfur form N,N′-disubstituted N-acylchloroformamides (see Table VI) the structures of which are confirmed by analysis and infrared spectroscopy. They are used as intermediates in the production of foam plastics, fireproofing agents, and dyes (191).

Oxalyl chloride reacts with carbodiimides to give cyclic adducts of type CCXXXVII (731, 784).

TABLE VI
EXAMPLES OF N,N'-DISUBSTITUTED N-ACYLCHLOROFORMAMIDES, RNYCX=NR

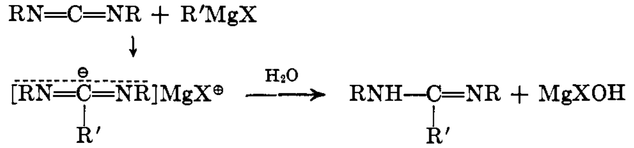
X	Y	Ref	X	Y	Ref
Cl	COR	245, 246	Cl	SOCl	191
Cl	CSCl	191	Cl	PCl_2	191
Cl	$POCl_2$	191, 783	Cl	SCl	191
Cl	COCl	189, 191, 245	Cl	SO_2	191



CCXXXVII

R = $(CH_3)_2CH$, C_6H_{11}, o-$CH_3C_6H_4$

Grignard reagents form adducts (CCXXXVIII) which on treatment with water yield alkylamidines (CCXXXIX) (98).

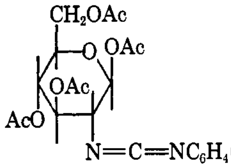


$$\begin{array}{l} RN{=}C{=}NR + R'MgX \\ \quad\downarrow \\ [R\overset{\ominus}{N}{=}\underset{R'}{C}{=}NR]MgX^{\oplus} \xrightarrow{H_2O} RNH{-}\underset{R'}{C}{=}NR + MgXOH \end{array}$$

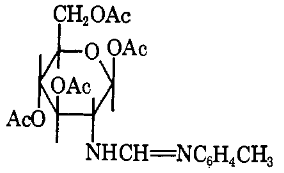
CCXXXVIII CCXXXIX

7. *Reduction*

Hydrogenation of carbodiimides yields the corresponding formamidine. Applied to N-(1,3,4,6-tetra-O-acetyl-β-D-glucos-2-yl)-N'-p-tolylcarbodiimide (CCXL), the reaction gives the formamidine (CCXLI) (305, 306).



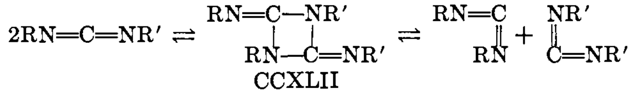
CCXL



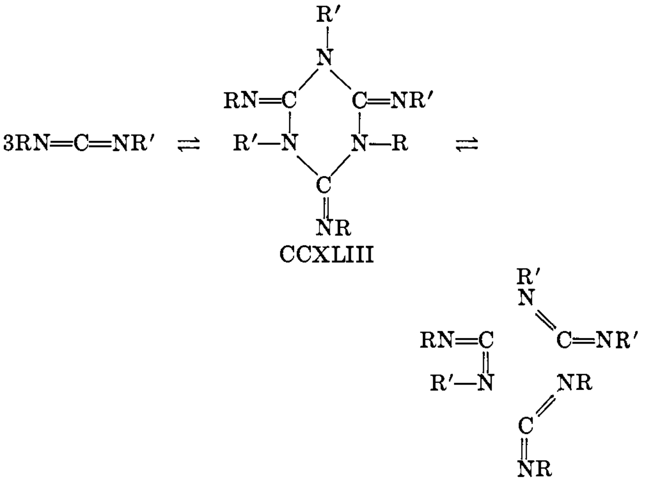
CCXLI

8. *Disproportionation of Unsymmetrical Carbodiimides*

Although unsymmetrical carbodiimides may be distilled unchanged at low pressure, they disproportionate when heated at atmospheric pressure to give a mixture of three carbodiimides, together with polymers (256, 719, 785). Thus, N-isopropyl-N'-phenylcarbodiimide boils unchanged at 111–112° (14 mm) but yields, on being distilled at atmospheric pressure, N,N'-diisopropyl-, N,N'-diphenyl-, and N-isopropyl-N'-phenylcarbodiimide, and some polymeric residue (256). The disproportionation probably proceeds by way of cyclic dimers (CCXLII) (256) or trimers (CCXLIII) (719).



CCXLII



CCXLIII

VI. POLYCARBODIIMIDES

Polycarbodiimides (CCXLIV) are compounds containing two or more carbodiimide groups per molecule; they thus differ from polymeric carbodiimides, which are di- or trimeric forms (CCXLII or CCXLIII) of these compounds.

$$+X{-}N{=}C{=}N+_n$$

CCXLIV

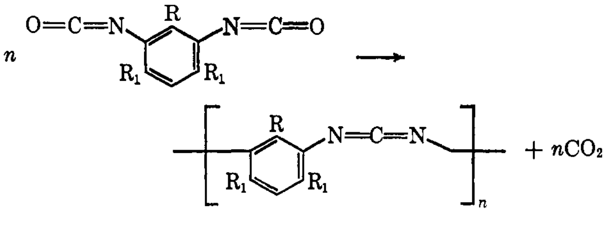
Polycarbodiimides are obtainable from polyisocyanates and polythioureas by the same reactions that furnish monocarbodiimides (36, 105, 107, 109, 163, 190, 193, 425, 509, 518, 625, 704, 709). (For examples, see equations below.) Aliphatic diisocyanates normally react more slowly than the corresponding aromatic ones (425). In reactions employing substituted aromatic diisocyanates, steric factors may retard the polymerization (425).

A recent patent has claimed (585) the production of polycarbodiimides by the polymerization of the monomers under the influence of suitable catalysts (*viz.*, organometallic compounds of groups Ia–IIIa, *e.g.*, phenyllithium, diethylzinc). Further confirmation of the assigned structures, particularly their distinctness from polymeric forms of carbodiimides (*e.g.*, CCXLII or CCXLIII), would appear desirable.

Polycarbodiimides show the characteristic absorption band due to the N=C=N– grouping at 4.70–

$$R_3CNHCSNH(CH_2)_nNHCSNHCR_3 \xrightarrow{-2H_2S} R_3CN{=}C{=}N(CH_2)_nN{=}C{=}NCR_3$$

$$nRN{=}C{=}NR + nOCN{-}X{-}NCO \longrightarrow +N{=}C{=}N{-}X+_n + 2nRNCO$$

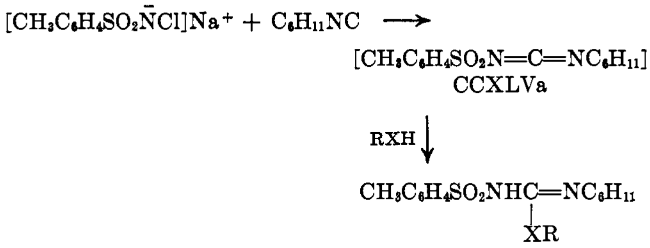


4.80 μ. They can be melt-pressed into clear, pale yellow films on a Carver press at about 250° and 10,000 psi. These films are resistant to aqueous acids and alkalis; this is claimed to be due to the hydrophobic nature of the polymer (425). Under special conditions, polycarbodiimides react with water, hydrogen sulfide, alcohols, and amines to give polyureas, polythioureas, poly-O-alkylisoureas, and polyguanidines, respectively (425).

VII. N-SULFONYLCARBODIIMIDES

An N-sulfonylcarbodiimide of the type CCXLV was first encountered by Aumuller (22) as an intermediate (CCXLVa) in the reaction of Chloramine T and cyclohexylisonitrile.

$$\mathrm{RSO_2N{=}C{=}NR'}$$
CCXLV



$$[\mathrm{CH_3C_6H_4SO_2\bar{N}Cl}]\mathrm{Na^+} + \mathrm{C_6H_{11}NC} \longrightarrow \underset{\text{CCXLVa}}{[\mathrm{CH_3C_6H_4SO_2N{=}C{=}NC_6H_{11}}]} \xrightarrow{\mathrm{RXH}} \mathrm{CH_3C_6H_4SO_2NH}\underset{\mathrm{XR}}{\underset{|}{\mathrm{C}}}\mathrm{{=}NC_6H_{11}}$$

$\mathrm{RX = CH_3C_6H_4SO_2NH,\ CH_3O,\ C_2H_5O}$

Ulrich and Sayigh (779) succeeded in preparing this class of carbodiimides (CCXLV) in 40–80% yield from the corresponding sulfonylthiourea and phosphorus pentachloride or phosgene. Desulfurization by mercuric oxide gave only low yields (12–18%) (505).

Anders and Kühl (17) have recently obtained sulfonylcarbodiimides in excellent yields by treatment of a sulfonyl isocyanide dichloride (CCXLVII) (itself prepared by chlorinating potassium N-(dithiomethylene)sulfonamide (CCXLVI) in carbon tetrachloride) with primary amine hydrochloride in an inert solvent at 100–140°.

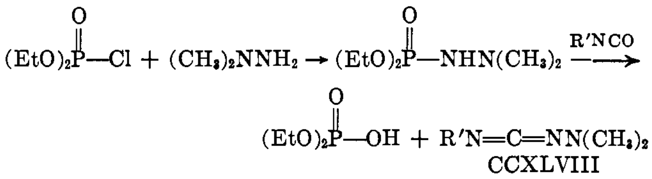
$$\underset{\text{CCXLVI}}{\mathrm{RSO_2N{=}C(SK)_2}} + \mathrm{4Cl_2} \rightarrow \underset{\text{CCXLVII}}{\mathrm{RSO_2N{=}CCl_2}} + \mathrm{2SCl_2} + \mathrm{2KCl}$$

$$\mathrm{RSO_2N{=}CCl_2} + \mathrm{R'NH_2{\cdot}HCl} \rightarrow \mathrm{RSO_2N{=}C{=}NR'} + \mathrm{3HCl}$$

Sulfonylcarbodiimides are crystalline solids or oils (17); they are fairly stable (17, 505, 779) but some tend to polymerize (17, 23). They add water rapidly, even in the absence of acids, to form N-sulfonylureas (17, 23).

VIII. N-AMINOCARBODIIMIDES

Wadsworth and Emmons (800) have recently reported the preparation of N-*t*-octyl-N′-dimethylaminocarbodiimide (CCXLVIII) (60%) from N,N-dimethylhydrazine and *t*-octyl isocyanate in the presence of diethyl phosphorochloridate as catalyst.



$$\mathrm{(EtO)_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{{-}Cl} + \mathrm{(CH_3)_2NNH_2} \rightarrow \mathrm{(EtO)_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{{-}NHN(CH_3)_2} \xrightarrow{\mathrm{R'NCO}} \mathrm{(EtO)_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{{-}OH} + \underset{\text{CCXLVIII}}{\mathrm{R'N{=}C{=}NN(CH_3)_2}}$$

R′ = *t*-octyl

This carbodiimide is a distillable liquid which slowly dimerizes to a crystalline product, the structure of which has as yet not been assigned with certainty. The dimer is depolymerized to the monomer on heating.

An attempt to desulfurize 1-(1,3,4,6-O-tetraacetyl-β-D-glucos-2-yl)-4-phenyl-3-thiosemicarbazide with mercuric oxide to the corresponding aminocarbodiimide is reported to have failed (305).

IX. N,N′-DISILYLCARBODIIMIDES

In recent years, an increasing number of investigations has been devoted to carbodiimides that incorporate silicon instead of carbon directly linked to each of the central nitrogen atoms. These compounds are generally known as silylcarbodiimides.

A. PREPARATION

1. *From Silyl Halide and Cyanamide*

By passing gaseous silyl iodide (CCXLIX, R = H; X = I) over silver cyanamide, Ebsworth and May (166) isolated the compound $\mathrm{(SiH_3)_2CN_2}$, which they showed later (167, 168) to be N,N′-disilylcarbodiimide (CCL, R = H) and not the corresponding cyanamide (CCLI, R = H) (166). Trialkyl- (or alkoxy-) silyl halides (CCXLIX, X = Br, Cl; R = alkyl, alkoxy) similarly yield the appropriate substituted analogs (59, 559–561); these are also accessible in excellent yield by replacing the silver cyanamide by cyanamide and triethylamine (59).

When dialkyldichlorosilanes (CCLII) are used, polysilylcarbodiimides of type CCLIII are obtained (558).

$$\underset{\text{CCXLIX}}{\mathrm{2R_3SiX}} + \mathrm{Ag_2NCN} \rightarrow \underset{\text{CCL}}{\mathrm{R_3SiN{=}C{=}NSiR_3}} + \mathrm{2AgX}$$

$$\underset{\text{CCLI}}{\mathrm{(R_3Si)_2NCN}}$$

$$\underset{\text{CCLII}}{n\mathrm{RR'SiCl_2}} + n\mathrm{Ag_2NCN} \rightarrow \underset{\text{CCLIII}}{(\mathrm{{-}SiRR'N{=}C{=}N{-}})_n} + 2n\mathrm{AgX}$$

2. *From Corresponding Thioureas*

Because of the great sensitivity to hydrolysis of silylcarbodiimides, the use of the oxides of mercury or lead for desulfurizing the corresponding thioureas is inadmissible, water being liberated during this reaction. This difficulty is ingeniously overcome by employing silver imidazole in ether (59).

$$\mathrm{R_3SiNHCSNHSiR_3} + \mathrm{2AgC_3H_3N_2} \rightarrow \mathrm{R_3SiN{=}C{=}NSiR_3} + \mathrm{Ag_2S} + \mathrm{2C_3H_4N_2}$$

3. *From Corresponding Ureas*

In boiling benzene, N,N′-di(trialkylsilyl)urea, phenyllithium, and trialkylsilyl chloride react to yield the silylcarbodiimide (CCL) in yields greater than 80% (560). The use of sodamide instead of phenyllithium, however, greatly reduces the yield (to approximately 12%).

4. *From Bis(trialkylsilyl)amines*

The sodium derivatives of bis(trialkylsilyl)amines (CCLIV) are convertible into silylcarbodiimides (CCL) by a variety of reagents, including (i) phosgene (560, 561), (ii) carbon dioxide (560, 561, 810), (iii) silicon tetraisocyanate (560, 561, 809), or trialkylsilyl isocyanate (559, 809), (iv) cyanogen halide (59, 284), and (v) thiocyanogen (623). The reactions are expressed by the following equations.

$$\underset{\text{CCLIV}}{2(R_3Si)_2NNa} + COCl_2 \rightarrow \underset{\text{CCL}}{R_3SiN{=}C{=}NSiR_3} + (R_3Si)_2O + 2NaCl \quad \text{(i)}$$

$$2(R_3Si)_2NH + COCl_2 \rightarrow R_3SiN{=}C{=}NSiR_3 + (R_3Si)_2O + 2HCl$$

$$2(R_3Si)_2NNa + 2CO_2 \rightarrow R_3SiN{=}C{=}NSiR_3 + (R_3Si)_2O + Na_2CO_3 \quad \text{(ii)}$$

$$(R_3Si)_2NNa + 2Si(NCO)_4 \rightarrow R_3SiN{=}C{=}NSiR_3 + [Si(NCO)_3]_2O + NaCNO \quad \text{(iii)}$$

$$(R_3Si)_2NNa + 2R_3SiNCX \rightarrow R_3SiN{=}C{=}NSiR_3 + (R_3Si)_2X + NaCNX$$

$$X = O, S$$

$$(R_3Si)_2NNa + BrCN \rightarrow R_3SiN{=}C{=}NSiR_3 + NaBr \quad \text{(iv)}$$

$$4(R_3Si)_2NNa + 3(NCS)_2 \rightarrow 2R_3SiN{=}C{=}NSiR_3 + 2[(R_3Si)_2NS]_2 + 4NaCNS \quad \text{(v)}$$

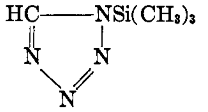
5. *By an Exchange Reaction*

Heating bis(trimethylsilyl)carbodiimide with triphenylsilyl chloride at 245–250°, and continually removing by distillation the trimethylchlorosilane formed, yields bis(triphenylsilyl)carbodiimide (75%) (559).

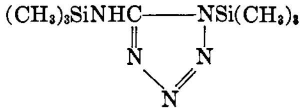
$$2Ph_3SiCl + Me_3SiN{=}C{=}NSiMe_3 \rightarrow Ph_3SiN{=}C{=}NSiPh_3 + 2Me_3SiCl$$

6. *From Silyl Derivatives of Tetrazoles*

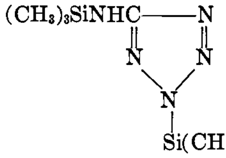
Silyl derivatives of tetrazoles, unlike comparable pyrrole, pyrazole, imidazole, and 1,2,4-triazole derivatives, are unstable to heat (57, 58, 60). Thus 1-trimethylsilyltetrazole (CCLV) decomposes at about 135° into bis(trimethylsilyl)carbodiimide (CCL, R = CH_3), nitrogen, and polymeric cyanamide (58, 60). The same carbodiimide (CCL, R = CH_3), together with trimethylsilyl azide and polymeric cyanamide results in the pyrolysis of 1-trimethylsilyl-5-trimethylsilylaminotetrazole (CCLVI) (58, 60) and its 3-trimethylsilyl isomer (CCLVII) (57).



CCLV



CCLVI



CCLVII

B. PHYSICAL PROPERTIES

With the exception of the solid bistriphenyl compound (CCL, R = C_6H_5; mp 118–121°), silylcarbodiimides so far reported are colorless mobile liquids of characteristic odor that generally distil undecomposed at ordinary pressure up to 240°. Vinyl homologs are partially polymerized during distillation. Their viscosity, unlike that of liquid carbodiimides, does not increase on storage (559). The measurement of Trouton constants of silylcarbodiimides indicates little association in the liquid phase (166, 559). Nmr spectra of bis(trimethylsilyl)carbodiimide display only one resonance peak at +325 ppm; this provides proof of its carbodiimide structure (compare dicyclohexylcarbodiimide, having a peak at 240 ppm). The infrared (ν 2190 cm^{-1}, very strong) and Raman spectra of the silylcarbodiimide also favor the carbodiimide structure (167, 559). Proton resonance spectra of some silylcarbodiimides have been reported (167, 559).

C. CHEMICAL PROPERTIES

In the homogeneous phase (*e.g.*, aqueous acetone), silylcarbodiimides are quickly hydrolyzed by water (559).

$$Ph_3SiN{=}C{=}NSiPh_3 + 2H_2O \rightarrow 2Ph_3SiOH + NH_2CN$$

Disilylcarbodiimide is cleaved by hydrogen chloride, silver thiocyanate, and silver chloride into the appropriate monosubstituted silane and cyanamide derivative (see equations below) (166). Its reaction with boron trifluoride is complex and not fully elucidated (166).

$$H_3SiN{=}C{=}NSiH_3 + 4HCl \rightarrow 2SiH_3Cl + NH_2CCl_2NH_2$$

$$H_3SiN{=}C{=}NSiH_3 + 2AgSCN \rightarrow 2SiH_3(NCS) + Ag_2NCN$$

$$H_3SiN{=}C{=}NSiH_3 + 2AgCl \rightarrow 2SiH_3Cl + Ag_2NCN$$

Silylcarbodiimides do not bring about condensation of amino acids to peptides, nor do they react with hydrogen sulfide, aniline, phenylhydrazine, etc. (261). Lithium aluminum hydride splits the silylcarbodiimide into substituted silane and metal cyanamide (559).

$$4Me_3SiN{=}C{=}NSiMe_3 + 2LiAlH_4 \rightarrow 8Me_3SiH + Li_2NCN + Al_2(NCN)$$

X. N,N′-DISTANNYLCARBODIIMIDES

Triphenylstannyl chloride reacts with sodium cyanamide to yield bis(triphenylstannyl)carbodiimide (326).

$$2Ph_3SnCl + NaNHCN \rightarrow Ph_3SnN{=}C{=}NSnPh_3 + HCl + NaCl$$

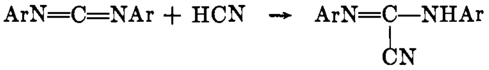
XI. ESTIMATION OF CARBODIIMIDES

Zetzsche and Fredrich (855) first described a method for the estimation of the carbodiimide grouping (–N=C=N–) based on the quantitative evolution of carbon monoxide when carbodiimide reacts with oxalic acid in an anhydrous medium (see also ref 144).

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

More recently, Zarembo and Watt (851) have developed two additional procedures based on the above reaction: (i) the volume of the gases evolved is measured by a gas-chromatographic procedure involving a column of 0.25% Apiezon L grease on 80–100 mesh glass beads, with helium as carrier gas; (ii) the carbodiimide is allowed to react with a known excess of oxalic acid in dry dioxane and the remaining acid back-titrated in the absence of air and moisture with standard sodium methoxide using thymol blue as indicator.

Hunig, *et al.* (285), have developed a volumetric estimation applicable to monomeric aromatic carbodiimides, the nitrogen atoms of which were more basic than those of diphenylcarbodiimide. The carbodiimide is treated with an excess of standard cyanide solution and the unreacted cyanide is back-titrated with standard mercuric nitrate, using diphenylcarbazide as indicator.



$$ArN{=}C{=}NAr + HCN \rightarrow ArN{=}\underset{\displaystyle CN}{\underset{|}{C}}{-}NHAr$$

XII. PHYSIOLOGICAL PROPERTIES

A. TOXICITY AND MISCELLANEOUS PROPERTIES

The toxicity and antitumor properties of some carbodiimides have been examined using seven bacterial species; di(triphenylmethyl)carbodiimide was far more toxic to a malignant than to a normal cell line; dicyclohexylcarbodiimide showed antitumor activity in mice (584). The mammalian toxicity of some carbodiimides was low (LD_{50} of dicyclohexylcarbodiimide (rats) 2.6 g/kg) (22).

N-Cyclohexyl-N′-(2-morpholinoethyl)carbodiimide has been employed in histology for detecting carbonyl groups (212, 213).

B. USE OF CARBODIIMIDES IN IMMUNOLOGY

The formation in animals of antibodies to substances of low molecular weight can often be elicited by injecting such substances conjugated to proteins. Goodfriend, Levine, and Fasman (225) have synthesized conjugates of proteins and biologically active polypeptides using soluble carbodiimides. Thus, protein–hapten conjugates, prepared from rabbit serum albumin and synthetic bradykinin and angiotensin, when injected in rabbits produced specific antibodies to bradykinin and angiotensin.

XIII. INDUSTRIAL USES

Carbodiimides have found a number of industrial applications which are covered by a fairly extensive patent literature. Their chief industrial uses are as follows.

A. AS POLYMER STABILIZERS

The products obtained from sulfur dioxide and diene elastomers or natural rubber are stabilized against breakdown on storage or exposure to heat or light by treatment with a carbodiimide (230). Many types of polyolefins (542), polyesters (192, 511, 513, 576), polyacrylonitriles (492), resins (513, 514), fibers (513), cellulose esters (510, 595), and foam materials (made from polyesters or polyesters modified with polyurethans) (271, 577, 802) are similarly stabilized against deterioration due to heat and hydrolysis by means of carbodiimides, particularly sterically hindered polycarbodiimides (513). This stabilization is attributed to the special reactivity of carbodiimides with free carboxyl groups which are formed during heating, molding etc., and which catalyze the degradation of the polymers (510, 513).

The washfastness of dyes on protein and polyamide fibers is greatly increased by treatments with carbodiimides (39).

On treatment with carbodiimides, soda cellulose gives a modified cellulose which is useful in textile sizes, coating compounds, and molding powers (480).

B. AS POLYMERIZATION PROMOTORS

Polyoxymethylenes have been prepared by polymerizing anhydrous monomeric formaldehyde with catalytic amounts of diisopropylcarbodiimide in an inert solvent such as toluene (178, 801). Linear polymers containing carboxyl or sulfonic acid groups are cross-linked by addition of a carbodiimide. This type of cross-linking is especially useful in vulcanizing rubbers containing small amounts of organic acids (89).

Polycarbodiimides, obtained from organic triisocyanate or polymers containing three or more isocyanate groups per molecule, have been found to be particularly useful in the preparation of shaped cellular foamed objects (109).

Dicyclohexylcarbodiimide has been used to produce neutral lubricating oils; it functions by combining free carboxyl and amino groups in the oil to neutral amide groups (26).

An infusible, insoluble mass is obtained by using a carbodiimide as the curing agent for the resinous polysilanes (632).

C. IN THE DYE INDUSTRY

Cellulose (natural or regenerated) and its derivatives (nitrocellulose or cellulose acetate) containing free hydroxyl groups react with carbodiimides in the presence of a copper salt to form products which are suitable for being dyed with acid dyes (632).

Polyformaldehyde is stabilized by additional esterification of end hydroxyl groups by anhydride or ketene using a carbodiimide as catalyst (436).

D. IN PHOTOGRAPHY

Treatment of photographic gelation emulsions with carbodiimides, or their soluble salts such as methiodide or methosulfate, results in a number of improvements in the desired properties of the emulsion (133, 694).

E. AS HERBICIDES, INSECTICIDES, ETC.

Cycloaliphatic carbodiimides have been reported to be effective post-emergence herbicides in agricultural crops (22). Some of these carbodiimides show insecticidal activity (*Musca domestica*, etc.) (624) and acraicidal activity (*Tetranychus urticae*), and some are effective fungicides (*Peronospora*) and nematocides (*Aphelenchoides ritzemabosi*) (22, 624).

F. MISCELLANEOUS USES

Carbodiimides have been used as depolarizers in electrochemical cells (431).

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