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# Cyclobutane Derivatives from Thermal Cycloaddition Reactions

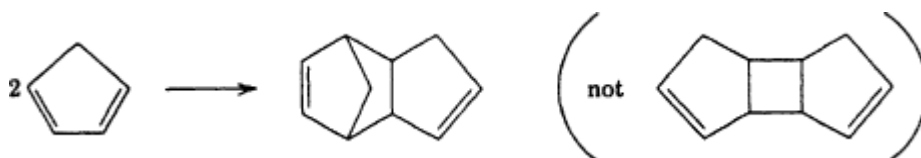
## 1. Introduction

Preparation of substituted cyclobutanes and cyclobutenes by cycloaddition reactions of alkene to alkene and alkene to alkyne has become an important synthetic reaction and, in fact, where applicable, is now the method of choice for synthesis of four-membered carbon ring compounds. Such cycloadditions may be achieved thermally under autogenous pressure in the presence of free-radical inhibitors or photochemically by irradiation with visible or ultraviolet light. This chapter does not include photochemical cycloadditions or the thermal dimerizations of ketenes since these have been well reviewed elsewhere.<sup>1-3</sup>

Historically, the establishment of cyclobutane structures for cycloaddition products provides an enlightening example of the waxing and waning of fashions in the interpretation of organic reactions.

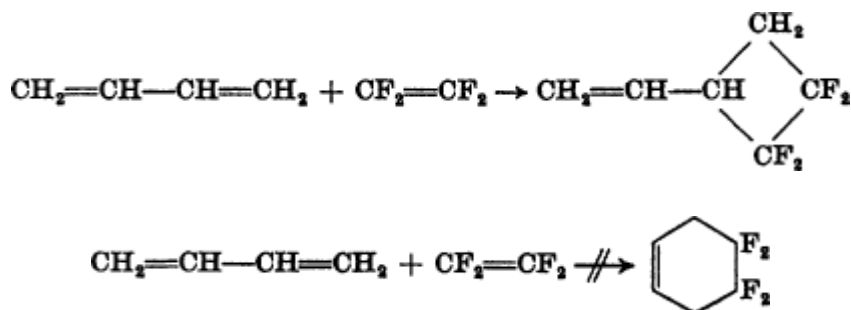
Some of the interesting and important landmarks will be briefly noted here.<sup>\*</sup> First, the early work of Liebermann<sup>4</sup> (1889) on the truxillic acids provided a strong measure of confidence for later workers in assigning cyclobutane structures to a variety of cycloadducts, and, when Kraemer<sup>5</sup> discovered dicyclopentadiene (1896), he suggested that it was a cyclobutane derivative. This was followed by proposals of cyclobutane structures for dimers from 1,5-cyclooctadiene (Willstätter,<sup>6</sup> 1905), substituted ketenes (Staudinger,<sup>7</sup> 1906–1912), unsaturated acids (Doebner,<sup>8</sup> 1907), and allenes (Lebedev,<sup>9</sup> 1911–1913). Publication by Staudinger<sup>10</sup> of *Die Ketene* in 1912 appeared to complete the conditioning of chemical thought, and postulation of formation of cyclobutanes by cycloaddition reactions was both fashionable and respectable over the next two decades.

The skies darkened briefly in 1928 when Diels and Alder<sup>11</sup> demonstrated the generality of their reaction and suggested that dicyclopentadiene resulted from 1,4 and not 1,2 addition. However, Bergel<sup>12</sup> in 1928 reaffirmed faith in the cyclobutane structure, and comparative peace reigned until 1931 when Alder and Stein<sup>13</sup> proved beyond reasonable doubt that dicyclopentadiene actually had the bridged-ring structure. With this development, cyclobutane structures for cycloadducts rapidly became unfashionable and fell into general disfavor. The tide was partially stemmed in 1934 when Cupery and Carothers<sup>14</sup> oxidized the dimer of divinylacetylene to cyclobutane-1,2-dicarboxylic acid—the first time a cyclobutane derivative of known structure was isolated as a degradation product of a cycloadduct. None the less, the tenor of thought in the late thirties was such that when Simonsen<sup>15</sup> showed that Staudinger's diphenyl-ketene-cyclopentadiene adduct contained a four-membered ring, this result was “not anticipated.” The pessimism which then prevailed is well illustrated by Bergmann's review article of 1939<sup>16</sup> in which many postulated cyclobutane structures (some correct, some incorrect) were flatly rejected. The era of doubt drew to a close late in the forties when new experimental results led to general recognition of the usefulness of thermal cycloaddition reactions as a synthetic route to cyclobutane derivatives.

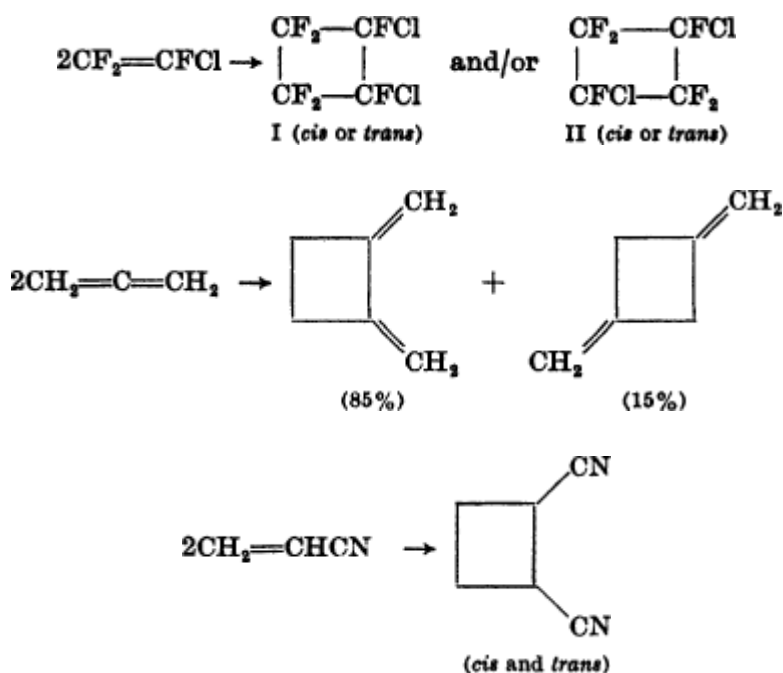


The breakthrough was greatly facilitated by the discovery by du Pont research groups<sup>17, 18</sup> that octafluorocyclobutane can be formed readily by thermal dimerization of tetrafluoroethylene. This development inspired several extensive investigations of cycloadditions involving fluoroalkenes. A typical reaction is the addition of tetrafluoroethylene to 1,3-butadiene at 125° to afford 3-vinyl-1,1,2,2-

tetrafluorocyclobutane in 90% yield.<sup>19</sup> This cycloaddition illustrates two important points. First, fluorinated alkenes may add to non-fluorinated unsaturated compounds much more readily than they dimerize. Second, when fluorinated alkenes are given a choice between four- and six-membered ring formation, as is possible with a conjugated diene, the formation of the four-membered ring is favored. It seems significant that ethylene<sup>20</sup> and tetracyanoethylene<sup>21</sup> apparently give only the normal Diels-Alder, six-membered ring products with butadiene.

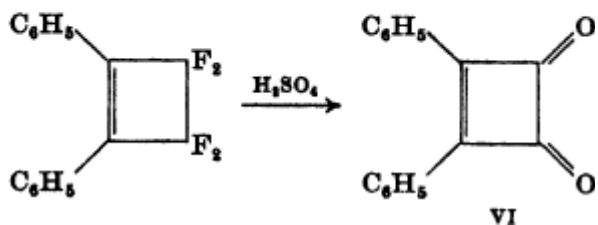
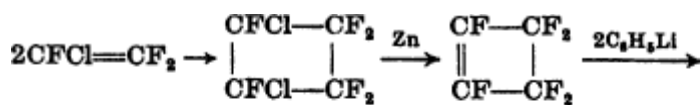
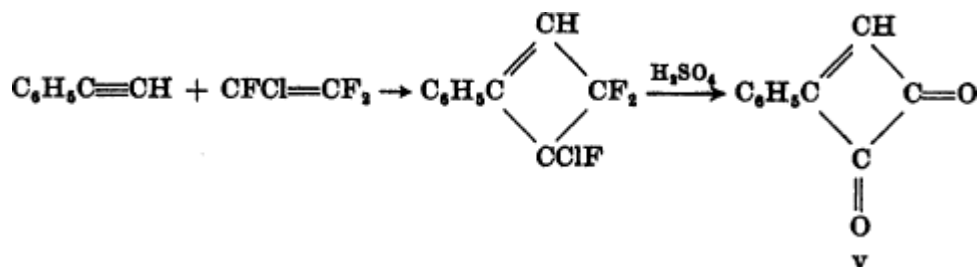
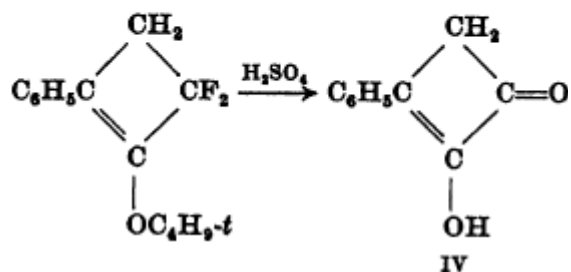
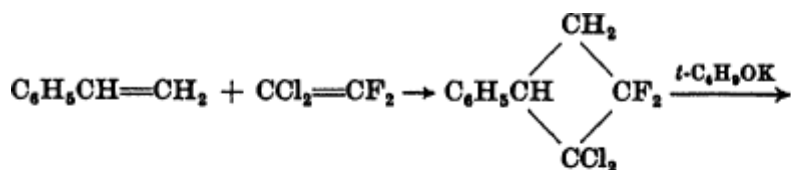
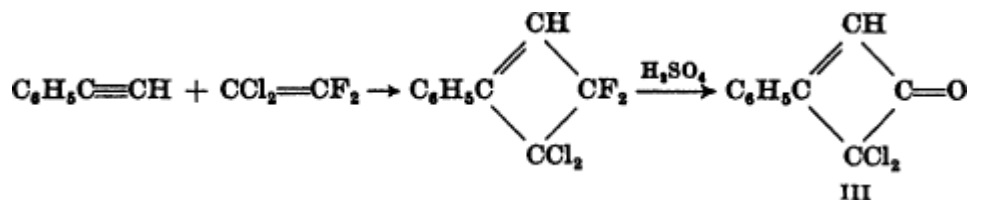


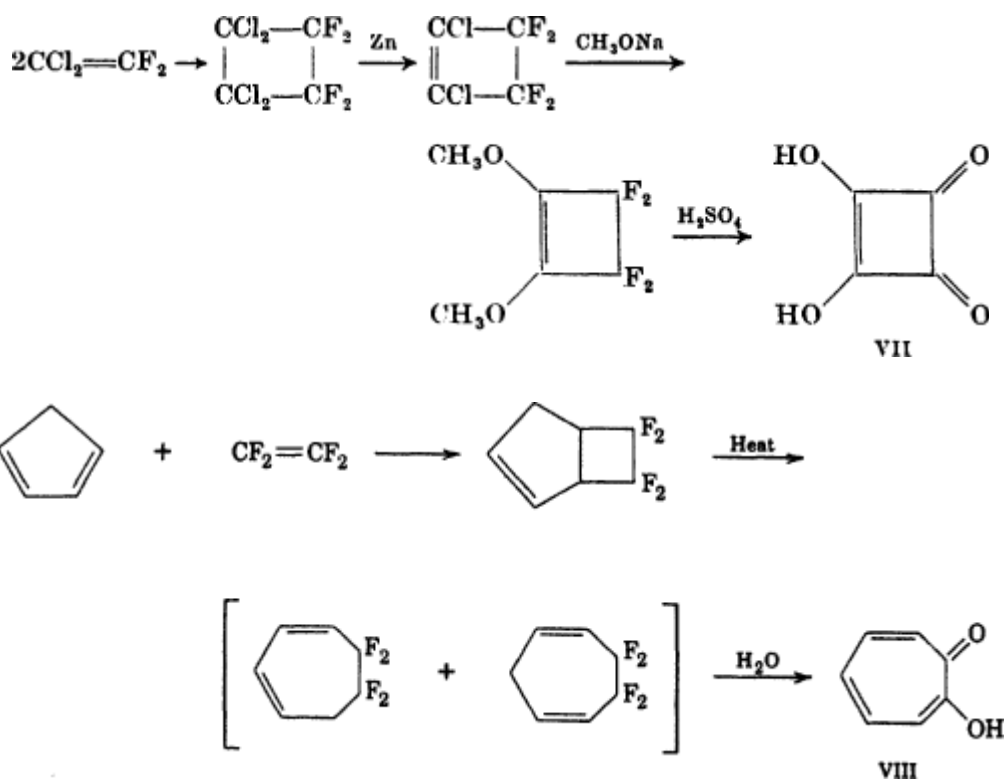
The experimental conditions for the addition of tetrafluoroethylene to butadiene are very similar to those commonly used for Diels-Alder reactions involving volatile addends, and a further similarity is provided by the aforementioned fact that two dissimilar compounds, tetrafluoroethylene and butadiene, are found to react with each other much more readily than they react with themselves. Like Diels-Alder reactions,<sup>22</sup> the cycloadditions leading to four-membered rings may present orientational and stereochemical problems. For example, dimerization of trifluorochloroethylene can give two structural isomers, the “head-to-head” (I) and “head-to-tail” (II) adducts, and each of these may be the *cis* or the *trans* isomer. It is of considerable practical and theoretical significance that the principal product in this<sup>23</sup> and other cases is the result of head-to-head addition (I) with the chlorine atoms predominantly *cis* to one another. This mode of addition is not at all peculiar to fluoroalkenes. Allene dimerizes to give predominantly 1,2-dimethylenecyclobutane<sup>9, 24</sup> (head-to-head), and acrylonitrile affords *cis*- and *trans*-1,2-dicyanocyclobutane.<sup>25</sup> As will be shown, these facts are strong evidence against ionic mechanisms for this type of cycloaddition (except possibly ketene dimerizations); in addition, they may well provide new understanding of factors governing cycloadditions in general, including the Diels-Alder reaction.



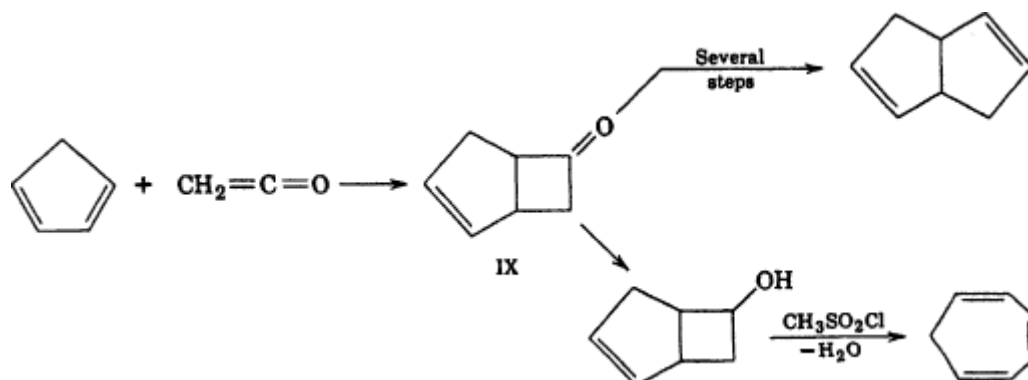
The cycloaddition reactions of fluoroalkenes have provided a dazzling array of unusual fluorinated cyclobutane and cyclobutene derivatives that would be extraordinarily difficult to synthesize by conventional means. Many of these substances possess great intrinsic interest; but, generally speaking,

they are not useful intermediates for the synthesis of nonfluorinated cyclobutanes since almost all contain gem-fluorine atoms that are characteristically rather inert chemically. None the less, some success has been achieved in utilizing the beneficial effect of gem-fluorine atoms on formation of four-membered rings and then removing the fluorine by hydrolysis to yield carbonyl groups. In this way, practical laboratory syntheses have been developed of substituted cyclobutenones (III, IV),[26-28](#) cyclobutenediones (V to VII),[29-31](#) and tropolone (VIII),[32](#) as illustrated in the following equations.

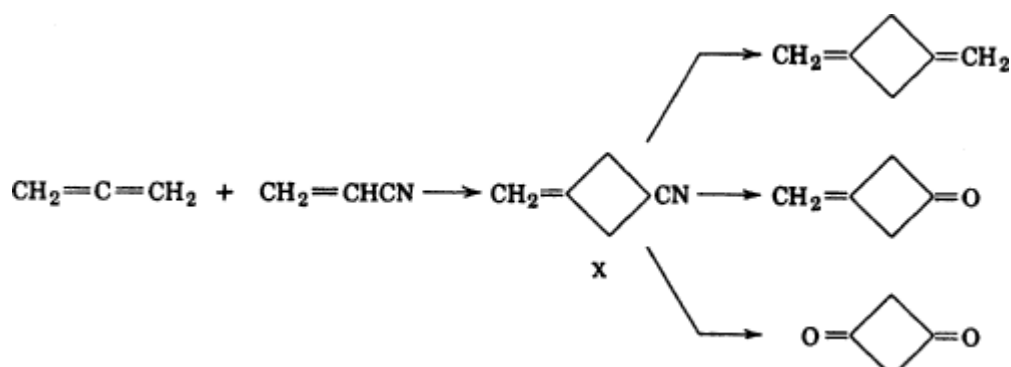




The cycloadduct IX from ketene and cyclopentadiene, even though formed in rather poor yield, has been used as an intermediate for the synthesis of a bicyclo[3.3.0]octadiene as part of a projected route to pentalene<sup>33</sup> and has also been converted to cycloheptatriene.<sup>34</sup>

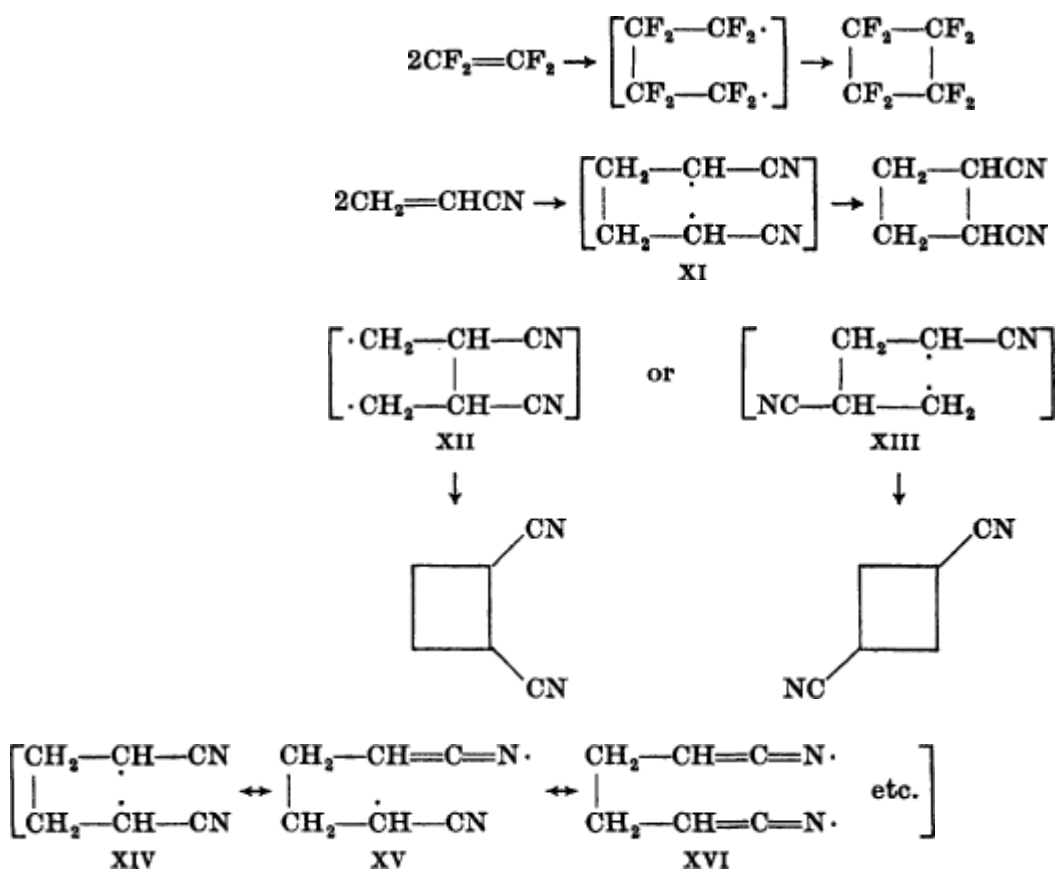


The very reasonable yields of cyclobutane derivatives recently demonstrated for the addition of allene to various substituted alkenes<sup>35</sup> have substantially broadened the synthetic usefulness of the cycloaddition reaction for the preparation of non-fluorinated, four-membered-ring compounds. The adduct X from allene and acrylonitrile has already proved useful in syntheses for 1,3-dimethylenecyclobutane,<sup>36, 37</sup> 3-methylenecyclobutanone,<sup>38</sup> and 1,3-cyclobutanedione.<sup>39</sup>

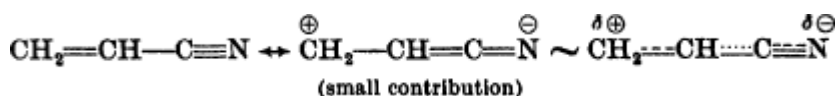


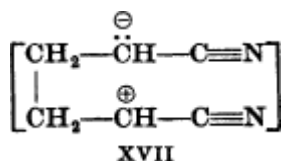
## 2. Reaction Mechanism

It has been suggested that formation of octafluorocyclobutane from tetrafluoroethylene during the pyrolysis of polytetrafluoroethylene (Teflon) involves a diradical intermediate.<sup>18</sup> A similar explanation was offered to account for the head-to-head dimerization of acrylonitrile.<sup>25</sup> Formation of the diradical XI was expected to be substantially more favorable than formation of the diradical XII, which would also lead to head-to-head cycloaddition, or XIII, which would give the head-to-tail product because of stabilization resulting through interaction of the unpaired electrons with the adjacent unsaturated cyano groups as may be symbolized by the resonance forms XIV to XVI, etc. Such stabilization would be possible for only one of the unpaired electrons of diradical XIII and would be impossible for XII.

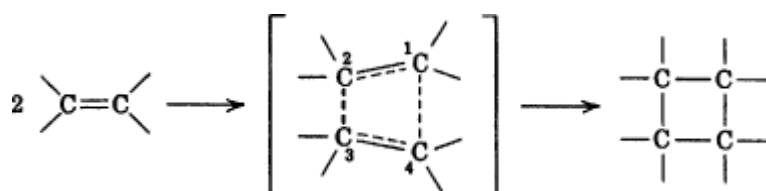


The head-to-head orientation produced with acrylonitrile appears to exclude an ionic mechanism since the electrical polarization of the double bond by the cyano group would be expected to lead exclusively to head-to-tail addition. Furthermore, an ionic intermediate (XVII) analogous to the diradical XI would have a cationic center immediately adjacent to a cyano group, and there seems to be no reason to suppose that this unfavorable juxtaposition of electron-withdrawing groups would necessarily be more than counterbalanced by the concomitant establishment of an anionic center adjacent to the other cyano group. An additional argument against ionic mechanisms is that these cycloadditions proceed well in non-polar solvents and with fluoroalkenes even in the gas phase.<sup>23</sup>





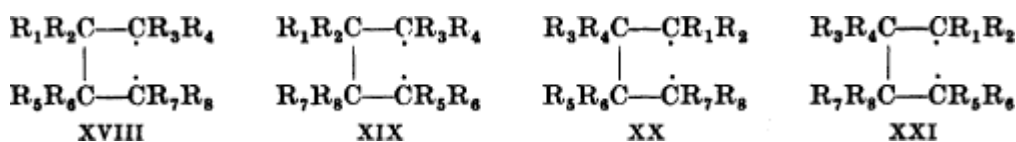
The reasonable alternative to the stepwise diradical mechanism is a more or less concerted breaking of the multiple bonds of the addends and formation of the new bonds of the adduct. If the 1,4 bond has only a very slight single-bond character in the transition state when formation of the 2,3 bond is nearly complete, we have what might be termed a “virtual” diradical mechanism. The distinction between this formulation and the “bona fide” diradical process proposed by Coyner and Hillman<sup>25</sup> is that the electrons are regarded as remaining paired at all times in the concerted mechanism and sufficient bonding exists between C-1 and C-4 to prevent free rotation about the 1,2 and 3,4 bonds. The free-valence index at the 1 and 4 positions in the transition state might well be sufficiently great that predictions of orientation can be made for unsymmetrical alkenes on the same successful basis as is possible with the diradical mechanism (see later).

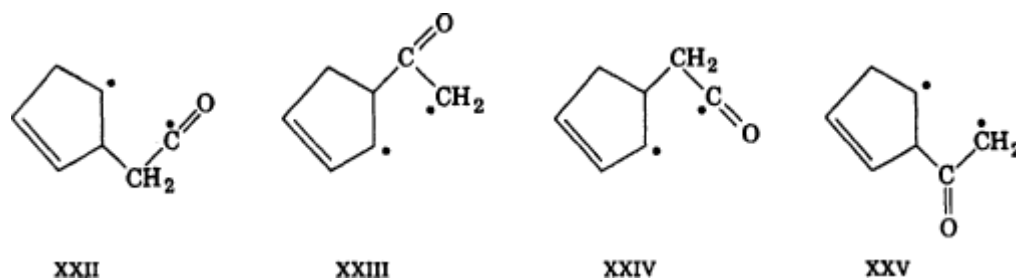


The possible role of charge-transfer complexes of the type postulated for the Diels-Alder reaction<sup>40</sup> as intermediates in formation of cyclobutane derivatives by cycloaddition reactions is by no means clear. Tetrafluoroethylene and similar substances are hardly expected to function well as both donor and acceptor moieties in forming charge-transfer complexes. None the less, such substances may dimerize smoothly to cyclobutane derivatives. On this basis, it seems best to conclude that formation of charge-transfer intermediates should not be regarded as a necessary condition for cycloaddition. However, as mentioned earlier, tetrafluoroethylene and butadiene react with each other more easily than either reacts with itself. This fact indicates that mutual polarization (or something akin to charge transfer) aids in stabilizing the cycloaddition transition state whatever the detailed features of the reaction mechanism may be.

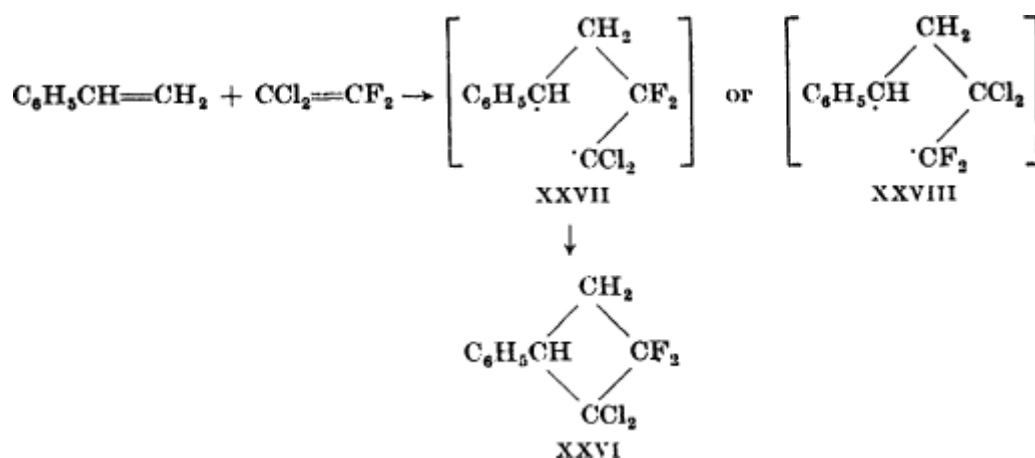
Second-order kinetics have been established for the gas-phase dimerization of some fluoroalkenes,<sup>23</sup> and activation parameters are available.<sup>23</sup> The results provide no help for distinguishing between the stepwise and concerted mechanisms.

The diradical mechanism for cycloaddition possesses the virtue of being extremely useful for predicting the course of cycloaddition with unsymmetrical ethylenes. For the general case of addition of  $\text{R}_1\text{R}_2\text{C}=\text{CR}_3\text{R}_4$  to  $\text{R}_5\text{R}_6\text{C}=\text{CR}_7\text{R}_8$ , one can write four possible diradical intermediates XVIII to XXI. The problem of predicting the direction of addition then reduces to the problem of predicting which of the diradicals would be the most stable on electronic or steric grounds or both. Usually it appears as though electronic considerations are the more important. As an example, consider the addition of ketene to cyclopentadiene. The four possible diradicals are XXII to XXV. Of these, XXIII is expected to be most stable because both odd electrons could be stabilized by interaction with an unsaturated group. The product obtained, IX, is that expected from a ring closure involving XXIII.





Similar arguments applied to the addition of dichlorodifluoroethylene to styrene suggest that the adduct should be XXVI, which is expected to arise from the diradical XXVII. The formulation XXVII is considered to be more favorable than XXVIII on the basis that a difluoromethyl radical should be less stable than a dichloromethyl radical.<sup>41</sup> The observed cycloaddition product is XXVI,<sup>27</sup> in accord with predictions.

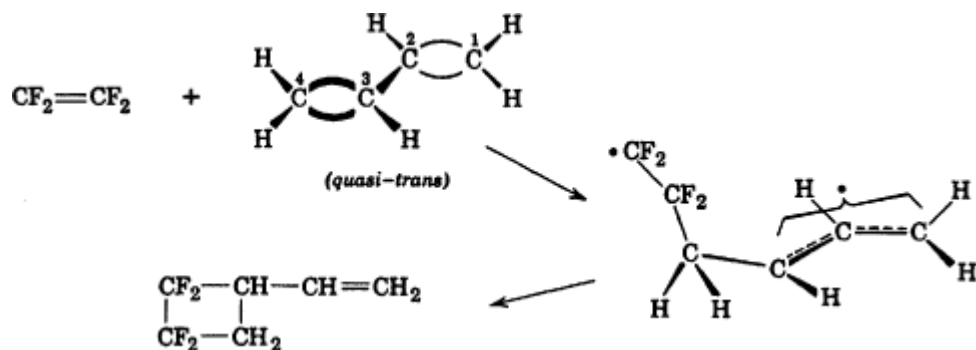


This approach has wide utility and seems to fail badly only for ketene dimerizations, which give the head-to-tail products (perhaps by an ionic mechanism; see later discussion). Tentative structures for some cycloaddition products are assigned in the tables at the end of the chapter on the basis of the diradical mechanism.

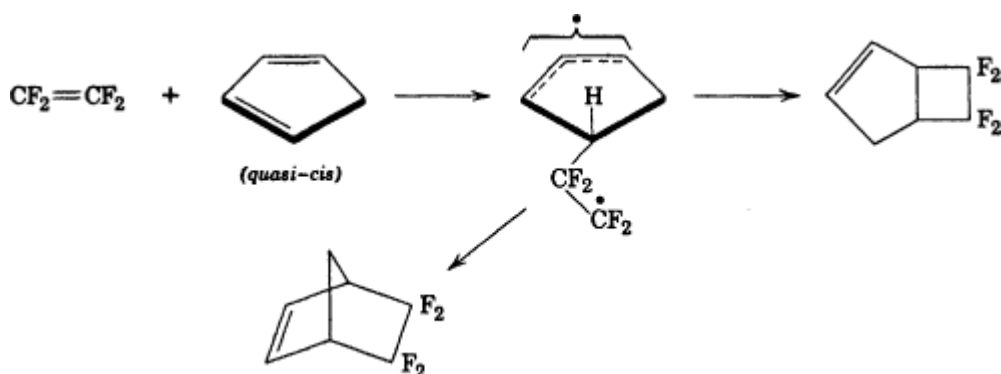
Whether or not bona fide diradicals with unpaired electrons are actually the reaction intermediates is very difficult to determine. The same problem has arisen before in connection with the mechanisms of the thermal polymerization of alkenes and the Diels-Alder addition.<sup>42</sup> It is clear that the absence of accelerating effects produced by the usual free radical initiators or of retarding influences by free-radical inhibitors is no proof against the diradical mechanism, since we are dealing with a reaction for which no obvious accelerating function can be seen for initiators and which need not be retarded by inhibitors because it is not a chain process. It may be that no single interpretation can be put in words which will satisfy everyone; at least, before final attempts are made to rationalize these cycloadditions, some additional experimental evidence and new ideas will be required.

A possible, but by no means compelling, argument in favor of the diradical mechanism follows. Butadiene and tetrafluoroethylene appear to give exclusively the four-membered-ring adduct,<sup>19</sup> while cyclopentadiene gives a mixture of four- and six-membered-ring products.<sup>32</sup> If tetrafluoroethylene (unlike dienophiles such as maleic anhydride<sup>42</sup>) were able to add to butadiene molecules in the more stable quasi-trans configuration to give diradicals, the resonance stabilization of the odd electrons in the butadiene half of any given diradical would tend to confer double-bond character on the 1,2 and 2,3 bonds so as to hold the diradical in the extended structure. This would greatly favor formation of a four-membered ring, since a six-membered ring could only be formed if (1) the allyl-type radical were to lose momentarily its resonance stabilization through a twist about the 2,3 C single bond, or (2) a six-membered ring containing a trans double bond were formed.

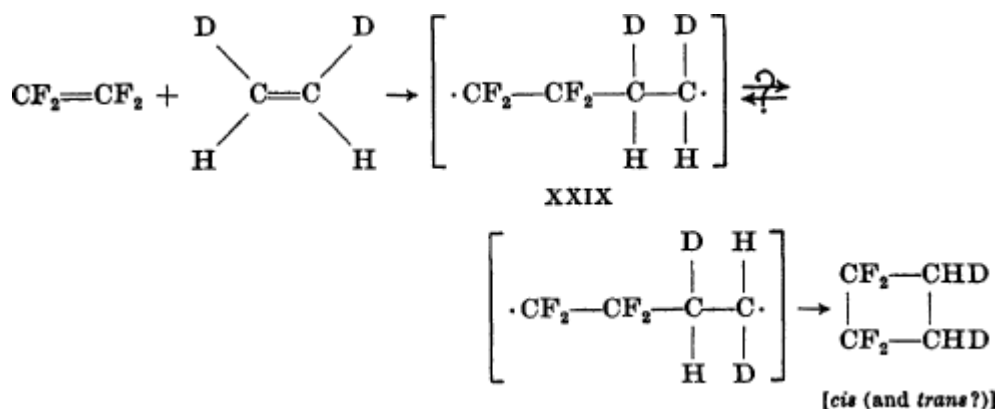




With cyclopentadiene, the double bonds can have only the quasi-cis relationship to one another; thus the diradical would necessarily possess a configuration which could afford both four- and six-membered-ring products, as is observed.<sup>32</sup>



It needs to be determined whether or not one alkene adds to another cleanly in the cis manner; a nearly ideal case for the purpose would be afforded by the addition of cis(or trans-)1,2-dideuteroethylene to tetrafluoroethylene. The involvement of a bona fide diradical (XXIX) might well lead to non-stereospecific addition as the result of rotation about the bond connecting the CHD groups before ring closure.<sup>43</sup>



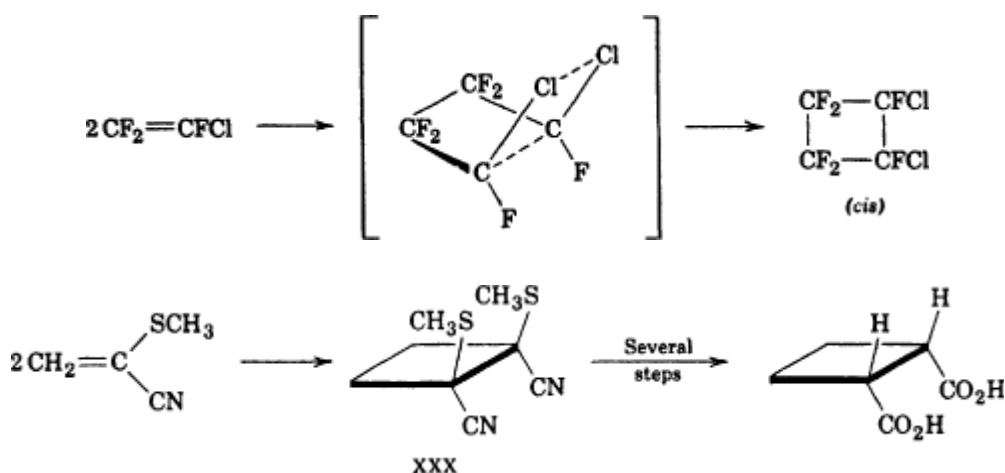
A number of other questions remain to be answered satisfactorily. Why are gem-fluoro compounds, allenes, and ketenes so peculiarly effective in forming four-membered rings even when six-membered rings can be formed, as for example with conjugated dienes? Why do the double and triple bonds in vinylacetylene react at about the same rate with tetrafluoroethylene?<sup>19</sup> Are there rules like the Alder rules governing the stereochemistry in cycloadditions leading to four-membered rings? Only tentative or partial answers to these questions can now be given.

The effectiveness of gem-fluorine atoms in promoting four-membered ring formation may be the result of non-bonding interelectronic repulsions between the fluorine atoms which could tend to increase the F

single bond C single bond F angle and hence diminish the angle between the other two valences of the carbon atom to which they are attached. Relief of the F single bond F repulsions would be thus expected to be substantially greater in formation of four-membered rings than of a six-membered ring. This rationalization is, of course, no help in accounting for the behavior of allenes and ketenes.

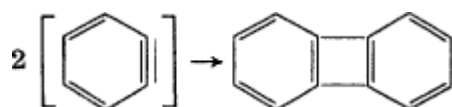
One thing is clear. Measurements of the activation energies for the forward and reverse processes have shown that the enthalpy of formation of octafluorocyclobutane from two molecules of tetrafluoroethylene is  $-50$  kcal.<sup>44</sup> This value is very much greater than the  $-25$  kcal estimated<sup>44</sup> for formation of cyclobutane from two molecules of ethylene, and it reflects a weak double bond in tetrafluoroethylene and/or a favorable disposition of the fluorine atoms and strong single bonds in octafluorocyclobutane.

Few quantitative data about the stereochemistry of additions to form cyclobutanes are available. With acrylonitrile, both *cis*- and *trans*-1,2-dicyanocyclobutane were reported.<sup>25</sup> With 1,3-butadiene, only *trans*-1,2-divinylcyclobutane was isolated along with vinylcyclohexene.<sup>45</sup> However, it is now clear that the *cis* compound is unstable under the reaction conditions and isomerizes to *cis-cis*-1,5-cyclooctadiene.<sup>46</sup> Consequently it seems probable that both isomers are actually formed. The dimerization of trifluorochloroethylene gives a 5 : 1 ratio of head-to-head addition products with preference for the *cis* isomer.<sup>23\*</sup> The predominance of *cis* addition here may be due to Cl single bond Cl dispersion forces operating in the transition state for ring closure<sup>47</sup> (regardless of whether by a concerted or stepwise mechanism) which tend to hold the chlorine atoms *cis* to one another. Similar considerations apply to the apparent formation of the *cis* head-to-head adduct XXX from  $\alpha$ -(methylthio)-acrylonitrile.<sup>48</sup>



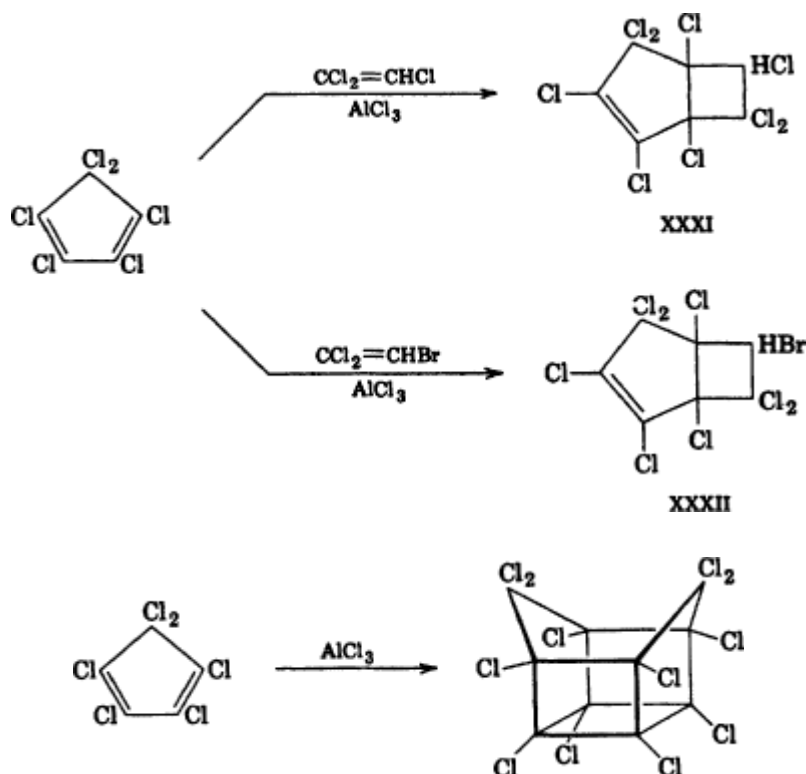
It is clear that some four-membered-ring cycloadditions may be subject to thermodynamic rather than kinetic control. With perfluoropropene, head-to-head addition with apparently a small preference for the *cis* product is observed at  $250^\circ$  while, at  $450^\circ$ , the head-to-tail adduct is formed in the larger amount and the *trans*-1,2 product is greatly favored over the *cis*.<sup>49</sup> Reversible dissociation of the cycloadduct was demonstrated at  $390^\circ$ .

A special cycloaddition reaction of considerable interest involves formation of biphenylene by presumed dimerization of benzyne. Biphenylene has been isolated in small to good yields from reactions in which benzyne was generated by heating  $[\text{C}_6\text{H}_4\text{Hg}]_6$  with copper<sup>50</sup> or silver<sup>51</sup> powder, the decomposition of *o*-fluorophenyllithium,<sup>52</sup> and the reaction of magnesium with *o*-bromiodobenzene.<sup>53</sup> It remains to be established whether or not the C single bond C bonds formed in these reactions are formed essentially simultaneously or in a stepwise manner through *o*, *o'*-biphenyl derivatives.<sup>51, 52</sup>

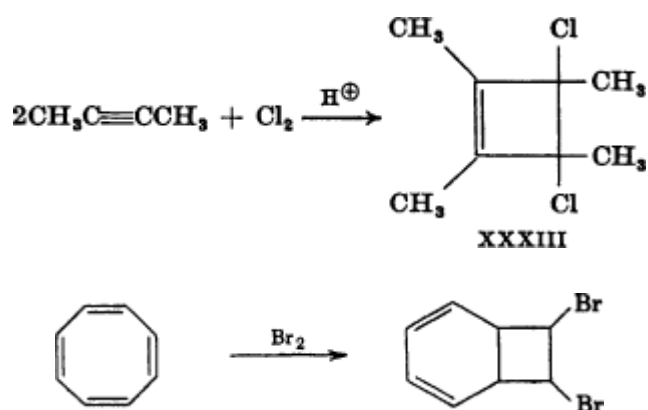


A few interesting cycloadditions require ionic catalysts. Thus hexachlorocyclopentadiene with

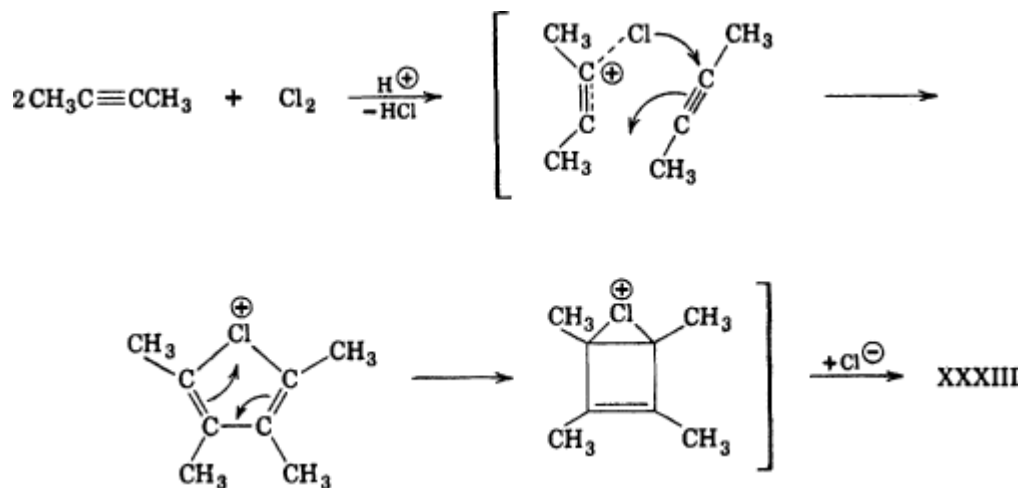
trichloroethylene and dichlorobromoethylene and aluminum chloride affords XXXI and XXXII, respectively.<sup>54</sup> Hexachlorocyclopentadiene itself is apparently converted with aluminum chloride to a dimer ( $C_{10}Cl_{12}$ ) with a caged structure possessing three cyclobutane rings.<sup>55</sup> The mechanisms of these processes are unknown, although they may be related to the cyclization reactions discussed below.



There are a few reactions, which might be classified as cycloadditions, in which cyclobutane derivatives are formed during additions to multiple bonds. The formation of XXXIII in the addition of chlorine (from sulfuryl chloride<sup>56</sup> or chlorine in the presence of acid<sup>57</sup>) to dimethylacetylene is one example, and the formation of a bridged dibromide in the addition of bromine to cyclooctatetrene is another.<sup>58</sup>



It is possible that the acid-induced<sup>57</sup> Smirnov-Zamkov reaction is the result of a "1,3 addition" of a dimethylacetylenechloronium complex to dimethylacetylene with a subsequent tautomeric shift and attack of chloride ion to give XXXIII. These non-thermal cycloaddition reactions have obvious synthetic utility but are beyond the scope of this chapter.



### 3. Scope and Limitations

The number of reported thermal cycloadditions which form four-membered rings is much smaller than the number reported for the similar and much studied Diels-Alder reaction.<sup>22, 40</sup> The known principal classes of substances which give successful dimerization reactions are included in the following list.

Fluoro- and fluorochloro-alkenes having a double bond substituted with a gem-fluoro group.

Allenes.

Ketenes (not covered in this chapter; see ref. 2).

Activated alkenes, dienes, and alkynes such as acrylonitrile, styrene, butadiene, and benzyne.

Cycloadditions involving two different alkenes or an alkene and an alkyne occur more or less well with the following combinations.

Fluoro- and fluorochloro-alkenes having a gem-fluoro substituted double bond with activated alkenes and alkynes, 1,3-dienes and allenes, and with ordinary alkenes. For the last group successful results have been reported so far only with tetrafluoroethylene.

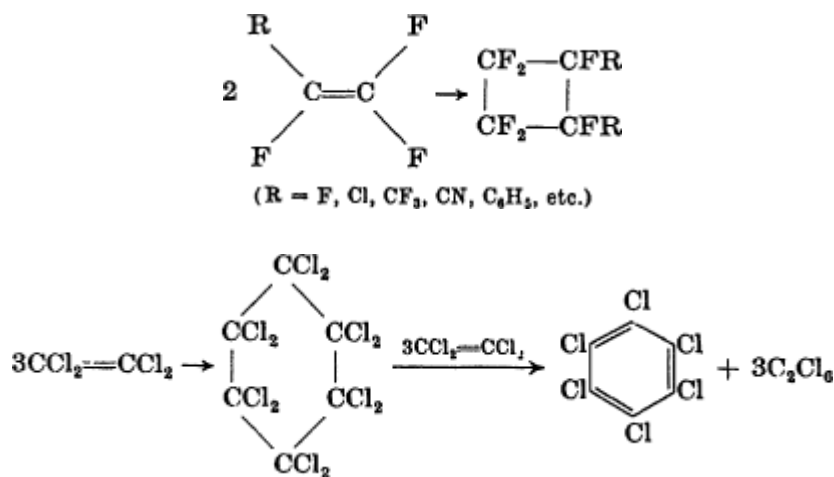
Allenes with activated alkenes and alkynes.

Ketenes with some activated alkenes, alkynes, and 1,3-dienes.

Each of the fundamental kinds of addends will be discussed separately.

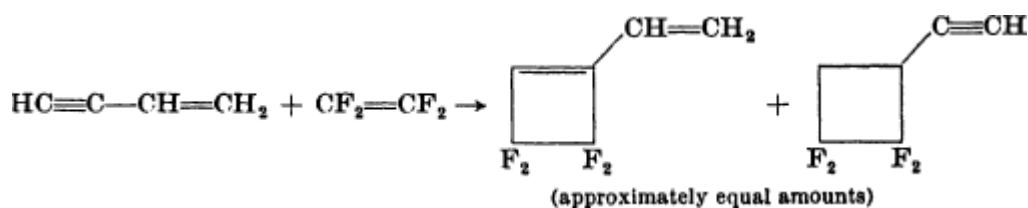
#### 3.1.1. Fluoro- and Fluorochloro-alkenes

A variety of fluoroalkenes of the following type have been found to dimerize in good yields at temperatures from 150° to 500° to give, apparently in all cases, the head-to-head adducts under conditions where kinetic rather than thermodynamic control of the products obtains. 1,1-Dichloro-2,2-difluoroethylene also forms a dimer in high yield. Tetrachloroethylene does not behave in the same way. After twelve days at 300°, the only products identified besides unreacted tetrachloroethylene were hexachloroethane and hexachlorobenzene.<sup>59</sup> Presumably these products arise by way of dodecachlorocyclohexane, which acts as a chlorinating agent for tetrachloroethylene.

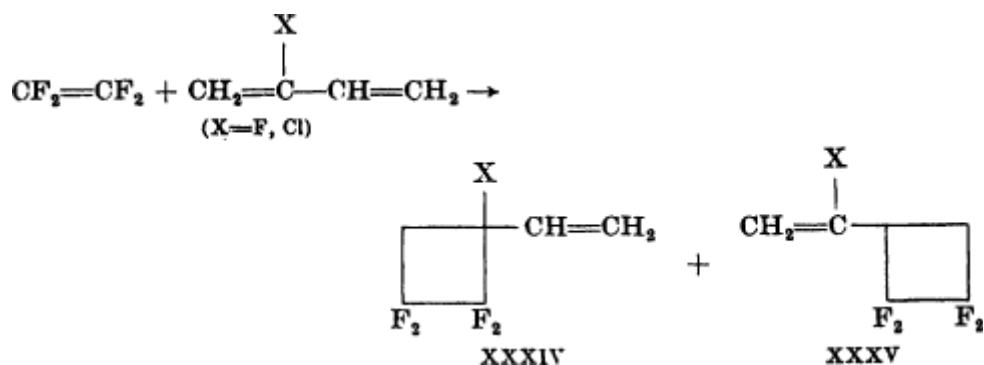


The general scope of the dimerizations of substituted fluoroalkenes is still undefined. A gem-fluoro group on the double bond appears to be very important, but other activation must also be supplied since vinylidene fluoride does not appear to dimerize to a cyclobutane.

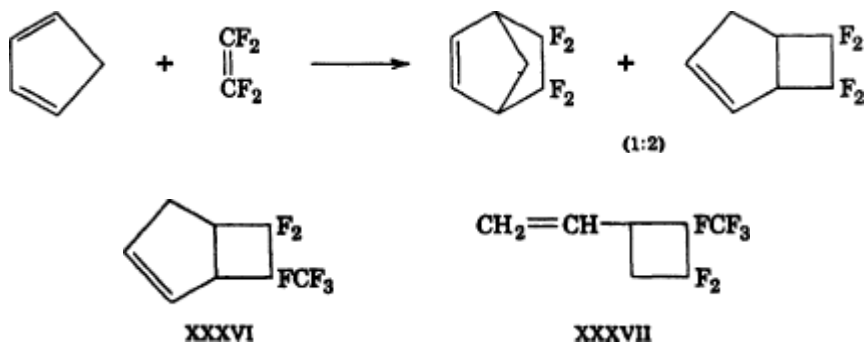
Tetrafluoroethylene adds well to a wide variety of multiple bonds.<sup>19</sup> Temperatures above 200° are usually required for simple alkenes, and 1-alkenes are more reactive than 2-alkenes. Activated alkenes like acrylonitrile react at much lower temperatures (~150°), while conjugated compounds like butadiene and vinylacetylene react at 100°. It is interesting and surprising that the double and triple bonds of vinylacetylene react at almost the same rate.



With chloroprene or fluoroprene, tetrafluoroethylene gives mixtures of monocycloadducts. The two products XXXIV and XXXV are formed in about the same ratio for fluoroprene, while XXXIV is favored by 5 : 1 for chloroprene.<sup>19</sup> This result can be rationalized on the basis of the mechanistic considerations discussed earlier.

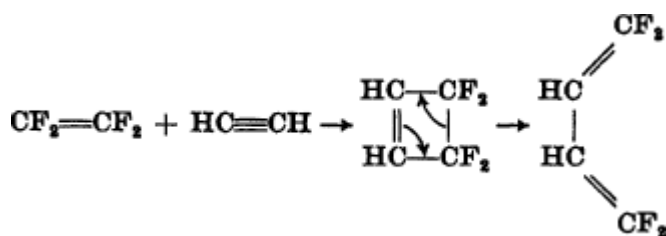


Six-membered ring compounds are not formed with fluoroalkenes and 1,3-dienes under conditions where kinetic control prevails. The only definite exception is the production of one part of 5,5,6,6-tetrafluorobicyclo[2.2.1]-2-heptene to two parts of the four-membered-ring cycloadduct with tetrafluoroethylene and cyclopentadiene.<sup>32</sup> The products from hexafluoropropene with cyclopentadiene and butadiene have been formulated as normal Diels-Alder products.<sup>60</sup> However, no compelling evidence was offered that the products are not actually XXXVI and XXXVII.



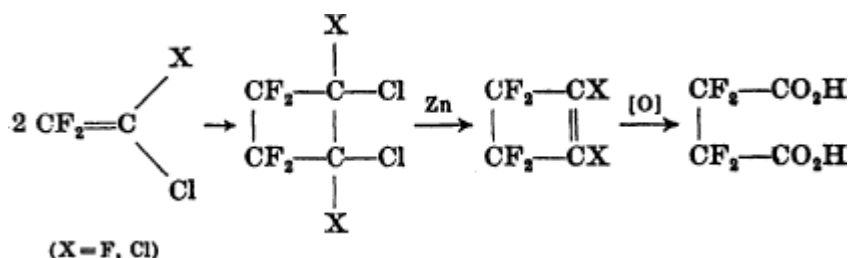
Conditions under which thermodynamic control of the products is exercised can be expected to lead to formation of six-membered-ring cycloadducts from fluoro- and fluorochloro-alkenes and 1,3-dienes because rearrangement of a variety of four-membered- to six-membered-ring adducts derived from such substances has been found to occur at 450–800°. [61](#)

Acetylene is reported to react with tetrafluoroethylene at 600° to give 1,1,4,4-tetrafluorobutadiene. [62](#) In this case the initially formed tetrafluorocyclobutene undergoes thermal ring opening in the manner shown by cyclobutene itself.

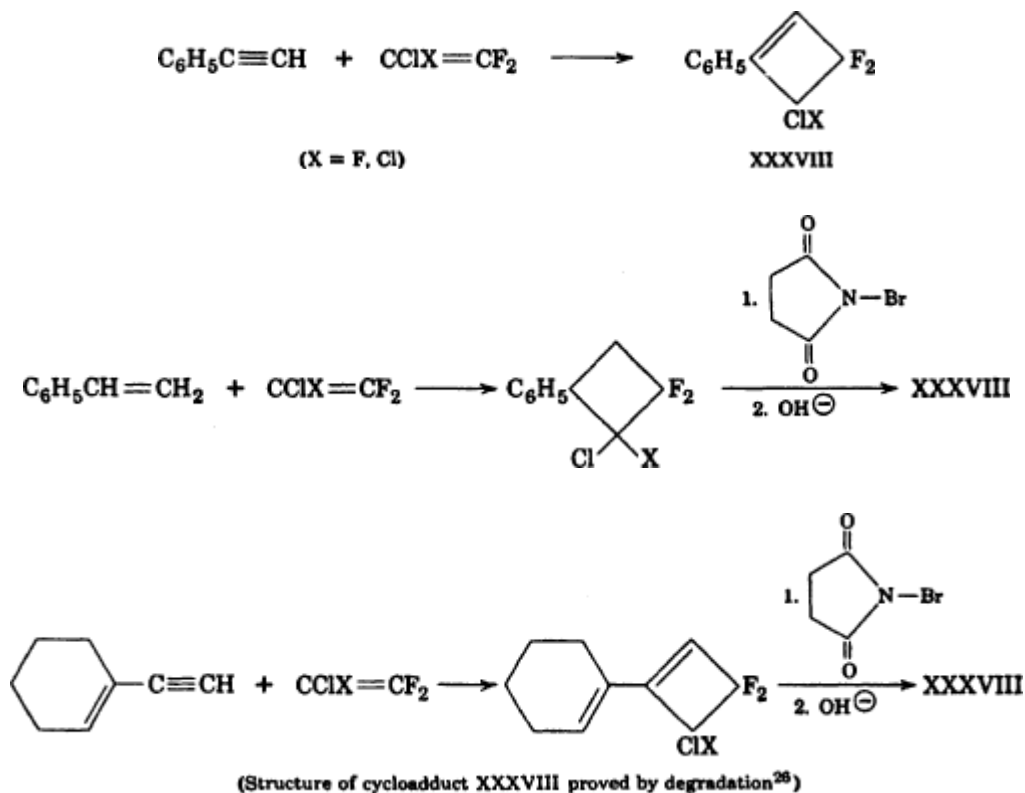


The fluorochloroalkenes with gem-fluorine atoms on the double bond usually add poorly, if at all, to the simple alkenes and alkynes but give excellent yields with 1,2- and 1,3-dienes and with reasonably activated alkenes and alkynes. If a poorly reactive addend is used, the fluorochloroalkenes undergo slow dimerization in competition with the desired cycloaddition. Vinylidene fluoride apparently does not add to styrene, [63](#) a fact which gives some indication of the degree of substitution required for facile addition. Likewise, it has been found that 1,2-difluoro-1,2-dichloroethylene does not add to phenylacetylene under conditions where 1,1-difluoro-2,2-dichloroethylene adds in 85% yields. [59](#) Symmetrical substitution in the addend may be undesirable. Thus diphenylacetylene gives no adduct with 1,1-difluoro-2,2-dichloroethylene [59](#) although, as mentioned, phenylacetylene adds readily.

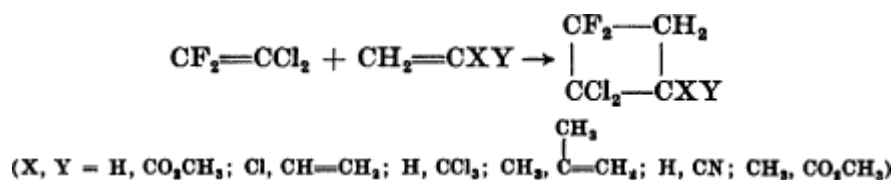
The head-to-head structures of the dimers of unsymmetrical fluorochloroethylenes have been proved by chemical means. [64-68](#)



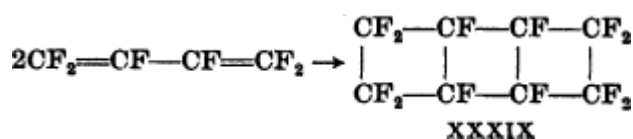
The mode of addition of trifluorochloroethylene and 1,1-difluoro-2,2-dichloroethylene to phenylacetylene, styrene, and 1-cyclohexenylacetylene has been established by degradation and interconversion reactions. [26](#), [69](#) In each case only one cycloadduct was formed, and its structure was in accord with predictions.



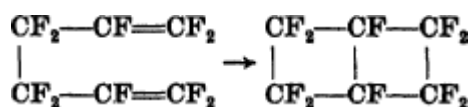
A study<sup>70</sup> of the cycloaddition reactions of 1,1-difluoro-2,2-dichloroethylene with various activated unsymmetrical alkenes and 1,3-dienes showed that only one compound was formed in each case. Although the structures of the products were not proved for each reaction, all the available data indicate that these adducts can be formulated as having the expected orientation.



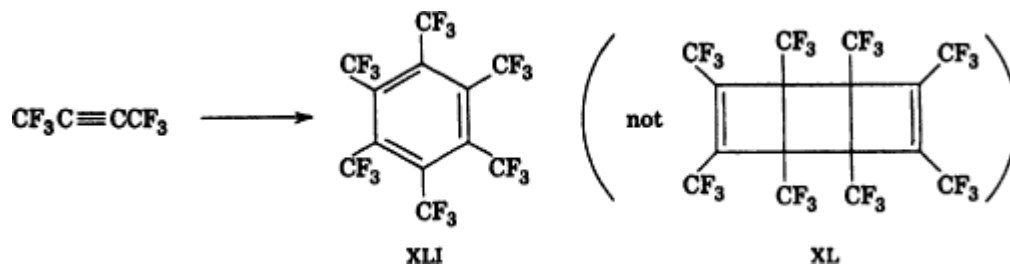
Dimerization of perfluoro-1,3-butadiene has been reported to afford the unusual and interesting tricyclic substance XXXIX.<sup>71</sup>



A similar structure has been written for the product of the intramolecular cyclization of perfluoro-1,5-hexadiene.<sup>72</sup>



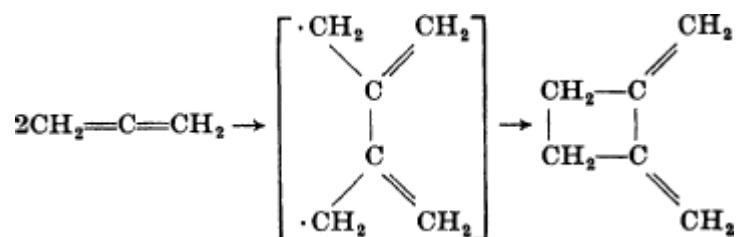
Perfluoro-2-butyne has been reported to give the tetramer XL,<sup>73</sup> but it now appears that the product is actually hexa(trifluoromethyl)benzene (XLI).<sup>74</sup>



Pyrolyses of polymers of fluoro- and fluorochloro-ethylenes have been found to give cyclobutane derivatives.<sup>17, 18, 75-77</sup> Presumably these are formed by cycloadditions of the alkenes formed by degradation.

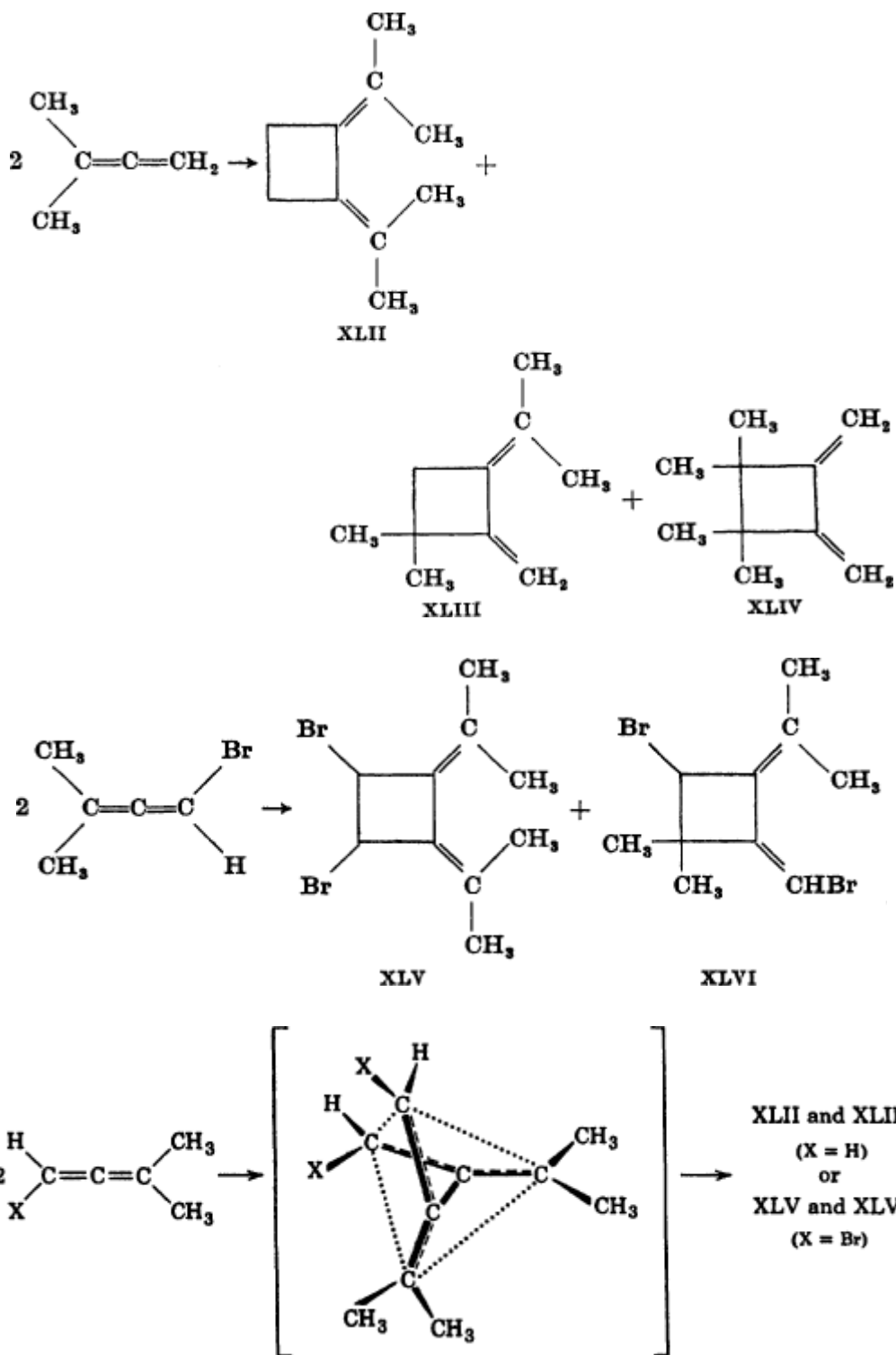
### 3.1.2. Allenes

Lebedev<sup>9, 78</sup> apparently was the first to observe the formation of cyclobutanes through dimerization of allenes. With allene itself, the product was reported to be 1,2-dimethylenecyclobutane, as expected from the diradical mechanism. At higher temperatures, in a flow system, the reaction appears to be less selective, and both the 1,2 and 1,3 adducts are formed in the ratio 85:15.<sup>24</sup> The over-all yield under these conditions is 50%.

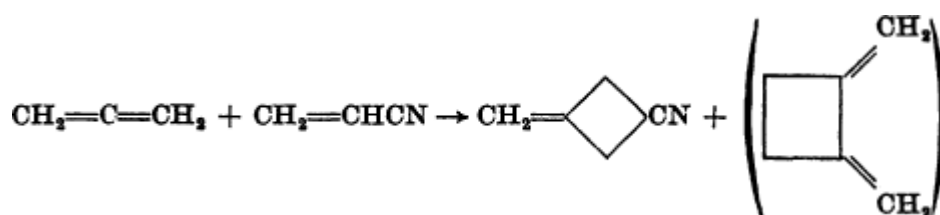


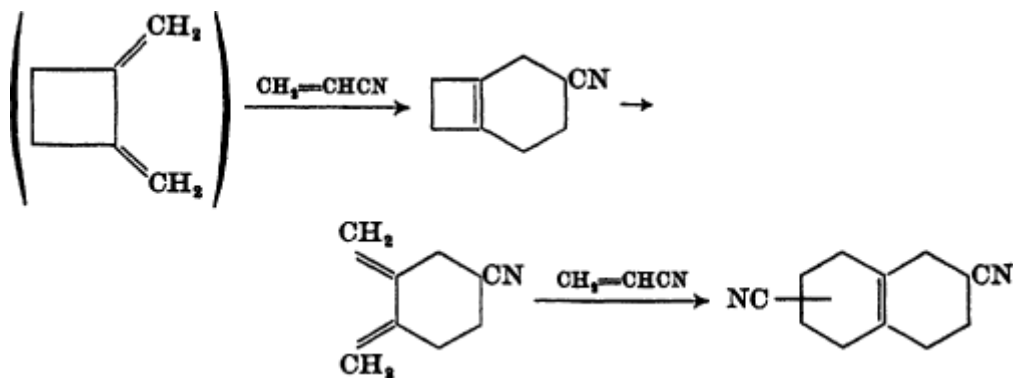
Lebedev has reported that 1,1-dimethylallene dimerizes to give at least two of the three possible head-to-head products XLII–XLIV.<sup>78</sup> The predominant products were assigned structures XLII and XLIII. Dimerization of 1,1-dimethyl-3-bromoallene affords XLV and XLVI in a ratio of 5:2.<sup>79</sup> Inspection of models suggests that hindrance between the methyl groups would make unlikely direct formation of XLII or XLV by way of a four-center transition state with the participating carbon atoms lying in one plane. Conceivably, the central carbon atoms could first be joined with the chains at or near right angles to one another, and then ring closure to the various possible products could take place by a partial rotation around the new C single bond C bond. Other mechanisms have been discussed by Petty.<sup>79</sup>



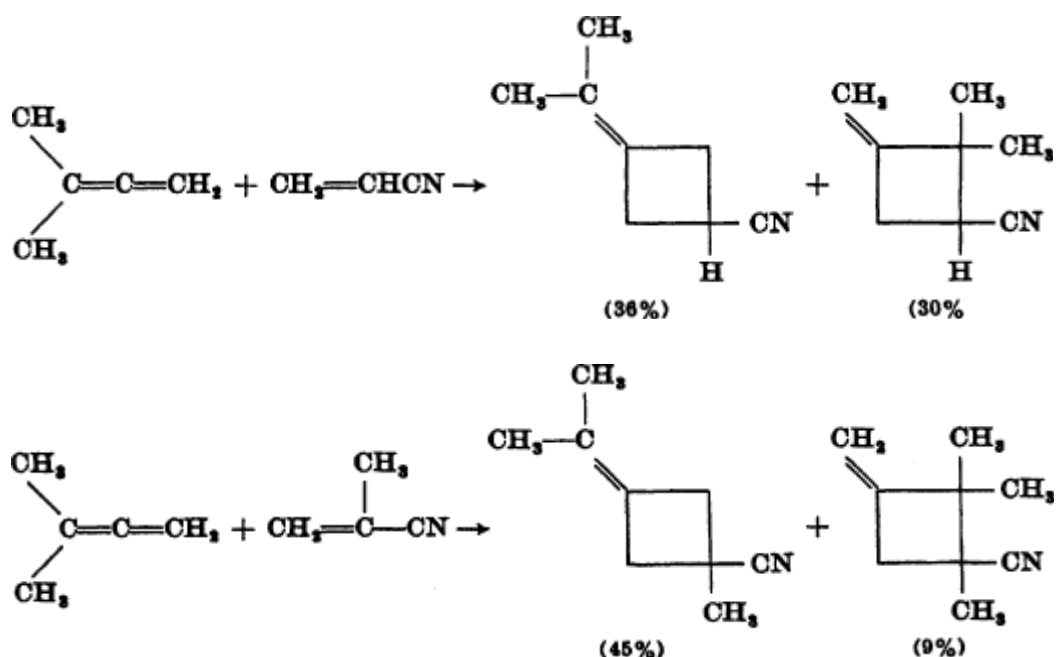


As mentioned earlier, the discovery that allene will undergo cycloaddition with a variety of activated alkenes is of considerable synthetic importance for the preparation of 1,3-disubstituted cyclobutanes.<sup>35, 37</sup> Generally there is concomitant formation of octahydronaphthalene derivatives from the allene dimer.<sup>35, 37, 80</sup> The reaction course with allene and acrylonitrile is typical.





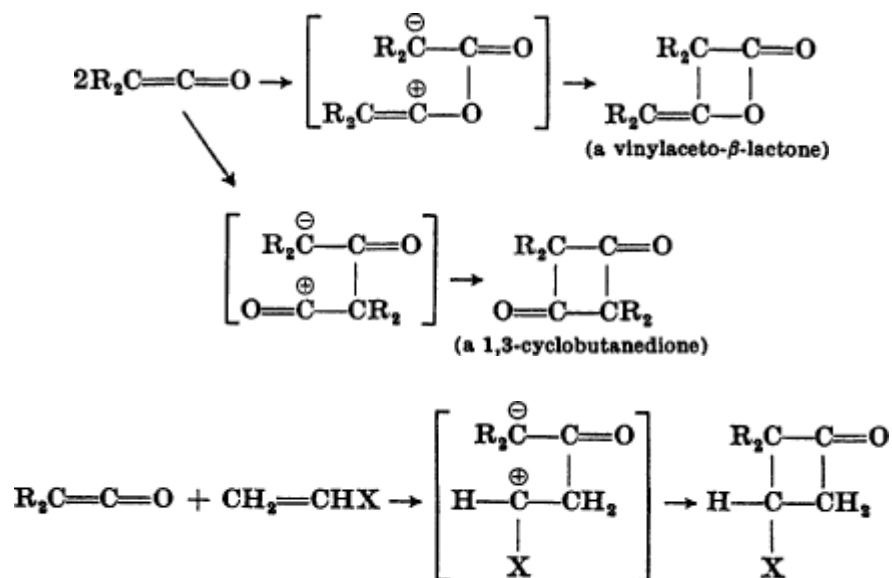
With unsymmetrical allenes and unsymmetrical alkenes, two different head-to-head cycloadducts can be formed. Although insufficient data are available for any final decision, it appears as though steric effects may be important in determining the product ratios. Thus comparison of the product ratios obtained with 1,1-dimethylallene and acrylonitrile<sup>37</sup> and methacrylonitrile<sup>37</sup> indicates a preference for formation of the product which has the smaller accumulation of adjacent methyl groups.



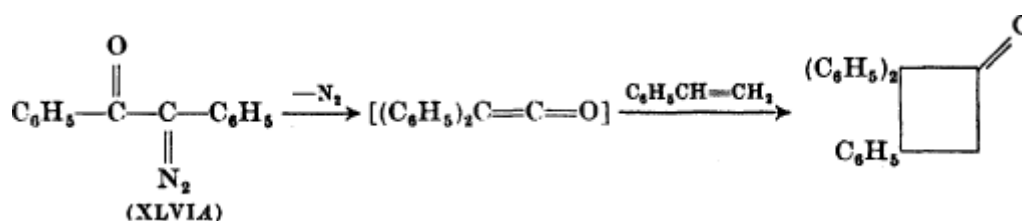
Addition of allene to acetylenes does not appear to work very satisfactorily. A yield of less than 1% of 1-phenyl-3-methylenecyclobutene was obtained from allene and phenylacetylene.<sup>81</sup>

### 3.1.3. Ketenes

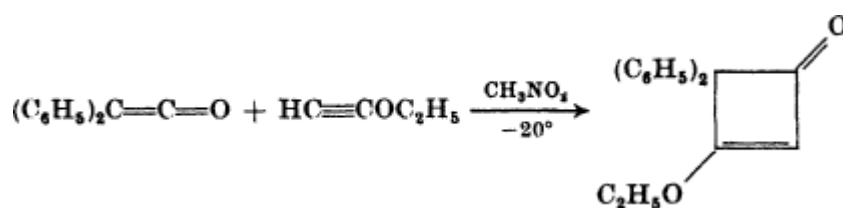
A number of cycloadditions of ketenes and alkenes to form cyclobutanes has been reported. In general, the products have the structures predicted by the diradical mechanism. This contrasts strongly with ketene dimerizations,<sup>2</sup> in which the reported products always have the head-to-tail structures regardless of whether a cyclobutanedione or a  $\beta$ -lactone is formed. The dimerizations can be reasonably formulated as having important contributions to their transition states of the indicated ionic structures. It is possible that the apparent conformity of the additions of ketenes to alkenes to predictions based on the diradical mechanism is illusory. The difficulty is that all the substituted alkenes so far employed (e.g., styrene, cyclopentadiene, vinyl ethyl ether) would be expected to give the same product by either the diradical mechanism or an ionic process wherein the alkene acts as a nucleophilic agent. Clearly, further research is needed to establish the mechanism of the ketene cycloadditions so that prediction of the orientations of the products to be expected can be put on a firmer basis.



Most of the reported ketene additions have been carried out with diphenylketene, and it appears that this substance gives better results than ketene itself. Azibenzil (XLVIA) can be used as a convenient source of diphenylketene. Thus, with styrene in dioxane, azibenzil gives a 58% yield of the cycloadduct.<sup>82</sup> Diphenylketene appears to give cycloadducts even with unactivated alkenes such as cyclopentene<sup>83</sup> and cyclohexene.<sup>83, 84</sup>



It adds also to ethoxyacetylene and similar substances in nitromethane at  $-20^\circ$  to afford interesting cyclobutenones.<sup>85, 86</sup>

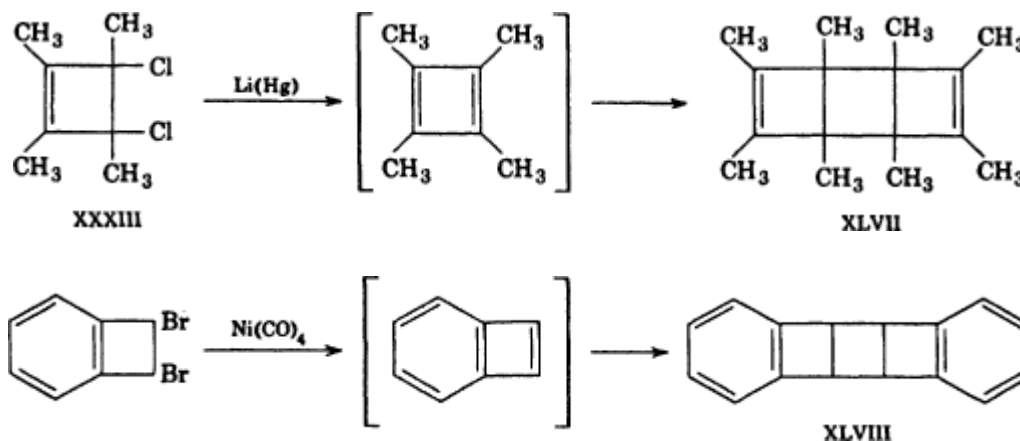


Ketene itself does not afford 3-phenylcyclobutenone when heated with phenylacetylene,<sup>87</sup> but it is now known<sup>88</sup> that the product is unstable under the reaction conditions.

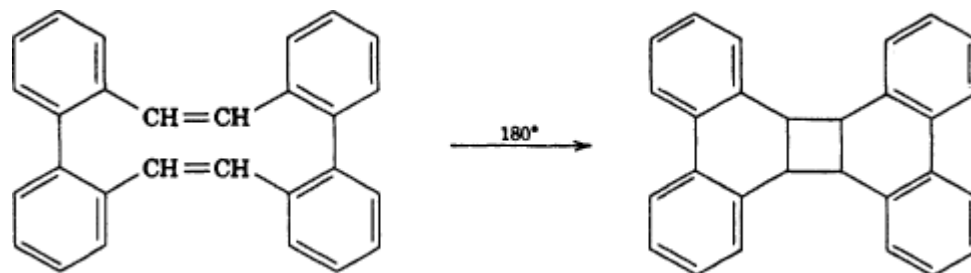
Dimethylketene appears to be less reactive than diphenylketene, and adducts have been reported only with vinyl ethyl ether and cyclopentadiene.<sup>89</sup>



intermediacy of cyclobutadiene derivatives.<sup>94, 95</sup> Thus Criegee<sup>94</sup> has demonstrated the formation of XLVII by treatment of the Smirnov-Zamkov<sup>56</sup> dichloride XXXIII with lithium amalgam, and Nenitzescu<sup>95</sup> has prepared XLVIII in a similar way. The generality of these reactions remains to be established.



An interesting internal thermal cycloaddition has been reported by Wittig, Koenig, and Claus.<sup>96</sup>



## 4. Experimental Conditions

### 4.1.1. Comparison of Addend Reactivities

The vast majority of successful cyclobutane-forming cycloadditions involve as one or both addends a fluorinated alkene, an allene, a ketene, or a similarly activated alkene.

For convenience, we shall call these “primary” addends. Primary addends can usually be added to one another and also undergo cycloaddition with a variety of substituted alkenes, alkynes, conjugated dienes, and enynes. The latter substances can be called “secondary” addends, and among them are many of the usual Diels-Alder dienes and dienophiles. In general, the ease of reaction of the secondary addends decreases in the order: conjugated dienes and enynes > unsymmetrically substituted alkenes > symmetrically substituted alkenes. Among the primary addends, the fluoroalkenes appear to react more readily than allenes. Although the number of reported ketene cycloadditions is too small to permit much generalization, ketenes seem to add to alkenes under milder conditions than those commonly used for adding fluoroalkenes to alkenes.

### 4.1.2. Reaction Conditions

Most cycloadditions are carried out at 100–225° under autogenous pressure of reactants in sealed glass tubes or steel autoclaves. Solvents are usually not beneficial but are sometimes recommended for safety reasons. It is common to use a polymerization inhibitor such as hydroquinone or terpene B,<sup>19</sup> but this is probably only of psychological value in the absence of important competing free-radical thermal polymerization reactions. As inhibitors do not appear to affect the cycloaddition reaction, inclusion of an inhibitor is unlikely to be positively harmful. Exclusion of oxygen may be generally desirable; but, except for a few instances where tetrafluoroethylene<sup>19</sup> and other monomers subject to oxygen-initiated polymerization have been employed, it does not seem to be customary practice to degas the reactants.

### 4.1.3. Safety Precautions

Low-molecular-weight fluorinated alkenes, ketenes, and allenes are usually gases at room temperature. Consequently it is desirable to use a well-ventilated area for handling the reactants—particularly because tetrafluoroethylene, trifluorochloroethylene, and ketene may present toxicity hazards comparable to or even greater than those of phosgene. Fluorinated alkenes and their cycloadducts should be handled with care, especially if there is a possibility of the presence (even in trace amounts) of certain olefins that contain fluorine linked to the doubly bonded carbon atoms. Fluorinated olefins generally should be regarded as highly toxic materials. Perfluoroisobutylene in particular is a deadly poison and exerts its effects in an insidious manner without warning. Perfluoroisobutylene is known to arise from thermal transformations of tetrafluoroethylene and polytetrafluoroethylene.

The usual precautions should be taken with reactions run in sealed glass tubes. After a reaction is complete, sealed tubes should be allowed to cool and should be vented before handling to remove hydrogen fluoride, hydrogen chloride, or other gases which often form in reactions involving fluoro- and fluorochloro-alkenes.

Steel or other metallic autoclaves are potentially more hazardous than glass tubes, and equipment capable of withstanding operating pressures of 500 atm. is necessary if tetrafluoroethylene is used.<sup>19</sup> The hazards of allene cycloadditions have been pointed out,<sup>36, 37</sup> and the use of an inert solvent as a diluent to diminish the possibility of violent decomposition is recommended.

Addition reactions with fluoroalkenes in metal vessels may also be hazardous. For example, the addition of trifluorochloroethylene to 1-cyclohexenylacetylene in a 1-1. stainless steel Parr bomb was carried out twice without difficulty, but in a third run the head gasket ruptured and the bomb was ruined by the reaction of the expanding hot gases with exposed stainless steel surface.<sup>69</sup>

## 5. Experimental Procedures

### 5.1.1. 1,1,2,2-Tetrafluoro-3,3,4,4-tetrachlorocyclobutane<sup>66</sup>

Four hundred grams of 1,1-difluorodichloroethylene was agitated at 200° for 12 hours in a stainless steel bomb. The unchanged monomer (75 g.) was recovered by distillation. The residue was taken up in ether and then distilled to give 313 g. of crystalline dimer: b.p. 131–132° and m.p. 84.8°. The conversion was 80%, and the yield 92%.

### 5.1.2. 1,1-Difluoro-2,2-dichloro-3-phenylcyclobutene<sup>26</sup>

A mixture of 18.4 g. (0.18 mole) of phenylacetylene, 24.0 g. (0.18 mole) of 1,1-difluoro-2,2-dichloroethylene, and 0.1 g. of hydroquinone was heated in a sealed glass tube at 130° for 2 hours. The crude product was flash-distilled under reduced pressure to remove some polymeric material and then fractionated through a 10-cm. Vigreux column. The yield of 1,1-difluoro-2,2-dichloro-3-phenylcyclobutene was 30.1 g. (71%), b.p. 109–111°/5 mm.,  $n_D^{25}$  1.5435.

### 5.1.3. 1,1,2-Trifluoro-2-chloro-3-(1-cyclohex-1-enyl)cyclobutene<sup>69</sup>

To each of four heavy-walled Pyrex tubes (19 × 25 × 615 mm.) was added 25.0 ml. (22.0 g., 0.208 mole) of 1-cyclohexenylacetylene. The tubes were cooled in a bath of isopropyl alcohol and solid carbon dioxide, and trifluorochloroethylene was passed in until 25 ml. (about 37 g., 0.32 mole) of liquid trifluorochloroethylene collected. The tubes were then sealed, allowed to warm to room temperature, and heated over a 4-hour period to 95°. After 20 hours at 95°, the tubes were cooled to room temperature and then to -78°, opened, and the excess trifluorochloroethylene allowed to escape as the material warmed to room temperature (hood). The crude adducts were combined and distilled through a Claisen head under reduced pressure to give 149 g. (79%) of 1,1,2-trifluoro-2-chloro-3-(1-cyclohex-1-enyl)cyclobutene, b.p. 71–73°/1 mm.,  $n_D^{25}$  1.4808. When cooled, the product crystallized as sharp white needles of m.p. 11–13°.

### 5.1.4. 3-Methylenecyclobutanecarbonitrile<sup>37</sup>

A 500-ml. stainless steel rocker bomb was charged with 212 g. (4 moles) of acrylonitrile, 40 g. (1 mole) of allene, and 2 g. of hydroquinone. The bomb was heated at 200° with agitation for 10.5 hours. The bomb was allowed to cool to room temperature, opened, and the contents distilled. After 120.4 g. of unreacted acrylonitrile, there was obtained 55.4 g. (60.4%) of 3-methylene-cyclobutanecarbonitrile, b.p. 64–65°/21 mm.,  $n_D^{25}$  1.4595. The distillation flask contained 32.5 g. of a tan solid residue, m.p. 138–143°. Several recrystallizations from acetone followed by one recrystallization from isopropyl alcohol gave white needles of 1,2,3,4,5,6,7,8-octahydronaphthalene-2,6-(and/or 2,7)-dicarbonitrile, m.p. 143.5–144.5°.

It may be generally advisable to run reactions of this type with an inert solvent as diluent even though the yields may be somewhat lower.<sup>36, 37</sup>

### 5.1.5. Bicyclo-[3.2.0]-2-hepten-6-one<sup>97</sup>

Approximately 0.65 mole of ketene was absorbed in a mixture of 50 ml. of toluene and 0.65–0.70 mole of freshly distilled cyclopentadiene contained in a bomb cooled by a solid carbon dioxide-isopropyl alcohol mixture. The sealed bomb was heated at 100° for 2 hours\* and then cooled to room temperature. The reaction mixtures from three such runs were combined, and on distillation (in a hood) 105 g. of crude ketone, b.p. 145–185°, was obtained. The impure ketone was purified through its semicarbazone. From 105 g. of crude ketone there was obtained 56 g. (17.4% based on ketene) of semicarbazone, m.p. 216.0–219.5°. After two recrystallizations from methanol-water (3:1), it melted at 219.0–220°.

The pure ketone, b.p. 62.0–63.5°/20 mm.,  $n_D^{20}$  1.4819, could be obtained in 85% yield by decomposition of the semicarbazone with phthalic anhydride and water.

### 5.1.6. 2,2,3-Triphenylcyclobutanone<sup>84</sup>

Equimolar portions of diphenylketene (8.0 g.) and styrene (4.5 g.) were heated in a sealed tube for 24 hours at 60°. The crude solid addition product crystallized as white needles from ethanol, m.p. 135–136°. The yield was 11.5 g. (93%).

## 6. Tabular Survey

Tables I through IV include cycloaddition reactions classified according to primary addend and reported to June, 1959.<sup>98</sup> An “early-position” principle was used in arranging the tables. Thus, since cycloadditions of fluoroalkenes are discussed before those of allene, the reaction of tetrafluoroethylene with allene is listed with the fluoroalkene adducts. The arrangement of compounds within any given table follows that of Beilstein. Familiarity with arrangement of the Beilstein volumes and the difference between “functioning” and “non-functioning” derivatives will permit any compound to be found quickly. The arrangement has the advantages of being specific and usually leading to close listings for similar compounds.

Table I. Cyclobutanes from Thermal Cycloaddition Reactions of Fluoro- and Fluorochloro-Alkenes

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[View PDF](#)

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Table II. Cyclobutanes from Thermal Cycloaddition Reactions of Allenes

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[View PDF](#)

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Table III. Cyclobutanes from Thermal Cycloaddition Reactions of Ketenes

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[View PDF](#)

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Table IV. Cyclobutanes from Thermal Cycloaddition Reactions of Activated Alkenes

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### End Notes

\*  
This paragraph and the following paragraph are based on a survey kindly provided by Dr. Edwin R. Buchman.

\*  
It is erroneously reported<sup>23</sup> that the symmetry numbers of the products should lead to predominance of cis over trans addition in the ratio of 2 : 1. This would be correct only if one optical antipode of the trans-dichloro compound were formed. The actual expected statistical ratio is 1 : 1.

\*  
It is recommended that reactions of this type be carried out behind a suitable barricade.



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*Actually, these workers only noted that the formation of dimeric 1,5-cycloöctadiene had a parallel in the dimerization of cyclopentadiene, and they referred to the paper by Kraemer and Spilker,<sup>[5]</sup> where a cyclobutane structure is suggested for dicyclopentadiene. The cyclobutane structure for dimeric 1,5-cycloöctadiene was not definitely proposed until much later by Ziegler, Sauer, Bruns, Froitzeim-Kühlhorn, and Schneider, *Ann.*, **589**, 122 (1954).*
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## References for Tables [I-IV](#)

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TABLE I

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Tetrafluoroethylene</i>						
Ethylene	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CH}_2$ (40)	0.13	None	200	7.5	19, 99
Tetrafluoroethylene	$\text{CF}_2\text{CF}_2\text{CF}_2\text{CF}_2$ (—)	—	None	200	13	64
Vinyl chloride	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCl}$ (23) (11)	0.24 1.0	None Gas	150 498–526	8 Flow system	19, 99 99
Trifluorochloroethylene	$\text{CF}_2\text{CF}_2\text{CF}_2\text{CFCl}$ (46)	0.84	None	150	13	100
1,1-Dichloroethylene	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CCl}_2$ (46)	0.39	None	150	8–12	19, 99
Trichloroethylene	$\text{CF}_2\text{CF}_2\text{CCl}_2\text{CHCl}$ (18)	0.79	None	225	8	19
Propylene	$\text{CH}_3\text{CHCF}_2\text{CF}_2\text{CH}_2$ (72)	0.17	None	225	9	19, 99
Allyl chloride	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCH}_2\text{Cl}$ (42)	0.30	None	150	8, 9.5	19, 99
2-Butene	$\text{CH}_3\text{CHCF}_2\text{CF}_2\text{CHCH}_3$ (5)	0.22	None	175	7.75	19, 99
Isobutylene	$(\text{CH}_3)_2\text{CCF}_2\text{CF}_2\text{CH}_2$ (30)	0.22	None	225	8.25	19, 99
Methallyl chloride	$\text{CF}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{Cl}$ (45)	0.34	None	150	8, 6.3	19, 99
$\text{CH}_3(\text{CH}_2)_n\text{CH}=\text{CH}_2$ ( $n = 11-19$ )	$\text{CH}_3(\text{CH}_2)_n\text{CHCF}_2\text{CF}_2\text{CH}_2$ (—) ( $n = 11-19$ )	~1.0	None	200–315	8	101
1-Tetradecene	$\text{CH}_3(\text{CH}_2)_{11}\text{CHCF}_2\text{CF}_2\text{CH}_2$ (35)	—	None	—	—	101
1-Octadecene	$\text{CH}_3(\text{CH}_2)_{15}\text{CHCF}_2\text{CF}_2\text{CH}_2$ (25)	—	None	283–305	8	101
Acetylene	$\text{CF}_2=\text{CH}-\text{CH}=\text{CF}_2$ (—)	—	None	600	4	62
Allene	$\text{CH}_2=\text{CCF}_2\text{CF}_2\text{CH}_2$ (14) (17)	1.00 1.00	None None	150 150	8 14	19 98
1,3-Butadiene	$\text{CH}_2=\text{CHCHCF}_2\text{CF}_2\text{CH}_2$ (90) (—)	0.43 —	None None	100–125 100	8 12	19 98, 99
2-Fluoro-1,3-butadiene	$\text{CH}_2=\text{CHCF}_2\text{CF}_2\text{CH}_2$ (35) $\text{CH}_2=\text{CFCHCF}_2\text{CF}_2\text{CH}_2$ (35)	0.56	None	100–125	8	19
2-Chloro-1,3-butadiene	$\text{CH}_2=\text{CHCClCF}_2\text{CF}_2\text{CH}_2$ (51) $\text{CH}_2=\text{CClCHCF}_2\text{CF}_2\text{CH}_2$ (10)	1.00	None	100	9.75	19, 98, 99
1,3-Pentadiene	$\text{CH}_3\text{CH}=\text{CHCHCF}_2\text{CF}_2\text{CH}_2$ (68) (—)	1.00 —	None —	100–125 100	8 9	19 99
2-Methyl-1,3-butadiene	$\text{CH}_2=\text{CHC}(\text{CH}_3)\text{CF}_2\text{CF}_2\text{CH}_2$ (83) (—)	1.00 —	None —	100–125 125	8 11.25	19 98, 99
Vinylacetylene	$\text{HC}\equiv\text{CCHCF}_2\text{CF}_2\text{CH}_2$ (35) $\text{CH}_2=\text{CH}-\text{C}=\text{CHCF}_2\text{CF}_2$ (35) $\text{CH}_2\text{CF}_2\text{CF}_2\text{CHC}=\text{CHCF}_2\text{CF}_2$ (3.5) $\text{C}_6\text{H}_5\text{CHCF}_2\text{CF}_2\text{CH}_2$ (3.5)	1.04	None	100	16	19, 98, 99

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE I—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES						
Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Tetrafluoroethylene (Continued)</i>						
Methyl vinyl ether	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHOCH}_3$ (13)	0.23	None	150	8-9.5	19, 99
Allyl alcohol	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCH}_2\text{OH}$ (45)	0.23	None	150	8	19
Dimethylallyl ether	$\text{CF}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{CH}_3)=\text{CH}_2$ (20)	0.42	None	100-125	8	19, 99
Acrolein	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCHO}$ (12)	0.22	None	150	8	19, 99
Methacrolein	$\text{CF}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CHO}$ (50)	0.28	None	150	8	19, 99
Methyl vinyl ketone	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCOCH}_3$ (18)	0.28	None	150	8	19, 99
Vinyl acetate	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHOCOCH}_3$ (27)	0.34	None	150	8-13	19, 99
Acrylonitrile	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCN}$ (84)	0.39	None	150	8	19, 99, 102
	(58)	0.50	None	125	17	103
Methyl $\alpha$ -chloroacrylate	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CClCO}_2\text{CH}_3$ (21)	0.90	None	150	8	19
Vinylacetonitrile	$\text{CF}_2\text{CF}_2\text{CH}_2\text{CHCH}_2\text{CN}$ (15)	0.27	None	150	8	19, 99
	(—)	—	None	125	17	103
Methyl methacrylate	$\text{CF}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CO}_2\text{CH}_3$ (84)	0.80	None	150	8-12	19, 99
Methacrylonitrile	$\text{CF}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CN}$ (—)	—	None	125	17	103

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$\begin{array}{c} \text{CH}_2\text{CF}_2\text{CF}_2\text{CH} \\   \\ (\text{CH}_2)_n \\   \\ \text{CH}_2=\text{CH} \\ (n = 10-18) \end{array}$	$\begin{array}{c} \text{CH}_2\text{CF}_2\text{CF}_2\text{CH} \\   \\ (\text{CH}_2)_n \text{ (—)} \\   \\ \text{CH}_2\text{CF}_2\text{CF}_2\text{CH} \\ (n = 10-18) \end{array}$	—	None	210-310	—	104	
Camphene	$\begin{array}{c} \text{CH}_2 \quad \text{CH}_2 \\   \quad   \\ \text{CH} - \text{CH}_2 - \text{CH} \\   \quad   \\ (\text{CH}_2)_2\text{C} \quad \text{CCF}_2\text{CF}_2\text{CH}_2 \end{array}$	(7)	1.00	None	150	8	19
Cyclopentadiene (see Dicyclopentadiene)							
1,3-Cyclohexadiene	$\text{CH}=\text{CHCH}_2\text{CH}_2\text{CHCHCF}_2\text{CF}_2$ (50)	2.00	None	100-125	8	19	
Dicyclopentadiene	$\text{CH}_2\text{CH}=\text{CHCHCHCF}_2\text{CF}_2$ (23)	2.00	None	190	8	19	
	$\text{C}_2\text{F}_2 \cdot \text{C}_{10}\text{H}_{12}$ (9)						
	$\text{CH}_2\text{CH}=\text{CHCHCHCF}_2\text{CF}_2$ (47)	2.00	Gas	470-480	Flow system	32	
	$\begin{array}{c} \text{CH} \\ / \quad \backslash \\ \text{CH} \quad \text{CF}_2 \\   \quad   \\ \text{CH} \quad \text{CH}_2 \quad \text{CF}_2 \\   \quad   \\ \text{CH} \quad \text{CF}_2 \end{array}$	(23)					

CYCLOBUTANES BY THERMAL CYCLOADDITION REACTIONS 37

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 0.

TABLE I—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES						
Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Tetrafluoroethylene (Continued)</i>						
Styrene	$C_6H_5CHCF_2CF_2CH_2$ (85)	0.42	None	175	13	19, 99
Phenylacetylene	$C_6H_5C=CHCF_2CF_2$ (—)	—	None	—	—	105
3,4-Epoxy-1-butene	$CF_2CF_2CH_2CHCH_2O$ (9)	1.32	None	135	10	19
2-Vinylfuran	$CF_2CF_2CH_2CHC=CHCH=CHO$ (77)	0.38	None	150	8	19, 99
Safrole	$CH_2O_2C_6H_3CH_2CHCF_2CF_2CH_2$ (18)	1.03	None	150	8	19
<i>Trifluorochloroethylene</i>						
Trifluorochloroethylene	$CF_2CFCICFCF_2$ (64) ( <i>cis and trans</i> )	—	None	200	11	64, 65
	(80)	—	None	200	8	66
	(—)	—	None	200	5-6	106
	(59)	—	None	220	12	107
	(<20)	—	Gas	680-760	Flow system	107
	(11)	—	Gas	550	Flow system	108
1,1-Difluoro-2,2-dichloroethylene	$CClFCF_2CF_2CCl_2$ (32)	1.13	None	200	18.5	67, 68
Isopropenylacetylene	$HC\equiv C(CH_3)CH_2CF_2CFCl$ (25) $H_2C=C(CH_3)C=CHCF_2CFCl$ (18) $CH_2CF_2CFClC(CH_3)C=CHCF_2CFCl$ (?) (4)	2.0	None	95	24	09
Ethyl acrylate	$CFCICF_2CH_2CHCO_2C_2H_5$ (56)	>1	None	180	24	109
Acrylonitrile	$CFCICF_2CH_2CHCN$ (—)	—	None	150	8	102
Ethyl propiolate	$CFCICF_2CH=CCO_2C_2H_5$ (29)	>1	None	180	24	109
1-Cyclohexenylacetylene	$C_6H_9C=CHCF_2CFCl$ (70-90)	1.01	None	95	24	69
Styrene	$C_6H_5CHCH_2CF_2CFCl$ (71)	1.14	None	120	23	27
Phenylacetylene	$C_6H_5C=CHCF_2CFCl$ (70)	1.01	None	120	24	29, 105
<i>1,1-Difluoro-2,2-dichloroethylene</i>						
1,1-Difluoro-2,2-dichloroethylene	$CF_2CCl_2CCl_2CF_2$ (—)	—	None	—	—	64
	(80-85)	—	None	200	12	66
	(90)	—	None	200	5-6	106
3,3,3-Trichloropropene	$CCl_2CF_2CH_2CHCCl_3$ (18)	1.03	None	131-135	19	70

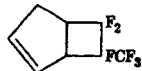
Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE I—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES						
Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>1,1-Difluoro-2,2-dichloroethylene (Continued)</i>						
2-Chlorobutadiene	$\left\{ \begin{array}{l} \text{CCl}_2\text{CF}_2\text{CH}_2\text{CClCH}=\text{CH}_2 \text{ § (90)} \\ + \\ \text{CCl}_2\text{CF}_2\text{CH}_2\text{CHC}(\text{Cl})=\text{CH}_2 \text{ (?) } \end{array} \right\}$	1.17	None	97-112	5.5	70
2,3-Dimethyl-1,3-butadiene	$\text{CCl}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{C}(\text{CH}_3)=\text{CH}_2 \text{ § (68)}$	1.00	None	96-115	5.5	70
2-Methyl-1-penten-3-yne	$\left\{ \begin{array}{l} \text{CCl}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{C}\equiv\text{CCH}_3 \text{ (63)} \\ \text{CCl}_2\text{CF}_2\text{CH}=\text{CC}(\text{CH}_3)=\text{CH}_2 \text{ § (?) } \end{array} \right\}$	0.92	None	140	70	110
Methyl acrylate	$\text{CCl}_2\text{CF}_2\text{CH}_2\text{CHCO}_2\text{CH}_3 \text{ § (48)}$	1.01	None	130 then 176	19 29	70
Acrylonitrile	$\text{CCl}_2\text{CF}_2\text{CH}_2\text{CHCN}$ (49)	0.98	None	133-139	20	70
Methyl methacrylate	$\text{CCl}_2\text{CF}_2\text{CH}_2\text{C}(\text{CH}_3)\text{CO}_2\text{CH}_3 \text{ § (74)}$	0.7	None	130-139	20.4	70
Styrene	$\text{C}_6\text{H}_5\text{CHCH}_2\text{CF}_2\text{CCl}_2$ (58)	1.01	None	130	3	27
Phenylacetylene	$\left\{ \begin{array}{l} \text{C}_6\text{H}_5\text{C}=\text{CHCF}_2\text{CCl}_2 \text{ (71)} \\ \text{(58)} \end{array} \right\}$	1.00 0.88	None None	130 95	2 48	26 110
<i>Perfluoropropylene</i>						
Perfluoropropylene	$\left\{ \begin{array}{l} \text{CF}_3\text{CFCF}_2\text{CF}_2\text{CFCF}_3 \text{ (98-100)} \\ + \\ \text{CF}_3\text{CFCF}_2\text{CF}(\text{CF}_3)\text{CF}_2 \text{ (96)} \end{array} \right\}$	—	None	250-450	19-24	49
1,3-Butadiene	$\left\{ \begin{array}{l} \text{CF}_2-\text{CFCF}_2 \text{ §   } \\   \\ \text{CH}_2-\text{CHCH}=\text{CH}_2 \end{array} \right\}$ (64)	1.1	None	180	24	60
Cyclopentadiene	 §    (60-69)	1.0-1.25	None	135-190	24-60	60
<i>Perfluoro-1,3-butadiene</i>						
Perfluoro-1,3-butadiene	$\left\{ \begin{array}{l} \text{CF}_3=\text{CFCF}_2\text{CF}_2\text{CFCF}=\text{CF}_2 \text{ (—)} \\ \text{CF}_2-\text{CF}-\text{CF}-\text{CF}_2 \\   \quad   \quad   \quad   \\ \text{CF}_2-\text{CF}-\text{CF}-\text{CF}_2 \end{array} \right\}$ (60)	—	None Gas	150 500	44 Flow system	71, 111 71, 111
<i>Perfluoro-1,5-hexadiene</i>						
Perfluoro-1,5-hexadiene	$\left\{ \begin{array}{l} \text{CF}_2-\text{CF}-\text{CF}_2 \\   \quad   \quad   \\ \text{CF}_2-\text{CF}-\text{CF}_2 \end{array} \right\}$ (70)	—	None	450	Flow system	72

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

§ This structure is based on mechanistic considerations and any available chemical evidence.

|| A different structure was assigned by the original investigators.



TABLE I—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES						
Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Perfluoroacrylonitrile</i>						
1,3-Butadiene	$\begin{array}{c} \text{CF}_2-\text{CFCN} \\   \quad   \\ \text{CH}_2-\text{CHCH}=\text{CH}_2 \end{array} \quad (88)$	0.75	None	40–50	8	112
Perfluoroacrylonitrile	$\text{NCCFCF}_2\text{CF}_2\text{CFCN}$ (100)	—	None	230	72	112
<i><math>\alpha,\beta</math>-Trifluorostyrene</i>						
$\alpha,\beta$ -Trifluorostyrene	$\text{C}_6\text{H}_5\text{CFCF}_2\text{CF}_2\text{CFC}_6\text{H}_5$ (15)	—	—	—	—	113

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE II

## CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ALLENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Allene</i>						
Allene	$\text{CH}_2=\text{CC}(\text{=CH}_2)\text{CH}_2\text{CH}_2$ (50) (5) (43)	— — —	Gas None None	500–510 140–150 400	4–6 sec. 82 Flow system	114 9 24
Methacrolein	$\text{CH}_2=\text{CCH}_2\text{C}(\text{=CH}_2)\text{CH}_2$ (7) $\text{CH}_2=\text{CCH}_2\text{C}(\text{CH}_3)(\text{CHO})\text{CH}_2$ (6.7)	0.5	Benzene	200	8	35, 37
Acrylic acid	$\text{CH}_2=\text{CCH}_2\text{CH}(\text{CO}_2\text{H})\text{CH}_2$ (21)	0.5	None	200	6	35, 37
Methyl acrylate	$\text{CH}_2=\text{CCH}_2\text{CH}(\text{CO}_2\text{CH}_3)\text{CH}_2$ (25)	0.25	None	200	13	35, 37
Acrylonitrile	$\text{CH}_2=\text{CCH}_2\text{CH}(\text{CN})\text{CH}_2$ (60) (57)	0.25 0.63	None Toluene	200 260–270	10.5 4	35, 37 36
Methyl methacrylate	$\text{CH}_2=\text{CCH}_2\text{C}(\text{CH}_3)(\text{CO}_2\text{CH}_3)\text{CH}_2$ (25)	0.5	None	200	8	35, 37
Methacrylonitrile	$\text{CH}_2=\text{CCH}_2\text{C}(\text{CH}_3)(\text{CN})\text{CH}_2$ (62)	0.17	None	225	12	35, 37

Note: References 99 to 127 are on p. 56.

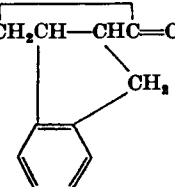
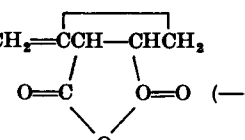
\* The yield is based on the addend used in smaller molal amount.

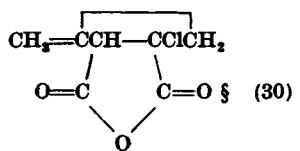
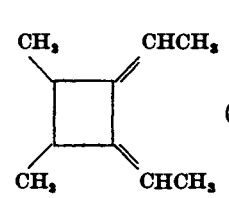
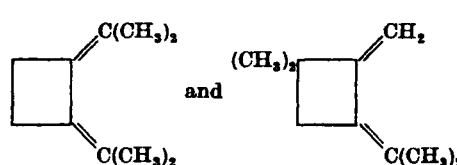
† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE II—Continued

## CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ALLENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Allene (Continued)</i>						
$\alpha$ -Acetoxyacrylonitrile	$\text{CH}_2=\text{CCH}_2\text{C}(\text{CN})(\text{OCOCH}_3)\text{CH}_2$ (20)	0.5	Benzene	200	6	35, 37
Diethyl fumarate	$\text{CH}_2=\text{CCH}(\text{CO}_2\text{C}_2\text{H}_5)\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)\text{CH}_2$ (11)	0.5	None	200	8	35, 37
Diethyl itaconate	$\text{CH}_2=\text{CCH}_2\text{C}(\text{CO}_2\text{C}_2\text{H}_5)(\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5)\text{CH}_2$ (32)	0.38	None	225	8	35, 37
Styrene	$\text{CH}_2=\text{CCH}_2\text{CH}(\text{C}_6\text{H}_5)\text{CH}_2$ (22)	1	Benzene	200	4	35, 37
$\alpha$ -Methylstyrene	$\text{CH}_2=\text{CCH}_2\text{C}(\text{CH}_3)(\text{C}_6\text{H}_5)\text{CH}_2$ (20)	0.67	None	190	4	35, 37
Phenylacetylene	$\text{CH}_2=\text{CCH}=\text{C}(\text{C}_6\text{H}_5)\text{CH}_2$ (<1)	1.2	None	150	24	81
Indene	$\text{CH}_2\text{CH}(\text{C}_6\text{H}_5)\text{CHC}=\text{CH}_2$ (28) 	0.33	None	200	8	35, 37
Maleic anhydride	$\text{CH}_2=\text{CCH}(\text{C}_6\text{H}_5)\text{CHCH}_2$  (—)	0.50	Benzene	200	8	35, 37

Chloromaleic anhydride		0.33	Benzene	200	5	35, 37
4-Vinylpyridine	$\text{CH}_2=\text{CCH}_2\text{CH}(\text{C}_5\text{H}_4\text{N})\text{CH}_2$ (23)	1.0	Benzene	200	8	35
1,3-Dimethylallene		(—)	None	150	—	115
1,1-Dimethylallene		(—)	None	130	—	78

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

§ This structure is based on mechanistic considerations; a less likely alternative is

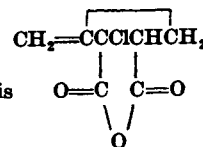
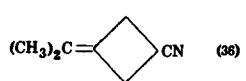
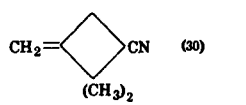
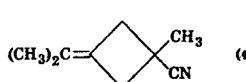
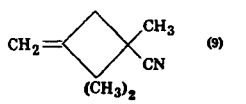
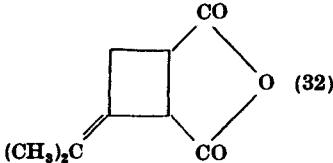
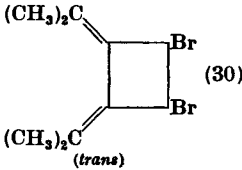
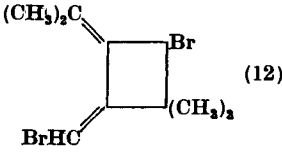
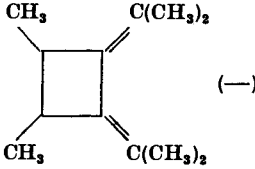
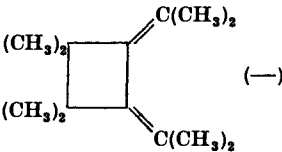


TABLE II—Continued

Addends	Product (Yield, %)*	CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ALLENES				
		Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
1,1-Dimethylallene (Continued)						
Acrylonitrile		0.3	None	200	8	35
						
Methacrylonitrile		0.33	None	200	8	35
						
Maleic anhydride		0.22	None	200	8	35

## 1,1-Dimethyl-3-bromoallene

1,1-Dimethyl-3-bromoallene	 <p>(30)</p>	—	None	60-80	—	79
	 <p>(12)</p>					
Trimethylallene	Mixture containing	—	None	150	—	115
	 <p>(—)</p>					
Tetramethylallene						
Tetramethylallene	 <p>(—)</p>	—	None	150	Various	116

Note: References 99 to 127 are on p. 56.


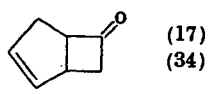
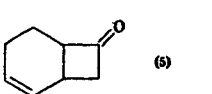
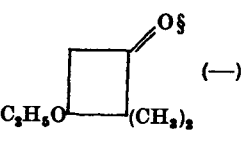
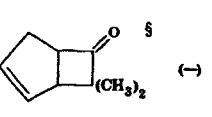
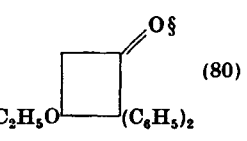
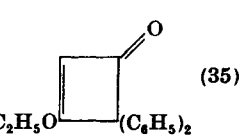
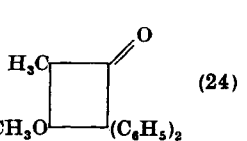
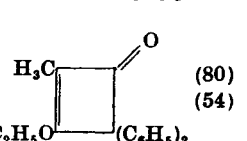
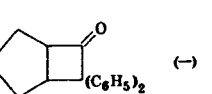
\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE III

## CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF KETENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Ketene</i>						
1,3-Butadiene	 (~1)	0.25	None	100	2	35
Cyclopentadiene	 (17) (34)	1.0	Toluene	100	2	97
		0.8	Toluene	100	1	117
1,3-Cyclohexadiene	 (6)	1.2	Toluene	100	4	97
<i>Dimethylketene</i>						
Ethyl vinyl ether	 (—)	1.0	None	-20	72-96	89
Cyclopentadiene	 (—)	0.63	None	-20	12	89
<i>Diphenylketene</i>						
Vinyl ethyl ether	 (80)	0.91	None	60	24	84
Ethoxyacetylene	 (35)	0.73	CH3NO2	-20	170	86
1-Methoxypropyne	 (24)	0.73	Benzene	60	3.5	86
1-Ethoxypropyne	 (80) (54)	—	Benzene	-20	—	86
		—	CH3NO2	-20	—	86
Cyclopentene	 (—)	—	—	—	—	118

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

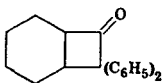
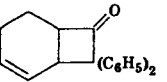
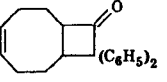
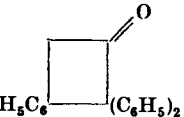
‡ Autogenous pressure is to be understood.

§ This structure is based on mechanistic considerations and any available chemical evidence.

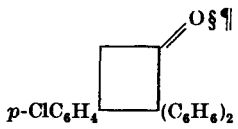
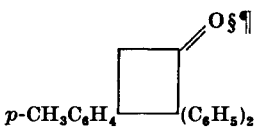
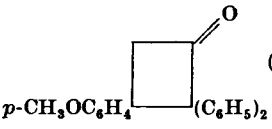
TABLE III—Continued

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## CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF KETENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Diphenylketene (Continued)</i>						
Cyclohexene	 (80)	1.0	None	100	240	83, 84
Cyclopentadiene	(89)	0.33	Pet. ether	Room	48	84,119,120
	(92)	0.33	Pet. ether	Room	24	121
	(82)	0.94	Pet. ether	Room	48	15
	(85)	—	—	—	—	83
1,3-Cyclohexadiene	 (—)	1.0	None	Room	12	83
1,5-Cyclooctadiene	 (80)	1.20	None	60	2	6
Styrene	 (93) (0-58)	1.0	None	60	24	84,120,122
		1.0	Dioxane	Reflux	1-96	82

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<i>p</i> -Chlorostyrene	 (82)	1.0	None	60	24	84
<i>p</i> -Methylstyrene	 (81)	1.0	None	60	24	84
Phenylacetylene	(—)	—	—	—	—	121
<i>p</i> -Methoxystyrene	 (84)	1.0	None	60	24	84

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood.

§ This structure is based on mechanistic considerations and any available chemical evidence.

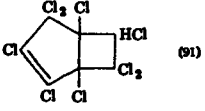
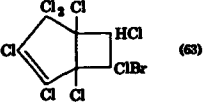
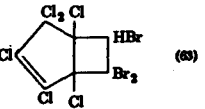
|| Azibenzil was used as a source of diphenylketene (see p. 26).

¶ A different structure was assigned by the original investigators.

CYCLOBUTANES BY THERMAL CYCLOADDITION REACTIONS 51

TABLE IV

## CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ACTIVATED ALKENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Trichloroethylene</i>						
Hexachlorocyclopentadiene	 (91)	1.0	None, AlCl <sub>3</sub> present	80	2	54, 55
<i>1,2-Dichlorobromoethylene</i>						
Hexachlorocyclopentadiene	 (63)	1.0	None, AlCl <sub>3</sub> present	75-78	2	54
<i>Tribromoethylene</i>						
Hexachlorocyclopentadiene	 (63)	1.0	None, AlCl <sub>3</sub> present	20-80	2	54
<i>1,3-Butadiene</i>						
1,3-Butadiene	$\text{CH}_2=\text{CHCH}(\text{CH}_2\text{CH}_2)\text{CH}=\text{CH}_2$ (4-5) ( <i>trans</i> )	—	None	150	18	45
<i>Vinylacetylene</i>						
Vinylacetylene	$\text{HC}\equiv\text{CCH}(\text{CH}_2\text{CH}_2)\text{C}\equiv\text{CH}$ (<1)	—	None	105	6	123
<i>Divinylacetylene</i>						
Divinylacetylene	$\begin{array}{c} \text{CH}_2-\text{CHC}\equiv\text{CCH}=\text{CH}_2 \\   \quad   \\ \text{CH}_2-\text{CHC}\equiv\text{CCH}=\text{CH}_2 \end{array}$ (<1)	—	None	81-82	5	14
<i>Ketene diethyl acetal</i>						
Benzalacetophenone	$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}-\text{CHCOC}_6\text{H}_5 \\   \quad   \\ \text{CH}_2-\text{C}(\text{OC}_2\text{H}_5)_2 \end{array}$ (?) (76)	1.6	None	Reflux	12	90
Dibenzalacetone	$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}-\text{CHCOCH}=\text{CHC}_6\text{H}_5 \\   \quad   \\ \text{CH}_2-\text{C}(\text{OC}_2\text{H}_5)_2 \end{array}$ (?) (87)	1.4	None	Reflux	12	90
<i>Acrylonitrile</i>						
Acrylonitrile	$\text{NCCH}(\text{CH}_2\text{CH}_2)\text{CHCN}$ (3-7) ( <i>cis</i> and <i>trans</i> )	—	None	195-300	1-24	25
<i>Methacrylonitrile</i>						
Methacrylonitrile	$\text{CH}_2\text{C}(\text{CN})(\text{CH}_2\text{CH}_2)\text{C}(\text{CN})\text{CH}_3$	—	<i>n</i> -Butyl acetate	240	40	128
<i>α-Methylmercaptoacrylonitrile</i>						
α-Methylmercaptoacrylonitrile	$\text{CH}_2\text{SC}(\text{CH}_3)(\text{CH}_2\text{CH}_2)\text{C}(\text{CN})\text{SCH}_3$ (65) ( <i>cis</i> )	—	None	Room	48	48

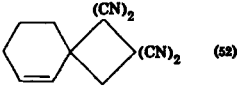
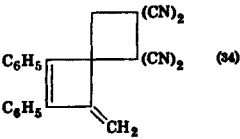
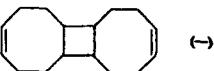
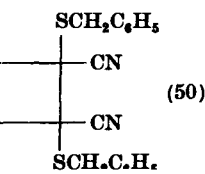
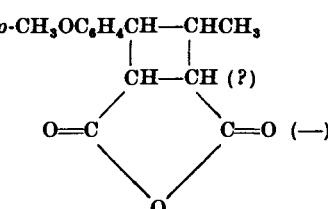
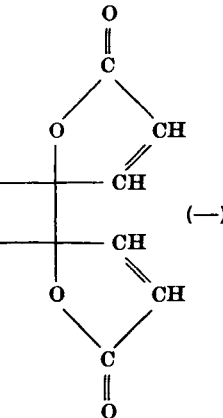
Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood.

TABLE IV—Continued

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
<i>Tetracyanoethylene</i>						
3-Methylenecyclohexene	 (52)	1.4	Benzene	Room	12	92
1,2-Dimethylene-3,4-diphenylcyclobutene	 (54)	1.8	Benzene	Room	12	92
<i>1,5-Cyclooctadiene</i>						
1,5-Cyclooctadiene	 (—)	—	None	Room	190	6
<i>Styrene</i>						
Styrene	$C_6H_5CHCH_2CH_2CH_2CH_2C_6H_5$ (<5)	—	None, I <sub>2</sub> added	150	24	91
1,1-Diphenylethylene						
1,1-Diphenylethylene	$(C_6H_5)_2CCH_2CH_2C(C_6H_5)_2$ (?) (2-4)	—	(CH <sub>3</sub> O) <sub>2</sub> SO <sub>2</sub>	50-55	2-5	93
<i>α-Benzylmercaptoacrylonitrile</i>						
α-Benzylmercaptoacrylonitrile	 (50)	—	None	Room	380	48, 124
<i>Anethole</i>						
Maleic anhydride	 (—)	—	—	—	—	125
<i>Protoanemonin</i>						
Protoanemonin	 (—)	—	None	Room	—	126, 127

Note: References 99 to 127 are on p. 56.

\* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood.



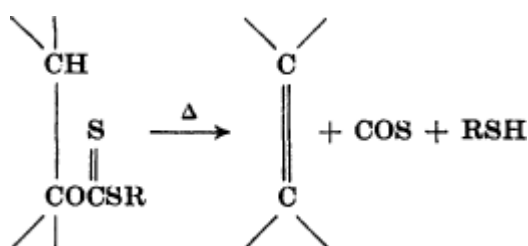
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# The Preparation of Olefins by the Pyrolysis of Xanthates. The Chugaev Reaction

## 1. Introduction

In this chapter the Chugaev reaction is defined as the thermal decomposition of the xanthate ester of an alcohol that contains at least one  $\beta$ -hydrogen atom, to produce one or more olefins, carbon oxysulfide, and a mercaptan.



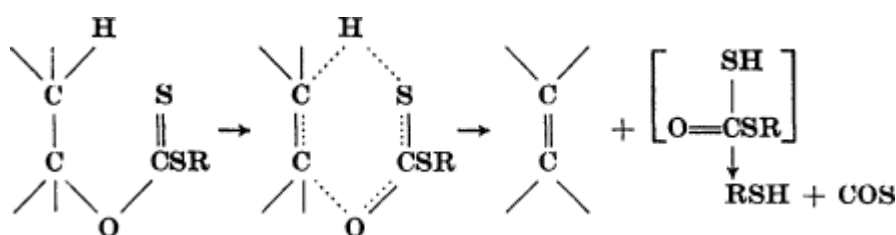
The formation of olefins by the pyrolysis of xanthates was discovered in 1899 by Chugaev<sup>1</sup> in connection with his studies on the optical properties of xanthates<sup>2</sup> and other compounds.<sup>3</sup> He subsequently employed the reaction in his investigations of terpenes and demonstrated both its utility as an olefin-forming reaction and its usefulness in structural determinations.

The reaction, which is particularly valuable for the conversion of sensitive alcohols to the corresponding olefins without rearrangement of the carbon skeleton,<sup>4, 5</sup> is analogous to the thermal decomposition of carboxylic esters of alcohols,<sup>6</sup> and of other related derivatives of alcohols, such as carbamates and carbonates,<sup>7</sup> to yield olefins.

## 2. Mechanism<sup>8</sup>

Considerable evidence indicates that the Chugaev reaction proceeds by the formation of a cyclic transition state involving a *cis*- $\beta$ -hydrogen atom of the alcohol moiety and the thion sulfur atom of the xanthate.

Subsequent decomposition, with simultaneous further bond making and breaking, gives the olefin and an unstable dithiocarbonate derivative which subsequently decomposes to carbon oxysulfide and a mercaptan.



Hückel, Tappe, and Legutke<sup>9</sup> appear to have been the first to note that the reaction involved a *cis*- $\beta$ -hydrogen atom, although Hurd and Blunck<sup>6</sup> had made a similar observation earlier with regard to

carboxylic esters. Hückel, Tappe, and Legutke postulated a concerted reaction in which the thiol sulfur atom, rather than the thion sulfur atom, attacked and removed the cis- $\beta$ -hydrogen atom.

This suggestion was modified by Barton<sup>10</sup> and by Cram,<sup>11</sup> who proposed that the reaction was completely concerted, involved a cis- $\beta$ -hydrogen atom in alicyclic compounds, and required that the more nucleophilic and less hindered thion sulfur atom attack the  $\beta$ -hydrogen atom. Evidence that the thion sulfur atom, rather than the thiol sulfur atom, attacked the  $\beta$ -hydrogen atom was obtained by Bader and Bourns<sup>12</sup> who made a study of sulfur and carbon isotope effects for the pyrolysis of trans-2-methyl-1-indanyl xanthate of natural isotopic abundance. Predicted isotope effects for the thiol sulfur, thion sulfur, and carbonyl carbon were obtained by use of the Bigeleisen equation.<sup>12</sup> As shown in Table I, the observed isotope effect agreed with the one predicted for the mechanism involving the thion sulfur atom.

Table I. Isotope Effects in the Pyrolysis at 80° of S-Methyl trans-2-Methyl-1-Indanyl Xanthate

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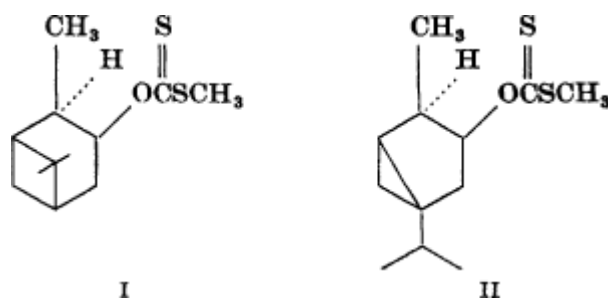
Cram, in his work on the methyl xanthates of the 3-phenyl-2-butanols<sup>11</sup> and 1,2-diphenyl-1-propanols,<sup>13</sup> also demonstrated that for acyclic compounds the same concerted reaction took place with a high stereospecificity, and that application of the principle of asymmetric induction led to the prediction of the configuration of the olefin.

Barton<sup>10</sup> proposed the term “molecular mechanism” for reactions such as the Chugaev reaction, carboxylic ester pyrolyses, and others, which proceed through a cyclic transition state involving neither ions nor radicals, but rather a redistribution of the electrons accompanied by bond making and breaking. He also correlated and predicted the configurations of a number of terpenes and other bicyclic compounds, using as a basis the preferred cis course of the Chugaev reaction.

Alexander and Mudrak<sup>14-16</sup> provided further convincing evidence for the cis elimination course. The methyl xanthates of cis- and trans-2-phenylcyclohexanol gave phenylcyclohexenes corresponding to cis elimination.<sup>14</sup> The methyl xanthate of cis-2-methyl-1-tetralol, which has no cis- $\beta$ -hydrogen atom, was stable to pyrolysis, whereas the trans isomer readily underwent pyrolysis to give 3,4-dihydro-2-methylnaphthalene.<sup>15</sup> Similar results were obtained with the methyl xanthates of the cis- and trans-2-methyl-1-indanols.<sup>16</sup>

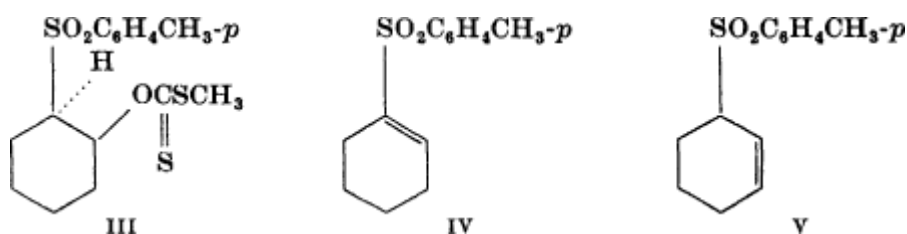
The concerted cis elimination mechanism of the Chugaev reaction requires that it be unimolecular and exhibit first-order kinetics. Evidence that this is so was provided by a kinetic study of the pyrolysis of a number of xanthates of 3 $\beta$ -cholestanol and cholesterol.<sup>7, 17</sup> All the compounds studied showed first-order kinetics for the pyrolysis reaction, and neither the rate nor the order of the reaction was affected by the addition of glass wool, a 2- and 3-cholestene mixture, or radical chain inhibitors such as hydroquinone, diphenylamine, and picric acid. Negative entropies of activation were obtained—an indication that the transition state was highly ordered, as would be expected of a concerted cyclic process.

Several details of the mechanism, however, still require further study. A number of xanthate pyrolyses have been reported in which significant amounts of trans elimination were observed. Included among the examples are the methyl xanthates of the  $\alpha$ -decalols,<sup>9</sup> pinocampheol (I)<sup>18</sup> and neothujol (II).<sup>19-22</sup>

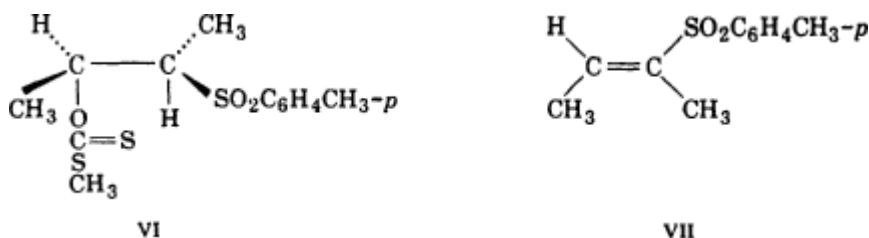


It is perhaps significant that all the xanthates that underwent trans elimination were liquids that could not be purified by distillation. Thus it is possible that some isomerization of the alkoxide ion occurred before the addition of carbon disulfide, and that the apparent trans elimination products actually arose from the presence of an isomeric xanthate.

Several unambiguous examples of trans elimination in xanthate pyrolyses have been reported by Bordwell and Landis.<sup>23, 24</sup> The methyl xanthate (III) of cis-2-p-toluenesulfonylcyclohexanol gave the trans elimination product, 1-p-toluenesulfonyl-1-cyclohexene (IV) in 40% yield, and little or none of the cis product, 3-p-toluenesulfonyl-1-cyclohexene (V).<sup>23</sup>



The methyl xanthate (VI) of (±) erythro-3-p-toluenesulfonyl-2-butanol gave cis-2-p-toluenesulfonyl-2-butene (VII), the trans elimination product, in 38% yield.<sup>24</sup>



Bordwell and Landis presented evidence that these eliminations proceed by initial ionization of the  $\beta$ -hydrogen atom, rendered more labile by the sulfonyl group on the same carbon atom, to give a dipolar ion intermediate. This intermediate then rearranges to the sterically more favored conformation before decomposing to give the olefin. In each of the cases above, the isomeric trans- or threo-xanthate gave the same olefin. The effect of other labilizing groups on the  $\beta$ -hydrogen atom has not been investigated.

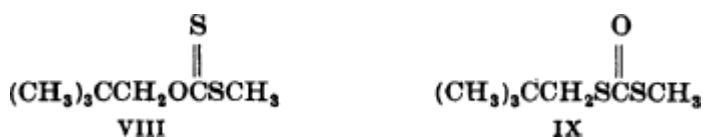
## 3. Scope and Limitations

Olefin-forming xanthates have been prepared (and pyrolyzed) from primary alcohols, secondary acyclic and alicyclic alcohols, tertiary acyclic and alicyclic alcohols, glycols, and dihaloalkanes. The S-methyl xanthates have been most frequently employed, but higher S-alkyl and S-benzyl and substituted S-benzyl xanthates have also been used.

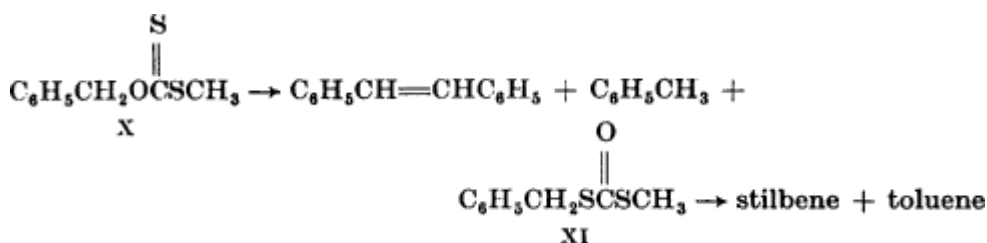
### 3.1. Xanthates of Primary Alcohols

Pyrolyses of xanthates of primary alcohols are surprisingly few in number. n-Amyl S-methyl xanthate gave 1-pentene (15%), and isoamyl S-methyl xanthate gave isopropylethylene (15%).<sup>25</sup> It was stated that these yields were minimal and could probably be doubled by more careful isolation of the olefins.

The methyl xanthate (VIII) of neopentyl alcohol, which has no  $\beta$ -hydrogen atom, rearranged on pyrolysis to give the more stable dithiocarbonate IX in 70% yield.<sup>26</sup>

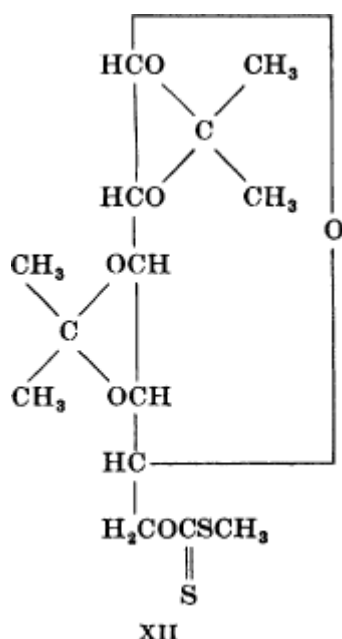


Benzyl S-methyl xanthate (X), which also has no  $\beta$ -hydrogen atom available for elimination, on pyrolysis at 160–185° gave stilbene (20–24%),<sup>27, 28</sup> toluene (20%),<sup>27</sup> and the dithiocarbonate XI.<sup>27</sup> The dithiocarbonate on pyrolysis at 290° gave stilbene (60%) and toluene (25%). Although these pyrolyses appear to involve free-radical intermediates, little direct evidence with respect to the mechanism is available.



The methyl xanthates of cyclohexylcarbinol and 4-methylcyclohexylcarbinol were pyrolyzed to give, in unstated yield, methylenecyclohexane and methylene-4-methylcyclohexane,<sup>29</sup> respectively.

The methyl xanthate (XII) of diacetone galactose underwent pyrolysis on heating, but the unidentified product was not an olefin.<sup>30</sup>



Although the statement has been made that xanthates of primary alcohols are more stable to pyrolysis

than those of secondary or tertiary alcohols,<sup>25</sup> there is not enough evidence to allow a comparison. In view of the lack of good methods for dehydrating primary alcohols under mild conditions, further study of the pyrolysis of xanthates of primary alcohols seems desirable. There is no obvious reason why xanthates of primary alcohols should be more stable than those of more highly substituted ones.

## 3.2. Xanthates of Secondary Alcohols

The Chugaev reaction has been widely employed for the conversion of both acyclic and alicyclic secondary alcohols to olefins.

### 3.2.1. Acyclic Alcohols

Depending on the degree of substitution on the carbon atoms adjacent to the carbinol carbon atom of acyclic alcohols, elimination may proceed in more than one direction to give structural isomers. These in turn may be mixtures of cis and trans forms. Where elimination is possible in only one direction, the olefin may be cis or trans, again depending on the degree of substitution.

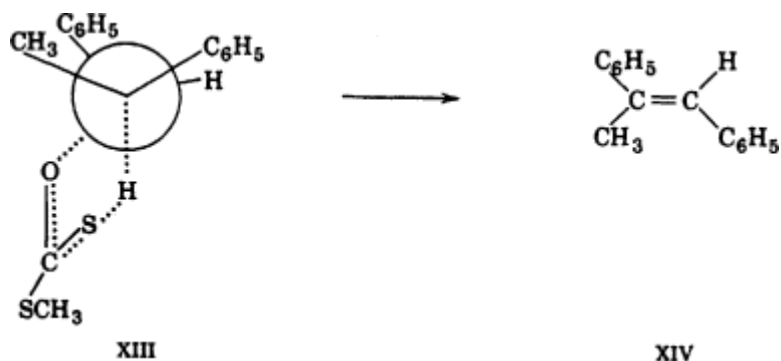
The configuration of the olefin is determined, in part, by the stereochemistry of the xanthate. In acyclic compounds the  $\beta$ -hydrogen atom and the xanthate group must be coplanar in the transition state, and this requirement in turn determines the configuration of the olefin. If more than one  $\beta$ -hydrogen atom is present, both the cis and the trans isomer may result, the proportion being partially dependent on the size of the other substituents on the two incipient olefin carbon atoms. When the steric factor is not dominant, the thermodynamically more stable trans olefin will predominate.

At least three factors determine the direction of elimination in xanthate pyrolysis (and ester pyrolyses in general): (1) the statistical, whereby the carbon atom carrying the greatest number of hydrogen atoms provides more chances for formation of the cyclic transition state; (2) the thermodynamic, whereby the more stable of the various possible olefins is preferred (the stability depending on the degree of "olefin-character" in the transition state), and (3) the steric, which affects the energies of the various possible transition states.

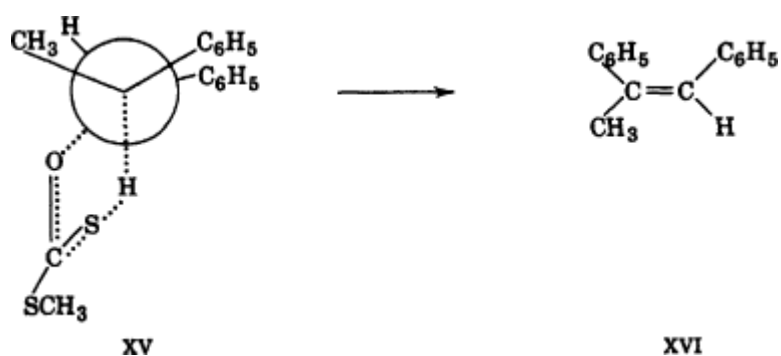
In many Chugaev reactions involving acyclic secondary alcohols, it is difficult to determine which of these three factors is dominant, and frequently one factor is excluded or is opposed by the other two. However, an understanding of them is useful in predicting the outcome of the Chugaev reaction.

The pyrolyses of the S-methyl xanthates of erythro- and threo-1,2-diphenyl-1-propanol, where elimination in only one direction is possible, afford an interesting example of the effect of steric factors on the ease of decomposition of the xanthate and provide good evidence that the Chugaev reaction proceeds by a cis elimination with acyclic compounds.<sup>13</sup>

In the cyclic transition state (XIII) for the S-methyl xanthate of erythro-1,2-diphenyl-1-propanol, the phenyl groups are on opposite sides of the incipient double bond; the only olefin isolated was trans- $\alpha$ -methylstilbene (XIV, 77%).<sup>13</sup>



Conversely, in the transition state (XV) for the threo-xanthate, the phenyl groups are on the same side of the incipient double bond; the only olefin isolated was *cis*- $\alpha$ -methylstilbene (XVI, 65%).<sup>13</sup>

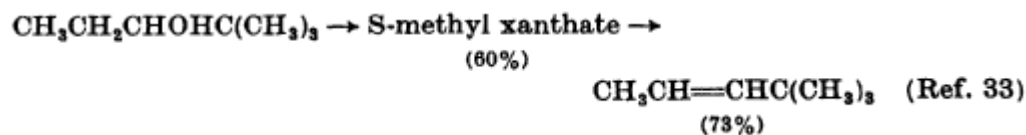
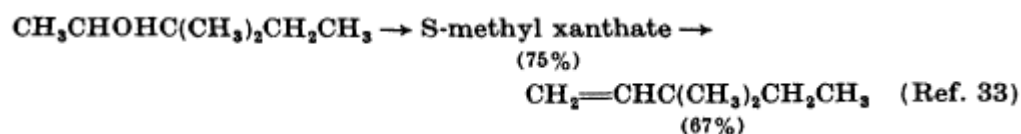
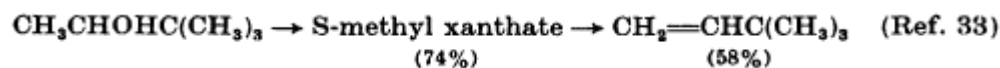


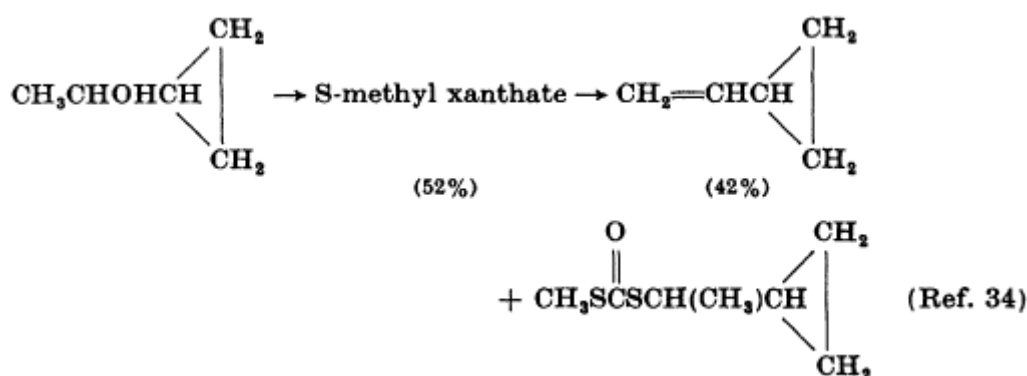
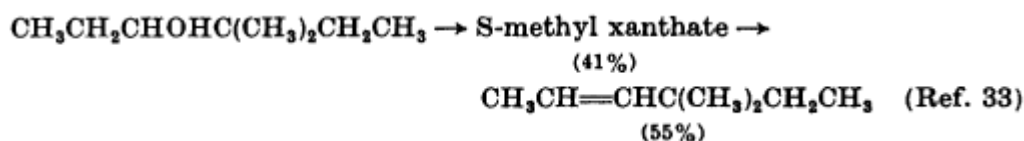
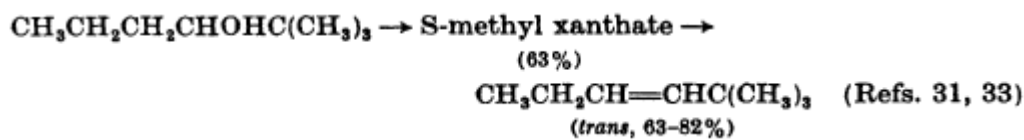
Decomposition of the erythro-xanthate began at 130°, and of the threo- at 145°, showing that the interference between the two phenyl groups increased the activation energy of the latter pyrolysis.

The pyrolysis of the methyl xanthate of diethylcarbinol gave *trans*-2-pentene in 55% yield (alkyl groups on opposite sides of the incipient double bond in the transition state) and *cis*-2-pentene in 33% yield<sup>31</sup> (alkyl groups on the same side), further illustrating the steric effects.

The methyl xanthate of di-undecylcarbinol gave 11-tricosene; the yield and configuration were not stated.<sup>32</sup>

The utility of the Chugaev reaction for the formation of olefins without rearrangement of the carbon skeleton is shown by the following examples.





Each of these alcohols is of the type which on non-pyrolytic dehydration gives rearranged olefins.<sup>35</sup> Thus methylcyclopropylcarbinol on dehydration with sulfuric acid gave vinylcyclopropane (8%), 1,4-pentadiene (0.4%), cyclopentene (0.9%), and 2-methyltetrahydrofuran (10%). The acetate of the same carbinol, in contrast to the xanthate, gave vinylcyclopropane (10%), cyclopentene (60%), 1,4-pentadiene (9%), and trace amounts of isoprene and trans-1,3-pentadiene.<sup>34</sup>

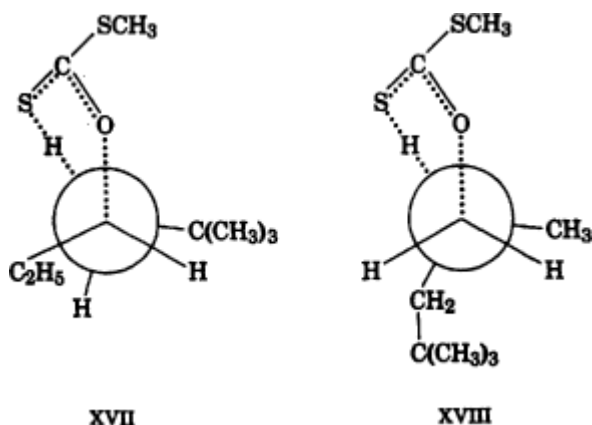
In three of the olefins above, cis-trans isomerism is possible, but only in the case of trans-2,2-dimethyl-3-hexene was the configuration determined. The bulk of the t-butyl and ethyl groups is apparently too large to permit the formation of the cis olefin. Presumably 2,2-dimethyl-3-pentene and 3,3-dimethyl-4-hexene also have the trans configuration for the same reason.

When elimination in more than one direction is possible, and more than one  $\beta$ -hydrogen atom is available on each carbon atom, the synthetic utility of the Chugaev reaction is greatly diminished by the formation of complex mixtures of olefins.

The S-methyl xanthate (25% yield) of 3-hexanol gave trans-3-hexene (28%), cis-3-hexene (13%), trans-2-hexene (29%), and cis-2-hexene (13%).<sup>31</sup> Similarly, the S-methyl xanthate (30% yield) of ethylisobutylcarbinol gave trans-2-methyl-3-hexene (43%), cis-2-methyl-3-hexene (5%), trans-2-methyl-4-hexene (28%), and cis-2-methyl-4-hexene (9%).<sup>31</sup> As expected, the direction of elimination in these examples conforms to statistical prediction, and the trans isomer predominates over the cis.

When the S-methyl xanthate of ethylneopentylcarbinol is pyrolyzed, a strong preference for elimination toward the bulky alkyl group is evidenced. Thus 2,2-dimethyl-3-hexene (58% trans, 2% cis) is formed in 60% yield and 2,2-dimethyl-4-hexene (21% trans, 5% cis) is formed in only 26% yield.<sup>31</sup> The explanation advanced for this behavior is that, when the xanthate moves into the transition state (XVII) for elimination toward the bulky alkyl group, some steric assistance is provided by the separation of the ester and t-butyl groups, or the ethyl and t-butyl groups, and this steric assistance is not provided when elimination proceeds in the other direction (XVIII).<sup>31</sup>

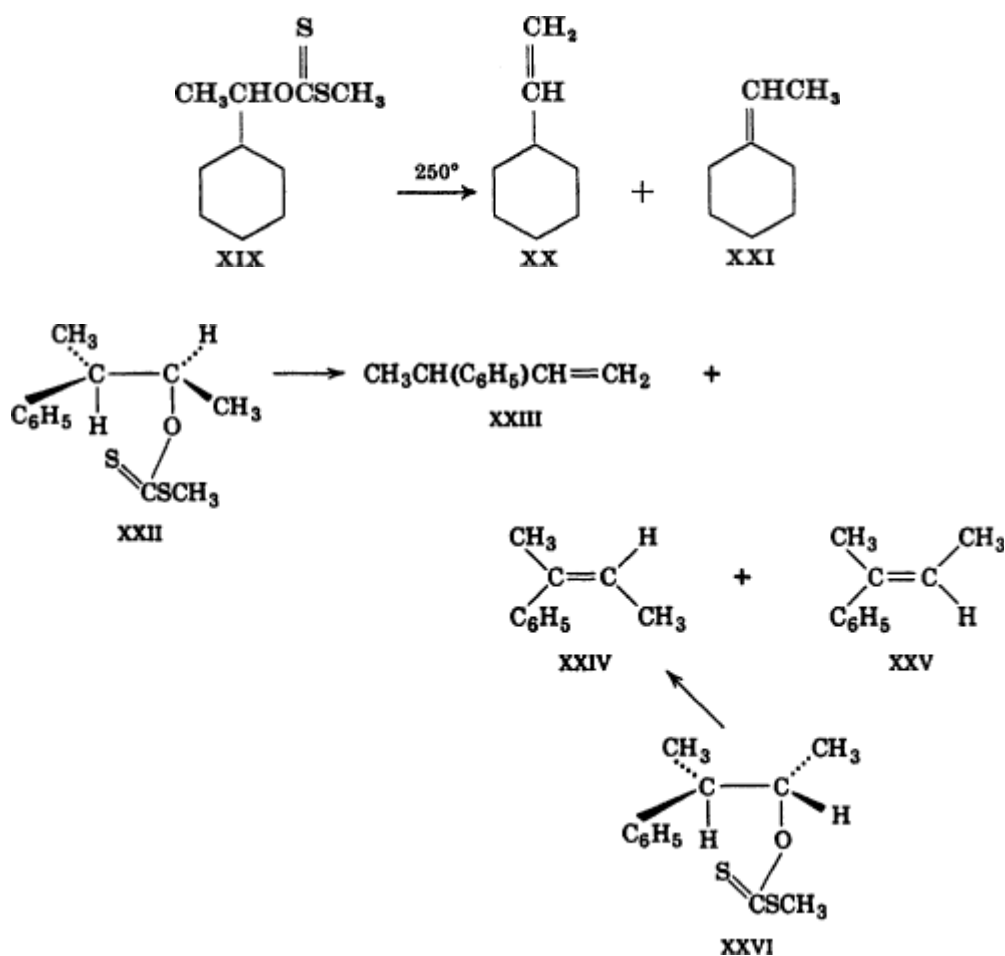




The pyrolysis of S-methyl sec-octyl xanthate gave a mixture of 2-octene (21–23%) and 1-octene (23–25%).<sup>25</sup> Although the terminal olefin is less stable, it is favored statistically because there are three hydrogen atoms available for elimination in this direction, compared to two in the other.

The S-methyl xanthate (XIX, 57% yield) of methylcyclohexylcarbinol gave a mixture consisting of cyclohexylethylene (XX, 32%), and ethylenecyclohexane (XXI, 20%).<sup>36</sup> Although the statistical factor favors the formation of cyclohexylethylene, no information about the relative stabilities of the two olefins is available.

The pyrolysis of the xanthates of erythro- and threo-3-phenyl-2-butanol<sup>11</sup> illustrates the difficulty of assessing all three of the factors (statistical, thermodynamic, and steric) involved in predicting the course of elimination. The S-methyl xanthate (XXII) of erythro-3-phenyl-2-butanol gave 2-phenyl-3-butene (XXIII, 32%), trans-2-phenyl-2-butene (XXIV, 45%), and cis-2-phenyl-2-butene (XXV, 5%).<sup>11</sup>

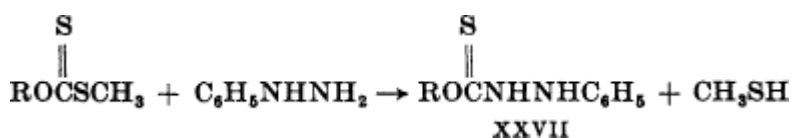


The yields of olefins from the corresponding threo-xanthate XXVI were 36% of the cis olefin XXV, 11%

of the trans olefin XXIV, and 37% of the terminal olefin XXIII. For each xanthate, the statistical factor favors terminal olefin, the thermodynamic factor favors internal olefin, and it is difficult to evaluate the steric factors.

The isolation of cis olefin (5%) from the erythro-xanthate and trans olefin (11%) from the threo-xanthate appears to indicate a trans elimination path for the Chugaev reaction. However, several other explanations may be suggested. The pyrolysis could have proceeded by an inter-, rather than an intra-molecular path.<sup>11</sup> Little or no evidence is available to indicate whether such a route is available for pyrolytic eliminations, however.

A second explanation lies in the fact that the xanthates were liquids, purified by distillation, and each may not have been free of the other isomer. In the first step in the preparation of the xanthates the corresponding alcohol was heated under reflux with potassium metal. It is well known that metal alkoxides can undergo epimerization under these conditions.<sup>37</sup> The presence of a small amount of the isomeric xanthate would be difficult to detect, although its presence might be shown by conversion to the corresponding phenylhydrazine derivative (XXVII),<sup>38</sup> followed by fractional crystallization or chromatography.



It is also possible that a portion of the xanthate decomposes by a reaction path involving the formation of the dipolar ion type of intermediate,<sup>24</sup> discussed previously, which leads to olefins by a route quite different from the concerted Chugaev reaction.

Finally, a portion of the xanthate decomposition may be peroxide induced, again following a different path, as discussed below for the case of (-)-menthyl S-methyl xanthate. Other examples of apparent trans Chugaev decompositions will be noted, and the same possible explanations may be applied. Further study is obviously necessary to determine the correct explanation.

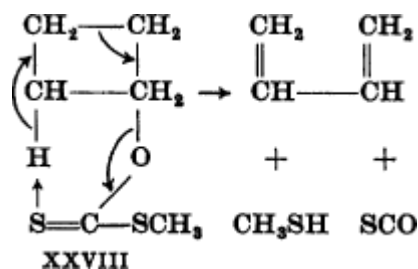
Similar results were obtained with the S-methyl xanthate of erythro-2-phenyl-3-pentanol, which gave 2-phenyl-3-hexene (37%), trans-2-phenyl-2-hexene (27%), and cis-2-phenyl-2-hexene (4%), the last compound corresponding to a trans Chugaev elimination.<sup>11</sup>

### 3.2.2. Alicyclic Alcohols

In the pyrolysis of the xanthates of alicyclic secondary alcohols, an additional restriction on the stereochemistry is imposed if the Chugaev reaction is to proceed by the cis elimination path. Coplanarity of the  $\beta$ -hydrogen atom and the xanthate group is required in the cyclic transition state, and, in order to avoid high energies due to bond and ring distortion, the groups must be cis to each other. For six-membered rings, this requires that one group be axial and the other equatorial. It has been pointed out<sup>39</sup> that theoretically the two groups can be trans and diequatorial, but that considerable ring distortion is required for coplanarity in the transition state. This high energy requirement makes trans elimination unlikely under the usual conditions of the Chugaev reaction.

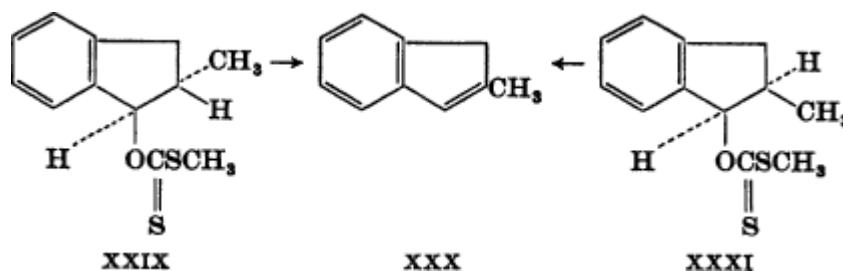
The reaction thus becomes a useful method for determining the configuration of cyclic  $\beta$ -substituted alcohols, since the relationship of the hydroxyl and substituent is readily ascertainable by observation of the direction of elimination of the xanthate. The steric course also has synthetic applications, since the position of the double bond to be introduced can be controlled by choosing the appropriate isomer for pyrolysis.

In the one reported example of the pyrolysis of a cyclobutyl xanthate, ring cleavage occurred. Cyclobutyl S-methyl xanthate (XXVIII, 84% yield) was pyrolyzed at 255° to give 1,3-butadiene in quantitative yield.<sup>40</sup> The reaction was pictured<sup>40</sup> as involving the simultaneous redistribution of electrons and bond making and breaking, as shown for XXVIII.

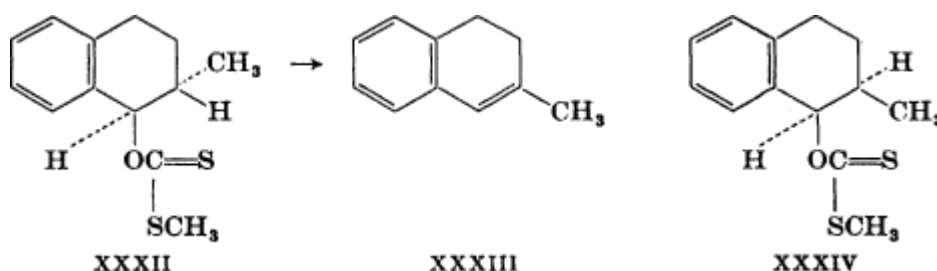


Several examples involving five-membered rings have been reported. The S-methyl xanthate (90% yield) of cyclopentanol at 255° gave cyclopentene in 70% yield.<sup>40</sup>

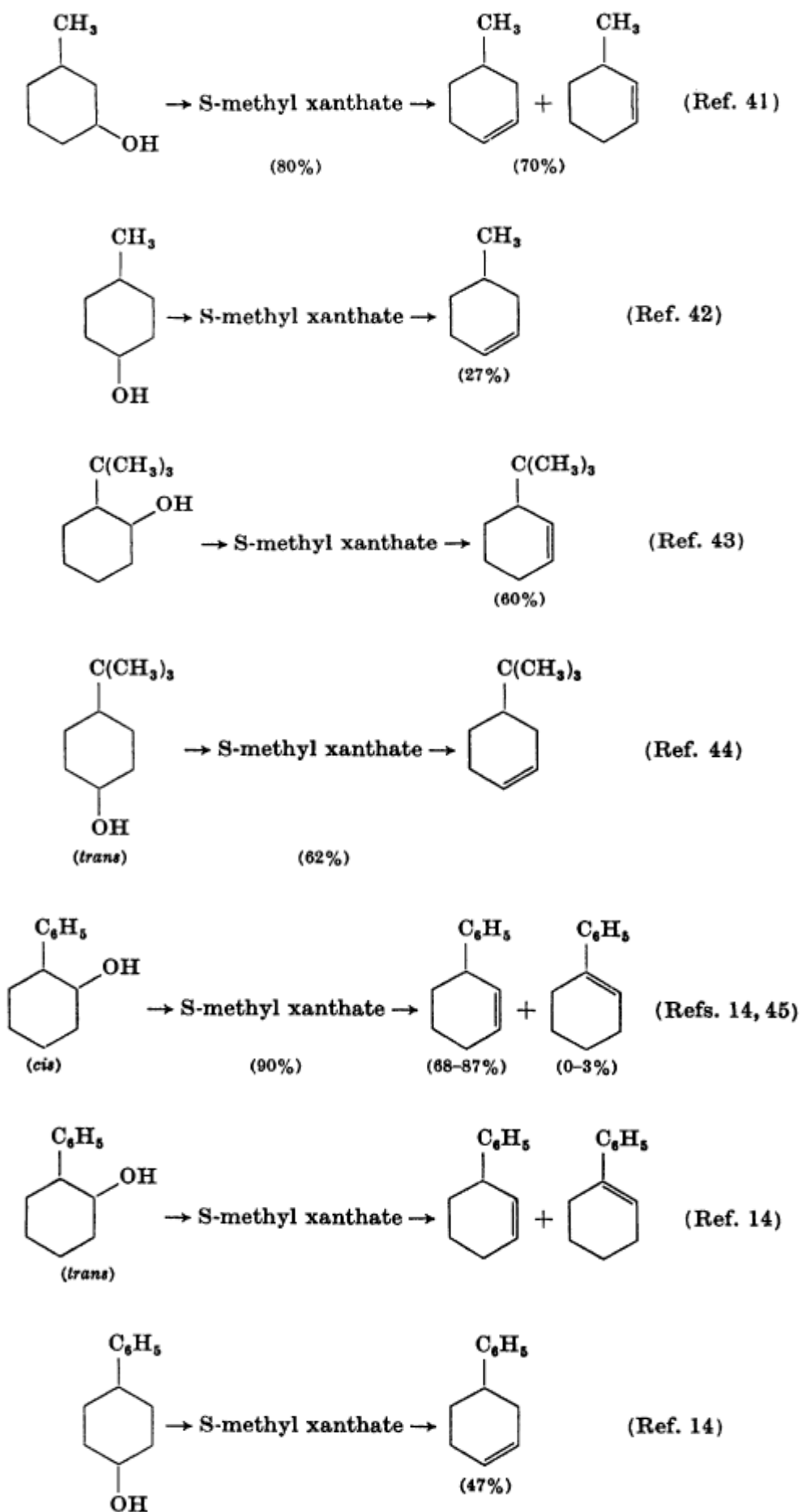
Pyrolysis of the S-methyl xanthate (XXIX) of trans-1-hydroxy-2-methylindane at 98–100° gave 2-methylindene (XXX) in 80% yield.<sup>16</sup> When the corresponding cis-xanthate (XXXI) was pyrolyzed at the same temperature, the yield of 2-methylindene was only 20%, regardless of the pyrolysis time,<sup>16</sup> suggesting the presence of an impurity in the xanthate. At higher temperatures, more deep-seated decomposition was observed, with no increase in yield of 2-methylindene.



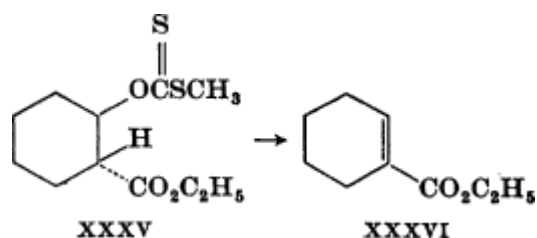
No such complications were encountered in the pyrolyses of the homologous tetralyl isomers.<sup>15</sup> trans-S-Methyl 2-methyl-1-tetralyl xanthate (XXXII) pyrolyzed readily at 98–100° to 2-methyl-3,4-dihydronaphthalene (XXXIII), while the cis isomer (XXXIV) was inert.



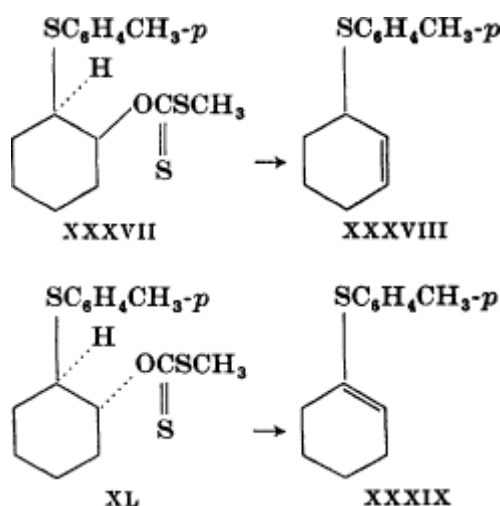
In general, xanthates derived from substituted cyclohexanols undergo the Chugaev reaction in the expected manner at temperatures in the range 100–250°, as shown by the following examples.



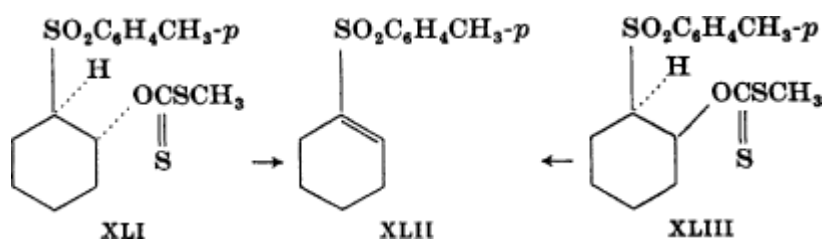
A few examples with substituents other than alkyl or aryl have been reported. The S-methyl xanthate (XXXV) of ethyl trans-cyclohexanol-2-carboxylate gave only ethyl 1-cyclohexenecarboxylate (XXXVI) in 34% yield.<sup>46</sup>



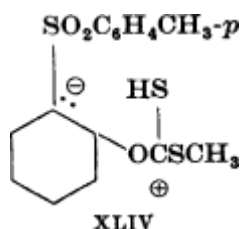
cis-2-p-Tolylthiocyclohexyl S-methyl xanthate (XXXVII) gave 3-p-tolylthio-1-cyclohexene (XXXVIII, 49–51%) accompanied by as much as 5–10% of the trans elimination product, 1-p-tolylthio-1-cyclohexene (XXXIX).<sup>23</sup> The isomeric trans-xanthate (XL) gave 1-p-tolylthio-1-cyclohexene (XXXIX, 85% yield).<sup>23</sup>



When the corresponding sulfones were pyrolyzed, the reaction appeared to follow a different course. trans-2-p-Tolylsulfonylcyclohexyl S-methyl xanthate (XLI) gave 1-p-tolylsulfonyl-1-cyclohexene (XLII, 77%), corresponding to cis elimination. However, the cis isomer XLIII gave almost exclusively the same olefin in 40% yield, corresponding to a trans elimination.<sup>23</sup>

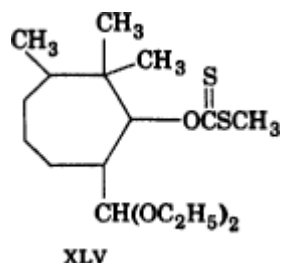


As in the case of the analogous acyclic sulfonyl-substituted compounds referred to earlier, the hypothesis has been advanced that the pyrolysis involves the formation of a dipolar ion XLIV, which decomposes to the olefin.<sup>23</sup> This stepwise decomposition is believed to be energetically more favorable than a concerted one because of the increased acidity of the  $\beta$ -hydrogen atom which is adjacent to the sulfonyl group.



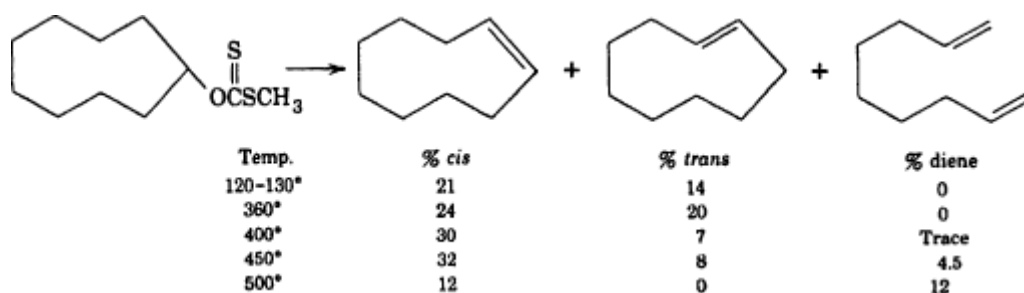
The cis- and trans- $\alpha$ - and - $\beta$ -decalyl S-methyl xanthates have been pyrolyzed at temperatures between 100° and 210° to yield mixtures of olefins.<sup>9, 47</sup>

One example of the pyrolysis of a cycloheptyl xanthate has been reported. The S-methyl xanthate of 1,1,7-trimethyl-2-hydroxy-3-diethoxymethylcycloheptane (XLV), heated at 200–210° in the presence of copper-bronze, gave in 50% yield an olefin of unknown structure, isomeric with the expected product.<sup>48</sup>



Pyrolysis of the S-methyl xanthates of cyclooctanol<sup>49a</sup> cyclononanol,<sup>49b</sup> and cyclodecanol<sup>49a, c</sup> points out that pyrolytic cis eliminations of alicyclic compounds give cis olefins only when the carbocyclic ring has eight or fewer carbon atoms. Thus cyclooctyl S-methyl xanthate when pyrolyzed at 135–290° gave cis-cyclooctene (88%) and no trans isomer.<sup>49a</sup>

Cyclononyl S-methyl xanthate gave mixtures of cis- and trans-cyclononene, and, above 400°, ring cleavage was observed in addition to the normal elimination.<sup>49b</sup> Two explanations were proposed for the formation of the 1,8-nonadiene. One explanation, that the diene is formed by rearrangement of cyclononenes, is supported by studies on the thermal decomposition of mixtures of the two cyclononenes at 500° which show that the cis and, especially, the trans isomer undergo transannular intramolecular rearrangement to the open-chain diene. The other, that the reaction goes through a six-membered cyclic transition state involving the oxygen atom and a hydrogen on the C-4 carbon atom, is suggested because such a transition state appears quite feasible sterically.<sup>49b</sup> Apparently neither route is energetically as favored as the Chugaev reaction at temperatures below 450°.



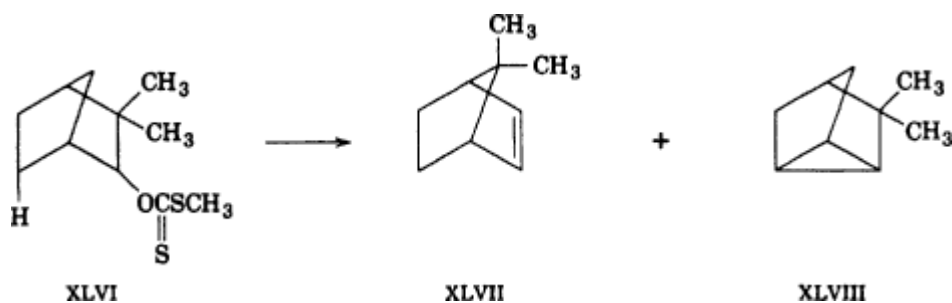
When cyclodecyl S-methyl xanthate is pyrolyzed (135–220°), the trans olefin (38–50%) predominates over the cis (6–11%).<sup>49a, c</sup>

The Chugaev reaction has had wide application in the study of both synthetic and structural problems in the terpenoid field. The reaction has been used to determine the configuration of hydroxyl groups; and, conversely, when configuration was known, the position of the double bond introduced by pyrolysis of the xanthate has been inferred on the basis of the preferred cis course of the Chugaev reaction.<sup>10</sup>

The availability of gas chromatography and nuclear magnetic resonance should stimulate and facilitate reinvestigation of those examples of the Chugaev reaction with terpenoids where the stereochemistry of the alcohol and the composition (presence of isomers) of the alcohol or olefin were not known with certainty.

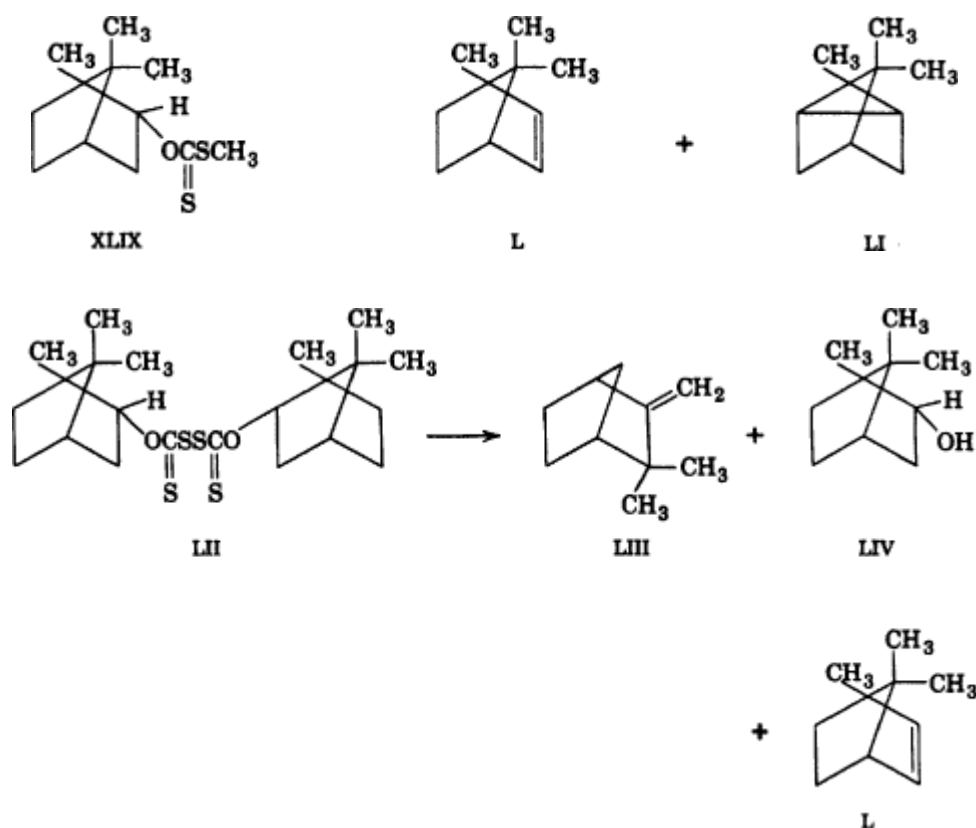
Camphenyl S-methyl xanthate (XLVI) was pyrolyzed to give, in unstated yield, apobornylene (XLVII),

with<sup>50</sup> or without<sup>51</sup> the additional product, apocyclene (XLVIII).

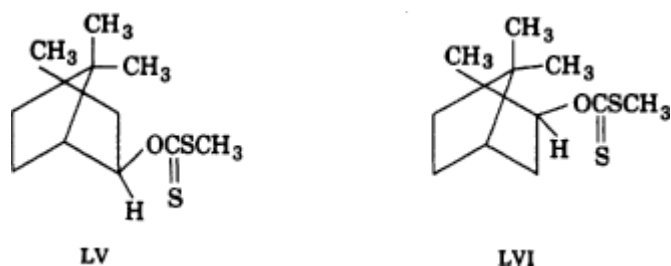


Apobornylene represents a rearrangement product, while the apocyclene indicates elimination of a hydrogen atom from a carbon atom  $\beta$  to the xanthate-bearing carbon atom of the ring. In a sense this hydrogen atom is equivalent to a  $\beta$ -hydrogen atom. It is known that compounds of these types may be in equilibrium at elevated temperatures in the presence of silica and alumina,<sup>52, 53</sup> and thus one of these products may be an artifact rather than a true Chugaev product.

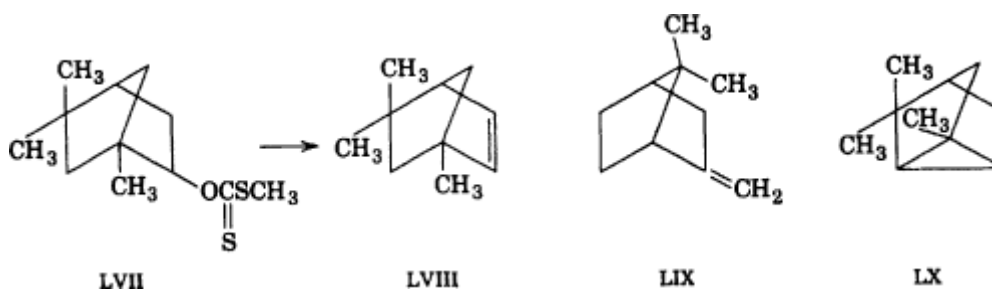
No rearrangement occurred with (-)-bornyl S-methyl xanthate (XLIX), which gave (+)-bornylene (L)<sup>54-56</sup> in yields up to 96%,<sup>56</sup> or (+)-bornylene and tricyclene (LI).<sup>57, 58</sup> However, the pyrolysis of (-)-bornyl dioxanthide (LII) gave camphene (LIII)<sup>59</sup> in addition to (+)-bornylene (L) and (-)-borneol (LIV).



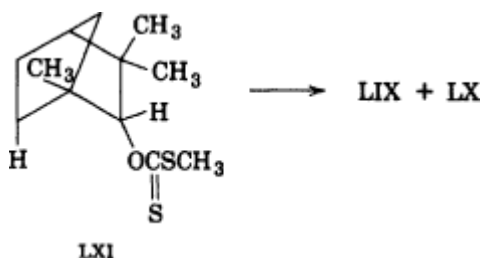
(+)-Bornyl<sup>55</sup> and (-)-epibornyl (LV)<sup>60</sup> S-methyl xanthates gave only (-)-bornylene (L), but isobornyl S-methyl xanthate (LVI) gave only the rearranged product, camphene (LIII),<sup>61</sup> again indicating rearrangement during or after the elimination.



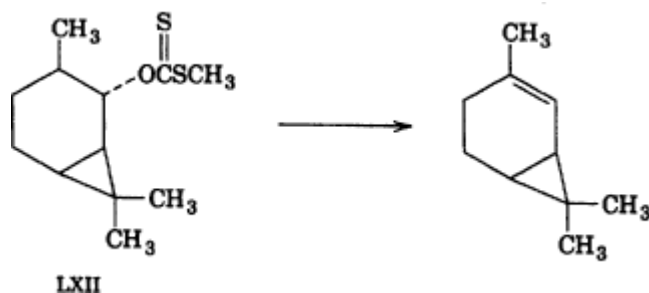
Pyrolysis of the S-methyl xanthate (LVII) of  $\alpha$ -isofenchyl alcohol gave isofenchylene (LVIII)<sup>62-64</sup> and, in one instance,  $\alpha$ -fenchene (LIX) and cyclofenchene (LX).<sup>65</sup>



The S-methyl xanthate (LXI) of  $\alpha$ -fenchyl alcohol should be incapable of undergoing the Chugaev reaction, since there are no hydrogen atoms, cis or trans, on either of the carbon atoms adjacent to the one carrying the xanthate group. However, it has been reported<sup>26, 64-66</sup> to give  $\alpha$ -fenchene (LIX) and cyclofenchene (LX) in yields up to 72%<sup>64</sup> for the mixture of olefins. Cyclofenchene results from elimination of a hydrogen atom from a  $\gamma$ -carbon atom, while  $\alpha$ -fenchene must arise by rearrangement.

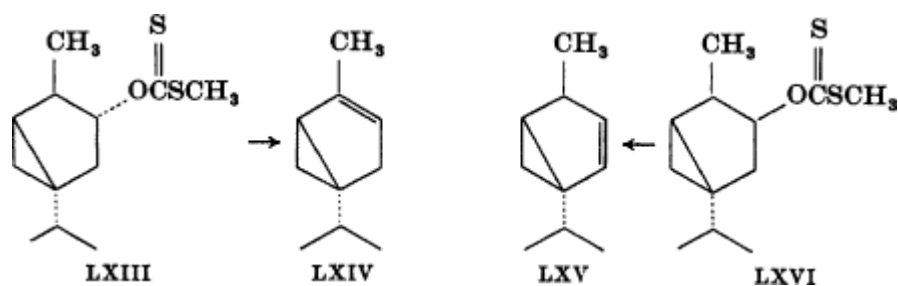


Several examples from the terpene field further illustrate the stability of three- and four-membered rings at the temperatures necessary for pyrolysis of xanthates. (-)-Caryl S-methyl xanthate (LXII), when heated to its boiling point, gave  $\Delta^4$ -carene.<sup>67</sup>



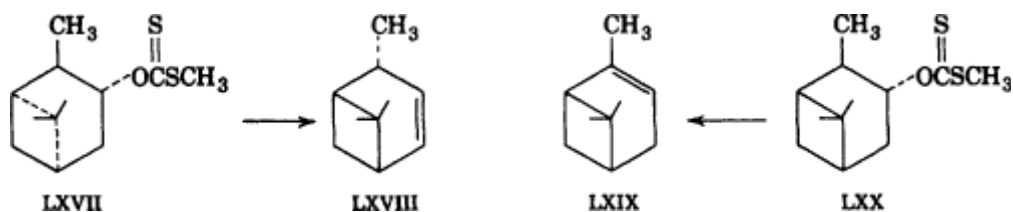
There are several reports of the pyrolysis, at temperatures up to 190°, of the S-methyl xanthate (LXIII) of thujyl alcohol (of uncertain configuration) to give  $\alpha$ -thujene (LXIV), and  $\beta$ -thujene (LXV).<sup>19, 31, 22, 68-70</sup>



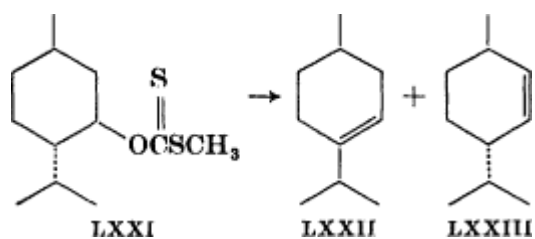


The formation of  $\alpha$ -thujene indicates that the xanthate and methyl groups must be trans to each other, and this assignment is supported by the fact that the S-methyl xanthate (LXVI) of (-)-neothujyl alcohol gave only  $\beta$ -thujene (LXV).<sup>10, 20</sup>

The S-methyl xanthate (LXVII) of (-)-pinocampheol gave mixtures of  $\Delta$ -pinene (LXVIII) and  $\alpha$ -pinene (LXIX),<sup>18, 71</sup> the yields in one experiment being 21 and 17%, respectively.<sup>72</sup> The S-methyl xanthate (LXX) of isopinocampheol gave  $\alpha$ -pinene (LXIX) in 38% yield.<sup>72</sup> No other olefins were reported.

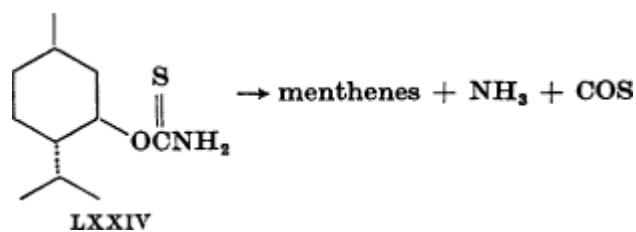


The most thoroughly studied terpenoid xanthate is (-)-menthyl S-methyl xanthate (LXXI), which on pyrolysis gives in 51% yield a 3:1 mixture of 3-menthene (LXXII) and 2-menthene (LXXIII).<sup>9, 73</sup>

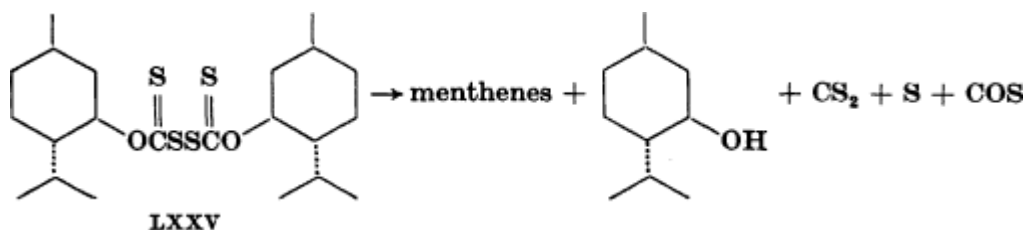


The occurrence of an unstable form of the xanthate,<sup>54, 74</sup> which decomposed at lower temperatures than did the normal xanthate, was shown to be due to the presence of peroxidic impurities.<sup>73</sup> An unstable form of the S-methyl xanthate (XLIX) of (-)-borneol was also noted.<sup>74</sup> The cause of the instability has not been established, although it is probably the same as that for the menthyl xanthate. Little is known about the effect of peroxides on xanthate pyrolyses.

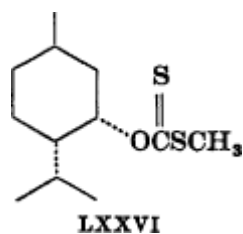
The effect of varying the S-alkyl group on the stability of the xanthate toward pyrolysis was shown qualitatively by using (-)-menthyl xanthates.<sup>74</sup> An S-isopropyl group increased the stability relative to an S-methyl group, while an S-benzyl group decreased the stability, and an S-p-nitrobenzyl group decreased it still more, suggesting that electronegative groups on the thiol sulfur decrease the activation energy for the Chugaev reaction. Replacement of the S-methyl portion by an amide group appeared to increase the stability, for temperatures in the range 200–220° were necessary for pyrolysis of the xanthogen amide LXXIV.<sup>75</sup>



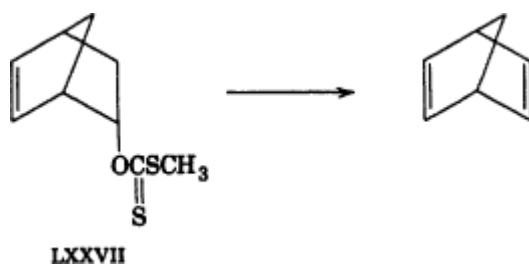
The dixanthide LXXV appeared to be less stable than the S-methyl xanthate, but only one of the menthyl groups underwent elimination, the other giving (-)-menthol.<sup>1, 59</sup>



The S-methyl xanthate (LXXVI) of (+)-neomenthol gave only 2-menthene in 80% yield.<sup>9</sup>



The S-methyl xanthate (LXXVII) of endo-5-hydroxybicyclo-[2.2.1]-2-heptene proved difficult to pyrolyze, giving at 250° only a 5% yield of bicyclo-[2.2.1]-2,5-heptadiene.<sup>76</sup> The corresponding acetate and trimethylammonium hydroxide failed completely to undergo pyrolysis at the same temperature.<sup>76</sup>



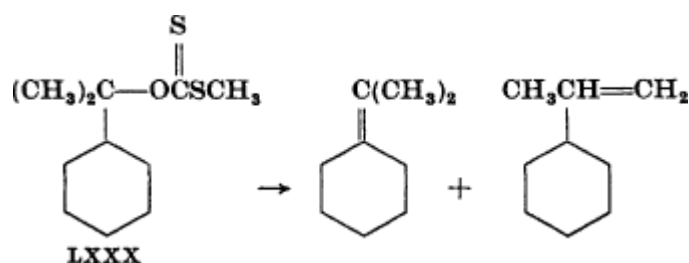
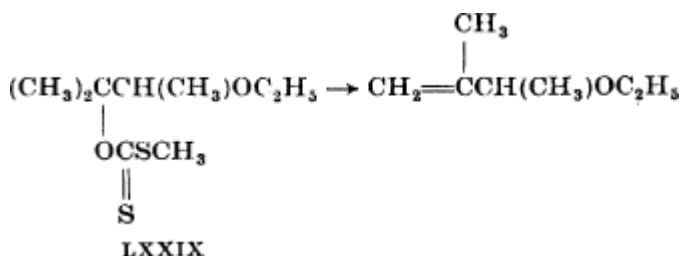
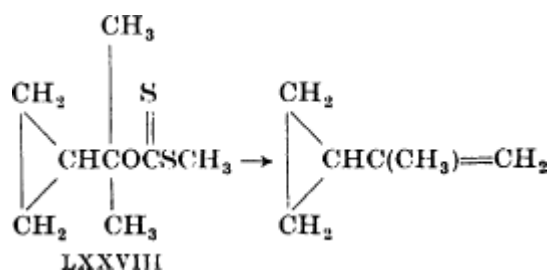
The Chugaev reaction has not been widely employed in the steroid field, but in the cases studied the yields of olefins were generally high. Cholesteryl S-methyl xanthate gave 3,5-cholestadiene in yields up to 93%.<sup>17, 77</sup> Good yields (65–90%) were also obtained with a variety of other alkyl groups on the thiol sulfur atom.<sup>7</sup> Rate studies on the decomposition of these xanthates showed that an increase in the electronegativity of the S-alkyl group decreased the stability of the xanthate in the following order.<sup>7</sup>

### 3.3. Xanthates of Tertiary Alcohols

The behavior of tertiary alcohols in the Chugaev reaction is comparable to that of primary and secondary alcohols, although very few examples have been reported.

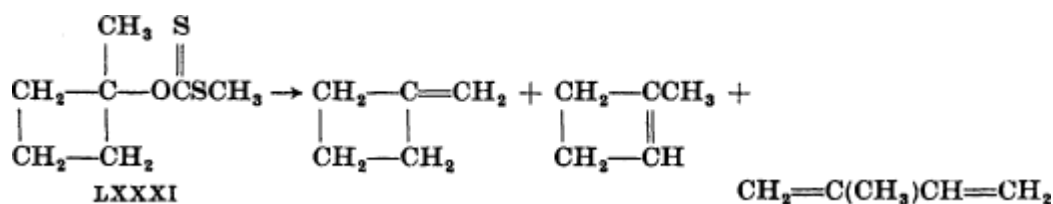
### 3.3.1. Acyclic Tertiary Alcohols

Xanthates of only four acyclic tertiary alcohols have been pyrolyzed. The S-methyl xanthate (LXXVIII) of dimethylcyclopropylcarbinol was pyrolyzed at 130–135° in xylene to give isopropenylcyclopropane in 24% yield.<sup>78</sup> The S-methyl xanthate of dimethylcyclobutylcarbinol was pyrolyzed at 100–120° to give a mixture of isopropenylcyclobutane and isopropylidenecyclobutane.<sup>79</sup> The S-methyl xanthate of (–)-3-ethoxy-2-methyl-2-butanol (LXXIX) gave (+)-3-ethoxy-2-methyl-1-butene in 71% yield.<sup>5</sup> The S-methyl xanthate (LXXX) of dimethylcyclohexylcarbinol was pyrolyzed at 150° to give both the exo olefin (11%) and the methylene compound (40%).<sup>36</sup>



### 3.3.2. Alicyclic Tertiary Alcohols

The pyrolysis at 255° of 1-methylcyclobutyl S-methyl xanthate (LXXXI) gave results comparable to those obtained with cyclobutyl S-methyl xanthate. The product, obtained in 86% yield, consisted of methylenecyclobutane (15%), 1-methylcyclobutene (21%), and isoprene (49%).<sup>80</sup>

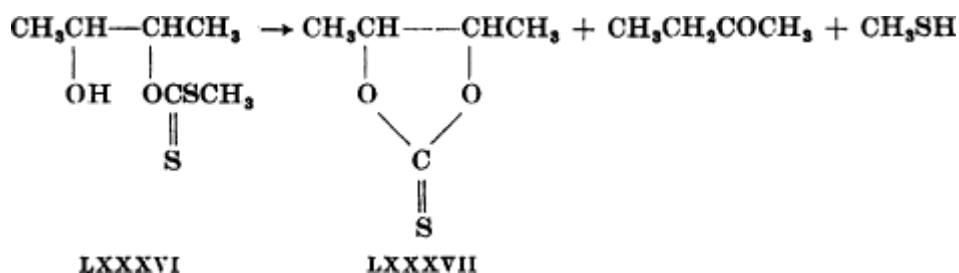


The pyrolysis of the S-methyl xanthates of several 1-alkylcyclohexanols gave olefin mixtures in yields of 46–51%.<sup>36</sup> Analysis of the olefin mixtures showed that the elimination proceeded so as to avoid forming a double bond exo to the six-membered ring, and that increasing substitution on the carbinol carbon atom,

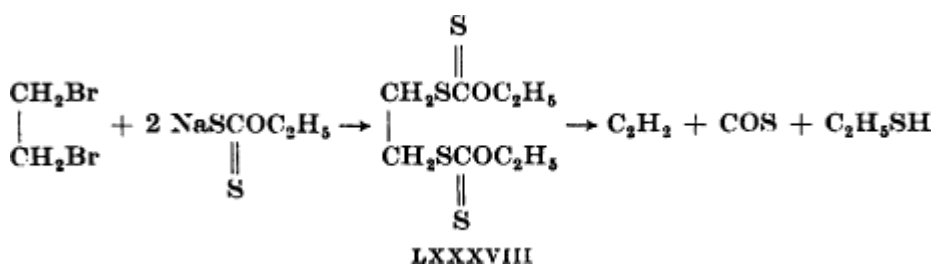
or the carbon atom adjacent to it, decreased the stability of the xanthate, probably owing to relief of steric crowding in the olefin.

### 3.4. Xanthates of Glycols

The only unambiguous example of the use of a glycol in the Chugaev reaction is the pyrolysis of the mono-S-methyl xanthate (LXXXVI) of 2,3-butanediol.<sup>82, 83</sup> The major product after extended heating at 200° was the cyclic thionocarbonate LXXXVII<sup>82, 83</sup> accompanied by a trace of methyl ethyl ketone presumably derived from the enol formed by elimination.<sup>83</sup>

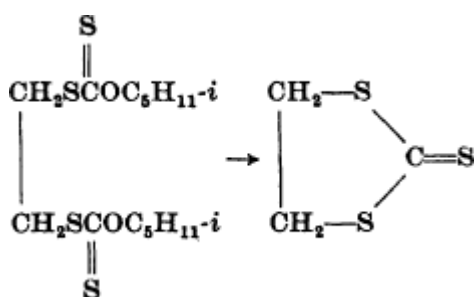


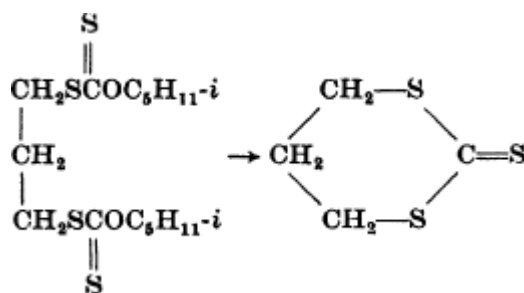
Several xanthates of 1,2-dithioglycols reportedly gave acetylenes and a variety of other products. Ethylene dibromide was treated with sodium O-ethyl xanthate, and the resulting dixanthate LXXXVIII was pyrolyzed at 200–270° to give acetylene (26%), carbon oxysulfide, and ethyl mercaptan.<sup>84, 85</sup>



In a similar fashion, 1,2-dibromopropane gave a dixanthate which yielded methylacetylene, carbon disulfide, carbon oxysulfide, ethanol, and ethyl mercaptan;<sup>84, 85</sup> and 1,2-dibromobutane afforded ethylacetylene.<sup>84</sup> 2,3-Dibromobutane, treated in the same manner, gave butadiene,<sup>84</sup> as did 1,4-dibromo-2-butene.<sup>85</sup> The formation of ethyl mercaptan in these pyrolyses suggests that the xanthate is partially undergoing pyrolysis in the normal fashion, and that ethylene and a 1,2-dithiol should also be formed.

In direct contrast to these pyrolyses, the pyrolysis of the xanthates shown below gave cyclic trithiocarbonates and other unidentified products.<sup>86</sup> A number of related xanthates were also prepared, but the pyrolyses were not described.





Further investigation of the use of glycols in the Chugaev reaction seems desirable, since potentially the reaction could provide a good synthetic route to acetylene derivatives and conjugated dienes.

## 4. Comparison with Other Methods of Dehydration

The most general and widely used method for dehydration of alcohols to olefins is to use an acid, such as sulfuric, phosphoric, or p-toluenesulfonic. Since these reagents may promote a carbonium ion type of reaction under the usual conditions, rearrangement of the carbon skeleton frequently occurs.<sup>34</sup> Solvolytic eliminations employing sulfonate esters of alcohols possess the same disadvantage. In such cases, the Chugaev reaction is quite valuable since rearrangements are rare.

If other acid-sensitive functional groups are also present in the alcohol, the Chugaev reaction, utilizing basic conditions, is advantageous.

Although vapor phase dehydration of alcohols over aluminum oxide may be superior to acid dehydration in the liquid phase, the high temperatures required (300–500°) render the method useless for compounds which cannot be vaporized readily or undergo decomposition or rearrangement.<sup>87</sup> These disadvantages are minimized at the much lower temperatures (100–250°) employed for the Chugaev method.

A dehydration method closely related to the Chugaev reaction is the pyrolysis of carboxylic esters, commonly the acetate esters. Although such esters undergo elimination via the same type of cyclic transition state as do xanthates, they are more stable to pyrolysis and require temperatures in the range 300–600°. They offer the considerable advantages, however, that in general they are much easier to prepare from alcohols than are the xanthates, and the olefins are less likely to be contaminated by the other decomposition products. A serious disadvantage of the Chugaev reaction is that the olefins are frequently contaminated by sulfur containing impurities, which are usually removed by distillation from sodium metal with an accompanying decrease in yield.

Carbonate and carbamate esters<sup>7</sup> fall between the xanthate and carboxylic esters in stability toward pyrolysis and are easier to prepare than xanthates. The carbonate esters possess the additional advantage that the other decomposition products, carbon dioxide and an alcohol (commonly ethyl), are neutral, do not react with the olefins formed, and do not have offensive odors. However, these esters have not found widespread use.

Esters of boric acid are sometimes quite easy to pyrolyze,<sup>88</sup> but further investigation of this method is necessary before its generality can be assessed.

In summary, the Chugaev reaction offers advantages when it is necessary to employ low temperatures, basic reaction conditions, or to avoid rearrangements. The disadvantages are the difficulties sometimes encountered in the preparation and purification of the xanthate esters, and in the removal of sulfur-containing impurities from the olefin.

In general, ester pyrolyses of all types offer high stereo-selectivity because of the restrictions on the

orientation of groups necessary to form the cyclic transition state. The combination of the pyrolysis method with the base-catalyzed trans elimination of sulfonate esters of alcohols provides two stereospecific methods for obtaining cis or trans eliminations.

## 5. Experimental Conditions

### 5.1. Preparation of the Xanthates

The utility of the Chugaev reaction is partially dependent upon the ease of formation and purification of the xanthate. The most commonly encountered difficulty in the preparation of xanthates is formation of the metal salt of the alcohol. The method usually employed consists in heating a solution of the alcohol in ether, benzene, or toluene under reflux with metallic sodium or potassium. The substitution of sodium hydride<sup>40, 49c, 80</sup> for the metal may result in higher yields, especially with less reactive alcohols such as sterols.<sup>17</sup> The use of sodium amide in toluene has also been reported,<sup>9</sup> and the method is convenient in that salt formation can be followed by observing the ammonia evolution.

Sodium salt formation has also been accomplished by means of the exchange reaction between potassium sec-amyloxide<sup>89</sup> or t-amyloxide.<sup>33, 90</sup>

It was reported that the yield of xanthate produced by use of powdered sodium or potassium hydroxide with an excess of the required alcohol was superior to that produced by use of sodium or potassium metal.<sup>25</sup> However, in a later study it was stated that no essential difference in yield of xanthate was obtained.<sup>36</sup>

In one instance, where sodium hydride was used to form the sodium salt of the alcohol, epimerization of the alcohol was observed. When  $\alpha$ -cholestanol in benzene was heated under reflux with sodium hydride and then treated with carbon disulfide and methyl iodide,  $\beta$ -cholestanyl S-methyl xanthate was obtained in 65% yield.<sup>17</sup> When the reaction was attempted under an atmosphere of dry nitrogen, only  $\alpha$ -cholestanol was recovered.

Such epimerization of alcohols may occur more frequently than is realized, and the presence of the isomeric xanthate could account for some of the reports of apparent trans Chugaev eliminations.

Once the metal salt is obtained, difficulty is rarely encountered in the subsequent reactions with carbon disulfide and the alkyl halide (usually methyl iodide). However, in the attempted preparation of cholesteryl S-isobutyl xanthate, no xanthate could be obtained, probably owing to steric hindrance to back-side attack by the sodium xanthate on the isobutyl iodide.<sup>7</sup>

Difficulty is frequently encountered in the purification of the xanthate. Many xanthates are too unstable to permit purification by distillation, even under reduced pressure. Unless these xanthates can be obtained in crystalline form, purification is limited to washing with water to remove inorganic salts and unreacted alcohols of low molecular weight. Occasionally chromatography on alumina can be used for purification of liquid xanthates. Many of the xanthates listed in Tables II through IV were liquids which could not be purified, and the crude xanthates were pyrolyzed directly.

Table II. Pyrolysis of S-Methyl Xanthates of Acyclic Alcohols

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[View PDF](#)

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Table III. Pyrolysis of Xanthates of Alicyclic Alcohols

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[View PDF](#)

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Table IV. Pyrolysis of Xanthates of Glycols and Related Compounds

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[View PDF](#)

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In at least one case [(–)-menthyl S-methyl xanthate] instability of the xanthate to ultraviolet light was noted.<sup>73</sup> This observation suggests that, if a xanthate is to be stored for any length of time before pyrolysis, it should be protected from light.

## 5.2. Decomposition of the Xanthates

The pyrolysis of the xanthate is usually carried out by distilling it under atmospheric pressure. Depending on the pyrolysis temperature and the boiling point of the olefin, it will either distil with the other decomposition products or remain behind in the reaction flask. Sulfur-containing impurities may be removed by heating the olefin under reflux with sodium metal.

It is sometimes advantageous to conduct the pyrolysis under reduced pressure, thus ensuring that the olefin and other decomposition products are removed as fast as they are formed. This method reduces the contamination of the olefin by sulfur-containing impurities since it is known that mercaptans will add to olefins at elevated temperatures.<sup>91</sup>

If the stability of the olefin is such that it distils unchanged at its boiling point, decomposition can be effected by dropwise addition of the xanthate to boiling diphenyl ether<sup>40</sup> or some other high-boiling inert compound.

## 6. Experimental Procedures

### 6.1.1. (–)-Menthyl S-Methyl Xanthate (Use of Metallic Sodium)<sup>1, 73</sup>

To a solution of 50 g. (0.31 mole) of (–)-menthol in 50 ml. of toluene is added 8 g. (0.35 gram atom) of sodium. The mixture is heated under reflux for 32 hours. The mixture is then cooled in an ice bath, the unreacted sodium is removed with a wire, and 125 ml. of anhydrous ether is added followed by 45 g. of carbon disulfide. When the resultant reaction has subsided, 45 g. of methyl iodide is added, the mixture is heated under reflux for 1 hour and then cooled and filtered. The precipitated sodium iodide is washed with ether and the washings added to the filtrate. The solvent is then removed at 40°/20 mm. and the residue is taken up in 100 ml. of ethanol. Water is added to the point of cloudiness, crystallization is induced by scratching, and the mixture is cooled. The first crop, 33.4 g., has m.p. 40–40.5°,  $[\alpha]_D - 80^\circ$  (1% in  $\text{CHCl}_3$ ); the second crop, 10 g., m.p. 40–40.5°,  $[\alpha]_D - 84^\circ$  (1% in  $\text{CHCl}_3$ ); the third crop, 7 g., m.p. 39–40.5° (total yield, 65%).

A 10.0-g. (0.041 mole) sample of the xanthate is heated under reflux at 145–155° for 6 hours. The residue is then distilled through an efficient semimicro column<sup>92</sup> to give 3.23 g. (56%) of menthenes, b.p. 64.5–65°/22 mm.,  $n_D^{25} 1.4500$ ,  $[\alpha]_D + 117^\circ$  (1% in  $\text{CHCl}_3$ ). After a sample is epimerized,<sup>93</sup> it has  $[\alpha]_D + 32^\circ$  (1% in  $\text{CHCl}_3$ ), which corresponds to 24% of 2-menthene in the original mixture.



### 6.1.2. Cyclobutyl S-Methyl Xanthate (Use of Sodium Hydride)40

To a stirred suspension of 3.5 g. (0.146 mole) of sodium hydride in 100 ml. of dry ether is added dropwise 8 g. (0.11 mole) of cyclobutanol. The resulting mixture is heated under reflux for 3 hours. Then 9.7 g. (0.135 mole) of carbon disulfide is added, the mixture is heated under reflux for 3 hours, 19.2 g. (0.135 mole) of methyl iodide is added, and the mixture is heated under reflux for an additional 3 hours. Water is then added to dissolve the solid material, the ether layer is separated and dried, and the ether removed. Distillation at 67°/1.5 mm. yields 14.3 g. (84%) of the xanthate.

The xanthate is pyrolyzed by adding it dropwise to boiling biphenyl to yield butadiene, collected as a gas at atmospheric pressure. The yield is quantitative.

Cyclopentanol, when subjected to the same procedure, gives the xanthate, b.p. 88°/2.5 mm., in 90% yield. Pyrolysis of the xanthate furnishes cyclopentene, collected as the dibromide, in 70% yield.

### 6.1.3. Methyl-t-butylcarbinyl S-Methyl Xanthate (Use of Potassium t-Amyloxyde)33

A mixture of 42.9 g. (1.1 gram atoms) of potassium, 85.8 g. (1.1 moles) of t-amyl alcohol, and 1.5 l. of toluene is boiled under reflux until the potassium has reacted. Then 102 g. (1 mole) of methyl-t-butylcarbinol is added to the hot solution. The solution is cooled and 115 g. (1.5 moles) of carbon disulfide is slowly added, causing the precipitation of the yellow potassium xanthate and the evolution of much heat. The mixture is cooled to room temperature, 156 g. (1.1 moles) of methyl iodide is added, and the mixture is heated on a steam bath for 4–5 hours. The mixture is then filtered to remove the potassium iodide, and the filtrate is distilled at 70 mm. to remove toluene and alcohol. The residue is distilled in a Claisen flask to give the xanthate, b.p. 85–87°/6 mm., in 74% yield. The methyl iodide may be replaced by an equivalent amount of dimethyl sulfate with equally good results.

The xanthate is pyrolyzed by distillation at atmospheric pressure to give t-butylethylene in 58% yield.

When the same procedure is applied to methyl-t-amylcarbinol, ethyl-t-butylcarbinol, ethyl-t-amylcarbinol, and n-propyl-t-butylcarbinol, the xanthates are obtained in yields of 41–75%, and on pyrolysis they give the corresponding olefins in yields of 55–73%.

### 6.1.4. Isoamyl S-Methyl Xanthate (Use of Sodium Hydroxide)25

A mixture of 40.5 g. (1 mole) of finely pulverized sodium hydroxide, 89 g. (1 mole) of isoamyl alcohol, 50 ml. of carbon tetrachloride, and 600 ml. of ether is stirred for 30 minutes, and then 76 g. (1 mole) of carbon disulfide is added, followed by 149 g. (1.05 mole) of methyl iodide. Distillation gives 126 g. (71%) of isoamyl S-methyl xanthate, b.p. 100–102°/10 mm.,  $n_D^{20}$  1.5234.

The substitution of potassium hydroxide for sodium hydroxide does not affect the yield; elimination of the solvent and the use of excess alcohol gives a slightly higher yield. The use of potassium metal, isoamyl alcohol, and xylene gave the same xanthate in 65% yield.

The xanthate (216 g., 1.2 moles) is heated at its boiling point under partial reflux for 7.5 hours and 45 g. of distillate is collected. After purification by three extractions with 40% potassium hydroxide solution and one with saturated mercuric chloride solution, distillation gives isopropylethylene, b.p. 19–20°/740 mm., in 15% yield.



### 6.1.5. 3 $\beta$ -Cholestanyl S-Methyl Xanthate<sup>17</sup>

A mixture of 1.0 g. (2.6 mmoles) of 3 $\beta$ -cholestanol, 500 mg. (20.8 mmoles) of sodium hydride, and 50 ml. of dry benzene is stirred and heated under reflux for 24 hours. The reaction mixture is then allowed to cool to room temperature, 4 ml. of carbon disulfide is added, and the resulting red mixture is stirred under reflux for 24 hours. It is then cooled to room temperature, 4 ml. of methyl iodide is added, and the mixture is stirred and heated under reflux for 24 hours. Water is added dropwise to decompose the excess sodium hydride, the organic layer is washed with water, dried over anhydrous sodium sulfate, and the solvent is evaporated on a steam bath. The residue is taken up in 10 ml. of petroleum ether (b.p. 30–60°) and chromatographed on 10 g. of aluminum oxide (Merck, for chromatographic adsorption). On elution with 50 ml. of petroleum ether the xanthate is obtained as a yellow oil which crystallizes when solvent-free. Recrystallization from 2:1 acetone-ethanol gives 950 mg. (77%) of 3 $\beta$ -cholestanyl S-methyl xanthate, m.p. 86–87°,  $[\alpha]_D + 5^\circ$  (1%, CHCl<sub>3</sub>).

One more recrystallization from 1:1 acetone-ethanol gives 800 mg. (65%) of analytically pure material, m.p. 87.5–88°,  $[\alpha]_D + 2^\circ$ .

The xanthate (214 mg., 0.447 mmole) is pyrolyzed by heating at 230°/20 mm for 2.5 hours, and the residue is dissolved in petroleum ether and chromatographed on alumina. Petroleum ether elutes 156 mg. (94%) of a one-to-one mixture of 2- and 3-cholestene, m.p. 68–69°,  $[\alpha]_D + 64^\circ$ , after one recrystallization from one-to-one alcohol-acetone.

## 7. Tabular Survey

In Table [II](#) and [III](#) are listed the xanthates of alcohols that have been pyrolyzed to yield olefins. Table [IV](#) is a list of xanthates of glycols and dithioglycols.

Arrangement of compounds within a table is in the order: primary, secondary, and tertiary alcohols. Within each group the compounds are listed according to the number of carbons in the parent alcohol.

The literature has been searched through 1958, but some later references are included.

### End Notes

- \*
- Although there are several spellings of Chugaev, the two most common are Tschugaeff and Chugaev. The latter was chosen for this chapter because of its simplicity.

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TABLE I  
ISOTOPE EFFECTS IN THE PYROLYSIS AT 80° OF S-METHYL  
*trans*-2-METHYL-1-INDANYL XANTHATE

	Per Cent Isotope Effect, $100(k^L/k^H - 1)^a$		
	Thiol Sulfur $S^{32}/S^{34}$	Thion Sulfur $S^{32}/S^{34}$	Carbonyl Carbon $C^{12}/C^{13}$
Predicted			
Thiol sulfur	~ 1.2	~ 0.0	3.0-4.0
Thion sulfur	~ 0.0	0.7-1.0	~ 0.0
Found	$0.21 \pm 0.07$	$0.86 \pm 0.16$	$0.04 \pm 0.06$

<sup>a</sup>  $k^L/k^H$  is the ratio of the pyrolysis rate constants for the light and heavy isotopes.

TABLE II

## PYROLYSIS OF S-METHYL XANTHATES OF ACYCLIC ALCOHOLS

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
<i>Primary Alcohols</i>					
C <sub>5</sub>	<i>n</i> -Amyl alcohol	57, 62	Reflux	1-Pentene (15)	25
	Isoamyl alcohol	*	Reflux	Isopropylethylene (15)	25
	Neopentyl alcohol	*	Heat	No olefin, xanthate rearranged to dithiocarbonate (70)	26
C <sub>7</sub>	Benzyl alcohol	29	Not given	Stilbene (24)	28
		—	160–185	Stilbene (20)	27
	Cyclohexylcarbinol	*	>200	Methylenecyclohexane	29
C <sub>12</sub>	4-Methylcyclohexylcarbinol	†	Not given	Methylene-4-methylcyclohexane	29
	Diacetone galactose	*	Not given	Unidentified products	30
<i>Secondary Alcohols</i>					
C <sub>4</sub>	3,3,4,4,4-Pentafluoro-2-butanol	50	151–152	No reaction	94
C <sub>5</sub>	3-Pentanol	28	250	2-Pentene ( <i>cis</i> , 33; <i>trans</i> , 55)	31
	Methylcyclopropylcarbinol	52	130–230	Vinylcyclopropane (42), 1,4-pentadiene, 1-cyclopropylethyl methyl dithiocarbonate	34
C <sub>6</sub>	3-Hexanol	25	250	3-Hexene ( <i>cis</i> , 13; <i>trans</i> , 28), 2-hexene ( <i>cis</i> , 13; <i>trans</i> , 29)	31
	Methyl- <i>t</i> -butylcarbinol	74	160–175	<i>t</i> -Butylethylene (71)	4, 33
C <sub>7</sub>	Ethylisobutylcarbinol	30	200	2-Methyl-3-hexene ( <i>cis</i> , 5; <i>trans</i> , 43), 4-methyl-2-hexene ( <i>cis</i> , 9; <i>trans</i> , 28)	31

Note: References 94 to 109 are on p. 100.

\* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

OLEFINS BY PYROLYSIS OF XANTHATES

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TABLE II—Continued

## PYROLYSIS OF S-METHYL XANTHATES OF ACYCLIC ALCOHOLS

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
<i>Secondary Alcohols (Continued)</i>					
C <sub>7</sub> (Cont.)	Methyl- <i>t</i> -amylcarbinol	75	Not given	<i>t</i> -Amylethylene (67)	33
	Ethyl- <i>t</i> -butylcarbinol	60	Not given	2,2-Dimethyl-3-pentene (73)	33
C <sub>8</sub>	Trifluoromethyl- <i>n</i> -hexylcarbinol	*	241–243	No reaction	95
	Methylcyclohexylcarbinol	57	250	Cyclohexylethylene (32), ethylidenecyclohexane (20)	36
	2-Octanol	†	165	1-Octene (23–25), 2-octene (21–23)	25
	Ethylneopentylcarbinol	†	150	2,2-Dimethyl-3-hexene ( <i>cis</i> , 2; <i>trans</i> , 58), 2,2-dimethyl-4-hexene ( <i>cis</i> , 5; <i>trans</i> , 21)	31
	2,2-Dimethyl-3-hexanol	63	200	<i>trans</i> -2,2-Dimethyl-3-hexene (63–82)	31, 33
C <sub>10</sub>	3,3-Dimethyl-4-hexanol	41	Not given	3,3-Dimethyl-4-hexene (55)	33
	<i>erythro</i> -3-Phenyl-2-butanol	85	180	2-Phenyl-2-butene ( <i>cis</i> , 5; <i>trans</i> , 45), 3-phenyl-1-butene (32)	11
	<i>threo</i> -3-Phenyl-2-butanol	80	180	2-Phenyl-2-butene ( <i>cis</i> , 27; <i>trans</i> , 8), 3-phenyl-1-butene (28)	11
C <sub>11</sub>	<i>erythro</i> -2-Phenyl-3-pentanol	75	200	2-Phenyl-2-pentene ( <i>cis</i> , 4; <i>trans</i> , 27), 2-phenyl-3-pentene (37)	11
	<i>threo</i> -3- <i>p</i> -Tolylthio-2-butanol	†	200–220	<i>cis</i> -2- <i>p</i> -Tolylthio-2-butene (77)	24

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	<i>erythro</i> -3- <i>p</i> -Tolylthio-2-butanol	†	200-220	<i>trans</i> -2- <i>p</i> -Tolylthio-2-butene (58)	24
	<i>threo</i> -3- <i>p</i> -Tolylsulfonyl-2-butanol	†	200-220	<i>cis</i> -2- <i>p</i> -Tolylsulfonyl-2-butene (58)	24
	<i>erythro</i> -3- <i>p</i> -Tolylsulfonyl-2-butanol	†	200-220	2- <i>p</i> -Tolylsulfonyl-2-butene ( <i>cis</i> , 38; <i>trans</i> , 10)	24
C <sub>12</sub>	1,2-5,6-Diacetone glucose	*	290-300	Xanthate rearranged to dithiocarbonate (30)	30
	2,3-5,6-Diacetone mannose	*	Not given	Unidentified product	30
C <sub>13</sub>	Benzhydrol	†	190-260	Tetraphenylethylene	96
	Phenylcyclohexylcarbinol	70	160-175	Benzalicyclohexane (20)	97
C <sub>15</sub>	<i>threo</i> -1,2-Diphenyl-1-propanol	71	145-195	<i>cis</i> -1,2-Diphenyl-1-propene (65)	13
	<i>erythro</i> -1,2-Diphenyl-1-propanol	70	130-195	<i>trans</i> -1,2-Diphenyl-1-propene (77)	13
C <sub>23</sub>	12-Tricosanol	†	Not given	11-Tricosene	32
	<i>Tertiary Alcohols</i>				
C <sub>6</sub>	Dimethylcyclopropylcarbinol	†	130-135	Isopropenylcyclopropane (24)	78
C <sub>7</sub>	(-)-2-Methyl-3-ethoxy-2-butanol	†	Not given	(+)-2-Methyl-3-ethoxy-2-butene (71)	5
	Dimethylcyclobutylcarbinol	†	100-120°	Mixture of isopropylidenecyclobutane and isopropenylcyclobutane (27%)	79
C <sub>9</sub>	Dimethylcyclohexylcarbinol	57	150	Isopropylidenecyclohexane (11), 2-cyclohexylpropene (40)	36

Note: References 94 to 109 are on p. 100.

\* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

TABLE III  
 PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS  
 (The S-methyl xanthate was used unless otherwise specified.)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
<i>Secondary Alcohols</i>					
C <sub>4</sub>	Cyclobutanol	84	255	Butadiene (100)	40
C <sub>5</sub>	Cyclopentanol	90	255	Cyclopentene (70, as dibromide)	40
C <sub>7</sub>	endo-5-Hydroxybicyclo-[2.2.1]-2-heptene	†	250	Bicyclo-[2.2.1]-2,5-heptadiene (5)	78
	3-Methylcyclohexanol	80	Not given	Mixture of 3- and 4-methylcyclohexene (70)	41
	4-Methylcyclohexanol	†	175-178	4-Methylcyclohexene (27)	42
C <sub>8</sub>	Cyclooctanol	*	135-290°	<i>cis</i> -Cyclooctene (88)	49a
C <sub>9</sub>	Camphenilol	59	Reflux	Mixture of apobornylene and apocyclene (55)	50, 51
	<i>trans</i> -2-Carboethoxycyclohexanol	†	210-235	Ethyl cyclohexenecarboxylate (34)	46
	Cyclononanol	*	120-130	Cyclononene ( <i>cis</i> , 21; <i>trans</i> , 14)	49
			360	Cyclononene ( <i>cis</i> , 24; <i>trans</i> , 20)	
			400	Cyclononene ( <i>cis</i> , 30; <i>trans</i> , 7), 1,8-nonadiene	
			450	Cyclononene ( <i>cis</i> , 32; <i>trans</i> , 8), 1,8-nonadiene (5)	
			500	<i>cis</i> -Cyclononene (12), 1,8-nonadiene (12)	
C <sub>10</sub>	<i>cis</i> -2-Methyl-1-indanol	*	98-100	2-Methylindene (20)	16
	<i>trans</i> -2-Methyl-1-indanol	*	98-100	2-Methylindene (80)	16
	<i>cis</i> - $\alpha$ -Decalol-(I) (m.p. 93°)	25	180	1(9)-Octalin and 2-octalin	9, 47
	<i>trans</i> - $\alpha$ -Decalol-(I) (m.p. 49°)	†	205-210	1(9)-Octalin (3), <i>trans</i> -1-octalin (14)	9
	<i>trans</i> - $\alpha$ -Decalol-(II) (m.p. 63°)	†	100-200	<i>cis</i> - and <i>trans</i> -2-octalin, 9,10-octalin	9, 47
	<i>trans</i> - $\beta$ -Decalol-(II) (m.p. 75°)	†	150-200	1- and 2-Octalin	9, 47
	Cyclodecanol	*	135-220°	Cyclodecene ( <i>cis</i> , 6-11; <i>trans</i> , 38-50)	49a,c
	(-)-Borneol	†	Not given	Bornylene (90-96)	56
			Not given	Bornylene and tricyclene	57, 58
			220-230	(+)-Bornylene	55
		*	190-200 (reduced pressure)	Bornylene (50), "stable xanthate" (50)	54
		Dixanthide†	155-160	Camphene, bornylene, (-)-borneol	59
	(+)-Borneol	*	220-230	(-)-Bornylene	55
	Isoborneol	†	140-175	Camphene	61
	(-)-Epiborneol	†	Not given	(-)-Bornylene	60
	(-)-Carol	†	"Distil"	(-)-4-Carene	67
	(+)-Dihydrocarveol	†	"Distil"	Limonene, (-)-isolimonene	55, 98, 99
	(-)-Dihydrocarveol	†	170-200	(+)-Isolimonene	18
	$\alpha$ -Fenchol	90	230	Mixture (72) of cyclofenchene and $\alpha$ -fenchene	26, 64-66
	Isofenchol	†	160-230	$\alpha$ -Fenchene, cyclofenchene, iso-fenchylene	62-65
	(-)-Pinocampheol	*	170-190	$\delta$ - and $\alpha$ -Pinene (17, 21)	18, 71, 72
	Isopinocampheol	†	Not given	$\alpha$ -Pinene (38)	72
	Thujol	†	160-190	$\alpha$ - and $\beta$ -Thujene	19, 21, 22, 68, 69
	(+)-Thujol	†	138	$\alpha$ -Thujene	70
	(-)-Thujol	†	183	$\beta$ -Thujene	70
	(-)-Neothujol	†	Not given	$\beta$ -Thujene	20
	Verbanol	*	Not given	"Pinene" (18)	100

Note: References 94 to 109 are on p. 100.

\* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.



TABLE III—Continued

 PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS  
 (The S-methyl xanthate was used unless otherwise specified.)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
<i>Secondary Alcohols (Continued)</i>					
C <sub>10</sub> (Cont.)	(-)-Menthol	84 ("Stable" xanthate)	145-155	2-Menthene (14), 3-menthene (37)	73
		("Unstable" xanthate)*	145-155	2-Menthene (14), 3-menthene (43)	73
		("Unstable" xanthate)*	130-140°/10 mm.	2- and 3-Menthene; "stable" xanthate (40-50)	54, 73
		66	130-200	Menthenes	1, 9, 54, 101-103
		(S-Ethyl)*	Not given	Menthenes	102
		50 (S-Isopropyl)	170	Menthenes	74
			Distillation under reduced pressure	Menthenes; "stable" xanthate (12)	74
		40 (S-Benzyl)	160	Menthenes	74
		(S-p-Nitrobenzyl)*	135	Menthenes	74
		(Dixanthide)†	120	Menthenes, (-)-menthol	1, 59
		(Xanthogen amide)†	200-220	Menthenes	75
		(+)-Neomenthol	†	185-220	2-Menthene (80)
	trans-4-t-Butylcyclohexanol	62	208	4-t-Butylcyclohexene	44
	2-t-Butylcyclohexanol	†	200-205	3-t-Butylcyclohexene (60)	43
	Cyclodecanol	†	135-205	Cyclodecene ( <i>cis</i> , 6; <i>trans</i> , 38)	49c
	2,2,6,6-Tetramethylcyclohexanol	†	230	No olefin, rearranged to dithiocarbonate (70-80)	26
C <sub>11</sub>	Thujamenthol	†	Not given	Thujamenthene	104
	cis-2-Methyl-1-tetralol	*	98-100	No reaction	15
	trans-2-Methyl-1-tetralol	*	98-100	2-Methyl-3,4-dihydronaphthalene	15
	4-Methylborneol	†	Not given	4-Methylbornylene	105
	4-Methylisborneol	†	Not given	4-Methylbornylene	105
C <sub>12</sub>	6-Methylborneol	†	210-215	6-Methylbornylene (52)	106
	cis-2-Phenylcyclohexanol	90	210-240	2-Phenylcyclohexene (0-3), 3-phenylcyclohexene (68-87)	14, 45
	trans-2-Phenylcyclohexanol	†	110-175	2- and 3-Phenylcyclohexene	14
C <sub>13</sub>	4-Phenylcyclohexanol	†	230-240	4-Phenylcyclohexene (47)	14
	cis-2-p-Tolylthiocyclohexanol	†	190-210	p-Tolylthiocyclohexene (3-5), 3-p-tolylthiocyclohexene (49-51)	23
	trans-2-p-Tolylthiocyclohexanol	†	190-210	p-Tolylthiocyclohexene (85)	23
	cis-2-p-Tolylsulfonylcyclohexanol	†	210-215	p-Tolylsulfonylcyclohexene (40)	23
	trans-2-p-Tolylsulfonylcyclohexanol	†	210-215	p-Tolylsulfonylcyclohexene (77)	23
C <sub>15</sub>	1,1,7-Trimethyl-2-hydroxy-3-diethoxymethylcycloheptane	†	200-210	Unidentified olefin (50)	48
C <sub>27</sub>	Cholesterol	85	200-220	3,5-Cholestadiene (78-93)	7, 17, 77, 89, 107, 108
		80 (S-Ethyl)	200-220	3,5-Cholestadiene (86)	7, 108
		(S-n-Propyl)†	200	3,5-Cholestadiene	108
		92 (S-Benzyl)	220	3,5-Cholestadiene (90)	7
		85 (S-p-Nitrobenzyl)	220	3,5-Cholestadiene (90)	7
		85 (S-p-Chlorobenzyl)	220	3,5-Cholestadiene (88)	7
		70 (S-p-Methoxybenzyl)	220	3,5-Cholestadiene (84)	7

Note: References 94 to 109 are on p. 100.

\* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

TABLE III—Continued  
 PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS  
 (The S-methyl xanthate was used unless otherwise specified)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
<i>Secondary Alcohols (Continued)</i>					
C <sub>27</sub> (Cont.)	Cholesterol (Continued)	80 (S-2,4-Dinitrophenyl)	220	3,5-Cholestadiene (65)	7
		80 (S-Diphenylmethyl)	220	3,5-Cholestadiene (72)	7
		72 (S-Triphenylmethyl)	220	3,5-Cholestadiene (65)	7
		92 (Trithiocarbonate)	220	3,5-Cholestadiene (80)	7
	3β-Cholestanol	77	230	2- and 3-Cholestene (94)	17
	87 (S-Benzyl)	230	2- and 3-Cholestene (92)	17	
<i>Tertiary Alcohols</i>					
C <sub>5</sub>	1-Methylcyclobutanol	78	255	Methylenecyclobutane (15), 1-methylcyclobutene (21), isoprene (49)	80
C <sub>7</sub>	1-Methylcyclohexanol	†	200	Methylenecyclohexane (10), 1-methylcyclohexene (39)	26, 36
C <sub>8</sub>	1-Ethylcyclohexanol	†	200	Ethylidenecyclohexane (6), 1-ethylcyclohexene (46)	36
C <sub>9</sub>	1-Isopropylcyclohexanol	†	100	Isopropylidenecyclohexane (10), 1-isopropylcyclohexene (36)	36
	(+)-1-(1'-Methoxyethyl)cyclohexanol	†	Distilled	(-)-1-(1'-Methoxyethyl)cyclohexene	81

Note: References 94 to 109 are on p. 100.

† The crude xanthate was pyrolyzed.

TABLE IV

## PYROLYSIS OF XANTHATES OF GLYCOLS AND RELATED COMPOUNDS

Xanthate	Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
$\begin{array}{c} \text{CH}_2\text{SCSOC}_2\text{H}_5 \\   \\ \text{CH}_2\text{SCSOC}_2\text{H}_5 \end{array}$	*	200-270	Acetylene (26), ethyl mercaptan	84, 85
$\begin{array}{c} \text{CH}_3 \\   \\ \text{CHSCSOC}_2\text{H}_5 \\   \\ \text{CHSCSOC}_2\text{H}_5 \end{array}$	†	Not given	Methylacetylene, ethanol, ethyl mercaptan, carbon disulfide, carbon oxysulfide	84, 85
$\begin{array}{c} \text{CHCH}_2\text{SCSOC}_2\text{H}_5 \\    \quad (?) \\ \text{CHCH}_2\text{SCSOC}_2\text{H}_5 \end{array}$	†	Not given	Butadiene, ethyl mercaptan, carbon oxysulfide	85
$\begin{array}{c} \text{C}_2\text{H}_5 \\   \\ \text{CHSCSOC}_2\text{H}_5 \\   \\ \text{CH}_2\text{SCSOC}_2\text{H}_5 \end{array}$	†	Not given	Ethyl acetylene, ethyl mercaptan, carbon oxysulfide	84
$\begin{array}{c} \text{CH}_3\text{CHSCSOC}_2\text{H}_5 \\   \\ \text{CH}_2\text{CHSCSOC}_2\text{H}_5 \end{array}$	†	Not given	Butadiene	84
$\begin{array}{c} \text{CH}_2\text{CHOH} \\   \\ \text{CH}_2\text{CHOCSCH}_3 \\    \\ \text{S} \end{array}$	†	200	Cyclic thionocarbonate, methyl ethyl ketone	82, 83, 109

Note: References 94 to 109 are on p. 100.

\* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

## REFERENCES FOR TABLES II-IV

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<sup>98</sup> Pigulevskii and Gorbunova, *Compt. rend. acad. sci. (U.R.S.S.)*, **54**, 499 (1946) [*C.A.*, **41**, 6551 (1947)].  
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# The Synthesis of Aliphatic and Alicyclic Nitro Compounds

## 1. Introduction

This chapter is concerned with the synthesis of nitro compounds in which the nitro group is on a saturated carbon atom. The most important methods available involve:

1. Treatment of alkyl halides with silver nitrite, a reaction useful only for synthesizing primary nitro compounds.
2. The reaction of alkyl bromides and iodides with sodium nitrite, a method of considerable value for the preparation of primary and secondary nitroparaffins and a wide variety of  $\alpha$ -nitro esters.
3. The oxidation of amines, a general and very useful means of preparing tertiary nitro compounds which also shows promise as a way of preparing secondary nitro compounds.
4. The oxidation of oximes, a method of value for the preparation of a variety of primary and secondary nitro compounds.
5. The nitration of active methylene compounds using nitrate esters under basic conditions.
6. The nitration of active methylene compounds with nitric acid.

The discussion of these methods for introducing a nitro group is followed by a section which takes note of miscellaneous reactions of rather limited utility or reactions about which not much can be said for want of data.

Finally, a comparison of the utility of the various methods in the synthesis of particular types of nitro compounds is given (pp. 129–130).

Preparations of nitro compounds which employ other nitro compounds as starting materials, e.g., Michael condensations of the salts of nitroparaffins and Diels-Alder reactions of nitroolefins, are not discussed. Nor are the liquid or vapor phase nitrations of hydrocarbons taken up, for these usually produce mixtures of products and the emphasis in this chapter is on reactions that readily lead to pure products.

## 2. The Reaction of Alkyl Halides with Silver Nitrite

In 1872 Victor Meyer and Stüber<sup>1</sup> reported that on refluxing isoamyl iodide with silver nitrite a mixture of the nitro compound and isoamyl nitrite was produced. Separation of the mixture was readily achieved as a consequence of the considerable difference in boiling points. Other examples were soon forthcoming, and the reaction has come to be regarded as a general one.

### 2.1. Scope and Limitations

Until recently the reaction was usually conducted in the neighborhood of 80° to 110°. However, in 1947 it was shown that the reaction of 2-bromoöctane with silver nitrite at such temperatures gives 2-nitroöctane, 2-octyl nitrite, 2-octyl nitrate, 2-octanol, 2-octanone, and other, unidentified, products.<sup>2</sup> Soon after, analogous results were obtained with 2-iodobutane.<sup>3</sup> The formation of nitrate esters as by-products in the reaction of cyclopentyl and cyclohexyl iodides with silver nitrite has also been demonstrated recently.<sup>4</sup>

The incursion of side reactions is not limited to reactions in which secondary halides are employed. Thus, after a benzene solution of 1-bromoheptane is heated with silver nitrite at ca. 85°, pure 1-heptyl nitrate is easily isolated.<sup>5</sup>

Nitrate ester formation is a consequence of the thermal instability of silver nitrite which decomposes as follows at 80° or above.<sup>2</sup>



The silver nitrate thus produced reacts readily with alkyl halides to give nitrate esters. Because nitrate esters, in contrast to nitrite esters, are not readily separated from the corresponding nitro compounds by distillation, their formation constitutes a considerable liability.

### 2.1.1. Primary Nitro Compounds

With primary bromides and iodides side reactions are completely suppressed by starting the reaction at 0° and allowing it to proceed to completion at room temperature.<sup>6</sup> This is an excellent way to prepare pure primary nitro compounds. For example, 1-nitroöctane is obtained in 80% yield from 1-bromoöctane, and 1-iodoheptane gives 1-nitroheptane in 82% yield.<sup>6</sup> In contrast, primary chlorides are unaffected by silver nitrite at room temperature.



Good yields of nitroparaffins are also obtained with branched-chain primary bromides and iodides in which the branching is  $\beta$  to the carbon atom holding the halogen. Thus isoamyl bromide and iodide give 3-methyl-1-nitrobutane in 72% and 78% yield, respectively. However, branching  $\alpha$  to the carbon atom holding the halogen has a deleterious effect. The reaction employing isobutyl iodide produces a distinctly lower yield (55–63%) of nitro compound. When isobutyl bromide is treated with silver nitrite, even after five days only 37% of the bromide has reacted. Finally, neopentyl iodide is not noticeably affected by silver nitrite after three days at room temperature; by this time a typical straight-chain primary iodide has reacted completely.<sup>6</sup> In acetonitrile (see p. 108), at 40°, the reaction between neopentyl iodide and silver nitrite is 85% complete after five days. Only 3% of the product is soluble in base, and efforts to isolate nitroneopentane did not succeed.<sup>7</sup> It is highly unlikely that the reaction of neopentyl iodide with silver nitrite will serve as a means of preparing nitroneopentane.

With para-substituted benzyl bromides, as shown in Table I, the relative proportions of nitro compound and nitrite ester produced depend on the electrical character of the substituent.<sup>8</sup>

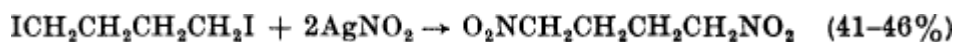
Table I. Products of the Reaction of Silver Nitrite with Benzyl Bromides

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A number of  $\alpha,\omega$  dinitro compounds have been prepared by the Victor Meyer reaction. A typical example is the synthesis of 1,4-dinitrobutane.<sup>9</sup>

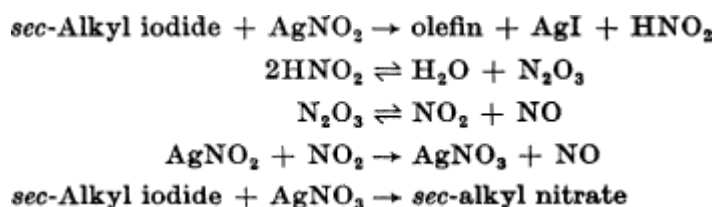


### 2.1.2. Secondary Nitro Compounds

The reaction of secondary halides with silver nitrite gives poor yields (ca. 15% on the average) of pure nitroparaffins despite the use of temperatures in the range from 0° to 25°. <sup>10</sup> There are several reasons for this behavior.

With secondary halides, nitrite ester formation is more important than in reactions employing primary halides. A second, and major, complication is dehydrohalogenation, which leads to two additional side reactions: (a) the “low-temperature” formation of nitrate esters, and (b) the addition of oxides of nitrogen to the olefin. <sup>10</sup>

The following sequence, which accounts for the “low-temperature” production of alkyl nitrates, is consistent with all the facts<sup>\*</sup> and invokes only reactions known to occur under the conditions employed.



Actually, the yields of nitrate esters are usually less than 10%, but their removal from nitro compounds requires a chemical separation which gives the pure nitroparaffin but significantly depresses the yield. <sup>2, 11</sup>

The addition of oxides of nitrogen to the olefin formed by dehydrohalogenation is evidenced by the formation of relatively non-volatile, thermally unstable products. In several instances crystalline compounds having the composition and properties of N<sub>2</sub>O<sub>3</sub>-olefin adducts have been isolated. <sup>10</sup> That these adducts are produced under the conditions of the Victor Meyer reaction is not surprising since, under similar conditions, nitrogen trioxide and nitrogen tetroxide readily add to olefins giving nitroso-nitro compounds, nitroso-nitrates, nitro-nitrites, nitro-nitrates, and dinitro compounds. <sup>12</sup>

### 2.1.3. Tertiary Nitro Compounds

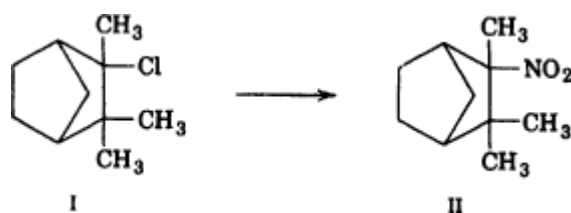
The reaction of tertiary halides with silver nitrite is of no value for the synthesis of tertiary nitro compounds. <sup>10</sup> At best, the nitro compound is obtained in 5% yield; usually none can be isolated.

Tertiary chlorides, in contrast to primary and secondary chlorides, react readily. Here, and with tertiary bromides, the major product is the nitrite ester (ca. 50–60% yield). Just as with secondary halides, blue-green nitrogen oxide-olefin adducts are also produced in appreciable amounts.

When t-butyl iodide is treated with silver nitrite at 0° a rapid reaction takes place. Iodine (50% yield) and a colorless unidentified gas are produced, <sup>10</sup> but the tertiary nitrobutane is not found and the product does not possess the characteristic ultraviolet absorption spectrum of t-butyl nitrite.

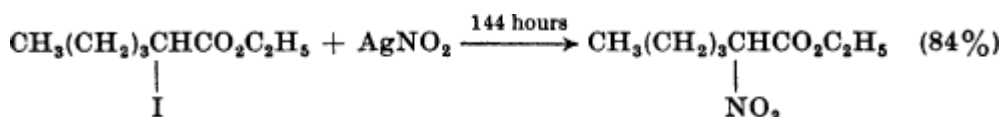
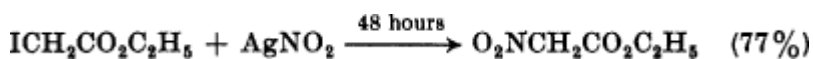
It has been reported that camphene hydrochloride I gives the tertiary nitro compound II on treatment with silver nitrite. <sup>13</sup> Actually, the nitro compound is not isolated. Instead the crude reaction product is reduced with sodium and isoamyl alcohol to 3-aminoisocamphane which is isolated in an over-all yield of about

4%. For a tertiary halide to give the nitro compound is of interest; but even more interesting is the production of the unrearranged product in a system notorious for ease of rearrangement.



#### 2.1.4. $\alpha$ -Nitro Esters

The reaction of  $\alpha$ -bromo esters with silver nitrite is so slow as to be completely impractical. Thus, after six and one-half days at room temperature, ethyl bromacetate and ethyl  $\alpha$ -bromopropionate reacted only to the extent of 12–15%. In contrast, when straight-chain  $\alpha$ -iodo esters of low molecular weight are employed, the reaction proceeds at a useful rate and produces excellent yields of pure  $\alpha$ -nitro esters.<sup>14</sup>



It is not known whether still longer reaction times are necessary with the higher homologs. However, the alternative procedure, the reaction between the readily available  $\alpha$ -bromo esters and sodium nitrite (p. 112), is so rapid and gives such good yields of  $\alpha$ -nitro esters that it is the method of choice. The sole exception is ethyl nitroacetate, which is easily obtained by the silver nitrite reaction but which cannot be prepared by the sodium nitrite process.<sup>15</sup>

## 2.2. Stereochemistry and Mechanism

When optically active 2-bromoöctane is allowed to react with silver nitrite in diethyl ether, 2-nitroöctane and 2-octyl nitrite are produced with inversion of configuration. The same result is obtained with optically active 2-iodoöctane.<sup>16</sup> If the reaction is conducted in cyclohexane, benzene, or acetonitrile, the 2-nitroöctane and 2-octyl nitrite are again of the inverted configuration.<sup>17</sup> The importance of nucleophilic attack rearward to the carbon-halogen bond by nitrite ion is also evident from the fact that neopentyl iodide is inert to silver nitrite under conditions which result in complete reaction with other primary iodides.

The reaction of silver nitrite with aliphatic halides, while possessing these  $\text{S}_{\text{N}}2$  attributes, simultaneously exhibits the characteristics of an  $\text{S}_{\text{N}}1$  process.<sup>8</sup> Thus the reaction rate increases on going from primary to secondary halides. Then, too, the variations in rates and products of the reaction of silver nitrite with benzyl bromides as a function of the para substituent (cf. Table I) become intelligible on the basis that the transition state of these reactions possesses carbonium ion character. That the formation of a silver-halogen bond furnishes an important part of the driving force for these reactions is clear from the failure of sulfonate esters to react with silver nitrite.

Because of these and a number of other facts, the reaction of alkyl halides with silver nitrite is regarded as one in which the pull of the silver on the halogen and the push of the nitrite ion are both important in the



transition state; the proportions of  $S_N1$  and  $S_N2$  character vary as a function of the structure of the halide and the nature of the reaction medium, and the products of the reaction reflect this variation in character: the greater the carbonium contribution to the transition state, the greater is the yield of nitrite ester and the smaller is the yield of nitroparaffin.<sup>8</sup>

In contrast, the reaction of optically active  $\alpha$ -phenylethyl chloride and silver nitrite proceeds with retention of configuration in ethyl ether or benzene but with inversion in cyclohexane.<sup>17</sup> These facts are interpreted to mean that, whereas in cyclohexane the graded  $S_N1$ – $S_N2$  path is followed, in diethyl ether (and in benzene) the reaction proceeds via the  $\alpha$ -phenylethyl carbonium ion. A detailed discussion of the stereochemistry and mechanism of the reaction of silver salts with organic halides will be published shortly.<sup>17</sup>

## 2.3. Experimental Conditions

It is good practice to maintain the reaction mixture in the neighborhood of  $0^\circ$  for the first 24 hours. After this the ice bath is removed and the reaction is allowed to proceed to completion at room temperature. The system should be protected from light until the silver salts are removed by filtration. Also, since nitrite esters are photochemically unstable, it is best to minimize exposure to light until they have been removed from the reaction mixture by distillation.

It is more difficult to remove an alcohol from the corresponding nitroalkane than it is to separate the nitrite ester. Minimal exposure to a moist atmosphere is, therefore, desirable.

Anhydrous diethyl ether is an excellent medium for these reactions. Petroleum ether, cyclohexane, and benzene have also been employed. In all these media silver nitrite is virtually completely insoluble. In contrast, silver nitrite dissolves in acetonitrile, and when such a solution is treated with 1-iodoheptane the yield of 1-nitroheptane is 60–64% and that of 1-heptyl nitrite is 23–33%.<sup>18</sup> Since the reaction of silver nitrite with 1-iodoheptane in diethyl ether gives 78–82% yields of 1-nitroheptane, and only 7–12% yields of 1-heptyl nitrite, it is clear that there is no advantage in carrying out the reaction in acetonitrile.

Indeed, the use of acetonitrile as a solvent is disastrous when a primary nitro compound of relatively high acidity is being produced. Thus, whereas the reaction of *p*-nitrobenzyl bromide with silver nitrite gives *p*-nitrophenylnitromethane in 75% yield in diethyl ether,<sup>8</sup> in acetonitrile no *p*-nitrophenylnitromethane is isolated.<sup>19</sup> Instead, a complex mixture is obtained. Enough is known about the mixture to suggest that the *p*-nitrophenylnitromethane initially formed is converted to the salt by dissolved nitrite ions; the anions of *p*-nitrophenylnitromethane are then oxidized by the silver ions or else undergo nitrosation.<sup>19</sup> In diethyl ether, presumably because of the insolubility of silver nitrite and the much smaller dielectric constant, *p*-nitrophenylnitromethane is not converted to the salt and side reactions are thereby averted.

It is important to recognize that many of the older preparations (prior to 1947) of nitro compounds are likely to be contaminated with the corresponding nitrate esters.<sup>2</sup> Indeed, if in the preparation of a nitro compound the reaction temperature exceeds  $30^\circ$ , the product should be scrutinized carefully to ensure that the corresponding nitrate ester is not present. With a secondary halide, even when the temperature is maintained between  $0^\circ$  and  $25^\circ$ , small amounts of nitrate esters are likely to be formed. Gross contamination by alkyl nitrates is easily demonstrated by shaking the product with 10–20% aqueous alkali; any nitrate ester present remains undissolved. The infrared spectra of nitrate esters are characterized by two sharp, intense, absorption bands close to  $6.14 \mu$  and  $7.84 \mu$ , and a third, intense but broad band centered around  $11.5$ – $11.7 \mu$ .<sup>20</sup> These bands provide a valuable means of detecting even small amounts of alkyl nitrates in nitroalkanes.

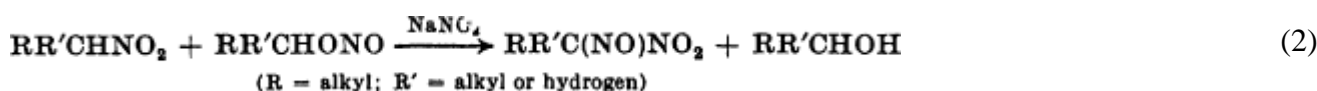
## 3. The Reaction of Alkyl Halides with Sodium Nitrite

The widely held view that the reaction of alkali metal nitrites with alkyl halides produces nitrite ester, with little or none of the nitro compound being formed,<sup>\*</sup> has recently been shown to be erroneous.<sup>21</sup> Actually, the nitro compound and nitrite ester are both produced, but the nitro compound is the major product so that the reaction employing sodium nitrite provides a simple and effective means of preparing aliphatic and alicyclic nitro compounds.

### 3.1. Scope and Limitations

Unless appreciable amounts of both the alkali metal nitrite and the alkyl halide are in solution the reaction does not occur. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) are among the few solvents which dissolve significant amounts of sodium nitrite and alkyl halides, and this is one of the reasons the synthesis of nitroparaffins from sodium nitrite and alkyl halides is conducted in these solvents.

A second reason for employing DMF or DMSO is that the reaction of alkali nitrites with alkyl halides is exceptionally fast in these media.<sup>21, 22</sup> The great speed of reaction (1) in DMF and DMSO makes it possible to minimize the side reaction (2) whose existence has been established recently.<sup>23</sup>



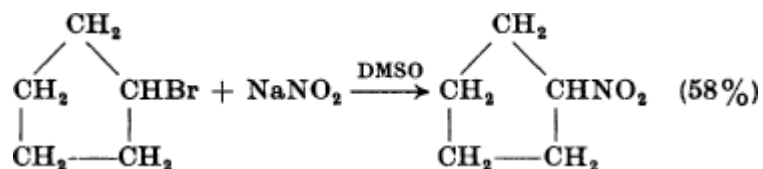
Even in DMF, sodium nitrite has a rather limited solubility, and this prevents realization of the reaction of nitrite ion with an alkyl halide at a rate which is anticipated from the kinetics in dilute solution. None the less, the reaction of a primary bromide or iodide with sodium nitrite is so much faster than the competing side reaction (2) that the side reaction can be effectively forestalled by working up the reaction mixture promptly.

With secondary bromides and iodides, nitrosation of the initially formed nitroparaffin would become a serious problem in the absence of several simple devices. The addition of urea to DMF markedly increases the solubility of sodium nitrite and, in reactions employing secondary alkyl iodides, this is all that is required to prevent the nitrosation process of equation (2).

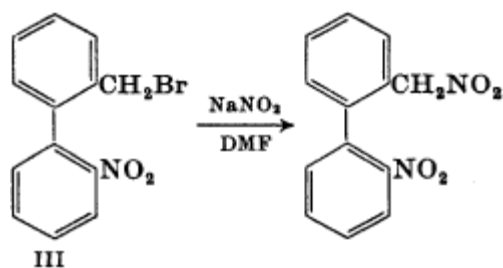
With secondary bromides and also cyclopentyl and cycloheptyl iodides, it becomes desirable not only to add urea but also a nitrite ester scavenger. Compounds such as phloroglucinol, catechol and resorcinol can be used for this purpose. Of these, phloroglucinol is the most effective.<sup>21</sup> Sodium nitrite is so soluble in DMSO that urea is never added when DMSO is the reaction medium.<sup>22</sup>

Alkyl bromides and iodides are equally useful for the preparation of primary and secondary nitroparaffins.<sup>21</sup> In contrast, alkyl chlorides react too slowly to be useful.

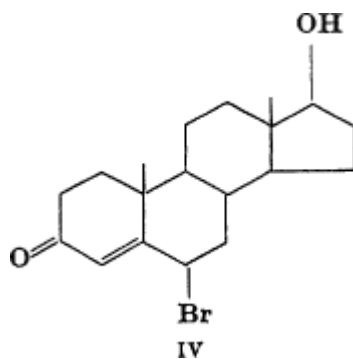




It is noteworthy that the yield of nitro compound obtained from benzyl bromide is slightly, but unmistakably, lower than that obtained from strictly aliphatic primary bromides while the yield from *p*-nitrobenzyl bromide is much lower. Undoubtedly related is the difficulty experienced in obtaining a pure product from the halide III.<sup>24</sup> The generalized significance of these results is discussed in the section dealing with the preparation of  $\alpha$ -nitro esters (p. 113).



The reaction of sodium nitrite with *t*-butyl bromide, *t*-butyl chloride, cyclohexyl bromide, and cyclohexyl iodide fails to give nitro compounds; instead isobutylene and cyclohexene are obtained.<sup>21</sup> The recent report that 6 $\beta$ -bromotestosterone IV does not yield a nitro steroid on treatment with sodium nitrite in DMF<sup>25</sup> is not surprising. It is of interest that bromocycloheptane and iodocycloheptane give 55% and 58% yields, respectively, of nitrocycloheptane.<sup>21</sup>



Sulfonate esters may also be employed in the sodium nitrite reaction. Without any attempt to establish optimum conditions, *n*-octyl tosylate and *n*-butyl methanesulfonate were converted to the corresponding nitroparaffins in 43–46% yields.<sup>21</sup> The use of sulfonates would, of course, be advantageous when dealing with alcohols that rearrange on conversion into halides. In this connection it should be recalled that the conversion of secondary alcohols to the corresponding bromides, using hydrobromic acid or phosphorus

tribromide, produces significant amounts of isomeric secondary bromides; e.g., from 2-pentanol between 10% and 28% of the product is 3-bromopentane.[26](#)

## 3.2. The Relative Value of Silver Nitrite and Sodium Nitrite for the Synthesis of Particular Types of Nitro Compounds

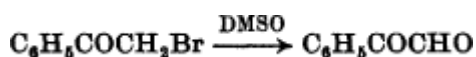
In the synthesis of saturated primary nitro compounds, silver nitrite gives nitroparaffins in about 80% yields as against about 60% yields obtained with sodium nitrite. While silver nitrite is, therefore, the reagent of choice here, the lower cost and ready availability of sodium nitrite, the not very large disparity in yield, and the shorter reaction time all combine to make sodium nitrite an excellent second choice. If, however, the primary nitro compound is of the type A single bond CH<sub>2</sub>NO<sub>2</sub>, where A is carbethoxy, p-nitrophenyl, or some other powerful electron-withdrawing group, silver nitrite is greatly preferred.

Sodium nitrite is far superior to silver nitrite for the synthesis of all types of secondary nitro compounds.

## 3.3. Experimental Conditions

The reaction of alkyl halides with sodium nitrite is generally carried out at room temperature; with benzylic halides a temperature in the neighborhood of -20° is employed. Since DMSO freezes at 18°, it cannot be employed at low temperatures; the importance of this restriction may be appreciated from the results obtained on converting α-phenyl-ethyl bromide to the nitro compound. In DMF at -18° a 43% yield of pure product is isolated, whereas in DMSO at 11° the yield is only 22%.[35](#)

In general, DMF and DMSO are about equally useful as solvents. It should be remembered, however, that DMSO is not a completely inert solvent. For example, it has been found that, at room temperature, DMSO oxidizes phenacyl bromides to the corresponding glyoxals.[36](#)



In the synthesis of nitro compounds from α-halo esters, secondary bromides, and alicyclic iodides, phloroglucinol is added to prevent the nitrosation process from destroying the nitro compound. With phloroglucinol present excessive reaction time is no longer critical, the only requirement being that sufficient time be given for the halide to react completely.

When phloroglucinol is not employed it is necessary to work up the reaction mixture promptly to prevent nitrosation. In DMF, primary bromides need a reaction time of 6 hours and primary iodides require 2½ hours; the addition of urea, by solubilizing the sodium nitrite, halves the reaction time. Because sodium nitrite is considerably more soluble in DMSO than in DMF, much more concentrated solutions can be prepared and this makes possible shorter reaction times. Reference should be made to the original papers[21](#), [22](#) for further details concerning reaction times. A convenient means of following the reaction is to titrate the liberated halide ion.

Lithium and potassium nitrites are as effective as sodium nitrite; the preference for sodium nitrite is based on price and availability.

## 4. The Oxidation of Amines

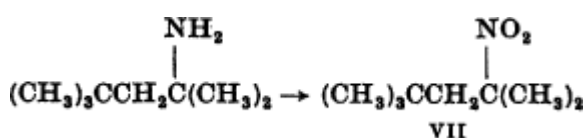
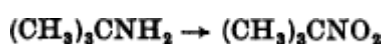
Although tertiary nitroparaffins have been known for many years, they have never been obtained by reactions which could be regarded as synthetically useful. Thus liquid phase nitration generally involves heating small amounts of a hydrocarbon in sealed tubes with dilute nitric acid to 130–150° for prolonged

periods. A large number of tubes are required, and they need to be opened for periodic relief of pressure; complex mixtures are produced, and the yields of pure tertiary nitro compounds are poor.[37](#)

The vapor phase nitration process devised by Hass, Hodge, and Vanderbilt,[38](#) despite its commercial importance, can hardly be regarded as a laboratory synthesis, the more so because it gives rise to complex mixtures. Finally, the classical reaction of silver nitrite with alkyl halides is worthless for the preparation of tertiary nitroparaffins.[10](#)

A simple and reliable procedure for oxidizing tertiary carbinamines,  $RR\phi R^2CNH_2$ , to the corresponding tertiary nitro compounds at 25–30° has recently been devised.[39](#) This procedure, which employs potassium permanganate, has the virtue of being applicable, without alteration, to a wide variety of amines; furthermore, it gives excellent yields of pure tertiary nitroparaffins. The method also has the advantage of starting with tertiary carbinamines, substances which have become easily accessible.[40](#)

The permanganate oxidation of t-butylamine in aqueous solution gives the tertiary nitrobutane in 83% yield. Amines of higher molecular weight which are insoluble in water are dissolved in a mixture of 80% acetone and 20% water, and the pH is controlled by adding magnesium sulfate. A typical example is the synthesis of the tertiary nitroöctane VII in 77% yield.[39](#)



Primary amines of the type  $RCH_2NH_2$  or  $R_2CHNH_2$  have not been tried in reaction with potassium permanganate, although it is presumed they will not give nitro compounds. The ability of a primary amine to be oxidized by permanganate to a nitro compound (which was reduced back to the original amine) has been used as a diagnostic for the t-carbinamine structure,  $RR\phi R^2CNH_2$ .[13](#)

In only one instance does the permanganate oxidation fail to give the desired t-nitro compound. When oxidation of triphenylmethanamine to triphenylnitromethane is attempted the only product isolated, aside from a 40% recovery of the amine, is triphenylcarbinol (33% yield based on the amine which reacted). This failure could have been anticipated from the report that triphenylnitromethane is readily decomposed by moisture.[41](#)

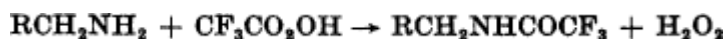
Emmons[42](#) has briefly examined the oxidation of aliphatic amines with peracetic acid. Although the oxidation of t-octylamine gives an 87% yield of the tertiary nitroöctane VII, Emmons regards the permanganate oxidation of t-carbinamines to tertiary nitro compounds as a more convenient preparation.

It is significant that peracetic acid can be employed for the synthesis of secondary nitroparaffins. Thus nitrocyclohexane is obtained in 70% yield on oxidizing cyclohexylamine, while 2-nitrobutane is isolated in 65% yield from 2-aminobutane. Although these were the only amines studied, oxidation with peracetic acid appears very much worth considering for the preparation of secondary nitro compounds. Indeed, except for the oxidation of oximes (p. 119), this is the only laboratory method available for introducing a nitro group into the cyclohexane nucleus.

The preparation of only one primary nitro compound by the use of peracetic acid is reported. n-Hexylamine gives 1-nitrohexane in 33% yield.[42](#)

Attempts to oxidize aliphatic amines with trifluoroacetic acid lead to the formation of the amine trifluoroacetate salts. Solutions of trifluoroacetic acid always contain considerable quantities of

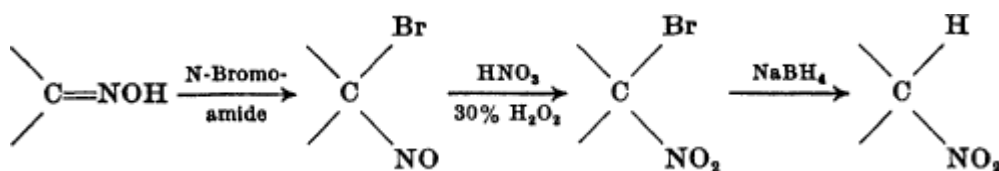
trifluoroacetic acid; as this is a strong enough acid to protonate virtually all the amine, the oxidation does not take place. When a sodium carbonate buffer system is present it is possible to obtain a reaction between an aliphatic amine and trifluoroperacetic acid, but the product is the N-alkyl trifluoroacetamide.<sup>42</sup>



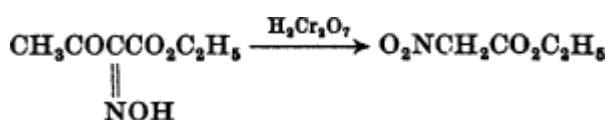
In a preliminary experiment t-butylamine was converted to 2-nitro-2-methylpropane in 31% yield by treatment with alkaline hydrogen peroxide.<sup>39</sup> Since hydrogen peroxide offers no advantage in the laboratory, its use has not been investigated further.

## 5. The Oxidation of Oximes

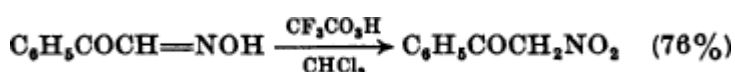
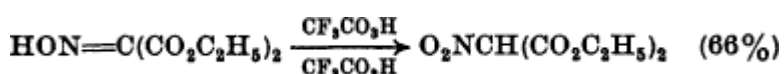
Two principal methods are available for oxidizing oximes to nitro compounds. One, developed by Emmons,<sup>43</sup> uses peroxytrifluoroacetic acid as the oxidant. The other, developed by Iffland,<sup>44-46</sup> involves three steps. The former method is the more generally useful one, but the latter procedure is preferable for the oxidation of sterically hindered oximes.



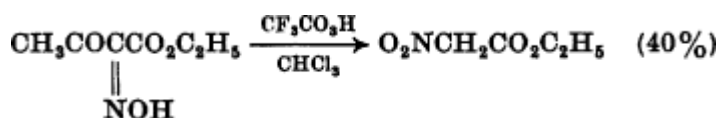
A third method, which seems to have been employed in only one instance, uses sodium dichromate in an aqueous acetic acid solution of sulfuric acid. In this way crude ethyl nitroacetate was obtained in 61% yield from ethyl  $\alpha$ -oximinoacetoacetate;<sup>47</sup> a slight modification of the reaction conditions furnished ethyl nitroacetate of high quality in 53% yield.<sup>48</sup>



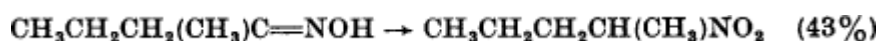
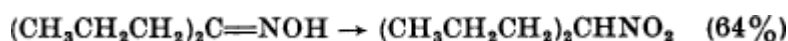
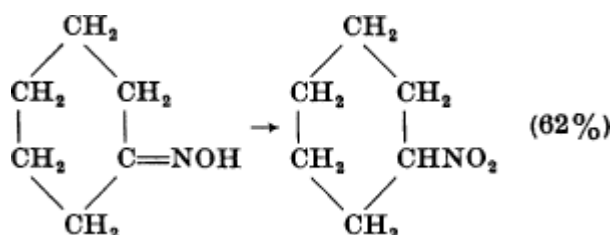
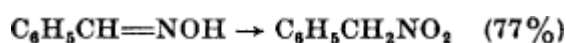
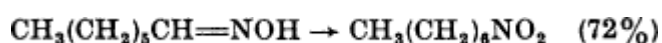
A wide variety of primary and secondary nitro compounds has been prepared by oxidation with peroxytrifluoroacetic acid; the yields range from 40% to 77%, the average being around 60%.<sup>43</sup> The preparation of nitro compounds in which the nitro group is alpha to a carbonyl group is conducted either in trifluoroacetic acid or in chloroform. Some typical results are given in the accompanying equations. It is presumed that the aci forms of these nitro compounds, e.g.,  $\text{HO}_2\text{N}=\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2$ , are the first products of oxidation and that, because of resonance stabilization, they are not destroyed before isomerization to the nitro form takes place.







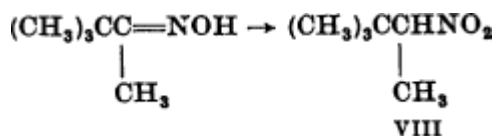
For the preparation of nitro compounds from monofunctional oximes, e.g., n-octanal oxime, the peroxytrifluoroacetic acid oxidation procedure must be modified in two ways. Acetonitrile is employed as the solvent and a buffer is added. Sodium bicarbonate is a satisfactory buffer in the oxidation of aliphatic oximes, while disodium hydrogen phosphate is used with aromatic and alicyclic oximes. The addition of small amounts of urea for scavenging any nitrogen oxides increases the yields significantly. Oxidation normally is carried out by the slow addition of an anhydrous solution of peroxytrifluoroacetic acid in acetonitrile to an acetonitrile solution of the oxime in which the buffer is slurried. Gentle reflux is maintained throughout the addition; too rapid addition of the peracid or overheating lowers the yield of nitroparaffin markedly. Some typical results are shown in the accompanying equations.



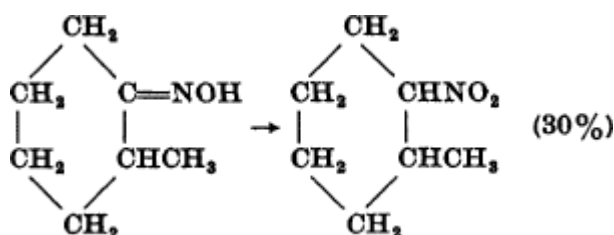
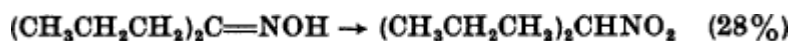
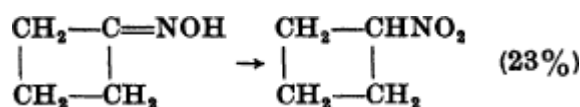
The preparation of nitrocyclohexane is especially noteworthy, for neither the sodium nitrite nor the silver nitrite reaction with cyclohexyl halides gives nitro compounds. Aside from the Iffland method of oxidizing oximes (which gives a 50% yield of nitrocyclohexane), the only other example of a laboratory procedure for the introduction of a nitro group into a cyclohexane nucleus is the peracetic acid oxidation of cyclohexylamine,<sup>42</sup> which gives a 70% yield of nitrocyclohexane (see p. 117). But, more often than not, the requisite amine would be obtained by reduction of the oxime.

The preparation of  $\alpha$ -phenylnitroethane in 69% yield suggests that the Emmons-Pagano peroxytrifluoroacetic acid oxidation procedure may prove especially valuable for the synthesis of nitro compounds such as  $\text{ArCH(R)NO}_2$ .

The peroxytrifluoroacetic acid oxidation of oximes is rather sensitive to steric hindrance. Neither pinacolone oxime nor trimethylacetaldehyde oxime is oxidized successfully by this procedure. In both cases most of the oxime is recovered. In contrast, Iffland and Yen<sup>46</sup> have converted pinacolone oxime to the pure nitro compound VIII in 36% yield by the three-step procedure. It is unlikely that any other method of preparing nitroparaffins would be a practical route to this compound.

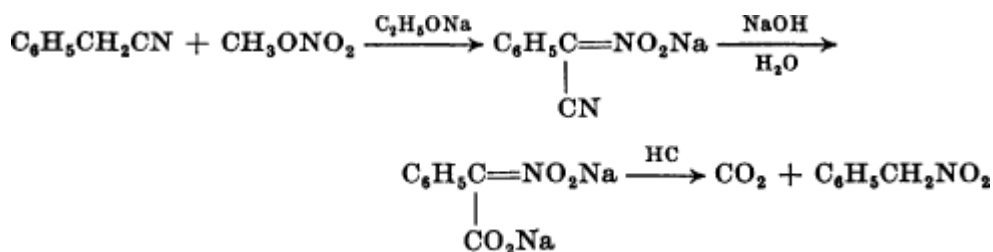


In the three-step sequence the oxime is first treated with either N-bromosuccinimide or N-bromoacetamide, and the resulting bromo nitroso compound is then oxidized to the bromo nitro compound by a mixture of nitric acid and 30% hydrogen peroxide. The bromo nitro compound is debrominated with sodium borohydride. It is not necessary to isolate or purify any of the intermediates. The procedure can be used only for the synthesis of nitrocycloalkanes and secondary nitroalkanes; it fails completely with aldoximes and aromatic ketoximes. As noted earlier, cyclohexanone oxime gives nitrocyclohexane in 50% yield; this and the 55% yield obtained in preparing nitrocyclopentane are the best yields which have been obtained. The accompanying equations illustrate some more typical results.



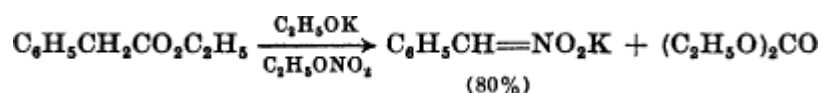
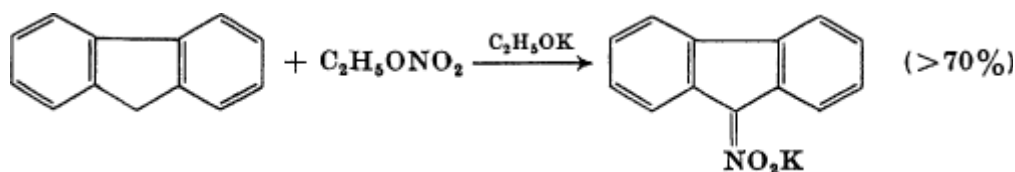
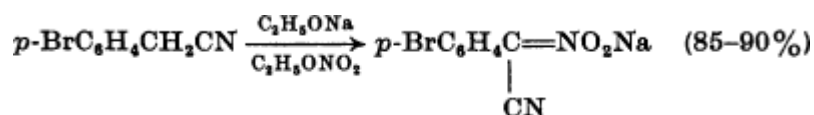
## 6. The Reaction of Active Methylene Compounds with Nitrate Esters

The nitration of an active methylene compound by the action of a nitrate ester under basic conditions has found some use in synthesis. Indeed, the preparation of phenylnitromethane described in Organic Syntheses<sup>49</sup> employs this reaction and provides phenylnitromethane in an over-all yield of 50–55%.



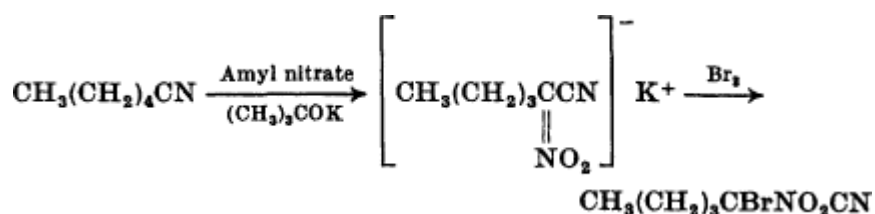
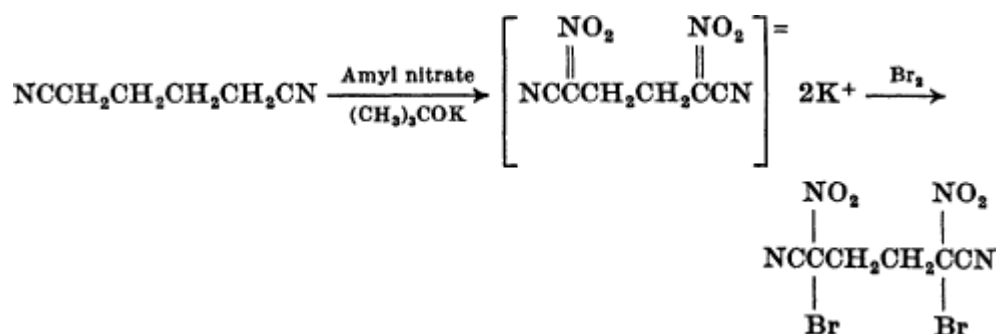
Early in the present century Wislicenus and his students showed that arylacetonitriles such as p-bromophenylacetonitrile,<sup>50</sup> arylacetic esters,<sup>51</sup> and fluorene<sup>52</sup> could be nitrated with ethyl nitrate, often in excellent yields. A distinguishing feature of the reaction with arylacetic esters is the loss of the ester group as diethyl carbonate. Thus, from the ethyl ester of phenylacetic acid, the product is the salt of phenylnitromethane.<sup>51</sup>





It is difficult to evaluate this method. Yields, when reported, are usually based on the crude salt of the nitro compound. Nitro salts are, in general, not easy to purify, and those derived from nitrated active methylene compounds are even more likely to be labile and difficult to purify. In addition, many of these salts are hygroscopic. The generation of the nitro compound from its salt by acidification involves the risk that some decomposition to the corresponding aldehyde or ketone (the Nef reaction) may take place.<sup>53</sup> And, finally, the nitro compounds derived from active methylene compounds are often intrinsically unstable.<sup>54-56</sup>

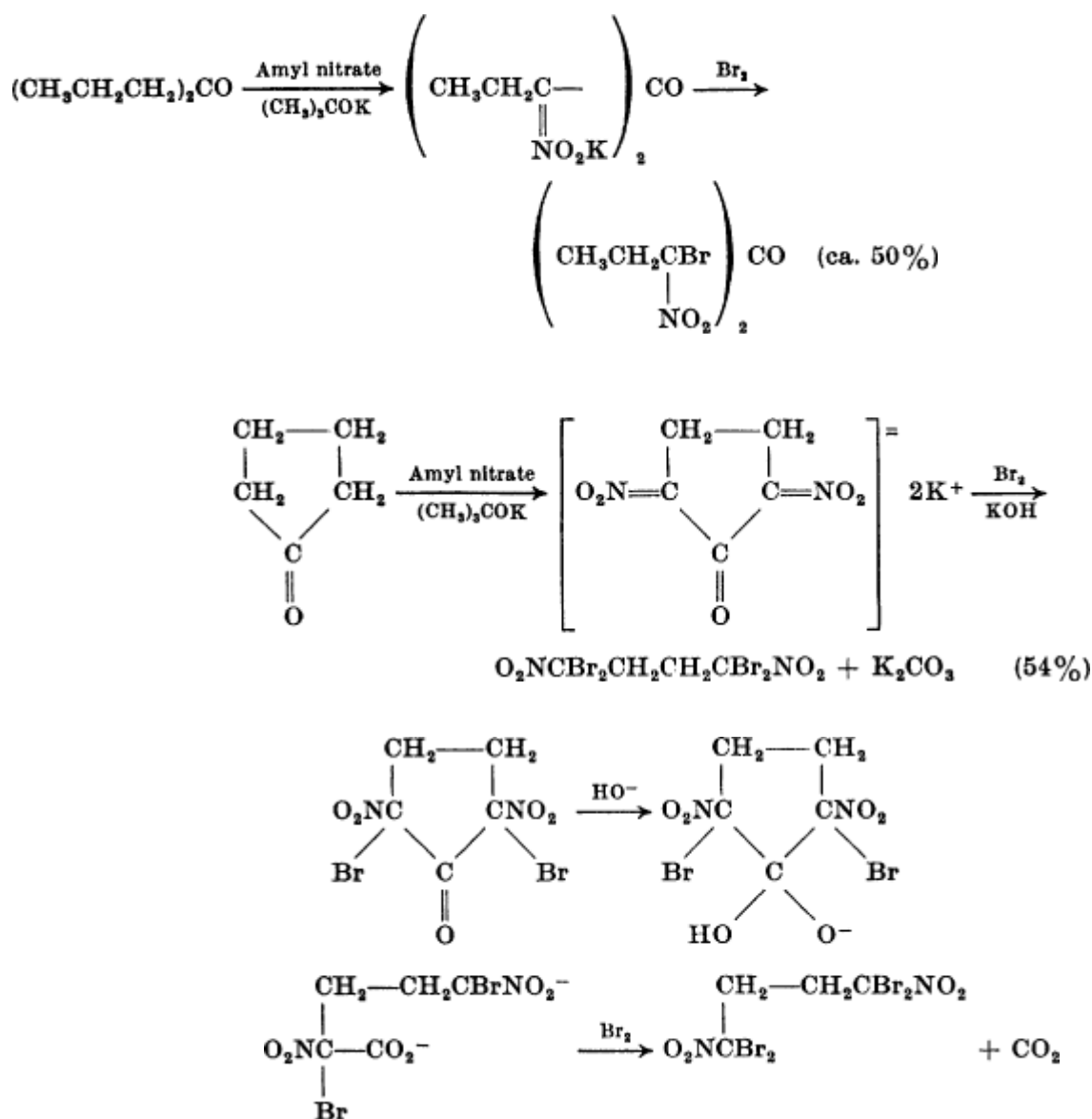
Bromination of the nitro salts has been employed as a device for identifying the nitration products and, since bromination of nitro salts is virtually a quantitative process, for determining yields.<sup>55-58</sup> Thus with adiponitrile the over-all yield of  $\alpha, \alpha\text{-}\delta$ -dibromo- $\alpha, \alpha\text{-}\delta$ -dinitroadiponitrile is 79%, while with hexanenitrile a 55% yield of the corresponding bromonitronitrile is isolated.<sup>56</sup> Lower limits for the yields of the corresponding nitronitrile salts are thereby established.



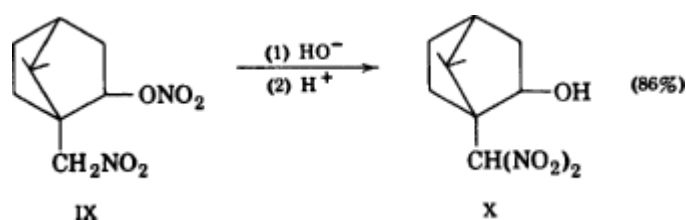
It was realized early that not all bases are equally useful in these reactions. In particular, it was recognized that potassium ethoxide is superior to sodium ethoxide in effecting nitrations. For example, *o*-bromophenylacetonitrile is nitrated by ethyl nitrate in the presence of sodium ethoxide to give the sodium salt of *o*-bromophenylnitroacetonitrile in 30% yield, whereas with potassium ethoxide the yield of the salt is 70%.<sup>59</sup> While fluorene gives a 70% yield of the potassium salt of 9-nitrofluorene when

potassium ethoxide is employed as the base, with sodium ethoxide no nitration occurs.<sup>52</sup>

Recent studies of the nitration of aliphatic nitriles,<sup>56</sup> ketones,<sup>56</sup> dinitriles,<sup>56</sup> and cyclic ketones<sup>55</sup> have dealt with the usefulness of various bases in these condensations, and with the influence of solvent, temperature, reaction time, and mode of addition. It has been found that sublimed potassium t-butoxide in tetrahydrofuran is the best reagent. The following equations are illustrative.<sup>55, 56</sup> The reaction with cyclopentanone is particularly interesting. Ring opening on bromination<sup>58</sup> has been shown to be a general reaction of the salts of  $\alpha, \alpha\phi$ -dinitrocycloalkanones.<sup>55</sup> Presumably the dibromodinitrocyclopentanone is an intermediate and reacts with hydroxide ion.

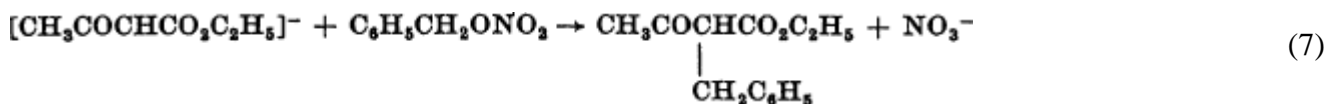
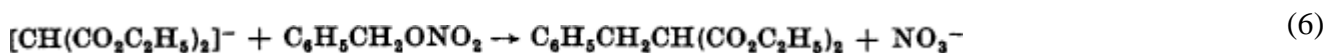


Nitration by a nitrate ester can be intramolecular. The 1,3-nitronitrate IX readily rearranges to the dinitro alcohol X in aqueous ethanolic potassium hydroxide.<sup>60</sup>

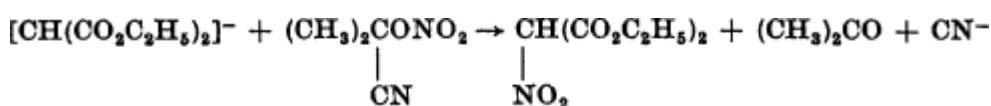


Nitration by nitrate esters involves, in essence, nucleophilic displacement by the carbanion being nitrated

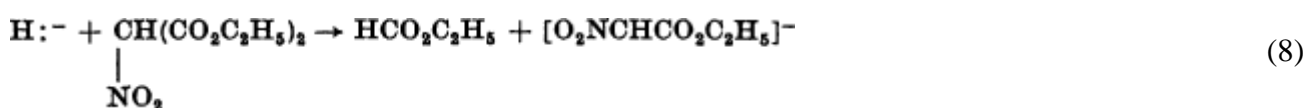
on the nitrogen of the nitrate ester (equation 5). But the alternative process of nucleophilic displacement on carbon is known; and, with the relatively weakly basic anions derived from malonic and acetoacetic esters, it is the latter mode of reaction which is observed (equations 6 and 7).<sup>61</sup>



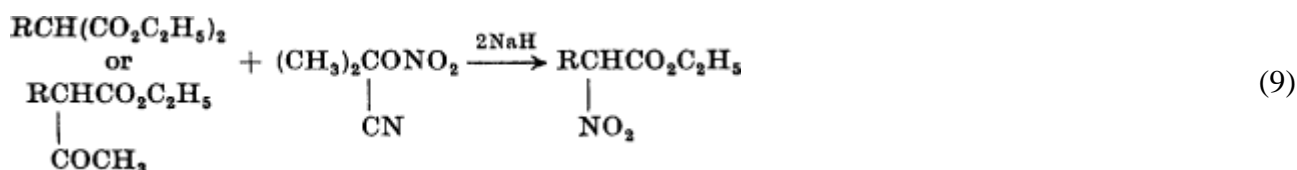
Nitration, rather than alkylation, of the anions of malonic and acetoacetic esters can be achieved by the use of acetone cyanohydrin nitrate.<sup>62</sup>



Since nitromalonic ester is a distinctly stronger acid than malonic ester, a second mole of base is needed to prevent destruction of an equivalent of sodiomalonic ester. But an excess of the base (sodium hydride) cannot be used as it degrades the nitromalonic ester to ethyl nitroacetate (equation 8); therefore an excess of sodiomalonic ester is employed. With a three-fold excess of sodiomalonic ester, diethyl nitromalonate is obtained in 45% yield. As a means of preparing nitromalonic ester, nitration with acetone cyanohydrin nitrate is inferior to the nitration of malonic ester with nitric acid, which consistently gives yields of over 90%<sup>63</sup> (see p. 136).



Nitration of monosubstituted malonic or acetoacetic esters with acetone cyanohydrin nitrate, in the presence of a 100% excess of sodium hydride, results in degradation to  $\alpha$ -nitro esters analogous to that described by equation 8 and constitutes a general synthesis of  $\alpha$ -nitro esters (equation 9).<sup>62</sup> The yields average 50–55% and are comparable from either type of ester. While this method will doubtless be useful in particular instances, it is greatly inferior to the general synthesis of  $\alpha$ -nitro esters which employs  $\alpha$ -halo esters and sodium nitrite (p. 112).<sup>27, 28</sup>

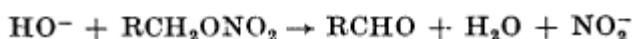
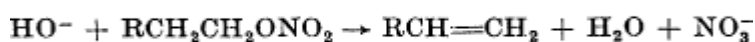
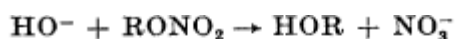


Acetone cyanohydrin nitrate is rapidly destroyed by metal alkoxides and, presumably, the same type of destructive process is responsible for the failure to nitrate the anions of such compounds as t-butyl acetate, acetophenone, and diethyl succinate.<sup>62</sup> Acetone cyanohydrin nitrate is thus of limited utility for

nitrating carbanions.

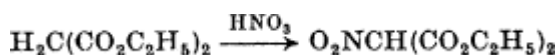
Self-condensation of the active methylene compound, which may become an important side reaction, can be minimized by completely converting the active methylene compound to its salt. For this purpose the strong base potassium t-butoxide and the non-protic solvent tetrahydrofuran serve very well.<sup>55</sup>

Nitrate esters are attacked by bases and, indeed, three reaction types are known. By way of illustration the reactions involving hydroxide ion are given.<sup>64</sup> These, presumably, are to a greater or lesser extent a source of difficulty in carrying out nitrations by nitrate esters under basic conditions.



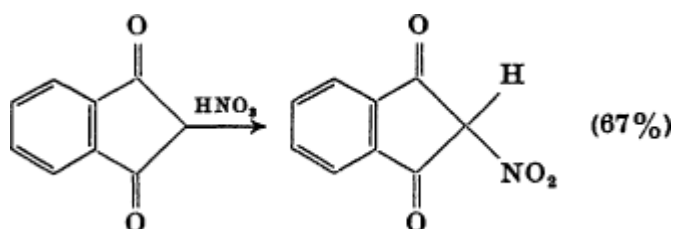
## 7. The Reaction of Active Methylene Compounds with Nitric Acid or Oxides of Nitrogen

Whereas the direct nitration of hydrocarbons with nitric acid or oxides of nitrogen is, at best, inconvenient for the preparation of pure compounds in the laboratory, high yields of pure products can be obtained from active methylene compounds under rather mild conditions. When diethyl malonate is treated with fuming nitric acid for several hours at 15–20°, diethyl nitromalonate is consistently obtained in about 92% yields.<sup>63, 65</sup>

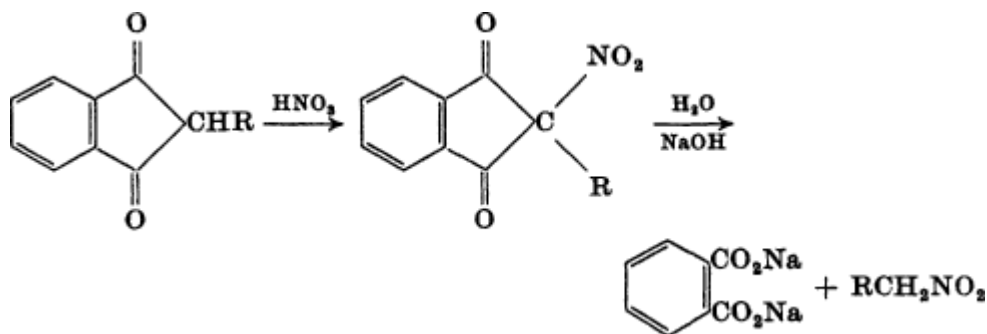


It is important to recognize that the nitro ester thus prepared is invariably contaminated by oxides of nitrogen which initiate autocatalytic decomposition of the nitro ester. These oxides, which cannot be removed by repeated washing and/or distillation, are completely removed by treatment with urea or acetamide. Diethyl nitromalonate so treated is stable over long periods of time.<sup>63</sup>

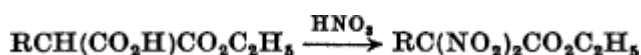
The nitration of indane-1,3-dione occurs readily at 40° on treatment with 90% nitric acid in acetic acid.<sup>66</sup>



The facility with which 1,3-indanediones can be nitrated has been employed in an ingenious manner by Zalukaev and Vanag for the synthesis of primary nitro compounds.<sup>67</sup> The 1,3-indanediones on which this synthesis is based are readily available, especially those in which R is a heterocyclic or aromatic nucleus. With R =  $\alpha$ -naphthyl, the nitration step occurs in 52–60% yield and hydrolysis by 5% aqueous sodium hydroxide gives pure  $\alpha$ -naphthylnitromethane in 57% yield. While  $\alpha$ -naphthylnitromethane can almost certainly be prepared more conveniently by a number of other methods, the Zalukaev procedure may well prove successful where other methods are inapplicable. For example, it is quite possible that nitroneopentane,  $(\text{CH}_3)_3\text{CCH}_2\text{NO}_2$ , can be prepared via an indanedione.



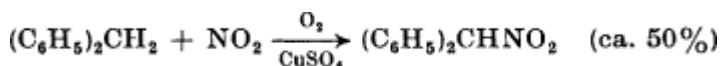
$\alpha$ ,  $\alpha$ -Dinitro esters can be obtained, although in poor yield, by nitration of half esters of malonic acids with 70% nitric acid.<sup>68</sup> In this way the dinitro esters in which R = H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, or n-C<sub>4</sub>H<sub>9</sub> have been prepared in 8–17% yields.



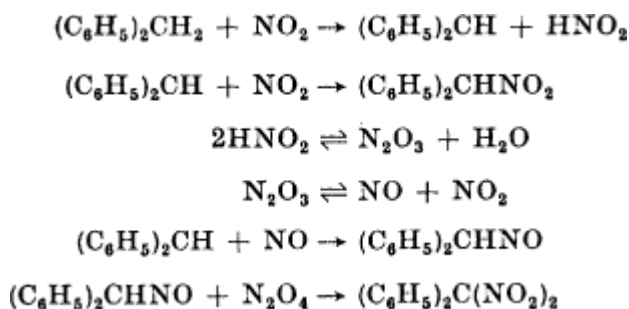
Nitration with oxides of nitrogen has had only limited use. Diphenylcyanonitromethane has been prepared by treating a chloroform solution of diphenylcyanomethane with dry nitrogen dioxide at 15–20°.<sup>69</sup>



Diphenylnitromethane has been obtained from diphenylmethane and nitrogen dioxide at 70–75° in carbon tetrachloride solution with anhydrous copper sulfate and oxygen present.<sup>70</sup>



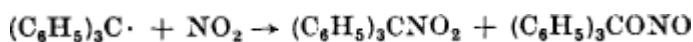
If oxygen is not available the reaction produces significant amounts of dinitrodiphenylmethane. The presence of oxygen is necessary to prevent build-up of the concentration of nitric oxide which, in conjunction with dinitrogen tetroxide, converts diphenylmethane to dinitrodiphenylmethane. The accompanying reaction scheme has been proposed to accommodate these facts.<sup>70</sup>



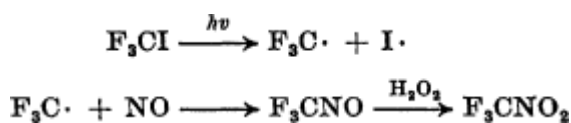
## 8. Miscellaneous Methods of Introducing a Nitro Group

This section briefly describes miscellaneous reactions of rather limited utility or reactions concerning which there are but few data.

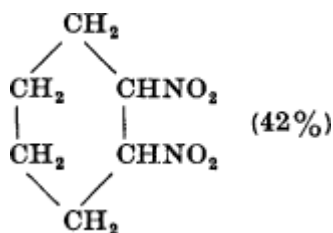
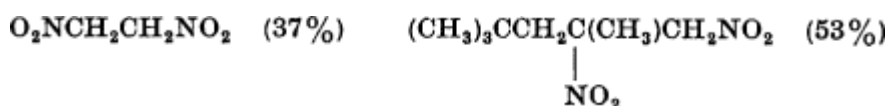
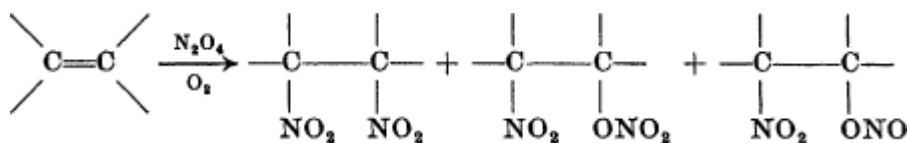
Triphenylnitromethane has been obtained by the reaction of triphenylmethyl radicals with nitrogen dioxide in diethyl ether solution.[41](#)



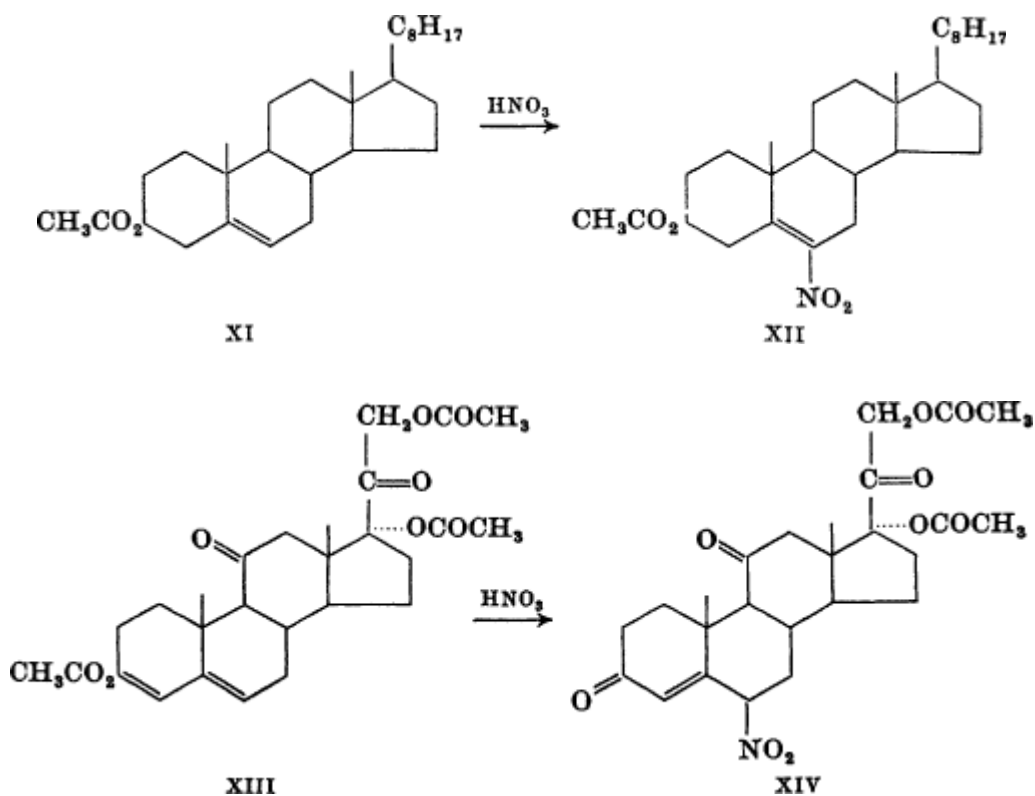
Ultraviolet irradiation of a gaseous mixture of a perfluoroalkyl iodide and nitric oxide in silica vessels, mercury being present to remove iodine, results in the replacement of iodine by a nitroso group. The yields are good. The nitroso compounds are oxidized by hydrogen peroxide to the corresponding nitro compounds.[71](#)



Addition of an olefin to a solution of pure nitrogen tetroxide in diethyl ether at 0° with oxygen present produces a mixture of the 1,2-dinitro compound, the nitroalkyl nitrate, and the nitroalkyl nitrite. Properly conducted, this can be a useful method for preparing 1,2-dinitro compounds.[12](#) Some typical nitro compounds obtained in this way are given below.



The nitration of unsaturated steroids is a useful reaction.[72](#) Thus, treatment of cholesteryl acetate XI in ether solution at 0° with fuming nitric acid affords pure 6-nitrocholesteryl acetate XII in 72% yield.[73](#) In the same way XIII is converted to XIV.[74](#) The importance of temperature control in these nitrations has been emphasized.[74](#)



## 9. Comparison of the Various Procedures for Introducing a Nitro Group

Certain generalizations are possible regarding the effectiveness of the various procedures for the preparation of particular types of nitro compounds. These are noted in the table below.

Nitro Compounds	Preferred Procedures
Primary nitroparaffins	Silver nitrite + alkyl halide
	Sodium nitrite + alkyl halide
	Aldoxime + peroxytrifluoroacetic acid
	Note: For the synthesis of $\text{ACH}_2\text{NO}_2$ , where A is a powerful electron-withdrawing group, e.g., carbethoxy, p-nitrophenyl, the use of sodium nitrite is to be avoided.
Secondary nitroparaffins	Sodium nitrite + alkyl halide (or sulfonate ester)
	Amine + peracetic acid
	Ketoxime + peroxytrifluoroacetic acid
	Ketoxime + N-bromosuccinimide followed by sodium borohydride
	Note: Sodium nitrite fails with cyclohexyl halides. Really pure secondary bromides are not likely to be obtained by the action of hydrobromic acid or phosphorus tribromide on secondary alcohols (p. 112). The ketoxime + N-bromosuccinimide procedure fails with aromatic ketoximes and is, in general, inferior to the peroxytrifluoroacetic acid method. However, in the oxidation of

	hindered oximes (where peroxytrifluoroacetic acid fails) the N-bromosuccinimide method is successful.
Tertiary nitroparaffins	Potassium permanganate + t-carbinamines
	Peracetic acid + t-carbinamines
$\alpha$ -Nitro esters	Sodium nitrite + $\alpha$ -halo esters
	Acetone cyanohydrin nitrate + sodium enolates of monosubstituted malonic or acetoacetic esters
	Silver nitrite + $\alpha$ -halo esters
	Note: Nitromalonic ester is best prepared by nitrating malonic ester with nitric acid.
$\alpha$ -Nitro nitriles	Nitrate ester + potassiumt-butoxide + nitrile
	Sodium nitrite + $\alpha$ -halo nitrile
$\alpha$ -Nitro ketones	Nitrate ester + potassiumt-butoxide + ketone
2-Nitro-1,3-diketones	Nitric acid + 1, 3-diketone

## 10. Experimental Procedures

### 10.1. Syntheses Employing Silver Nitrite

#### 10.1.1. Silver Nitrite

The preparation of this salt is given in Organic Syntheses.[75](#)

#### 10.1.2. 1-Nitroöctane

Detailed directions for the synthesis of this nitro-paraffin in 75–80% yield from 1-bromoöctane are given in Organic Syntheses.[75](#)

#### 10.1.3. 1,4-Dinitrobutane

The preparation of this dinitro compound in 41–46% yield from 1,4-diiodobutane is given in Organic Syntheses.[9](#)

#### 10.1.4. Phenylnitromethane<sup>8</sup>



A slurry of 100 g. of silver nitrite and 1 g. of calcium hydride in 250 ml. of anhydrous ether is cooled to 0° in a 500-ml. three-necked flask fitted with a dropping funnel, stirrer, and drying tube, and 85.5 g. (0.5 mole) of benzyl bromide ( $n_D^{20}$  1.5762) is added dropwise to the stirred mixture over a period of 1 hour. After stirring at 0° in the dark for a total of 25 hours, tests for unreacted halide using a saturated solution of silver nitrate in acetonitrile and the Beilstein test are negative. The reaction mixture is filtered, the silver salts are washed with ether, and the washings are added to the original filtrate. About 1 g. of calcium hydride is added to the ether solution and the ether is distilled at atmospheric pressure through a 1 × 50 cm. glass helix packed column; the bath temperature is maintained between 48° and 50°. The last of the ether is removed under the vacuum of a water pump and the residual liquid is distilled through a 6-in. Vigreux column. Nineteen grams (28% yield) of benzyl nitrite is obtained, b.p. 56–56.5°/8 mm.;  $n_D^{20}$  1.5006–1.5008. After a 3-g. interfraction there is obtained 41.4 g. (61% yield) of phenylnitromethane, b.p. 77–79°/1 mm.;  $n_D^{20}$  1.5315. The phenylnitromethane is completely soluble in 20% aqueous sodium hydroxide.

## 10.2. Syntheses Employing Sodium Nitrite

### 10.2.1. Ethyl $\alpha$ -Nitrobutyrate

Detailed directions for the synthesis of this  $\alpha$ -nitro ester in 68–75% yield from ethyl  $\alpha$ -bromobutyrate are given in Organic Syntheses.[27](#)

### 10.2.2. 1-Nitroöctane<sup>21</sup>

1-Bromoöctane (58 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of dimethylformamide (DMF) and 36 g. of sodium nitrite (0.52 mole) immersed in a water bath maintained at room temperature; stirring is continued for 6 hours. The reaction mixture is then poured into 1.5 l. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). The aqueous phase is extracted four more times with 100-ml. portions of petroleum ether, after which the combined extracts are washed with water and dried over anhydrous magnesium sulfate. The petroleum ether is removed by distillation under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to 65°. Rectification of the residue yields 13.6 g. (29%) of 1-octylnitrite (b.p. 37°/2 mm.;  $n_D^{20}$  1.4127), 2.8 g. of interfractions, and 28.2 g. (60%) of 1-nitroöctane (b.p. 60°/1 mm.;  $n_D^{20}$  1.4324). When 1-iodoöctane is used the reaction time is cut to 2½ hours.

### 10.2.3. 2-Nitroöctane

[A.22](#) 2-Iodoöctane (71.2 g., 0.30 mole) is poured into a stirred solution of 225 ml. of dimethyl sulfoxide (DMSO) and 36 g. of sodium nitrite (0.52 mole) contained in a 500-ml. flask immersed in a water bath held at room temperature. Stirring is continued for 4 hours. The reaction mixture is poured into 600 ml. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). The aqueous phase is separated and further extracted with four 100-ml. portions of petroleum ether. The combined extracts are washed with water and then dried over anhydrous magnesium sulfate. The petroleum ether solution is distilled through a small column, after which the residual liquid is rectified under reduced pressure. At 2 mm., 14.0 g. (30% yield) of 2-octyl nitrite ( $n_D^{20}$  1.4089) distills at 32°; this is followed by a small fraction (3.9 g.) (b.p. 53–56°/1 mm.;  $n_D^{20}$  1.4111–1.4382), after which 27 g. (58% yield) of 2-nitroöctane (b.p. 61°/1 mm.;  $n_D^{20}$  1.4281) is obtained.

B.21 2-Iodoöctane (72 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole), and 40 g. of urea (0.67 mole) in a 1-l. flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water bath maintained at room temperature, and stirring is continued for 4 hours. The reaction mixture is then poured into 1.5 l. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). After separation of the upper layer, the aqueous phase is extracted repeatedly with petroleum ether. The combined extracts are then washed with two 75-ml. portions of 10% aqueous sodium thiosulfate, with 150 ml. of water, and are dried over anhydrous magnesium sulfate.

Using a small column, the petroleum ether is stripped off under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to about 65°. The residual pale-blue liquid is transferred, with the aid of a little petroleum ether, to a 100-ml. flask, the column is attached, and the remaining solvent is removed under reduced pressure. Rectification of the residue yields 12.0–14.2 g. (25–30%) of 2-octyl nitrite (b.p. 30°/2 mm.;  $n_D^{20}$  1.4091), 0.9–3.3 g. of interfractions, and 27.2–28.1 g. (57–60%) of 2-nitroöctane (b.p. 57°/1 mm.;  $n_D^{20}$  1.4280).

#### 10.2.4. Nitrocyclopentane<sup>22</sup>

Cyclopentyl bromide (22.0 g., 0.15 mole) is treated with a solution of 18 g. of sodium nitrite in 100 ml. of DMSO for 3 hours at 15°. On working up the reaction mixture in the same way as in the preceding example, 9.9 g. (58% yield) of nitrocyclopentane is isolated (b.p. 62°/8 mm.;  $n_D^{20}$  1.4538).

#### 10.2.5. Phenylnitromethane<sup>21</sup>

Benzyl bromide (51.3 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole), and 40 g. of urea maintained at –20° to –15°. After 5 hours the reaction mixture is worked up as in the 1-nitroöctane preparation on p. 131 except that 700 ml. of diethyl ether is used for extraction. Rectification gives 13.1 g. (33% yield) of crude benzyl nitrite (b.p. 44°/5 mm.;  $n_D^{20}$  1.5010–1.5024), 1.7 g. of interfractions, and 22.1 g. (55% yield) of phenylnitromethane (b.p. 76°/2 mm.;  $n_D^{20}$  1.5316). The phenylnitromethane is completely soluble in 20% aqueous sodium hydroxide.

#### 10.2.6. (+)- $\alpha$ -Phenylnitroethane<sup>35</sup>

In a 1-l. flask equipped with a stirrer, a drying tube containing potassium hydroxide, and a dropping funnel are placed 550 ml. of DMF (dried over calcium hydride), 35.6 g. (0.534 mole) of dry sodium nitrite, and 47.4 g. of dry urea. The reaction vessel is placed in an ice-salt bath, stirring is begun, and the solution is cooled to –18°. (+)- $\alpha$ -Phenylethyl bromide (65.1 g., 0.352 mole;  $\alpha_D^{26} = +66.32$ ; neat, 1 dm.) is added dropwise over a 3- to 5-minute period. The flask is covered with a towel to exclude light. After 13 hours at –18° a negative test for organic halide\* is obtained showing that the reaction is complete.<sup>‡</sup> The reaction mixture is poured into 1 l. of ice water layered with 400 ml. of benzene. The aqueous layer is extracted with three 100-ml. portions of benzene and then with two 100-ml. portions of diethyl ether. The combined ether-benzene extracts are washed with four 75-ml. portions of water and dried over anhydrous magnesium sulfate. Removal of the solvents under reduced pressure leaves about 60 ml. of a yellow liquid which is distilled at 4 mm. (maximum bath temperature 85°; maximum boiling point 73°) in order to remove the nitrite ester. The residual crude nitro compound is shaken with two 100-ml. portions of 85% phosphoric acid and then with 100 ml. of 2,4-dinitrophenylhydrazine solution\* to which is added 50 ml. of 2N hydrochloric acid. The organic liquid is separated, 50 ml. of diethyl ether added, and the ether solution is washed with water and dried over anhydrous magnesium sulfate. The ether is removed under reduced

pressure and the residue rectified through a small column. The yield of pure (+)- $\alpha$ -phenylnitroethane (b.p. 74–75°/1 mm.;  $n_D^{20}$  1.5213;  $\alpha_D^{31} + 10.23^\circ$ ; neat, 1 dm.) is 22.9 g. (43%).

## 10.3. The Oxidation of Amines

### 10.3.1. 2-Nitro-2,4,4-trimethylpentane<sup>39</sup>

Twenty-five and eight-tenths grams (0.2 mole) of 2-amino-2,4,4-trimethylpentane (t-octylamine) is dissolved in 500 ml. of acetone in a 1-l. flask equipped with a Tru-bore stirrer and a thermometer. The solution is diluted with 125 ml. of water, and 30 g. of magnesium sulfate is added. The temperature is maintained at 25–30° and 190 g. (1.12 mole) of potassium permanganate is added portionwise, over a period of approximately  $\frac{1}{2}$  hour, to the well-stirred reaction mixture. Stirring is continued at 25–30° for 48 hours after the addition of the potassium permanganate and then, while stirring, most of the acetone is removed under the vacuum of a water aspirator at an internal temperature of about 30°. The resulting heavy sludge is steam distilled, and the pale blue distillate is extracted with petroleum ether (b.p. 35–37°) and dried over anhydrous sodium sulfate. The dried mixture is filtered and most of the petroleum ether is removed by distillation at atmospheric pressure. Rectification through a short column gives 24.3 g. (77%) of the colorless tertiary nitro compound; the material boils at 54°/3 mm. ( $n_D^{28}$  1.4314) and melts at 23.5–23.7°.

### 10.3.2. 2-Nitro-2-methylpropane<sup>39</sup>

In the course of 15 minutes 100 g. of t-butylamine is added to a stirred mixture of 650 g. of potassium permanganate and 3 l. of water; the temperature rises to 45°. The stirring is continued for 8 hours without external heating, and the mixture is then held at 55° $\pm$ 5° for another 8 hours. The product is isolated by steam distillation, washed with dilute hydrochloric acid, with water, and dried. Distillation gives 117 g. (83% yield) of the tertiary nitro compound (b.p. 127–128°;  $n_D^{28}$  1.3980; m.p. 25–26°).

### 10.3.3. 2-Nitrobutane<sup>42</sup>

With vigorous stirring, 65.2 ml. (2.4 moles) of 90% hydrogen peroxide is added dropwise fairly rapidly to 300 ml. of ice-cooled ethylene chloride. After addition of four drops of sulfuric acid catalyst, 292 g. (2.88 moles) of acetic anhydride is added to the cooled solution during 90 minutes. The mixture so obtained is stirred for 30 minutes at 0° and 30 minutes at room temperature. It is diluted with 200 ml. of ethylene chloride and heated rapidly to reflux. At this temperature a solution of 43.8 g. (0.6 mole) of sec-butylamine in 50 ml. of ethylene chloride is added dropwise over 1 hour. The reaction is very exothermic during this addition, and the system rapidly develops a blue color. After the amine has been added, the mixture is heated under reflux for 1 hour. It is then cooled, washed with two 500-ml. portions of cold 1:1 ammonia, and then with 500 ml. of water. The organic extract is dried over magnesium sulfate, and the major portion of solvent is removed by fractionation in a column packed with glass helices. The residue, still containing some solvent, is fractionated in a spinning band column; 40.2 g. (65%) of 2-nitrobutane (b.p. 64–66°/60 mm.;  $n_D^{20}$  1.4043) is obtained.

## 10.4. The Oxidation of Oximes

### 10.4.1. Phenylnitromethane<sup>43</sup>

A solution of peroxytrifluoroacetic acid is prepared from 5.5 ml. (0.2 mole) of 90% hydrogen peroxide, 34.0 ml. (0.24 mole) of trifluoroacetic anhydride, and 50 ml. of acetonitrile. This is added over a  $1\frac{1}{4}$  - hour period to a well-stirred mixture of 2.0 g. of urea, 78 g. (0.55 mole) of dibasic sodium phosphate, and 12.1 g. (0.1 mole) of benzaldehyde oxime in 200 ml. of acetonitrile. The mixture is heated under gentle reflux during the addition and for 1 hour after the addition has been completed. It is then cooled and added to 400 ml. of water. The resulting solution is extracted with four 100-ml. portions of methylene chloride. The combined extracts are washed with three 100-ml. portions of 10% sodium bicarbonate solution and dried over magnesium sulfate. The solvent is evaporated under reduced pressure and the residual liquid is fractionated through a semimicro column.<sup>76</sup> After a small forerun has distilled, there is obtained 10.6 g. (77%) of colorless phenylnitromethane, b.p. 97–99°/4.0 mm.

### 10.4.2. 4-Nitroheptane<sup>43</sup>

A solution of peroxytrifluoroacetic acid in acetonitrile prepared as described above is added over an 80-minute period to a well-stirred suspension of 47 g. (0.55 mole) of sodium bicarbonate in a solution of 2 g. of urea, 12.9 g. (0.1 mole) of di-n-propyl ketoxime, and 200 ml. of acetonitrile. Throughout the addition and for 1 hour after, the solution is heated under gentle reflux. It is then poured into 600 ml. of cold water and worked up as in the preceding preparation. Fractionation of the product through a semimicro column<sup>76</sup> yields 9.3 g. (64%) of 4-nitroheptane, b.p. 58–60°/3 mm.

### 10.4.3. Nitrocyclobutane<sup>44</sup>

A solution of 16.1 g. (0.19 mole) of cyclobutanone oxime and 40 g. (0.47 mole) of sodium bicarbonate dissolved in 230 ml. of water is added during 30 minutes to a stirred solution of 85 g. (0.47 mole) of N-bromosuccinimide dissolved in 200 ml. of water. The reaction mixture is maintained at 0–10° by an ice-salt bath and is stirred 30 minutes after addition of the oxime solution. The product is collected by five extractions with 50-ml. portions of petroleum ether (b.p. 20–40°). The combined extract is concentrated on a steam bath, and the blue oil is oxidized by shaking at room temperature with a mixture of 150 ml. of concentrated nitric acid (sp. gr. 1.42) and 70 ml. of 30% hydrogen peroxide until the blue color is completely removed. The reaction mixture is diluted with water and the bromonitrocyclobutane is extracted with petroleum ether (b.p. 20–40°). After washing with dilute sodium hydroxide solution and water, the solvent is removed by distillation. The crude bromonitro compound (about 23 g.) is added dropwise to a stirred refluxing mixture of 38 g. (1.0 mole) of sodium borohydride in 300 ml. of methanol and 100 ml. of water (about 30 minutes are required). The methanol is removed by steam distillation and the aqueous solution is acidified by addition of 75 g. of hydroxylamine hydrochloride. The nitro compound is collected by continuous extraction with petroleum ether (b.p. 20–40°). After drying over anhydrous sodium sulfate, the extract yields 42 g. (23%) of pure nitrocyclobutane (b.p. 77–78°/40 mm.;  $n_D^{25}$  1.4413).

## 10.5. Nitrations Employing Nitrate Esters

### 10.5.1. Phenylnitromethane

Benzyl cyanide is nitrated with methyl nitrate and the resulting salt is hydrolyzed and decarboxylated; the

over-all yield of phenylnitromethane is 50–55%. Detailed directions are given in Organic Syntheses.[49](#)

### 10.5.2. Dipotassium 2,5-Dinitrocyclopentanone[55](#)

A stirred solution of 18.45 g. (0.165 mole) of potassium t-butoxide (rendered free of t-butyl alcohol by sublimation at 220°/1 mm.) in 90 ml. of tetrahydrofuran (purified by refluxing over sodium hydroxide and then distilling from potassium metal under nitrogen) is cooled to –30° by means of a solid carbon dioxide bath, and 4.2 g. (0.05 mole) of cyclopentanone dissolved in 70 ml. of tetrahydrofuran is added dropwise over 30 minutes. A solution of 14.6 g. (0.11 mole) of amyl nitrate in 35 ml. of tetrahydrofuran is then added dropwise over 30 minutes with the temperature maintained at –30°. The bath is removed and the reaction mixture is allowed to warm to 25°, with stirring.

As soon as the reaction mixture reaches room temperature, it is filtered through a pressure filtration apparatus, nitrogen being used to supply the pressure. The residue, dipotassium 2,5-dinitrocyclopentanone, is washed successively with 70 ml. of tetrahydrofuran, 50 ml. of methanol, and 50 ml. of ether and is recrystallized from 30% aqueous potassium hydroxide. The green crystals are washed with methanol until the washings are colorless and neutral. The yield of analytically pure salt after drying at 56°/1 mm. is 55%.

## 10.6. Nitrations Employing Nitric Acid

### 10.6.1. Diethyl Nitromalonate[63](#)

Diethyl malonate (80.0 g., 0.5 mole) is placed in a 500-ml. three-necked flask fitted with dropping funnel, stirrer, thermometer, and an outlet protected by a drying tube. The flask is cooled by tap water at 12°, and 184 ml. of fuming nitric acid (d. 1.5) is added at a rate sufficient to maintain the temperature between 15° and 20°. The addition requires 1 hour, after which time the mixture is stirred for 3½ hours at 15°. The solution is poured onto 1 l. of ice and water and the ester extracted with a 200- and a 100-ml. portion of toluene.

The combined toluene extracts are washed twice with water and then with 200-ml. portions of 5% aqueous urea until a starch-potassium iodide test for oxides of nitrogen in the wash is negative. The toluene solution is extracted with 10% aqueous sodium carbonate in portions until acidification of a test portion of extract shows that it contains no nitro ester. The sodium carbonate extracts are combined and washed once with 200 ml. of toluene. The aqueous solution is then carefully acidified to Congo red paper with concentrated hydrochloric acid, with cooling by the occasional addition of ice.

The ester is collected by extraction with 500-, 200-, and 100-ml. portions of toluene. The toluene solution is washed with two 200-ml. portions of water and then with 5% aqueous urea, again being checked with starch-potassium iodide test paper for the complete absence of oxides of nitrogen. The toluene solution is dried over magnesium sulfate. The yield of ester is determined by weighing the toluene solution, taking an aliquot, adding an equal volume of ethanol, and titrating the nitro ester with N sodium hydroxide to a phenolphthalein end point. The assay shows that the yield is 94.1 g. or 91.7%. If analytically pure ester is desired, it may be obtained by concentrating and distilling. The pure ester ( $n_D^{21}$  1.4274) boils at 81–83°/0.3 mm.

## 11. Tabular Survey

Each of the following tables, [II](#) through [VII](#), is concerned with a general method of preparing nitro

compounds. Within a given table the nitro compounds are divided into three groups: primary, secondary, and tertiary. Within each of these groups (except in Table [VI](#)) compounds are listed in the following sequence:

- Straight-chain nitro compounds
- Branched-chain nitro compounds
- Alicyclic nitro compounds
- Unsaturated nitro compounds
- Benzylic and other arylated nitro compounds
- Nitro ketones
- Nitro acids
- Nitro esters
- Nitro nitriles
- Miscellaneous nitro compounds
- Dinitro compounds

Table II. Nitro Compounds Prepared with Silver Nitrite

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[View PDF](#)

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Table III. Nitro Compounds Prepared with Sodium Nitrite

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Table IV. Nitro Compounds Prepared by the Oxidation of Amines

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Table V. Nitro Compounds Prepared by the Oxidation of Oximes

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Table VI. Nitrations Employing Nitrate Esters

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[View PDF](#)

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Table VII. Nitro Compounds Prepared with Nitric Acid

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[View PDF](#)

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In Table [VI](#) the sequence is:

- Nitro compounds devoid of other functional groups
- Nitro ketones
- Nitro esters
- Nitro nitriles
- Miscellaneous nitro compounds

The literature through June, 1959, has been covered in this survey.

Throughout these tables a dash in the yield column corresponds to an unspecified yield and is different from 0% yield which, when established, is always explicitly stated.

#### End Notes

- \*  
Assistance from the Office of Ordnance Research under Contract DA 33-008-ORD-1808 is gratefully acknowledged.
- \*  
Among them is the fact that oxides of nitrogen are not observed in the reactions of primary straight-chain halides with silver nitrite, but they are regularly noted in reactions involving secondary bromides and iodides.
- \*  
Although statements to this effect occur in many textbooks and monographs, we have been unable to find any support for this view in the original literature.
- \*  
This test is carried out by shaking several drops of the reaction solution with a mixture of about 1 ml. of water and 1 ml. of petroleum ether (b.p. 35–37°). The petroleum ether layer is isolated, most of the petroleum ether is removed by evaporation, and a drop of a saturated solution of silver nitrate in acetonitrile is added. A precipitate shows the presence of organic halide, whereas a cloudy, or clear, solution signifies the absence of organic halide.
- †  
The reaction mixture is worked up in subdued light until the nitrite ester has been removed.
- \*  
This is prepared by saturating 2N hydrochloric acid with 2,4-dinitrophenylhydrazine at 0°.

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TABLE I  
PRODUCTS OF THE REACTION OF SILVER NITRITE  
WITH BENZYL BROMIDES

Bromide	Nitro Compound, %	Nitrite Ester, %
<i>p</i> -Nitrobenzyl	75	5
Benzyl	61	28
<i>p</i> -Methylbenzyl	45	37
<i>p</i> -Methoxybenzyl	26	55

TABLE II  
 NITRO COMPOUNDS PREPARED WITH SILVER NITRITE

Nitro Compound (Yield, %) RNO <sub>2</sub>	Halide Employed RX	Yield of Nitrite Ester, % BONO	References
CH <sub>3</sub> NO <sub>2</sub> (71)	I	16	77
C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub> (—)	I	—	1
<i>n</i> -C <sub>3</sub> H <sub>7</sub> NO <sub>2</sub> (67)	Br	19	78
(70)	I	—	79
<i>n</i> -C <sub>4</sub> H <sub>9</sub> NO <sub>2</sub> (0)	Cl	—	78
(73)	Br	13	6
(74)	I	12	6
<i>n</i> -C <sub>5</sub> H <sub>11</sub> NO <sub>2</sub> (67)	Br	—	80
<i>n</i> -C <sub>6</sub> H <sub>13</sub> NO <sub>2</sub> (0)	Cl	—	6
(76, 69)	Br	10	6, 8
(78)	I	13	6
<i>n</i> -C <sub>7</sub> H <sub>15</sub> NO <sub>2</sub> (79, 61)	Br	11	6, 80
(82)	I	10	6
<i>n</i> -C <sub>8</sub> H <sub>17</sub> NO <sub>2</sub> (0)	Cl	—	6
(80)	Br	14	75
(83)	I	11	6
<i>n</i> -C <sub>18</sub> H <sub>37</sub> NO <sub>2</sub> (—)	I	—	81
F(CH <sub>2</sub> ) <sub>3</sub> NO <sub>2</sub> (39)	Br	—	82
(76)	I	—	82
F(CH <sub>2</sub> ) <sub>4</sub> NO <sub>2</sub> (58)	Br	—	82
(76)	I	—	82
F(CH <sub>2</sub> ) <sub>5</sub> NO <sub>2</sub> (73)	Br	—	82
(70)	I	—	82
F(CH <sub>2</sub> ) <sub>6</sub> NO <sub>2</sub> (54)	Br	—	82
HOCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (62)	I	—	83
CH <sub>3</sub> CHOHCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (64)	I	—	33
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> NO <sub>2</sub> (18)*	Br	14	6
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> NO <sub>2</sub> (59, 44)	I	20	6, 80
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (72, 61)	Br	19	6, 80
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (78)	I	16	6, 1
(CH <sub>3</sub> ) <sub>3</sub> CCH <sub>2</sub> NO <sub>2</sub> (0)†	I	—	8, 6
CH <sub>2</sub> =CHCH <sub>2</sub> NO <sub>2</sub> (55)‡	Br	—	7
CH <sub>2</sub> =C(CH <sub>3</sub> )CH <sub>2</sub> NO <sub>2</sub> (40)	Br	—	84
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NO <sub>2</sub> (—)	Cl	—	85
(61)	Br	28	8
(—)	I	—	86
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (58)	Br	—	87
<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (75)	Br	5	8
(—)	I	—	88
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (26)	Br	55	8
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (45)	Br	37	8
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> NO <sub>2</sub> (66)	I	—	89
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>4</sub> NO <sub>2</sub> (50)	I	—	89
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>5</sub> NO <sub>2</sub> (55)	I	—	89
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>6</sub> NO <sub>2</sub> (70)	I	—	89
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>7</sub> NO <sub>2</sub> (50)	I	—	89
CH <sub>3</sub> COCH <sub>2</sub> NO <sub>2</sub> (—)	I	—	90
C <sub>6</sub> H <sub>5</sub> COCH <sub>2</sub> NO <sub>2</sub> (—)	I	—	91
O <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H (—)	I	—	92

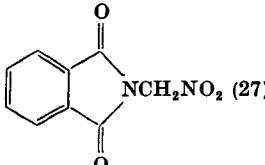
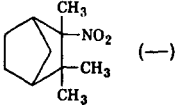
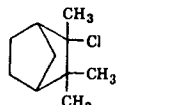
Note: References 77 to 108 are on p. 156.

\* After 5 days, 63% of the halide was recovered.

† After 3 days, 96% of the halide was recovered.

‡ This reaction was run in diethyl ether at 0° for 12 hours; b.p. of nitro compound, 39–40°/20 mm.; *n*<sub>D</sub><sup>20</sup> 1.4260.

TABLE II—Continued  
NITRO COMPOUNDS PREPARED WITH SILVER NITRITE

Nitro Compound (Yield, %) RNO <sub>2</sub>	Halide Employed RX	Yield of Nitrite Ester, % RONO	References
O <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (77)	I	—	14
O <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (—)	I	—	92
 NCH <sub>2</sub> NO <sub>2</sub> (27)	Br	—	93
O <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> § (—)	I(CH <sub>2</sub> ) <sub>2</sub> I	—	94
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub> NO <sub>2</sub> (37)	I(CH <sub>2</sub> ) <sub>3</sub> I	—	9, 95
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>4</sub> NO <sub>2</sub> (41–46)	I(CH <sub>2</sub> ) <sub>4</sub> I	—	9
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>5</sub> NO <sub>2</sub> (45)	I(CH <sub>2</sub> ) <sub>5</sub> I	—	9
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>6</sub> NO <sub>2</sub> (46–48)	I(CH <sub>2</sub> ) <sub>6</sub> I	—	9
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>7</sub> NO <sub>2</sub> (60)	I(CH <sub>2</sub> ) <sub>7</sub> I	—	96
O <sub>2</sub> N(CH <sub>2</sub> ) <sub>10</sub> NO <sub>2</sub> (50)	I(CH <sub>2</sub> ) <sub>10</sub> I	—	97
(CH <sub>3</sub> ) <sub>2</sub> CHNO <sub>2</sub> (0)	Cl	—	10
(19–26)	Br	24–34	10
(15–23)	I	25–35	10, 98
CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )NO <sub>2</sub> (0)	Cl	—	10
(19–24)	Br	27–37 ¶	10
(10–15)	I	30–35 ¶	10
(CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CHNO <sub>2</sub> (7–15)	Br	22–29 ¶	10
(9)	I	27 ¶	10
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH(CH <sub>3</sub> )NO <sub>2</sub> (0)	Cl	—	10
(17–23)	Br	18–25	10
(15–20)	I	17–25	10
(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub> CH(NO <sub>2</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> (11)	Br	34 ¶	10
(14)	I	30 ¶	10
Nitrocyclopentane ¶ (3)	I	—	99, 4
Nitrocyclohexane ¶ (—)	I	—	4, 99
C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )NO <sub>2</sub>    (3–12)	Cl	45	16, 11
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )NO <sub>2</sub>    (18)	Br	33	10
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHNO <sub>2</sub> ** (0)	Br	—	100
CH <sub>3</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (80)	I	—	14
CH <sub>3</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (75)	I	—	14
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (84)	I	—	14
(CH <sub>3</sub> ) <sub>3</sub> CNO <sub>2</sub> (4–6)	Cl	64	10
(0)	Br	64	10
(0)	I	0 ††	10
CH <sub>3</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> NO <sub>2</sub> (5–6)	Cl	58	10
CH <sub>3</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> NO <sub>2</sub> (0)	Br	50–60	10
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> C(NO <sub>2</sub> )(CH <sub>3</sub> ) <sub>2</sub> (0)	Cl	49	10
(0)	Br	33	10
(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> CNO <sub>2</sub> †† (0)	Cl	—	41
§§ (0)	Br	—	100
 (—)		—	13

Note: References 77 to 108 are on p. 156.

§ This product is probably not 1,2-dinitroethane; Levy *et al.*, *J. Chem. Soc.*, 1946, 1096.

|| Some nitrate ester was present.

¶ Some nitrate ester was isolated.

\*\* Dibenzhydryl ether was isolated in 60% yield.

†† A colorless gas and iodine were produced.

‡‡ Oxides of nitrogen were evolved and only triphenylcarbinol was isolated.

§§ Triphenylcarbinol was isolated in 94% yield.

TABLE III  
NITRO COMPOUNDS PREPARED WITH SODIUM NITRITE

Nitro Compound (Yield, %) RNO <sub>2</sub>	Halide Employed RX	Solvent	References
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> NO <sub>2</sub> (46)	Methanesulfonate	DMF	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> NO <sub>2</sub> (60)	Br	DMF	21
(61)	I	DMF	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> NO <sub>2</sub> (60)	Br	DMF	21
(66)		DMSO	22
(60)	I	DMF	21
(45)	Tosylate	DMF	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> NO <sub>2</sub> (57)	I	DMF	21
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NO <sub>2</sub> (55)	Br	DMF	21
<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (22)	Br	DMF	15
C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>5</sub> NO <sub>2</sub> (58)	I	DMF	21
CH <sub>3</sub> COCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (47)	Cl	DMF	81
CH <sub>3</sub> CH <sub>2</sub> COCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (48)	Cl	DMF	81
C <sub>6</sub> H <sub>5</sub> COCH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub> (87)	Br	DMF	81
O <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (0)	Br	DMF	15
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH(CH <sub>3</sub> )NO <sub>2</sub> (58)	Br	DMF	21
(46)		DMSO	22
(60)	I	DMF	21
(58)		DMSO	22
(CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CHNO <sub>2</sub> (61)	Br	DMF	21
(62)	I	DMF	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH(CH <sub>3</sub> )NO <sub>2</sub> * (—)	I	DMF	101
Nitrocyclopentane (57)	Br	DMF	21
(58)		DMSO	22
(55)	I	DMF	21

Nitrocyclohexane (0)	Br	DMF	21
(0)	I	DMF	21
Nitrocycloheptane (55)	Br	DMF	21
(58)	I	DMF	21
C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )NO <sub>2</sub> † (43)	Br	DMF	35
CH <sub>3</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (68)	Cl	DMSO	28
CH <sub>3</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (66)	Br	DMSO	28
(62)		DMF	28
CH <sub>3</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (62)	I	DMF	28
CH <sub>3</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (68-75)	Br	DMF	27, 28
(83)		DMSO	28
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (87)	Br	DMSO	28
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (76)	Br	DMSO	28
(74)		DMF	28
(CH <sub>3</sub> ) <sub>2</sub> CHCH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (75)	Br	DMSO	28
(67)		DMF	28
C <sub>6</sub> H <sub>5</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (70)	Br	DMF	28
(CH <sub>3</sub> ) <sub>3</sub> CNO <sub>2</sub> ‡ (0)	Cl	DMF	21
§ (0)	Br	DMF	21
(CH <sub>3</sub> ) <sub>2</sub> C(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (91)	Br	DMSO	28
(78)		DMF	28
(CH <sub>3</sub> ) <sub>2</sub> C(NO <sub>2</sub> )CN (52)	Br	DMF	19

Note: References 77 to 108 are on p. 156.

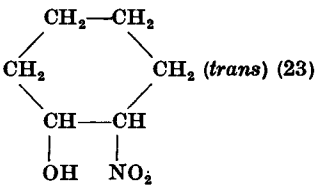
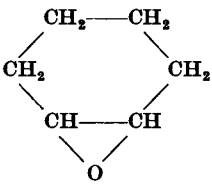
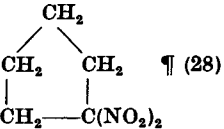
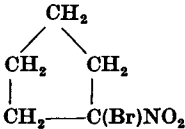
\* 2-Nitrotridecane has b.p. 122°/1 mm., *n*<sub>D</sub><sup>20</sup> 1.4421.

† This reaction was conducted at -18°. In DMSO, at 11°, a 22% yield of *α*-phenylnitroethane was obtained.

‡ Isobutylene was obtained in 69% yield.

§ Isobutylene was obtained in 73% yield.

TABLE III—Continued  
 NITRO COMPOUNDS PREPARED WITH SODIUM NITRITE

Nitro Compound (Yield, %) RNO <sub>2</sub>	Halide Employed BX	Solvent	References
 (CH <sub>3</sub> ) <sub>2</sub> C(NO <sub>2</sub> ) <sub>2</sub>    (45)	 (CH <sub>3</sub> ) <sub>2</sub> C(Br)NO <sub>2</sub>	DMSO	33
 ¶ (28)	 ¶ (28)	DMF	34

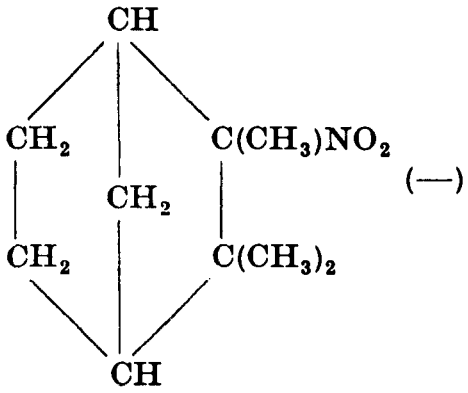
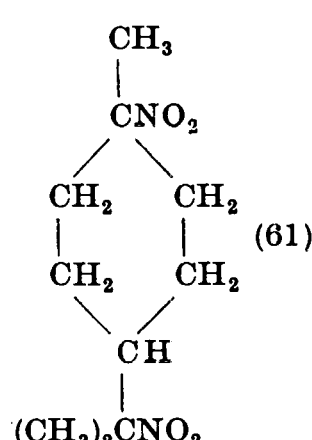
Note: References 77 to 108 are on p. 156.

|| Urea was added and the reaction was conducted at 70–80° for 1 day.

¶ Urea was added and the reaction was conducted at 40° for 4 days.

TABLE IV

NITRO COMPOUNDS PREPARED BY THE OXIDATION OF AMINES  
 $\text{RNH}_2^* \rightarrow \text{RNO}_2$

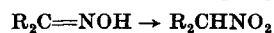
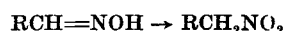
Nitro Compound (Yield, %)	Oxidizing Agent	Reference
$\text{CH}_3(\text{CH}_2)_5\text{NO}_2$ (33)	$\text{CH}_3\text{CO}_2\text{OH}$	42
$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{NO}_2$ (65)	$\text{CH}_3\text{CO}_2\text{OH}$	42
Nitrocyclohexane (70)	$\text{CH}_3\text{CO}_2\text{OH}$	42
$(\text{CH}_3)_3\text{CNO}_2$ (83)	$\text{KMnO}_4$	39
$(\text{CH}_3)_2\text{CHC}(\text{CH}_3)_2\text{NO}_2$ (71)	$\text{KMnO}_4$	39
$(\text{CH}_3)_2\text{CHCH}_2\text{C}(\text{CH}_3)_2\text{NO}_2$ (82)	$\text{KMnO}_4$	39
$(\text{CH}_3)_3\text{CCH}_2\text{C}(\text{CH}_3)_2\text{NO}_2$ (77)	$\text{KMnO}_4$	39
(87)	$\text{CH}_3\text{CO}_2\text{OH}$	42
1-Nitro-1-methylcyclopentane (72)	$\text{KMnO}_4$	39
1-Nitro-1-methylcyclohexane (73)	$\text{KMnO}_4$	39
1-Nitro-1,4-dimethylcyclohexane (70)	$\text{KMnO}_4$	39
	$\text{KMnO}_4$	13
	$\text{KMnO}_4$	39
$(\text{C}_6\text{H}_5)_3\text{CNO}_2$ (0)	$\text{KMnO}_4$	39

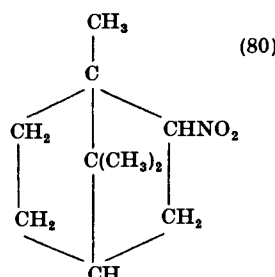
Note: References 77 to 108 are on p. 156.

\* The amine used corresponded in structure to the nitro compound formed.



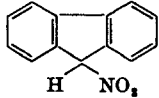
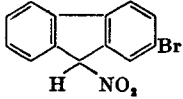
TABLE V  
NITRO COMPOUNDS PREPARED BY THE OXIDATION OF OXIMES

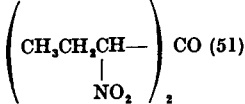
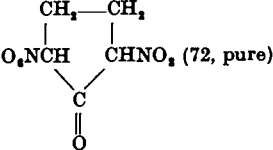
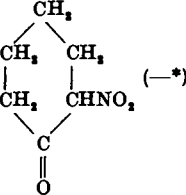
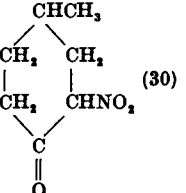


Nitro Compound (Yield, %)	Oxime Oxidized	Reagents, Remarks	Reference
1-Nitrobutane (0)	Butanal	NaOBr	45
1-Nitroheptane (72)	Heptanal	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
1-Nitroöctane (63)	Octanal	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
Phenylnitromethane (77)	Benzaldehyde	CF <sub>3</sub> CO <sub>3</sub> H + Na <sub>2</sub> HPO <sub>4</sub>	43
$\omega$ -Nitroacetophenone (76)	Phenylglyoxal aldoxime	CF <sub>3</sub> CO <sub>3</sub> H	43
Ethyl nitroacetate (40)	Ethyl $\alpha$ -oximinoacetoacetate	CF <sub>3</sub> CO <sub>3</sub> H	43
2-Nitropropane (0)	Acetone	NaOBr and then aqueous ethanolic KOH	45
2-Nitrobutane (47)	Butanone	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
2-Nitropentane (43)	Methyl <i>n</i> -propyl ketone	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
(38)		N-Bromosuccinimide and then NaBH <sub>4</sub>	46
3-Nitropentane (29)	Diethyl ketone	N-Bromosuccinimide and then NaBH <sub>4</sub>	46
2-Nitrohexane (19)	Methyl <i>n</i> -butyl ketone	N-Bromoacetamide and then NaBH <sub>4</sub>	46
3-Nitrohexane (25)	Ethyl <i>n</i> -propyl ketone	N-Bromoacetamide and then NaBH <sub>4</sub>	46
2-Nitroheptane (59)	2-Heptanone	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
(16)		N-Bromoacetamide and then NaBH <sub>4</sub>	46
3-Nitroheptane (29)	3-Heptanone	N-Bromoacetamide and then NaBH <sub>4</sub>	46
4-Nitroheptane (64)	4-Heptanone	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
(28)		N-Bromoacetamide and then NaBH <sub>4</sub>	46
2-Nitroöctane (10)	2-Octanone	N-Bromoacetamide and then NaBH <sub>4</sub>	46
2-Nitro-3-methylbutane (49)	Methyl isopropyl ketone	CF <sub>3</sub> CO <sub>3</sub> H + NaHCO <sub>3</sub>	43
(48)		N-Bromosuccinimide and then NaBH <sub>4</sub>	46
3-Nitro-2,2-dimethylbutane (36)	Pinacolone	N-Bromosuccinimide and then NaBH <sub>4</sub>	46
Nitrocyclobutane (23)	Cyclobutanone	N-Bromosuccinimide and then NaBH <sub>4</sub>	44
Nitrocyclopentane (60)	Cyclopentanone	CF <sub>3</sub> CO <sub>3</sub> H + Na <sub>2</sub> HPO <sub>4</sub>	43
(55)		N-Bromosuccinimide and then NaBH <sub>4</sub>	44
Nitrocyclohexane (62)	Cyclohexanone	CF <sub>3</sub> CO <sub>3</sub> H + Na <sub>2</sub> HPO <sub>4</sub>	43
(50)		N-Bromosuccinimide and then NaBH <sub>4</sub>	44
2-Nitro-1-methylcyclohexane (30)	2-Methylcyclohexanone	N-Bromosuccinimide and then NaBH <sub>4</sub>	44
4-Nitro-1-methylcyclohexane (22)	4-Methylcyclohexanone	N-Bromosuccinimide and then NaBH <sub>4</sub>	44
Nitrocycloheptane (51)	Cycloheptanone	CF <sub>3</sub> CO <sub>3</sub> H + Na <sub>2</sub> HPO <sub>4</sub>	43
(30)		N-Bromosuccinimide and then NaBH <sub>4</sub>	44
(80)			
	Camphor	KOH + Br <sub>2</sub> followed by aqueous alcoholic KOH	102
$\alpha$ -Nitroindanone (0)	$\alpha$ -Indanone	NaOH + Br <sub>2</sub>	45
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHNO <sub>2</sub> (0)	Benzophenone	NaOH + Br <sub>2</sub>	45
9-Nitrofluorene (0)	Fluorenone	NaOH + Br <sub>2</sub>	45
$\alpha$ -Phenylnitroethane (69)	Acetophenone	CF <sub>3</sub> CO <sub>3</sub> H + Na <sub>2</sub> HPO <sub>4</sub>	43
Diethylnitromalonate (66)	Diethyl mesoxalate	CF <sub>3</sub> CO <sub>3</sub> H	43
Nitromalonamide (49)	Mesoxalamide	CF <sub>3</sub> CO <sub>3</sub> H	43

Note: References 77 to 108 are on p. 156.

TABLE VI  
NITRATIONS EMPLOYING NITRATE ESTERS

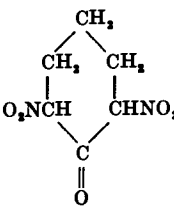
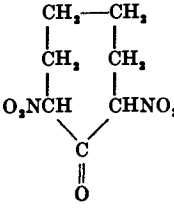
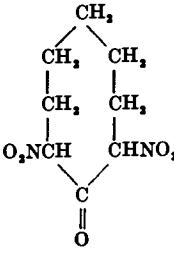
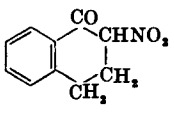
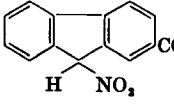
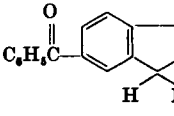
Salt of Nitro Compound (Yield, %)	Compound Nitrated	Base	Nitrate Ester	Reference
Nitrocyclopentadiene (—)	Cyclopentadiene	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	103
C <sub>5</sub> H <sub>7</sub> CH <sub>2</sub> NO <sub>2</sub> (ca. 80*)	Ethyl phenylacetate	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	51
C <sub>5</sub> H <sub>7</sub> CH <sub>2</sub> NO <sub>2</sub> (55*)	C <sub>5</sub> H <sub>7</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Methyl	49
(70*)		NaH	Acetone cyanohydrin	62
<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (ca. 50*)	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	104
<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	104
<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (42, * pure)	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	NaH	Acetone cyanohydrin	62
<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	105
<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	105
<i>m</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	105
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	Ethyl <i>p</i> -bromophenylacetate	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	51
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	50
α-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	α-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	104
β-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> NO <sub>2</sub> (—*)	β-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> CN	NaOC <sub>2</sub> H <sub>5</sub>	Ethyl	104
 (ca. 35, * pure)	Fluorene	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	52
 (63, pure)	2-Bromofluorene	KOC <sub>2</sub> H <sub>5</sub>	2-Octyl	106
C <sub>6</sub> H <sub>5</sub> COCH <sub>2</sub> NO <sub>2</sub> (41)	Acetophenone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	56

 CO (51)	4-Heptanone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	56
O <sub>2</sub> NCH <sub>2</sub> COCH <sub>2</sub> NO <sub>2</sub> (49, pure)	Acetone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	56
O <sub>2</sub> NCH <sub>2</sub> COCH(CH <sub>3</sub> )NO <sub>2</sub> (57, pure)	Ethyl methyl ketone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	56
 (72, pure)	Cyclopentanone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	55
 (—*)	Cyclohexanone	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	54
 (30)	4-Methylcyclohexanone	KOC <sub>2</sub> H <sub>5</sub>	2-Octyl	107

Note: References 77 to 108 are on p. 156.

\* This is the yield of the nitro compound, not its salt.

TABLE VI—Continued  
 NITRATIONS EMPLOYING NITRATE ESTERS

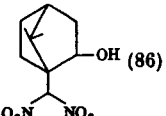
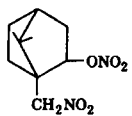
Salt of Nitro Compound (Yield, %)	Compound Nitrated	Base	Nitrate Ester	Reference
 (53, pure)	Cyclohexanone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	55
 (54, pure)	Cycloheptanone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	55
 (35, pure)	Cyclooctanone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	55
 (40, pure)	$\alpha$ -Tetralone	KOC(CH <sub>3</sub> ) <sub>3</sub>	Amyl	55
 (85)	2-Benzoylfluorene	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	108
 (65)	2,7-Dibenzoylfluorene	KOC <sub>2</sub> H <sub>5</sub>	Ethyl	108
<p><i>p</i>-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SCH(NO<sub>2</sub>)COC<sub>2</sub>H<sub>5</sub> (—*)            O<sub>2</sub>NCH<sub>2</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> (42, * pure)</p>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SCH <sub>2</sub> COC <sub>2</sub> H <sub>5</sub> Diethyl malonate	NaOC <sub>2</sub> H <sub>5</sub> NaH	Ethyl Acetone	65 62
O <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (52, * pure)	CH <sub>2</sub> COCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NaH	Acetone cyanohydrin	62
O <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> CMe <sub>2</sub> (0)	CH <sub>2</sub> CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub>	NaH	Acetone cyanohydrin	62
O <sub>2</sub> NCH(CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (0)	(CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	NaH	Acetone cyanohydrin	62
CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (56, * pure)	CH <sub>2</sub> CH(CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	NaH	Acetone cyanohydrin	62
CH <sub>2</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (51, * pure)	CH <sub>2</sub> CH <sub>2</sub> CH(CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	NaH	Acetone cyanohydrin	62
CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (46, * pure)	CH <sub>2</sub> COCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NaH	Acetone cyanohydrin	62

Note: References 77 to 108 are on p. 156.

\* This is the yield of the nitro compound, not its salt.

TABLE VI—Continued  
 NITRATIONS EMPLOYING NITRATE ESTERS

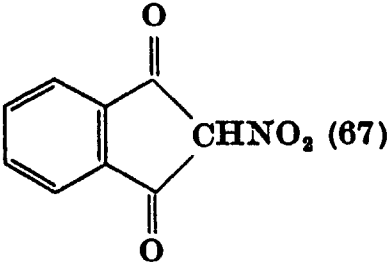
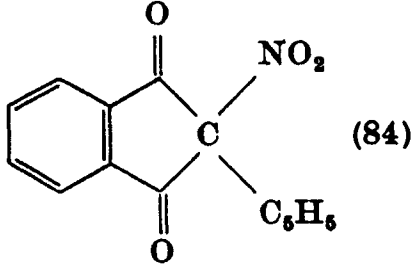
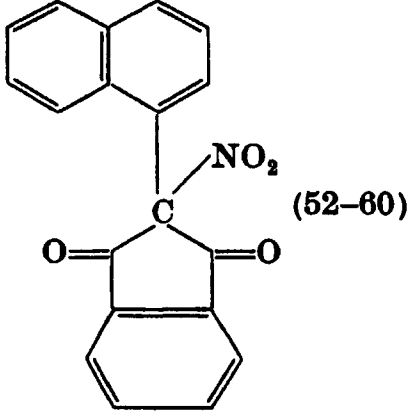
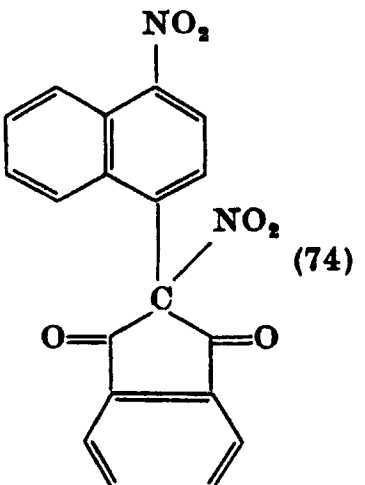
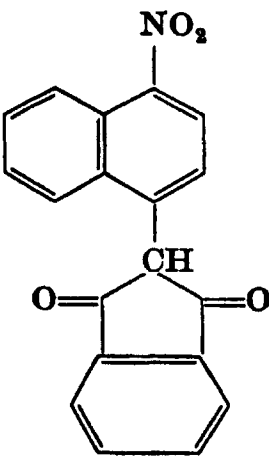
Salt of Nitro Compound (Yield, %)	Compound Nitrated	Base	Nitrate Ester	Reference
$n\text{-C}_4\text{H}_9\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (54,* pure)	$n\text{-C}_4\text{H}_9\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	NaH	Acetone cyanohydrin	62
$n\text{-C}_4\text{H}_9\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (50,* pure)	$\text{CH}_3\text{COCH}(n\text{-C}_4\text{H}_9)\text{CO}_2\text{C}_2\text{H}_5$	NaH	Acetone cyanohydrin	62
$n\text{-C}_5\text{H}_{11}\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (46,* pure)	$n\text{-C}_5\text{H}_{11}\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	NaH	Acetone cyanohydrin	62
$n\text{-C}_5\text{H}_{11}\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (70,* pure)	$\text{CH}_3\text{COCH}(n\text{-C}_5\text{H}_{11})\text{CO}_2\text{C}_2\text{H}_5$	NaH	Acetone cyanohydrin	62
$i\text{-C}_4\text{H}_9\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (47,* pure)	$i\text{-C}_4\text{H}_9\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	NaH	Acetone cyanohydrin	62
$i\text{-C}_5\text{H}_{11}\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (69,* pure)	$\text{CH}_3\text{COCH}(i\text{-C}_5\text{H}_{11})\text{CO}_2\text{C}_2\text{H}_5$	NaH	Acetone cyanohydrin	62
$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (40,* pure)	$\text{CH}_3\text{COCH}(\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl})\text{CO}_2\text{C}_2\text{H}_5$	NaH	Acetone cyanohydrin	62
$\text{CH}_2=\text{CHCH}_2\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (45,* pure)	$\text{CH}_2=\text{CHCH}_2\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	NaH	Acetone cyanohydrin	62
$\text{CH}_2=\text{CHCH}_2\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (53,* pure)	$\text{CH}_3\text{COCH}(\text{CH}_2\text{CH}=\text{CH}_2)\text{CO}_2\text{C}_2\text{H}_5$	NaH	Acetone cyanohydrin	62
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ (67,* pure)	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	NaH	Acetone cyanohydrin	62
$\text{O}_2\text{NCH}(\text{CO}_2\text{C}_2\text{H}_5)_2$ (54,* pure)	Diethyl malonate	NaH	Acetone cyanohydrin	62
$\text{O}_2\text{NCH}_2\text{CN}$ (0)	$\text{CH}_3\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{CH}_3\text{CH}_2\text{CH}(\text{NO}_2)\text{CN}$ (44, pure)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{CH}_3(\text{CH}_2)_4\text{CH}(\text{NO}_2)\text{CN}$ (55, pure)	$\text{CH}_3(\text{CH}_2)_4\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{O}_2\text{NCH}(\text{CN})\text{CH}_2\text{CH}_2\text{CH}(\text{CN})\text{NO}_2$ (93, pure)	$\text{NC}(\text{CH}_2)_4\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{O}_2\text{NCH}(\text{CN})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CN})\text{NO}_2$ (46, pure)	$\text{NC}(\text{CH}_2)_5\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{O}_2\text{NCH}(\text{CN})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CN})\text{NO}_2$ (67, pure)	$\text{NC}(\text{CH}_2)_6\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56

$\text{O}_2\text{NCH}(\text{CN})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CN})\text{NO}_2$ (49, pure)	$\text{NC}(\text{CH}_2)_6\text{CN}$	$\text{KOC}(\text{CH}_3)_3$	Amyl	56
$\text{C}_6\text{H}_5\text{CH}(\text{CN})\text{NO}_2$ (72-82)	Benzyl cyanide	$\text{NaOC}_2\text{H}_5$	Methyl	49
$o\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CN})\text{NO}_2$ ("Very good")	$o\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CN}$	$\text{NaOC}_2\text{H}_5$	Ethyl	104
$m\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CN})\text{NO}_2$ (ca. 75)	$m\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CN}$	$\text{NaOC}_2\text{H}_5$	Ethyl	104
$p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CN})\text{NO}_2$ (—)	$p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CN}$	$\text{NaOC}_2\text{H}_5$	Ethyl	104
$o\text{-BrC}_6\text{H}_4\text{CH}(\text{CN})\text{NO}_2$ (ca. 70, crude)	$o\text{-BrC}_6\text{H}_4\text{CH}_2\text{CN}$	$\text{KOC}_2\text{H}_5$	Ethyl	59
$p\text{-BrC}_6\text{H}_4\text{CH}(\text{CN})\text{NO}_2$ (over 90, crude)	$p\text{-BrC}_6\text{H}_4\text{CH}_2\text{CN}$	$\text{KOC}_2\text{H}_5$	Ethyl	50
$\alpha\text{-C}_{10}\text{H}_7\text{CH}(\text{CN})\text{NO}_2$ (—*)	$\alpha\text{-C}_{10}\text{H}_7\text{CH}_2\text{CN}$	$\text{NaOC}_2\text{H}_5$	Ethyl	104
$\beta\text{-C}_{10}\text{H}_7\text{CH}(\text{CN})\text{NO}_2$ (—)	$\beta\text{-C}_{10}\text{H}_7\text{CH}_2\text{CN}$	$\text{NaOC}_2\text{H}_5$	Ethyl	104
$p\text{-CH}_3\text{C}_6\text{H}_4\text{S}(\text{CH}_2)_2\text{NO}_2$ (—*)	$p\text{-CH}_3\text{C}_6\text{H}_4\text{SCH}_2\text{COC}_2\text{H}_5$	$\text{NaOC}_2\text{H}_5$	Ethyl	65
 (86)		KOH	Self	60

Note: References 77 to 108 are on p. 156.

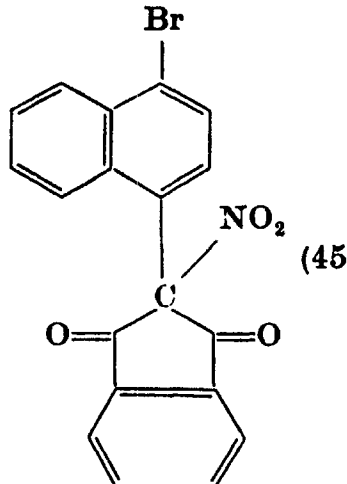
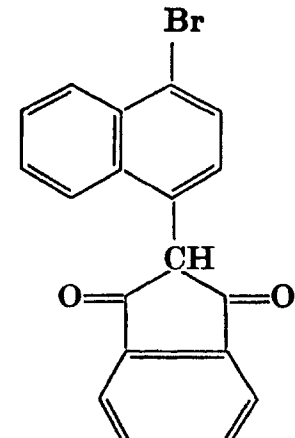
\* This is the yield of the nitro compound, not its salt.

TABLE VII  
NITRO COMPOUNDS PREPARED WITH NITRIC ACID

Nitro Compound (Yield, %)	Compound Nitrated	Reference
$(C_6H_5)_2CHNO_2^*$ (ca. 50)	$(C_6H_5)_2CH_2$	70
$O_2NCH(CO_2C_2H_5)_2$ (ca. 92)	Diethyl malonate	63
 $CHNO_2$ (67)	1,3-Indanedione	66
$HC(NO_2)_2CO_2C_2H_5$ (11)	$H_2C(CO_2H)CO_2C_2H_5$	68
 (84)	2-Phenyl-1,3-indanedione	67
 (52-60)	2-( $\alpha$ -Naphthyl)-1,3-indanedione	67
 (74)		67
		67

\* In this reaction nitrogen dioxide and oxygen were used in carbon tetrachloride at 70–75° with anhydrous cupric sulfate instead of nitric acid.

TABLE VII—*Continued*  
 NITRO COMPOUNDS PREPARED WITH NITRIC ACID

Nitro Compound (Yield, %)	Compound Nitrated	Reference
 <p>(45)</p>		67
$(C_6H_5)_2C(CN)NO_2$ † (57) $CH_3C(NO_2)_2CO_2C_2H_5$ (17) $C_2H_5C(NO_2)_2CO_2C_2H_5$ (17) $n-C_4H_9C(NO_2)_2CO_2C_2H_5$ (8) $(C_6H_5)_2C(NO_2)_2$ † (ca. 30)	$(C_6H_5)_2CHCN$ $CH_3CH(CO_2H)CO_2C_2H_5$ $C_2H_5CH(CO_2H)CO_2C_2H_5$ $n-C_4H_9CH(CO_2H)CO_2C_2H_5$ $(C_6H_5)_2CH_2$	69 68 68 68 70

Note: References 77 to 108 are on p. 156.

† Dry nitrogen dioxide in chloroform at 15–20° was used instead of nitric acid.

‡ Nitrogen dioxide and nitric oxide were used in carbon tetrachloride with calcium nitrate instead of nitric acid.

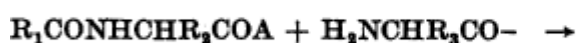
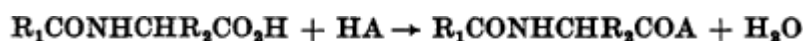
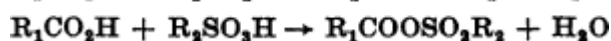
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<sup>78</sup> Reynolds and Adkins, *J. Am. Chem. Soc.*, **51**, 279 (1929).  
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<sup>96</sup> von Braun and Danziger, *Ber.*, **46**, 103 (1913).  
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<sup>102</sup> Forster, *J. Chem. Soc.*, **77**, 254 (1900).  
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# Synthesis of Peptides with Mixed Anhydrides

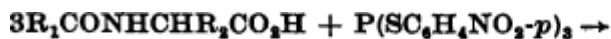
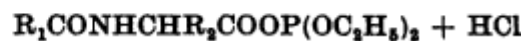
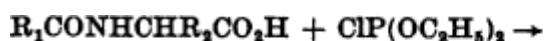
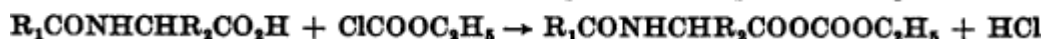
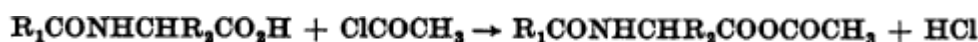
## 1. Introduction

A mixed acid anhydride, or mixed anhydride, is a dehydration product of two polyoxy acids. For a mixed anhydride to be of interest for peptide synthesis one of the component acids must, in general, be an  $\alpha$ -acylamino acid. The nature of the second component acid, HA, may vary widely.



In this chapter the term mixed anhydride will be used in a more general sense than ordinarily in order to emphasize the similarity of a number of procedures that have been found useful for the synthesis of peptides. Thus, in addition to conventional mixed anhydrides, derivable from polyoxy acids, reference will be made to "mixed anhydrides" otherwise recognizable as acyl halides, ethers, esters, thiol esters, O-acylisoureas and isoimides, etc.

In practice an  $\alpha$ -acylamino acid mixed anhydride is usually prepared by reaction of an  $\alpha$ -acylamino acid with an unsymmetrical anhydride that not only provides the second acid component but is also instrumental in causing the reaction to proceed in the desired direction.



This chapter is limited to a review of the chemistry of the acyclic  $\alpha$ -acylamino acid mixed anhydrides, excluding the well-known  $\alpha$ -acylamino acid chlorides and azides which have already been the subject of an excellent review.<sup>1</sup> In general, discussion of the application of  $\alpha$ -acylamino acid mixed anhydrides will be limited to non-polymeric peptide bond formation and will not be concerned with acylations other than those leading to the formation of a peptide bond.

## 2. General Considerations



## 2.1. Nature of the Reaction

### 2.1.1. Formation of the $\alpha$ -Acylamino Acid Mixed Anhydride

In general, in the displacement reaction between the  $\alpha$ -acylamino acid anion and an unsymmetrical anhydride the less reactive  $\alpha$ -acylamino anhydride is formed with the elimination of the stable anion corresponding to the stronger acid.[2](#)

### 2.1.2. Amide Bond Formation

In the reaction of the  $\alpha$ -acylamino anhydride with an amine, the amine behaves as the nucleophile and the acylating species as the electrophilic reagent. In an anhydride of the type  $R_1CONHCHR_2COOCOR_3$  the amine may attack at either anhydride carbonyl. If  $R_1CONHCHR_2-$  is the more strongly electron-attracting group, the adjacent carbonyl will be more positively charged than that adjacent to  $R_3$  and the desired amide bond formation will predominate.[3](#), [4](#) The base strength of the attacking amine may also be important in determining the major products of the reaction.[5](#)

The effect of the solvent upon the course of peptide synthesis has received little attention. However, in analogous reactions involving simpler unsymmetrical anhydrides, solvents are known to have considerable effect. The mixed anhydride of acetic and propionic acid reacts with aniline in an anhydrous medium to give a 90% yield of propionanilide, whereas in an aqueous medium propionylation decreases and the yield of acetanilide rises to 32%.[6](#) Similar results were obtained in the reaction of aniline with the mixed anhydride of acetic acid and chloroacetic acid; the ratio of chloroacetylation to acetylation decreased considerably with variation of the solvent in the order benzene, acetone, and aqueous acetone.[3](#), [4](#)

The yield of acylations carried out in water is influenced by the pH of the solution. In non-aqueous solvents the rate may be influenced by the addition of acids or bases. These factors will be considered more fully under the individual  $\alpha$ -acylamino mixed anhydrides.

## 2.2. Structural Factors

### 2.2.1. Structure of the Anhydride

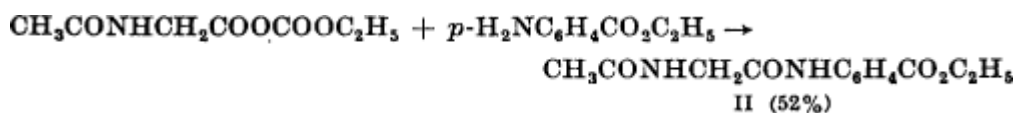
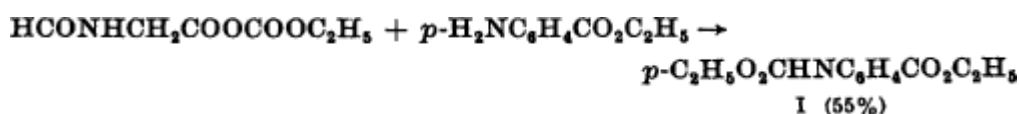
The effect of varying the alkyl group  $R_2$  in mixed  $\alpha$ -acylamino anhydrides of the general formula  $C_6H_5CH_2OCONHCHR_1COOCOR_2$  has been determined by reaction of 25 mixed anhydrides, derived from carbobenzyloxyglycine and various aliphatic acids, with aniline. The effectiveness of the mixed anhydride  $C_6H_5CH_2OCONHCHR_1COOCOR_2$  in producing carbobenzyloxyglycylanilide decreases with decreasing steric requirement of the group  $R_2$ . These results agree with those predicted by Newman's rule of six.[7](#) Thus Vaughan and Osato[8](#) found that those anhydrides, in which  $R_2$  is derived from diethylacetic acid and isovaleric acid, having the highest six number, gave the highest yield of carbobenzyloxyglycylanilide (85% and 83% respectively). The isocaproic and lauric acid mixed anhydrides with six numbers only half as great as isovaleric acid gave yields of the above anilide of only 36% and 31%, respectively. However, the anhydride from trimethylacetic acid (six number of zero) and

carbobenzyloxyglycine gave a 72% yield of carbobenzyloxyglycylanilide. In this instance, it is possible that the positive inductive effects of the alkyl groups play the major role in determining the course of the reaction.

No corresponding systematic study of the effect of changing the steric environment around the amino acid carbonyl by varying the amino acid side chain has yet been made.

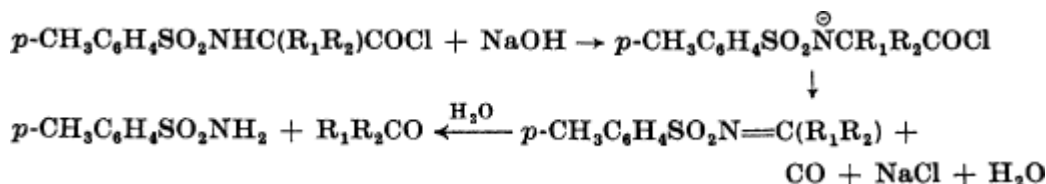
In most cases the  $\alpha$ -amino protecting group is carbobenzyloxy or carbobenzyloxyaminoacyl, although many others have been used. When the protecting group is trityl, steric hindrance generally prevents formation of an anhydride: trityl amino acids other than glycine or alanine apparently fail to form mixed anhydrides with ethyl chloroformate,<sup>9, 10</sup> although they will form mixed anhydrides with dicyclohexylcarbodiimide.<sup>11, 12</sup>

Formylglycyl ethyl carbonate reacts with ethyl *p*-aminobenzoate to form primarily the urethan I, whereas acetylglycyl ethyl carbonate forms the expected amide II.<sup>13</sup> However, other formylamino acid alkyl carbonates react in the normal manner although yields are frequently low.



Low yields (30–40%) of product have been obtained in the coupling of sodium glycinate with the mixed anhydrides  $\text{ClCH}_2\text{CONHCH}[\text{CH}_2\text{CH}_2\text{CH}(\text{SC}_2\text{H}_5)_2]\text{COOCOOC}_8\text{H}_{17}$ , and  $\text{ClCH}_2\text{CONHCH}_2\text{COOCOOC}_8\text{H}_{17}$  derived from the corresponding chloroacetyl amino acids.<sup>14</sup> Chloroacetyl amino acids would be expected to give unsaturated azlactones as by-products in many mixed anhydride syntheses.<sup>15</sup>

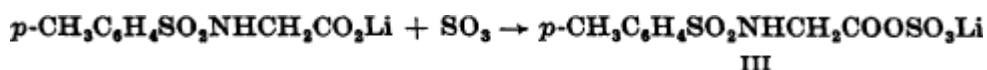
A remarkable reaction discovered by Beecham<sup>16, 17</sup> is probably applicable to a variety of  $\alpha$ -tosylamino acid mixed anhydrides. He observed that  $\alpha$ -tosylamino acid chlorides react with aqueous sodium hydroxide solution with evolution of carbon monoxide (86–99% yields) and the formation of an aldehyde (or ketone), *p*-toluenesulfonamide, and sodium chloride.



The reaction is slower with sodium carbonate than with sodium hydroxide and fails with sodium bicarbonate. With aqueous ammonia, but not with glycine or proline, a tosylamino acid amide results.  $\alpha$ -Tosyl-DL-valyl azide dissolved in aqueous sodium hydroxide with effervescence, and the odor of isobutyraldehyde was noticeable.<sup>16</sup> This suggests that the Beecham reaction may be fairly general for  $\alpha$ -tosylamino acid mixed anhydrides.

To avoid the Beecham reaction in the acylation of amino acid salts with  $\alpha$ -tosylamino acid alkyl carbonates it is merely necessary to control the pH of the solution by introducing magnesium oxide, sodium bicarbonate, or similarly weak alkaline reagents. However, even under mildly basic conditions  $\alpha$

-tosylamino acid alkyl carbonates do not always react smoothly.  $\alpha$ -Tosylisoleucine alkyl carbonates give less satisfactory results in peptide synthesis than do carbobenzyloxyisoleucine alkyl carbonates.<sup>18</sup> Various  $\alpha$ -tosylalanine phosphate esters in model coupling experiments with cyclohexylamine gave unpromising results (unpublished work, but see ref. <sup>19</sup>). Protection of the  $\alpha$ -amino group by groups other than tosyl was not investigated. On the other hand, the mixed anhydride of sulfuric acid and tosylglycine of Kenner<sup>5</sup> condensed with phenylalanine in 86% yield and with phenylalanyl glycine in 92% yield. This method differs from other mixed anhydride procedures in that the sulfuric acid mixed anhydride III is used in the form of its salt.



### 2.2.2. Structure of the Amine

The amine that is acylated may be either the salt or the ester of an amino acid or peptide. If an ester is employed, a neutral product is obtained from which the acidic and basic starting materials may be readily removed by extraction with sodium bicarbonate solution and dilute hydrochloric acid. The use of an alkali metal salt results in the formation of an acidic product which often requires counter-current distribution to separate it in a pure state from any of the original acylamino acid or peptide.

A number of carbobenzyloxyvaline dipeptides were prepared in one of two ways: (A) the mixed anhydride of carbobenzyloxy-DL-valine and ethyl chloroformate in ether was condensed with the ester of an amino acid and the product saponified with alkali; (B) the same mixed anhydride in dioxane was condensed with the sodium salt of an amino acid. The over-all yields were slightly higher by procedure A.<sup>20</sup> Vaughan and Osato<sup>21</sup> suggest that the lower yields obtained with salts are due to the use of an aqueous medium. Vigorous stirring is advisable when sodium salts are used, particularly if the anhydride was prepared in a water-immiscible solvent.

Davis found it impractical to condense carbobenzyloxy dipeptides with the sodium salt of an amino acid because of difficulties in purification.<sup>20</sup> Part of his difficulty could, however, have been due to the presence of mixtures of stereoisomers since he was working with DL-amino acids.

There are several reasons why it is more satisfactory to condense an acylamino acid with the sodium salt of a dipeptide than to condense the acylated peptide with the amino acid.

1. The sodium salt of the dipeptide will have a higher concentration of free amino groups and consequently will give a better yield of acylated product than the amino acid. At pH 7.4 glycyltryptophan has about twenty times the concentration of free amino groups as tryptophan, and the peptide reacts more smoothly with silver phenyl carbobenzyloxyglycylphosphate than tryptophan.<sup>22</sup>
2. The separation of an acyl tripeptide from an  $\alpha$ -acylamino acid will generally be easier than the separation of an acyl tripeptide from an acyldipeptide.
3. In condensing the carbobenzyloxy or phthaloyl derivatives of the  $\alpha$ -acylamino acid with the dipeptide, less racemization would be expected than in condensing the acylated dipeptide with the amino acid. Tri- and higher peptides, however, are more susceptible to racemization than dipeptides, and methods avoiding alkaline solution are usually necessary to retain optical purity.

If the ester of an amino acid or peptide is used as the amine component, the ester group must ultimately be

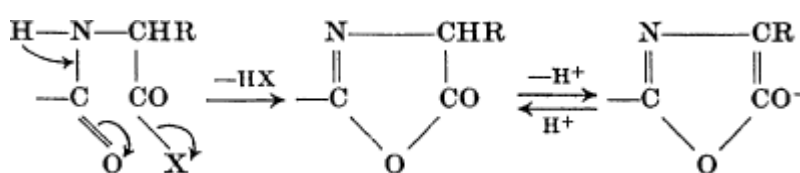
removed. Although saponification is commonly employed, the ester group may be removed without recourse to alkaline media. Esters such as methyl and ethyl will undergo hydrolysis in aqueous hydrochloric or hydrobromic acid,<sup>23, 24</sup> and esters such as benzyl, t-butyl, and cyclopentyl will undergo alkyl-oxygen fission with anhydrous halogen acids.<sup>25-29</sup> Benzyl esters are also converted to the acids by hydrogenolysis.<sup>30</sup>

Several instances have been cited where a mixed  $\alpha$ -acylamino anhydride will react with the ester of an amino acid and not with the sodium salt, or vice versa. Thus the mixed anhydride from tritylglycine and ethyl chloroformate reacts with ethyl glycinate to give ethyl tritylglycylglycinate in 63% yield, but the same anhydride does not react with an aqueous dioxane solution of sodium glycinate to give the trityldipeptide.<sup>9</sup> The acid chloride of L-3-formyl-2,2-dimethylthiazolidine-4-carboxylic acid could not be formed, but the mixed anhydride with carbonic acid acylated methyl glycinate in the normal manner<sup>31, 32</sup> but failed to acylate sodium glycinate.<sup>31</sup> The mixed anhydride of formylglycine and ethyl chloroformate acylated p-aminobenzoic acid in 47% yield but reacted with ethyl p-aminobenzoate to give the urethan in 55% yield.<sup>13</sup> These results were attributed to the abnormal behavior of the mixed anhydride in yielding the cation  $C_2H_5O_2C^{\Delta}$  instead of the expected cation  $HCONHCH_2CO^{\Delta}$ . The assumption that the reaction proceeds through an acyl carbonium intermediate does not explain its abnormal course. The solvent may play an important role in determining which way a mixed anhydride will react.<sup>3, 4, 6</sup>

## 2.3. Racemization

Greenstein<sup>33</sup> has calculated the probability that all the amino acid residues in a peptide of n residues are of a single optical configuration when the starting material is of various degrees of optical purity. For a decapeptide, the probability is 0.90 if 1% of optical enantiomorph is present in each starting amino acid, and 0.35 if 10% of enantiomorph is present. Since racemization likewise leads to introduction of the optical enantiomorph, it is apparent that even 5% racemization at each step is intolerable for the synthesis of higher peptides.

Compounds that possess the structural unit single bond  $CONHCHRCOX$  may undergo racemization as shown below.



Racemization of  $\alpha$ -acylamino acids via mixed anhydrides (of acetic acid) and azlactones (oxazolones) has been reviewed.<sup>34</sup> The nature of X has a considerable influence on the extent of racemization, but data are not available to make a comparison among the various anhydrides. The azide ( $X = N_3$ ) is remarkably resistant to racemization,<sup>35, 36</sup> and it is probably unique among mixed anhydrides in this respect. Thiol esters are relatively resistant to attack by alkoxide ion but are readily aminolyzed. Thus carbobenzyloxyglycyl-L-leucyl thiophenolate and sodium glycinate in aqueous tetrahydrofuran gave the carbobenzyloxy tripeptide with retention of activity in 70% yield.<sup>37</sup> However, the p-nitrophenyl thiol ester of carbobenzyloxyglycyl-L-alanine reacted with L-phenylalanyl glycine in aqueous dioxane to give a product containing 70% of the LL form and 30% of the DL form.<sup>38</sup>

Amino acids other than serine, threonine, or cysteine in which the amino group is protected by a carbalkoxyl, phthaloyl, p-toluenesulfonyl, or trityl group are generally not subject to racemization. However, all acyl peptides except those with a terminal carboxy group in a glycine, proline, or hydroxyproline residue may be racemized during anhydride formation. In the ethyl ester of carbobenzyloxy D-serylglycyl-L-alanine, the seryl residue is almost completely racemized in aqueous

methanol in the presence of triethylamine at room temperature.<sup>39</sup>

The rate of racemization usually increases as the time and temperature for anhydride formation are increased, but the most important factor is the nature of the solvent. Racemization is reduced in non-polar solvents and in the absence of base.<sup>5</sup> With  $\alpha$ -acylaminoacyl alkyl carbonates, tetrahydrofuran and toluene are particularly good solvents for diminishing the rate of racemization whereas chloroform<sup>40</sup> and dimethylformamide<sup>41</sup> are poor in this respect. Chloroform and dimethylformamide may dissolve the triethylamine hydrochloride formed during the preparation of the anhydride, and this salt may influence the rate of racemization. If this assumption is correct, tributylamine hydrochloride, which is soluble in many organic solvents, should increase the rate of racemization with benzene as the solvent. If the triethylamine hydrochloride is a major factor in causing racemization, it may prove advantageous to choose a different tertiary amine, or to select a different method of removing hydrogen chloride from the reaction mixture. The free base, or a salt of the  $\alpha$ -amino acid ester other than the hydrochloride, might be used.

Several physical methods have been utilized to determine the extent of racemization. Acetyl-L-leucine has been coupled with ethyl glycinate by a variety of procedures.<sup>35</sup> Because the optically pure product has a relatively high rotation, rotation can be used as a criterion of purity. A test that permits detection of less than 0.5% racemization involves the acylation of ethyl glycinate with carbobenzyloxyglycyl-L-phenylalanine and subsequent fractional crystallization of the product.<sup>42</sup> Countercurrent distribution may be used to separate the optical isomers.<sup>38</sup>

Enzymic methods have proved quite satisfactory for detecting racemization. The enzymes used are specific for hydrolysis of peptide bonds in which the newly liberated carboxyl groups are associated with  $\alpha$ -amino acid residues of the L configuration.<sup>43</sup> Histidylphenylalanylarginyl-tryptophylglycine was synthesized from L-amino acids using N, N'-dicyclohexylcarbodiimide for the coupling reagent.<sup>44</sup> Treatment of the pentapeptide with trypsin resulted in the formation of histidylphenylalanylarginine and tryptophylglycine together with much unhydrolyzed material as shown by paper chromatograms. Only 37% of the pentapeptide was cleaved. The enzyme leucine aminopeptidase gave histidine, phenylalanine, arginine, tryptophan, and glycine in the molar ratios 1:1:0.4:0.4:0.4. Thus both enzymic methods indicated that only about 40% of the all-L isomer was present. Leucine aminopeptidase was also used to demonstrate that the octapeptide occupying positions 6 to 13 of the ACTH molecule has been synthesized without racemization.<sup>45</sup>

The optical purity of eight tripeptides of D- and L-valine, prepared by the dicyclohexylcarbodiimide procedure, was demonstrated through the use of a microbiological assay for L-valine.<sup>46</sup>

Racemization can be avoided by condensing a carbalkoxy (or phthaloyl, tosyl, or trityl)amino acid with a peptide so as to lengthen the chain by one amino acid at a time. By this method histidylphenylalanylarginyltryptophylglycine was synthesized using dicyclohexylcarbodiimide to form most of the peptide bonds.<sup>47</sup> The product was completely hydrolyzed by trypsin to histidylphenylalanylarginine and tryptophylglycine; chymotrypsin gave histidylphenylalanine, arginyltryptophan, and glycine.

Coupling of larger peptide fragments at a glycine or proline residue, or synthesis through the azide, also avoids racemization.

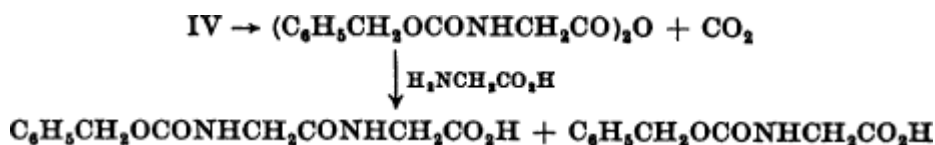
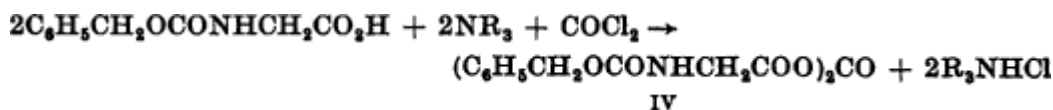
No systematic study of the effect of the  $\alpha$ -amino acid side chain on the rate of racemization has appeared.

## 2.4. Bis-( $\alpha$ -Acylaminoacyl)Carbonates

Carbobenzyloxyglycine reacts with phosgene in the presence of a tertiary base in an inert solvent to give a mixed anhydride which, when condensed with glycine, gave carbobenzyloxyglycylglycine in 40% over-all



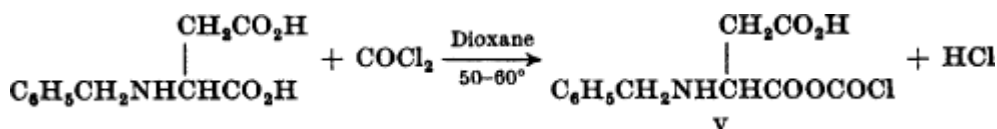
yield.<sup>48</sup> The proposed pathway is shown in the accompanying equations.



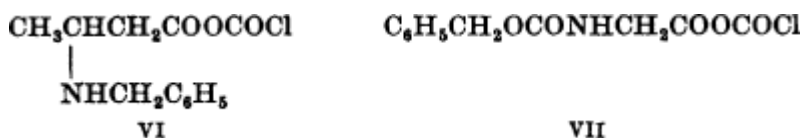
The yields could possibly be improved by operating at temperatures below zero, but the method would still be less convenient than others that are available.

### 3. $\alpha$ -Acylaminoacyl Chlorocarbonates

A mixed anhydride of N-benzyl-DL-aspartic acid and phosgene was reported to have the structure V.<sup>49</sup> This proposed structure seems open to considerable doubt since its formation would imply that: (1) a basic amine fails to react with the hydrogen chloride which is formed as a by-product, (2) the amino group is not acylated by an active acylating group in the same molecule, (3) excess phosgene fails to react with an available carboxyl group, and (4) both an acid and an anhydride coexist without reacting to liberate hydrogen chloride even though a base is present and the reaction product is in solution. The presumed mixed anhydride has been used to prepare both alpha and beta amides<sup>50</sup> and peptides.<sup>49, 51</sup>



Reaction of N-benzyl-DL- $\beta$ -aminobutyric acid with phosgene in dioxane at 60° was reported to give the mixed anhydride VI.<sup>52</sup> This structure is unlikely for some of the reasons just cited against the formation of a compound of structure V.

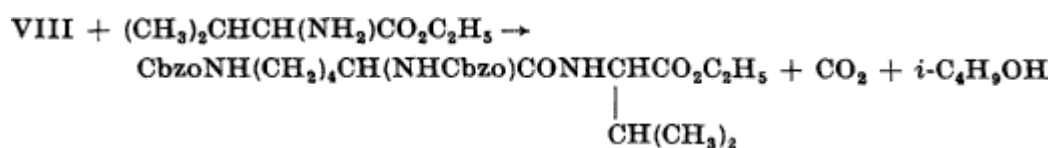
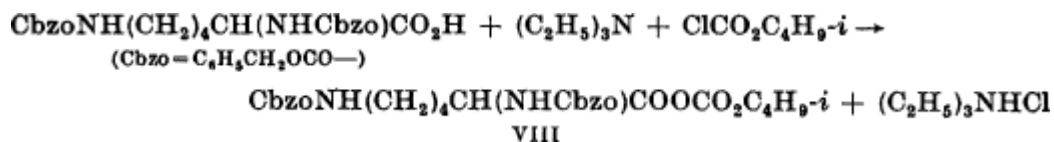


Carbobenzyloxyglycine reacts with phosgene at -70° to give the mixed anhydride VII. This decomposes at -5° to give the symmetrical carbobenzyloxyglycine anhydride. However, at -70° in pyridine carbobenzyloxyglycyl chlorocarbonate (VII) is more stable and has been used to acylate a phenolic hydroxyl group.<sup>53</sup> Presumably peptide syntheses could also be carried out at -70°.

### 4. $\alpha$ -Acylaminoacyl Alkyl Carbonates

The most widely used of the newer synthetic methods for forming a peptide bond involves a mixed carbonic-carboxylic acid anhydride and was developed in 1951 simultaneously in three different laboratories.<sup>48, 54-56</sup> Essentially the method consists of the formation of a mixed anhydride by the

reaction of a tertiary amine salt of an  $\alpha$ -acylamino acid or peptide with an alkyl chloroformate in an indifferent solvent at a low temperature. To this solution of mixed anhydride the amino acid or peptide ester that is to be acylated is then added. Isolation of the mixed anhydride is not necessary or even desirable, although it may be separated from the by-product ammonium salt. Thus treatment of dicarbobenzyloxy-L-lysine in toluene with triethylamine and isobutyl chloroformate gives the mixed anhydride VIII which reacts with ethyl valinate to give ethyl dicarbobenzyloxy-L-lysyl-L-valinate in 81% yield.<sup>57</sup>



The appeal of this method comes from the facts that it employs readily available reagents, is simple and rapid, may be run at low temperatures, and gives by-products that are ordinarily easy to separate.

## 4.1. Scope and Limitations

### 4.1.1. The Amine Component

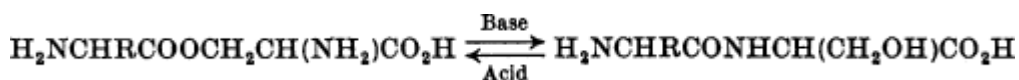
Any amino acid or peptide derivative having a free primary amino group may serve as the amine component. Secondary amines tend to react to give urethans. Poor results have been obtained in the acylation of sarcosine<sup>58</sup> and proline (both the acid and the ethyl ester),<sup>59</sup> and in the preparation of other N-substituted peptide linkages. However, in certain cases proline gives good results. Thus carbobenzyloxy-L-alanyl-L-phenylalanine, after conversion to the mixed carbonic anhydride, coupled with methyl L-prolyl-L-leucinate in 79% yield.<sup>60</sup>

The copper complex of lysine has been used to protect the  $\alpha$ -amino group, while the  $\epsilon$ -amino group was acylated by carbobenzyloxyamino acid ethyl carbonates.<sup>61</sup>

The synthesis of peptide intermediates in which a hydroxy amino acid is the amine component usually presents no special difficulties. However, the use of 2 moles of serine per mole of mixed anhydride is recommended to minimize side reactions with the hydroxyl group.<sup>18</sup> O-Acyl derivatives of serine which are of interest in the synthesis of azaserine may be prepared from a carbonic acid mixed anhydride and an N-protected serine.<sup>62-64</sup> The reaction of tritylglycine with N-trityl-DL-serine gives a quantitative yield of crude O-(N-tritylglycyl)-N-trityl-DL-serine.<sup>63</sup>

When the protecting groups are removed from peptide intermediates, acyl migration from oxygen to nitrogen (or vice versa) may occur when non N-terminal seryl or threonyl residues are present.<sup>62</sup> An example is shown in the accompanying reaction. An observation in this laboratory regarding this well-known reaction deserves comment. When an N-carbobenzyloxyaminoacyl serine or threonine is treated with hydrogen bromide in nitromethane,<sup>65</sup> the N-dipeptide hydrobromide usually precipitates as soon as it is formed and prevents rearrangement to the O-dipeptide. On the other hand, the use of

hydrogen bromide in glacial acetic acid<sup>26</sup> results in rearrangement and the O-dipeptide may be isolated. To avoid the risk of deamidation of asparagine or glutamine peptides in a subsequent ester saponification, the sodium salt of asparagine or glutamine may be used in place of the corresponding ester in the synthesis although the yields of product are then lower.<sup>66</sup>

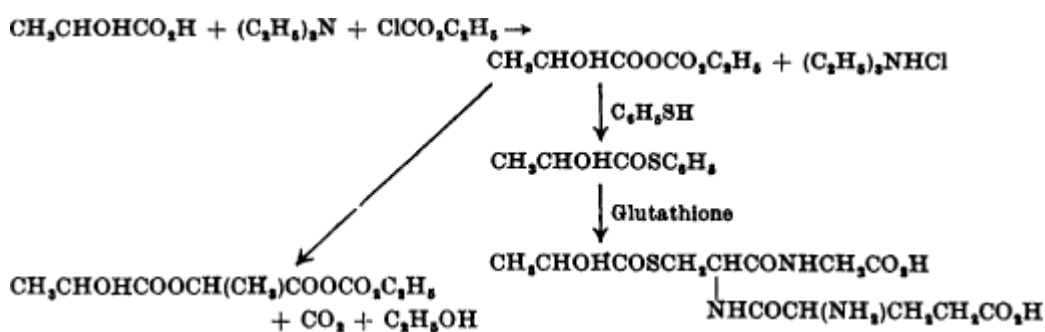


#### 4.1.2. Neutral Amino Acids

Glycine, alanine, valine, leucine, isoleucine, methionine, S-benzylcysteine, proline, phenylalanine, and tryptophan present no special difficulties in this reaction. Yields of recrystallized materials are usually about 70–80%. Carbobenzyloxy-D-alanine, however, as the mixed anhydride with isobutyl chloroformate reacts with ethyl L-alaninate to form a dipeptide intermediate in only a very low yield.<sup>67</sup> Halogenated, nitrated, unsaturated, or otherwise modified neutral amino acids may be employed. It is not necessary for the amine function to be in the  $\alpha$  position. However, the presence of a  $\gamma$ -tosylamido group will result in cyclization to the corresponding 1-tosyl-2-pyrrolidone. The cyclic intermediate will react with an amino acid ester to give the same product that would have been obtained had cyclization not occurred.<sup>68</sup>

#### 4.1.3. Hydroxy Amino Acids

The published data on the use of the carbonic anhydride method with hydroxy amino acids (serine, threonine, hydroxyproline) are limited. Carbobenzyloxy-DL-serine gives satisfactory results;<sup>41</sup> for example, it reacts with benzyl glycinate in 50% yield,<sup>69</sup> and with benzyl-L-leucinate in 55% yield.<sup>70</sup> Mixed anhydrides of serine and threonine generally couple with esters of amino acids to give crystalline products in about 50% yield,<sup>15</sup> but in a number of cases the intermediates could not be crystallized. Impurities arising from acylation of the hydroxyl group no doubt cause the difficulty. The synthesis of S-lactylglutathione,<sup>71</sup> illustrates such a reaction.



Oxy-DL-leucyl-DL-alanine has been obtained in 56% over-all yield from the carbobenzyloxy- $\beta$ -oxy-DL-leucine mixed anhydride with ethyl chlorocarbonate in tetrahydrofuran and DL-alanine followed by removal of the carbobenzyloxy group.

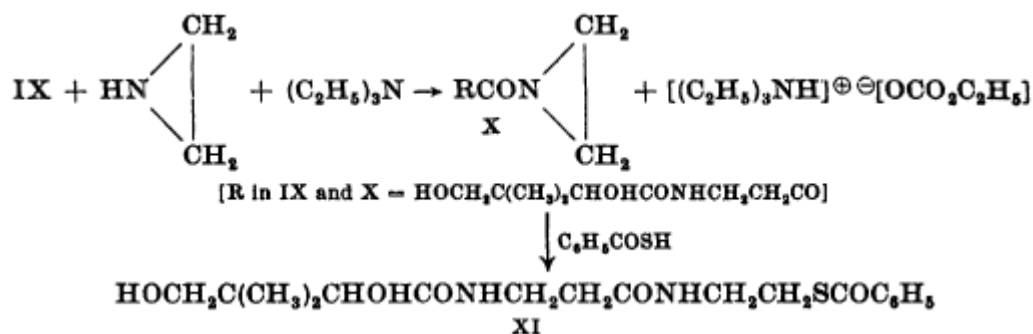
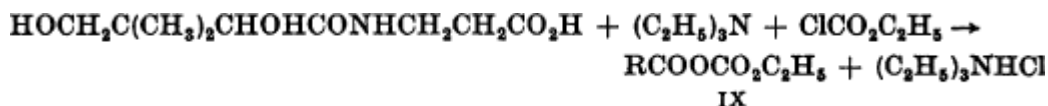
In syntheses involving hydroxy amino acids the amine component must be added as soon as the mixed anhydride has been formed.

Phthaloyl-L-threonine and isobutyl chloroformate react in chloroform to give a 40% yield of  $\beta$ -lactone. Phthaloyl-DL- $\beta$ -hydroxyvaline under the same conditions gives an 8% yield of lactone and a 25% yield of



the dimeric eight-membered-ring dilactone.[72](#)

Mixed carbonic anhydrides of pantothenic acid have been used to form amides,[73-77](#) These mixed anhydrides illustrate a type in which the acid contains primary and secondary hydroxyl groups. Of particular interest is the synthesis of benzoylpantethein.[74, 78](#) The mixed anhydride IX of triethylammonium pantothenate and ethyl chlorocarbonate reacts with ethylene imine to form pantothenyl ethylene imine (X), which is converted by means of thiobenzoic acid to benzoylpantethein (XI).



#### 4.1.4. Tyrosine

The presence of a phenolic group in the acid usually interferes with mixed anhydride formation since the phenolic group reacts with the alkyl chloroformate. Salicylic acid provides one example,[79](#) and carbobenzyloxytyrosine another.[80](#) It is necessary to block the phenolic group in tyrosine to obtain satisfactory results;[41](#) tosyl,[81](#) carbobenzyloxy,[82](#) and acetyl<sup>28</sup> derivatives have been used. On the other hand, no blocking is necessary with carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine. The mixed anhydride with ethyl -chloroformate is formed, and it couples with the methyl esters of leucine, valine, phenylalanine,[83](#) or isoleucine<sup>84</sup> in 60–75% yields. Likewise, both N-tosyl-S-benzyl-L-cysteinyl-L-tyrosine<sup>85</sup> and N-carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine<sup>82, 86</sup> react as the anhydride with isobutyl chloroformate with L-phenylalanyl-L-glutaminyll-L-asparagine to give 62–64% yields of crude product. The analogous anhydride of N-tosyl-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanine gives the peptide with L-glutaminyll-L-asparaginyll-S-benzyl-L-cysteine in 59% yield.<sup>87</sup> Because the presence of S-benzyl-L-cysteine adjacent to the tyrosine residue may reduce the reactivity of the phenolic hydroxyl group, it is unnecessary to protect it.

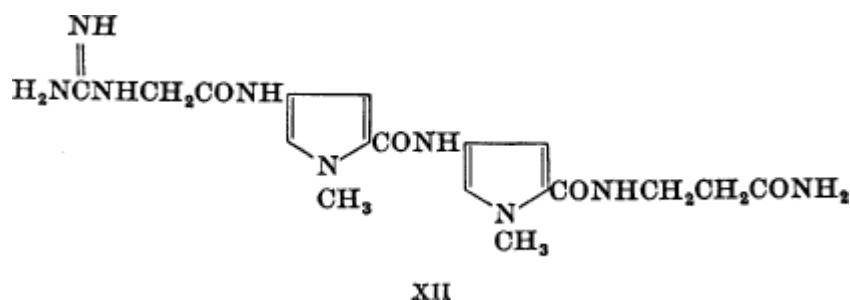
#### 4.1.5. Basic Amino Acids

If both amino groups of lysine are protected, there is no difficulty in coupling lysine through a mixed anhydride with other amino acids. The use of α-N-carbobenzyloxy-im-benzyl-L-histidine<sup>\*</sup> failed because of the insolubility of its triethylammonium salt.<sup>88</sup> However, with the same base dicarbobenzyloxy-L-histidine<sup>89, 90</sup> and dicarbocyclopentyloxy-L-histidine gave the mixed anhydride.<sup>15</sup>

Blocking the guanido group of arginine through formation of the ω-nitro derivative permits the formation of α-N-carbobenzyloxy-ω-nitro L-arginyl ethyl carbonate with no difficulty.<sup>91</sup> The hydrazide or acid chloride could not be prepared from α-N-carbobenzyloxy-ω-nitro-L-arginine.<sup>1</sup> The mixed anhydride of α-N-p-nitrocarbobenzyloxy-ω-nitro-L-arginine and ethyl chlorocarbonate has also been used to prepare arginine peptides.<sup>92</sup>

The protection of the guanido group of arginine by percarbobenzyloxylation has recently been accomplished.<sup>93, 94</sup> The resulting tricarbobenzyloxy-L-arginine (precise structure unknown) was converted to the mixed anhydride with ethyl chloroformate and used for peptide syntheses. Benzyl tricarbobenzyloxy-L-arginyl- $\omega$ -N-carbobenzyloxy-L-argininate was prepared in 73% yield, but for its isolation it was necessary to wash with aqueous triethylamine to remove tricarbobenzyloxy-L-arginine, rather than with aqueous carbonate or bicarbonate because of the high solubility of the sodium or potassium salts of tricarbobenzyloxy-L-arginine in chloroform and the relatively low solubility in water.

The use of the mixed carbonic anhydride of guanidoacetic acid to prepare the peptide XII in 10% yield has been reported.<sup>95</sup>

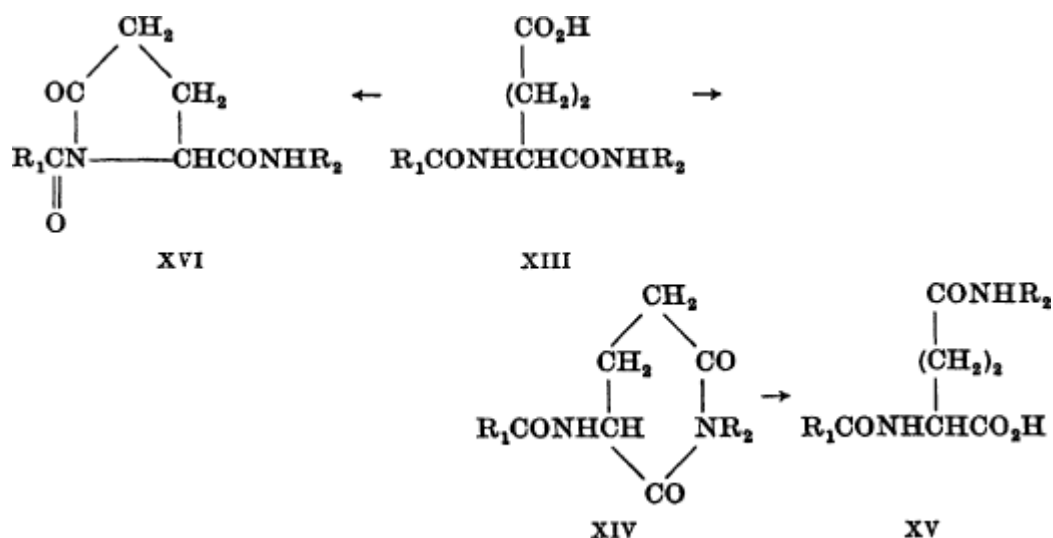


#### 4.1.6. Acidic Amino Acids and Their Amides

Conflicting claims appear in the early literature dealing with aspartic and glutamic acid peptides. The newer techniques of paper chromatography and countercurrent distribution show that when it is possible for a reaction to proceed by way of an acylglutamic acid anhydride or imide a mixture of products will be obtained, although either the  $\alpha$  or  $\omega$  isomer may predominate.<sup>96-99</sup> Even the reaction of the azide derived from carbobenzyloxy-L-glutamic acid- $\gamma$ -hydrazide with amino acid esters leads to a mixture of isomers.<sup>98, 100</sup> The mixed carbonic carboxylic anhydride method, however, applied to mono esters of acyl-L-glutamic acids gives homogeneous products.<sup>96, 97, 101, 102</sup>

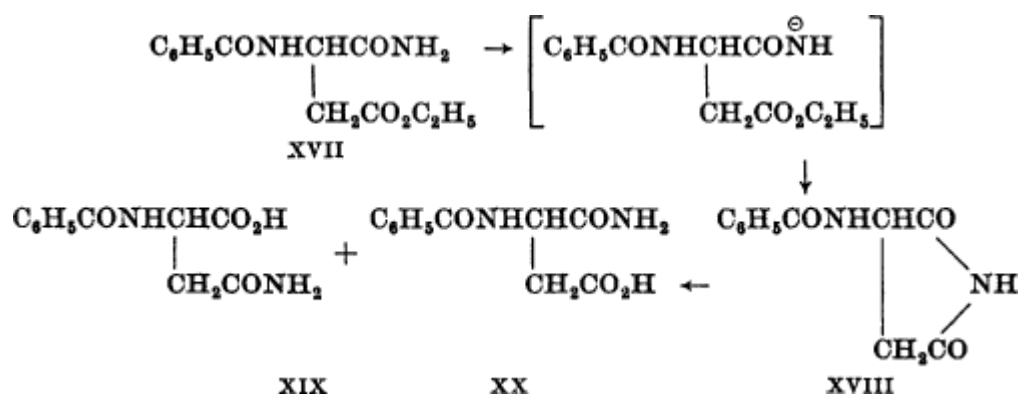
It has been suggested that where yield is not an important factor peptides of acylglutamic acids may be conveniently prepared by the use of one equivalent of both ethyl chloroformate and triethylamine. The mixture of  $\alpha$  and  $\gamma$  peptides which results may be separated by counter-current distribution or by fractional extraction or precipitation.

Acylglutamic acid amides of structure XIII were readily cyclized to the imides XIV with thionyl chloride and pyridine. Dilute alkali converts the imides XIV to the isomeric acids XV. Ring opening of XIV in the opposite direction occurs if the  $R_1CO$  group is replaced by a trityl group. This may be due to steric factors. Thus diethyl trityl- $\gamma$ -L-glutamylglycine gives, on saponification, trityl- $\alpha$ -L-glutamylglycine.<sup>103, 104</sup> With thionyl chloride at  $0^\circ$ , N-benzoyl- $\alpha$ -DL-glutamylglycine n-hexylamide (XIII;  $R_1 = C_6H_5$ ,  $R_2 = CH_2CONHC_6H_{13-n}$ ) cyclized to the acylpyrrolidone XVI, whereas the corresponding mixed carbonic anhydride cyclized in the opposite direction to give DL- $\alpha$ -benzamidoglutaryl-glycine n-hexylamide (XIV;  $R_1 = C_6H_5$ ,  $R_2 = CH_2CONHC_6H_{13-n}$ ).<sup>105</sup>



The acyl isoglutamine derivatives XIII cyclize “extremely easily” to the imides XIV,<sup>5</sup> for example with acetic anhydride.<sup>106</sup> Hydrolysis of the imides XIV leads to mixtures of isomeric acids XIII and XV.<sup>101, 106</sup> Such results support the statement that glutamine gives unsatisfactory results with the alkyl carbonic anhydride method.<sup>41</sup> However, the ethyl chloroformate mixed anhydride of carbobenzyloxy-L-glutamine couples with L-asparaginyl-S-benzyl-L-cysteine methyl ester to give a 72% yield of product<sup>84</sup> and with other amino acid and peptide esters in yields of 56–63%.<sup>83</sup> The first coupling reaction was carried out also with the anhydride from sec-butyl-chloroformate.<sup>107</sup>

Results with aspartic acid parallel those with glutamic acid. Both the acyl anhydride<sup>108</sup> and the imide<sup>84, 101, 109</sup> of aspartic acid may open to give a mixture of  $\alpha$  and  $\beta$  isomers; consequently syntheses must be designed to avoid these intermediates. The mono ester of an acylaspartic acid can be used for the synthesis of peptides. The resulting  $\beta$ -alkyl acylaspartyl peptide, however, is very unstable to alkali and is readily converted to the corresponding imide.<sup>101</sup> Benzoyl-L-isoasparagine ethyl ester (XVII) was converted through the intermediate imide XVIII to a mixture of benzoyl-L-asparagine (XIX) and benzoyl-L-isoasparagine (XX) by the use of either aqueous sodium hydroxide or warm 0.2N aqueous sodium carbonate. It is apparent that the coupling of an acylaspartic or acylglutamic acid with an amino acid or peptide in basic solution by any anhydride procedure may lead to rearranged products. If the coupling with an amino acid ester or peptide ester is performed in neutral solution, the normal product may be expected. However, saponification of ester groups may be accompanied by rearrangement.



The mixed carbonic anhydride procedure has failed for some workers<sup>66</sup> for the preparation of asparaginyl peptides, whereas others have reported successful results with yields up to about 50%. The carbobenzyloxy-L-asparagine mixed anhydride with ethyl chloroformate has been coupled with methyl L-serinate in 22% yield and with ethyl L-serylglycinate in 9% yield.<sup>110</sup> Carbobenzyloxy-L-asparaginyl-S-benzyl-L-cysteine methyl ester was prepared in essentially the same yield by the mixed carbonate (52%) and phosphorazo<sup>\*</sup> method (56%). The carbobenzyloxy-L-glutamyl-L-asparagine mixed anhydride with sec-butyl chloroformate was coupled with S-benzyl-L-cysteine methyl ester in 47% yield.<sup>107</sup> With the

latter two peptides it has been shown that dehydration of the amide bond of asparagine to the nitrile occurs to an appreciable extent when the pyrophosphite or dicyclohexylcarbodiimide method is employed, but it is not observed with the mixed carbonic anhydride procedure.

## 4.2. Side Reactions

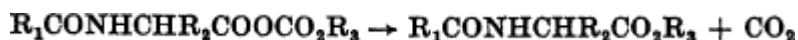
### 4.2.1. Disproportionation

The first side reaction observed in the use of mixed anhydrides of  $\alpha$ -acylamino acids and alkyl carbonates was disproportionation.<sup>48</sup> Since the symmetrical anhydride can acylate only half as much amine as can the mixed carbonic anhydride, disproportionation obviously results in decreased yield. Disproportionation is favored by a long reaction time in the anhydride-forming step. Carbobenzyloxyglycylglycine was converted to carbobenzyloxyglycylglycine anhydride when it was allowed to react for 65 minutes with benzyl chloroformate in diethylformamide, but gave the mixed anhydride when the reaction time was decreased to 5 minutes.<sup>111</sup> Low reaction temperatures lessen disproportionation.<sup>48</sup> It has been suggested that liberation of carbon dioxide during the preparation of the mixed anhydride indicates disproportionation, but this is not always true since carbon dioxide is also a by-product of a modified Dakin-West reaction as noted in the next section.

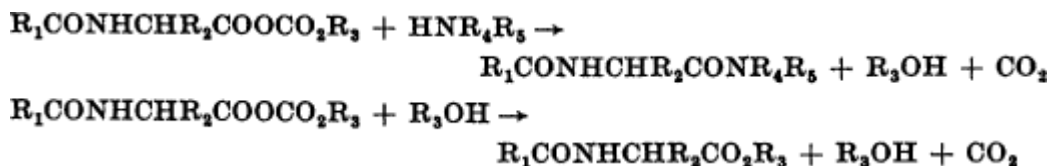


### 4.2.2. Ester Formation

In some reactions esters were isolated as byproducts when acylamino carboxylic alkyl carbonates were employed to acylate amines. The esters were considered to have been formed by the loss of carbon dioxide from the mixed anhydride.<sup>41</sup>



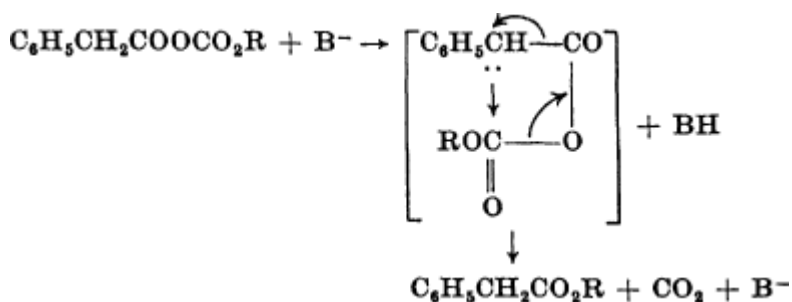
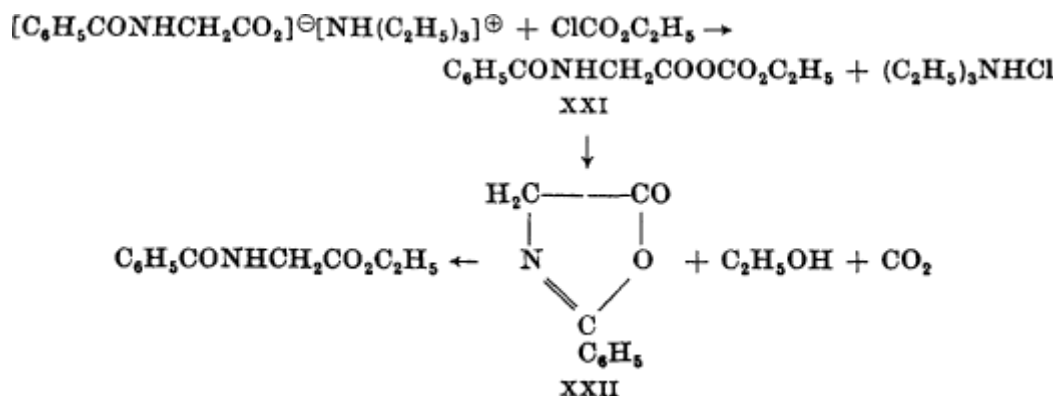
An alternative explanation would be that the mixed anhydride reacts with the alcohol liberated during amide formation. However, the formation of esters in the presence of a primary or secondary amine by acylation of alcohols formed as by-products could not account for any great amount of ester formation.



Where azlactone formation is possible, another pathway for ester formation is open. Hippuric acid reacts with ethyl chloroformate in the presence of triethylamine to give ethyl hippurate and carbon dioxide. Since, in the presence of benzaldehyde at 0°, 2-phenyl-4-benzylidenoxazol-5-one was obtained yield in addition to ethyl hippurate, the reaction was assumed to proceed via the mixed carbonic anhydride XXI and the azlactone XXII.<sup>112</sup> In this instance no amine was present to react with the mixed anhydride. (See

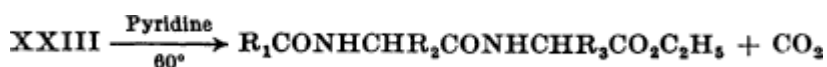
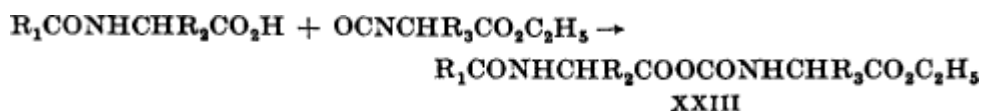
equations on p. 181.)

Still another method of formation of esters is possible. The addition of the sodium salt or ester of an amino acid to the mixed anhydride formed from phenylacetic acid and isobutyl chloroformate failed to result in any amide formation but gave instead an excellent yield of isobutyl phenylacetate.<sup>113</sup> This product may be explained as the result of a modified Dakin-West reaction in which an ester is formed instead of a ketone. The general mechanism proposed by King and McMillan for the Dakin-West reaction<sup>114, 115</sup> readily accommodates this extension of the reaction, although an intramolecular reaction involving a four-membered ring as shown appears more plausible.



Diphenylacetic acid, which does not undergo a Dakin-West reaction,<sup>114</sup> gives an isobutyl carbonate mixed anhydride that readily acylates amino acid esters with no evidence of ester formation. On the other hand, acylamino acids which readily undergo the Dakin-West reaction will also form esters with an alkyl chloroformate in the presence of base. Ester formation is not usually a serious side reaction; when it is, a mixed anhydride may be selected that will avoid it.

An obvious similarity exists between the formation of an ester from an  $\alpha$ -acylamino acid alkyl carbonate via a modified Dakin-West reaction and the formation of a peptide derivative from an acylamino acid and a carbonyl amino acid ester (isocyanate).<sup>116</sup>



The decomposition of the intermediate XXIII is catalyzed by pyridine,<sup>117</sup> the catalyst used in the original Dakin-West experiments.<sup>118</sup>





#### 4.2.4. Reactions with the Solvent

Dimethylformamide reacts exothermically with ethyl or isobutyl chloroformate to give an essentially quantitative yield of carbon dioxide.<sup>15</sup> Dimethylformamide has such unusual solvent properties that it is the favorite solvent for the preparation of mixed carbonic anhydrides of more complex products such as sodium or potassium benzylpenicillinate<sup>121</sup> (although methylene chloride is preferred when triethylammonium benzylpenicillinate is used), sodium pantothenate,<sup>73, 75, 122</sup> and the amino-nucleoside derived from puromycin.<sup>123</sup> Carbobenzyloxy puromycin was prepared in 64% yield from the anhydride of carbobenzyloxy-p-methoxy-L-phenylalanine and ethyl chloroformate with the amino-nucleoside in dimethylformamide, but attempts to prepare analogs of puromycin with phthaloylglycine or carbobenzyloxyglycine in the same manner gave poor yields and variable results.

No change in yield of phthaloylglycylanilide was observed when dimethylformamide was used in place of chloroform as a solvent.<sup>54</sup> Phthaloylglycyl-p-aminobenzoic acid appears to form anhydrides with both ethyl and isobutyl chloroformates in dimethylformamide, but the starting material is recovered unchanged after attempted couplings with glutamic acid and glycine.<sup>13</sup> However, the anhydride of carbobenzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanyl-glycine and isobutyl chloroformate reacted with benzyl L-prolinate in dimethylformamide to give a 60% yield of carbobenzyloxyhexapeptide ester.<sup>124</sup> Pantotheine also was prepared in 50% yield from the mixed anhydride obtained by treating a suspension of sodium pantothenate in dimethylformamide with ethyl chloroformate.<sup>75</sup>

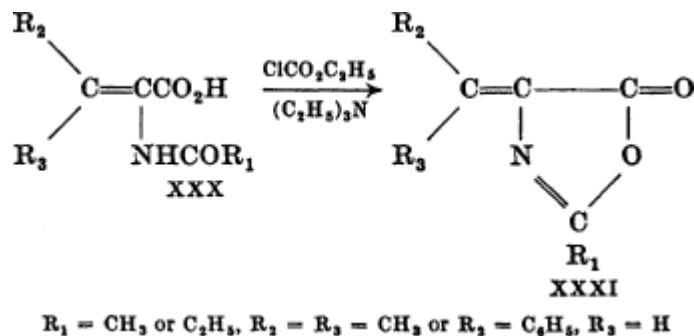
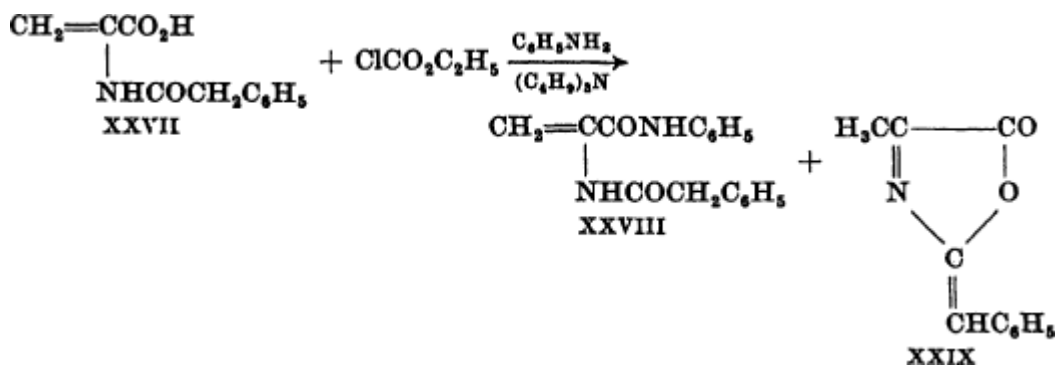
Reactions in dimethylformamide involve the competition between anhydride formation and decomposition of the alkyl chloroformate, and yields will probably depend upon the rate at which the acid reacts to form the anhydride. Difficulty in using dimethylformamide as a solvent would be anticipated only for those acids which react relatively slowly to form mixed anhydrides.

#### 4.2.5. Reactions with Tertiary Bases

Chloroformates react with tertiary bases to give products which include carbon dioxide, quaternary salts, and the tertiary base hydrochloride.<sup>125, 126</sup> This reaction is normally slow enough so that it causes no interference with the anhydride-forming step. However, ethyl chloroformate appears to react faster with triethylamine than with anions of hindered acids such as tritylvaline or tritylleucine. Although it was assumed that these tritylamino acids were converted to mixed anhydrides in benzene with ethyl chloroformate (because of the formation of triethylamine hydrochloride), the products failed to react with methylaniline or glycine ester even when heated for 1 hour on a water bath.<sup>9</sup> However, mixed anhydrides of tritylamino acids and dicyclohexylcarbodiimide react to form peptides in satisfactory yields.<sup>11, 103</sup> Thus the formation of triethylamine hydrochloride should not be interpreted as proof that anhydride formation has occurred.

#### 4.2.6. Azlactone Formation

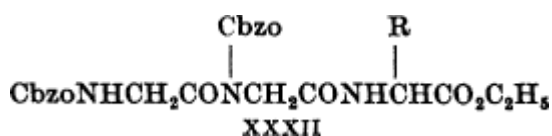
Reaction of 2-phenylacetamidoacrylic acid (XXVII) with ethyl chloroformate in chloroform at  $-18^{\circ}$  followed by the addition of aniline gave a 9% yield of the anilide XXVIII; the pseudo-azlactone XXIX was the major product.<sup>127</sup> Since the pseudoazlactone XXIX does not react with aniline, it was concluded that both the anilide XXVIII and the pseudo-azlactone XXIX were derived from the mixed carboxylic carbonic anhydride, but that cyclization of the mixed anhydride to the pseudo-azlactone was very rapid. Other  $\alpha,\beta$ -unsaturated  $\alpha$ -acylamino acids XXX readily gave azlactones XXXI. It has been suggested that amide bond formation via mixed carboxylic carbonic anhydrides may proceed partly via azlactones.<sup>127</sup>



When a solution of hippuric acid in acetone at  $-10^\circ$  was treated with triethylamine and isobutyl chloroformate and an aqueous solution of ethyl glycinate added 20 minutes later, 25% of the hippuric acid was isolated as 2-phenyl-4-isopropylidene-5-oxazolone. It was also found, as expected on the basis of Bergmann's work,<sup>128</sup> that chloroacetyl-DL-phenylalanine was readily converted by isobutyl chloroformate to 2-methyl-4-benzal-5-oxazolone.<sup>15</sup> Thus by-products may be anticipated when chloroacetyl amino acids are used to prepare mixed anhydrides.

#### 4.2.7. Diacylation

The mixed anhydride of carbobenzyloxyglycine and ethyl chloroformate reacts with diethyl L-glutamate to give a 36–41% yield of diethyl carbobenzyloxyglycyl-L-glutamate and a 17% yield of a by-product formulated as XXXII ( $\text{R} = \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ ), although the possibility that both carbobenzyloxyglycyl groups are on the nitrogen atom of diethyl glutamate has not been entirely excluded.<sup>129</sup> However, the same mixed anhydride reacts with ethyl glycinate to give a 30% yield of XXXII ( $\text{R} = \text{H}$ ).<sup>129a</sup> With excess ethyl glycinate this by-product is not obtained. Steric effects may lessen this side reaction with other amino acids. Peptide synthesis with phosphorus oxychloride has led to similar by-products.<sup>130</sup>



#### 4.2.8. Racemization

The general section on racemization at the beginning of this chapter should be consulted.

Racemization occurs with the mixed carboxylic carbonic anhydride procedure.<sup>40, 131</sup> A sample of optically pure  $\alpha$ -benzoyl-L-lysyl-L-lysyl-L-lysine was quantitatively hydrolyzed to  $\alpha$ -benzoyl-L-lysine and L-lysyl-L-lysine by trypsin, whereas the same benzoyl tripeptide prepared by the isobutyl chloroformate procedure<sup>132</sup> was hydrolyzed to only a small extent. Partial racemization also was observed when the



mixed anhydride prepared from formyl-L-phenylalanine and ethyl chloroformate was condensed with glycine anilide.[133](#)

A comparison between the use of the ester of an amino acid and its hydrochloride with triethylamine has been reported.[40](#) Ethyl glycinate gave a higher over-all yield of dipeptide (65%) but also more of the DL-peptide (30% of the total yield) than did ethyl glycinate hydrochloride and triethylamine (53% over-all, 17% of the product DL). These results are in conflict with those of workers who have used other mixed anhydrides and report that the presence of triethylamine hydrochloride leads to increased racemization.

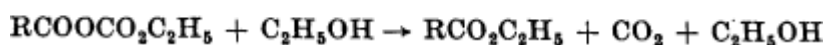
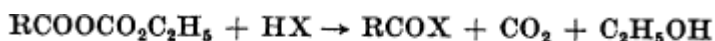
## 4.3. Miscellaneous Uses of $\alpha$ -Acylamino Alkyl Carbonates

### 4.3.1. Synthesis of Symmetrical Anhydrides

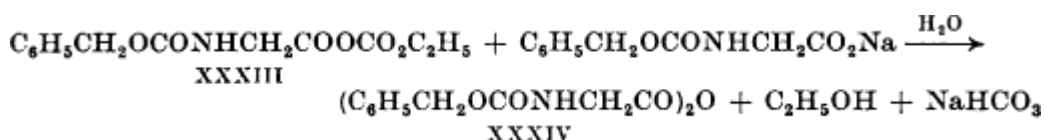
The formation of symmetrical anhydrides from  $\alpha$ -acylamino acid alkyl carbonates is ordinarily an undesirable side reaction that results in decreased yields in peptide syntheses. In most instances disproportionation of a mixed to a symmetrical anhydride has been inferred to explain carbon dioxide evolution and relatively poor yields of peptide.

Disproportionation is not the best method to prepare symmetrical anhydrides from acyl alkyl carbonates because ester formation is an important competitive reaction.[134](#) Heating ethyl benzoyl carbonate in ethyl chloroformate under refluxing conditions gave ethyl benzoate and benzoic anhydride in a 10:7 ratio.[135](#)

In view of the great reactivity of carbonic acid mixed anhydrides with compounds of the type HX (where HX is an acid, amine, alcohol, thiol, water, etc.) it is apparent that esters could be formed by a chain reaction. If HX is a carboxylic acid, RCO<sub>2</sub>H, and is added in stoichiometric amount the product, RCOX, will be a symmetrical anhydride. By this method and with dioxane as a solvent, phthaloylglycine anhydride was prepared in 93% yield and carbobenzyloxyglycine anhydride in 50% yield. The method was also applied to the preparation of symmetrical carbobenzyloxy peptide anhydrides including carbobenzyloxyglycylglycine anhydride, which may be recrystallized from ethanol without decomposition.[136](#)



The yield of carbobenzyloxyglycine anhydride was increased from 50% to 81% by conducting the reaction in water in the presence of one equivalent of sodium hydroxide. Addition of water to carbobenzyloxyglycine ethyl carbonate (XXXIII) gave a 25% yield of the anhydride XXXIV. This suggests that carbobenzyloxyglycine formed by hydrolysis of the mixed anhydride reacts faster with the mixed anhydride than either anhydride reacts with water. Benzoyl ethyl carbonate reacts with water to give benzoic anhydride, carbon dioxide, and ethanol.[137](#)



Symmetrical anhydrides have been employed in peptide synthesis.[136](#) For example,

carbobenzyloxyglycine anhydride (XXXIV) reacts with glycine in two equivalents of aqueous sodium hydroxide to give a 75% yield of carbobenzyloxyglycylglycine (XXXV). In the same manner carbobenzyloxy diglycylglycine was prepared in 50% yield and phthaloylglycylglycine in 53% yield. However, phthaloylglycine anhydride gave no isolable amounts of phthaloyltriglycylglycine on treatment with triglycine. Peptide syntheses by this procedure have the disadvantage of giving products from which by-products are difficult to remove.



### 4.3.2. Synthesis of Other Mixed Anhydrides

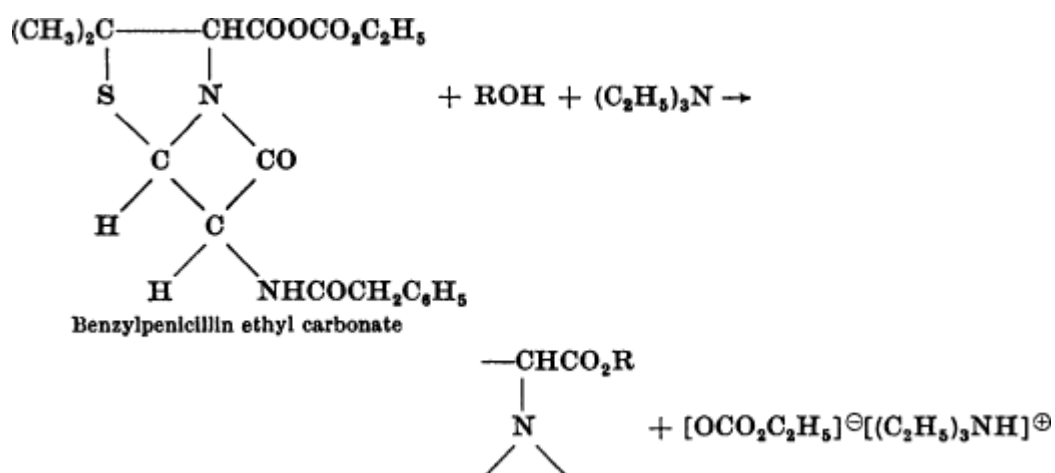
While reaction of an  $\alpha$ -acylamino acid alkyl carbonate with an acid will lead to a new mixed anhydride, the reaction is not ordinarily useful in peptide synthesis since it adds an extra step; the original mixed anhydride is normally as useful as any mixed anhydride derived from it would be. However, thiol esters do possess certain advantages over acyl carbonic anhydrides for some purposes (see pp. 241–255), and most of the literature on the preparation of new mixed anhydrides from acylamino acid alkyl carbonates pertains to the preparation of  $\alpha$ -acylamino thiol esters.

The preparation of  $\alpha$ -ketonitriles from acylamino acids via the mixed carbonic anhydride has not been reported, although it has been reported that  $\alpha$ -ketonitriles will acylate amines.<sup>138, 139</sup> Acylaminoacylcyanides would probably be unstable because of their tendency to polymerize.

### 4.3.3. Synthesis of Esters

It is occasionally desirable to esterify an amino acid. The synthesis of O-serine derivatives of  $\alpha$ -acylamino acids has already been mentioned.

One practical point in acylating hydroxyl groups with carbonic acid mixed anhydrides was noted in the synthesis of esters of benzylpenicillin.<sup>121</sup> As ordinarily carried out, an alcohol is one product of the acylation reaction with an acyl alkyl carbonate. To avoid the presence of two different alcohols in the reaction mixture one may add an additional equivalent of triethylamine.



### 4.3.4. Cyclic Peptides

In model experiments the addition of ethyl chloroformate to an equivalent mixture of phthaloylglycine and ethyl glycinate gave the desired mixed anhydride and ethyl glycinate hydrochloride;[140](#) salt formation between phthaloylglycine and glycine ester effectively prevented appreciable urethan formation. Subsequent addition of tributylamine to the reaction mixture resulted in peptide bond formation.

The preparation of cyclic peptides presents three additional factors which are not important in linear polypeptide synthesis. They are the tendency to form linear polymers rather than cyclic products, the insolubility of the starting polypeptide in any suitable solvent, and the ability of the amide bond to exist in either cis or trans conformation.[141](#)

The concentration of the peptide necessary to have an equal chance for chain formation and for cyclization at the start of the reaction, assuming limited association, was calculated from the dimensions of the polypeptide chain. The use of a relatively polar solvent such as dimethylformamide to lessen the initial association of peptide molecules and the use of dilute solution were expected to favor cyclization. Initially it was found that triglycylglycine and pentaglycylglycine were too insoluble to react with ethyl chloroformate. Since peptides containing different amino acids are generally more soluble than those containing a single amino acid, D-leucylglycylglycine was tried and found to be sufficiently soluble in dimethylformamide to react with ethyl chloroformate. Cyclization occurred upon the addition of tributylamine to give cyclo-(D-leucylglycylglycyl) in 37% yield.[140](#) The product gave no ninhydrin test and had no free amino or carboxyl group. Its solubility in butanol excluded the possibility of a long polymer chain. That the product might be a hexapeptide appeared to be statistically improbable.

More recent cyclization studies show that the character of the reaction product cannot be calculated on the assumption that chain length and dilution alone determine the reaction course. Polymerization of N-carboxyglycine anhydride[142](#) gave cyclo-(hexaglycyl) as the major cyclic product. Cyclization of triglycine azide, originally assumed to give cyclo-(triglycyl),[143](#) has been shown to give instead cyclo-(hexaglycyl).[144](#), [145](#) Cyclization of the p-nitrophenyl esters of glycyl-L-leucylglycine and of glycyl-L-leucylglycylglycyl-L-leucylglycine gave the same crystalline cyclohexapeptide.[146](#) It has been shown that doubling is to be expected in cyclizing peptides with an odd number of amino acids.[146-149](#) An excellent summary of the problems of synthesizing cyclic peptides has appeared.[149a](#)

## 4.4. Experimental Conditions

### 4.4.1. Order of Addition of Reactants

In the preferred method of synthesis the  $\alpha$ -acylamino acid is dissolved in an inert solvent in the presence of one equivalent of a tertiary base, the alkyl chloroformate added to form the mixed anhydride, and then the amine to be acylated is introduced. Changing the order of addition results in decreased yields. For example, the tri-n-butylammonium salt of phthaloylglycine when allowed to react with ethyl chloroformate and then with ethyl glycinate gave a 70% yield of ethyl phthaloylglycylglycinate. Reaction of the acid and glycine ester with ethyl chloroformate to give the mixed anhydride and ethyl glycinate hydrochloride followed by addition of tri-n-butylamine lowered the yield to 58%. Addition of ethyl chloroformate to a mixture of the other reactants gave a 27% yield.[140](#)

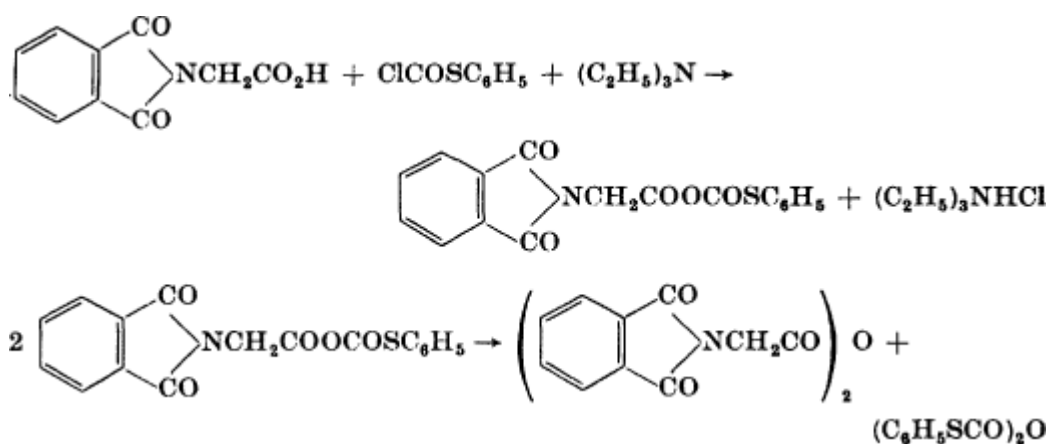
### 4.4.2. Alkyl Chloroformates

In non-aqueous solvents, branched-chain alkyl chloroformates would be expected to increase the electron density on the adjacent carbonyl group of the mixed anhydride and thus diminish the tendency toward urethan formation. The reaction of a series of carbobenzyloxy peptide alkyl carbonates with sodium glycinate in aqueous solution was investigated. The alkyl groups were methyl, ethyl, isopropyl, isobutyl, isoamyl, n-heptyl, n-octyl, benzyl, and phenyl; the acylated amino acids and peptides, carbobenzyloxyglycine, carbobenzyloxyglycylglycine, and carbobenzyloxydiglycylglycine.<sup>48</sup> The ethyl and isopropyl carbonates gave the highest yields of acylated dipeptide whereas the higher alkyl esters gave better results with the higher peptides. A poor yield of impure carbobenzyloxyglycylglycine was obtained with the methyl ester, and the phenyl ester failed. The anhydrides of phthaloylglycine with either methyl or ethyl chloroformate gave the same yield of phthaloylglycylanilide.<sup>54</sup> sec-Butyl and isobutyl carbonates were the most satisfactory.<sup>21, 56, 150-153</sup> The anhydride of dicarbobenzyloxy-L-2,4-diaminobutyric acid with carbobenzyloxy chloride was used to make peptides.<sup>154</sup>

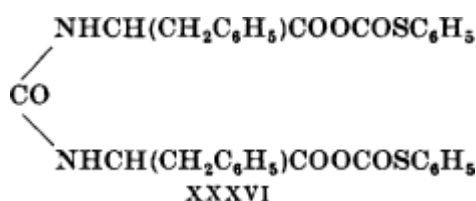
In addition to giving improved yields of peptides, mixed anhydrides formed from isobutyl chloroformate possess another practical advantage over those from ethyl chloroformate.<sup>41</sup> Neutral peptide intermediates are usually isolated by introduction of petroleum ether to an ethyl acetate solution. Any urethans formed as by-products will appear in the neutral fraction. The isobutyl urethans are more soluble in ethyl acetate-petroleum ether than are the ethyl urethans; thus purification of the product is easier.

A 50% excess of sec-butyl chloroformate in the formation of the anhydride with carbobenzyloxyglycine gave an impure product when coupled with ethyl-DL-phenylalaninate, but the amount of pure product obtained therefrom was not appreciably different from that obtained when a molar quantity of sec-butyl chloroformate was used in formation of the anhydride.<sup>21</sup>

Treatment of triethylammonium phthaloylglycinate with phenyl chlorothiolformate in cold chloroform leads to a rapid precipitation of phthaloylglycine anhydride, presumably via the pathway indicated.<sup>155</sup>



The use of n-hexyl chlorothiolformate in place of alkylchloroformates gave mixed anhydrides far less satisfactory for peptide bond formation.<sup>15</sup> The existence of phenyl thiolcarbonate XXXVI has been postulated as an intermediate in the reaction of phenylalanine with phenyl chlorothiolformate.<sup>156</sup>



#### 4.4.3. Tertiary Amines

Various tertiary amines may be employed to form the ammonium salts of the acylamino acid. Methyl- and ethylpiperidine are commonly used by European chemists, whereas triethylamine is preferred in the United States. The use of tri-n-butylamine was suggested because its salts are soluble in most organic solvents.<sup>54</sup> This very property, however, has led many investigators to use triethylamine. When the final reaction mixture is worked up, washing with dilute hydrochloric acid fails to remove the tri-n-butylamine from the organic layer. Concentration then gives a mixture (usually a solution) of product and tributylamine. Triisoamylamine proved to be even more difficult to remove. In the preparation of ethyl carbobenzyloxy-DL-phenyl-alanyl glycinate, removal of the solvent after washing with acid and base gave two layers. The product was isolated by decanting the upper layer of triisoamylamine and triturating the bottom layer with ether.<sup>157</sup>

Although a moderate excess of triethylamine<sup>21</sup> or tri-n-butylamine<sup>54</sup> has been reported to have no effect on yields, a large excess may be undesirable. Chloroformates react with tertiary amines,<sup>126</sup> and it is possible that mixed anhydrides will also be decomposed by an excess of triethylamine or other relatively strong bases.<sup>125</sup>

Dimethylaniline has been recommended as a substitute for triethylamine since it does not react with chloroformates at room temperature.<sup>125</sup>

The use of metallic salts of the acylamino component rather than the acid and an organic base has received little attention except for the preparation of penicillin derivatives, where dry metallic salts are commercially available. Metallic salts of acylamino acids are unavailable, are troublesome to prepare, and are less soluble in the available solvents than are amine salts.

#### 4.4.4. Solvents

A wide variety of solvents has been used for the preparation of mixed anhydrides, the more usual being dry chloroform, toluene, tetrahydrofuran, and dimethylformamide. The reaction fails in water,<sup>140</sup> and the use of moist chloroform or toluene results in a 10–15% decrease in yield.<sup>21</sup> However, mixed anhydrides of penicillin have been made in aqueous acetone,<sup>158, 159</sup> and, when dimethylaniline is used in place of the more usual triethylamine, reactions in aqueous solvents are possible.<sup>125</sup> Aqueous nitromethane proved to be better than water alone; as all the experiments were performed with glycine derivatives which form anhydrides relatively rapidly, it is not known whether this practice can be extended to other amino acids. Many reactions have been run in dioxane at 10°,<sup>54</sup> but the relatively high temperature dictated by the freezing point of dioxane sometimes resulted in disproportionation of the mixed anhydride. Better results were obtained in acetone at – 10°. <sup>65</sup> The anhydride of  $\alpha$ -tosyl- $\epsilon$ -carbobenzyloxy-L-lysine and ethyl chloroformate reacted with benzyl p-aminobenzoate to give a 21% yield of product in tetrahydrofuran, a 14% yield in dioxane, and an 11% yield in chloroform.<sup>160</sup> However, there is no reason to expect parallel changes in yield with other reactants in these solvents.

Racemization is greater in chloroform<sup>40</sup> and dimethylformamide<sup>41</sup> than in dioxane, toluene, tetrahydrofuran, or toluene-dioxane mixtures.

Isolation of the product is simplified when toluene and other water-immiscible solvents are used in place of dioxane, acetone, and like solvents. The reaction mixture may be washed directly with hydrochloric acid and sodium bicarbonate solution (in the case of neutral products) to remove by-products without the necessity of replacing the original solvent.

The amount of solvent appears to be unimportant.<sup>21</sup>

#### 4.4.5. Time, Temperature, and Stability

Temperature is reported to be the most critical factor in the preparation of mixed carbonic anhydrides; the anhydrides are too unstable to permit the use of temperatures above 15° and the reaction rate becomes too slow at temperatures below – 20°. [21](#) Although a number of peptide derivatives have been prepared at 10° in dioxane, [54](#) the importance of keeping the reaction temperature at 0° to minimize disproportionation must be stressed. [48](#) A temperature of – 5° permits the preparation of the mixed anhydride in good yield in 5 to 10 minutes in most cases. Carbobenzyloxyglycine forms a mixed carbonic anhydride within 30 seconds at – 5°, but more complex amino acids require a longer reaction period. Although no decrease in yield in the preparation of phthaloylglycylanilide was observed whether the aniline was added to the anhydride at 0° after 10, 30, or 60 minutes, [54](#) there appears to be no advantage in prolonging the anhydride-forming step beyond 20 minutes.

The carbobenzyloxy group was removed from the  $\alpha,\alpha$ -dimethyl ester of carbobenzyloxy- $\gamma$ -L-glutamyl-L-glutamyl ethyl carbonate, [161-163](#) as well as from its isomer involving mixed anhydride formation on the alpha carboxyl group, [164](#) by hydrogenolysis in cold dioxane or dimethylformamide with a palladium catalyst. The resulting mixed anhydrides were used for the preparation of polymers.

Mixed anhydrides formed between many types of organic acids and ethyl chloroformate in the presence of a tertiary base have been known for more than fifty years. [79](#) Their existence in solution was postulated as early as 1888. [137](#) Recently it has been found that many of these anhydrides are relatively stable compounds that may be distilled; [165](#), [166](#) one, p-nitrobenzoyl anisyl carbonate, has been recrystallized. [167](#) Various mixed anhydrides of benzylpenicillin have been obtained as gums in analytically pure form. [168](#) Phthaloylglycylglycyl ethyl carbonate has been obtained crystalline. [125](#)

#### 4.4.6. Amide-Forming Step

After the anhydride has been prepared, the amine to be acylated is added to the anhydride, the cooling bath removed, and the reaction mixture stirred for about 4 hours at room temperature or allowed to stand overnight. Ethyl carbobenzyloxy-L-leucylglycinate was formed in 86% yield from carbobenzyloxy-L-leucyl sec-butyl carbonate in  $\frac{1}{2}$  hour at room temperature. [169](#) The reaction time may be shortened to a few minutes by heating the reaction mixture rapidly to boiling and then cooling. [57](#)

The amine component may be dissolved in any suitable solvent. Amino acids and peptides are usually dissolved in normal aqueous sodium hydroxide; esters of amino acids or peptides may be dissolved in a solvent such as acetone, benzene, chloroform, dimethylformamide, dioxane, ether, ethyl acetate, or tetrahydrofuran. If the solvent used for the anhydride is immiscible with that used for the amine, vigorous stirring is necessary. Since carbon dioxide is formed during the acylation, care must be observed to avoid excessive foaming during the addition of the amine. With many organic solvents foaming is hardly noticed, but with toluene, or when an aqueous solution of the sodium salt of an amino acid is added to a mixed carbonic anhydride, brisk evolution of carbon dioxide results.

#### 4.4.7. Isolation of Product

A variety of procedures has been used to isolate the peptide intermediate. If a solid is present in the reaction mixture it may be recovered by filtration and examined for water solubility. In most instances the solid will prove to be the hydrochloride of the tertiary amine used to neutralize the acylamino acid and will dissolve completely in water. In some cases part of the desired product is recovered directly from the reaction mixture and may be washed with water to remove amine salts.

If the reaction solvent is immiscible with water and the product is neutral, the reaction mixture may be washed (after filtration) with dilute hydrochloric acid to remove any unreacted amino acid ester, and then with salt water, and with aqueous sodium bicarbonate, to remove any remaining acylamino acid. In the



synthesis of percarbobenzyloxy-L-arginine, triethylamine was used in place of aqueous sodium bicarbonate.<sup>94</sup> The use of salt water is usually advisable to avoid emulsions. The solution remaining after extraction is dried, filtered, and concentrated in vacuum. Neutral esters are best obtained crystalline by dissolving them in ethyl acetate and adding petroleum ether. Trituration with ether or nitromethane will sometimes bring about crystallization if ethyl acetate fails. If the product remains a syrup, it is normally pure enough to use for the next step, e.g., saponification, hydrogenation, deacylation.

When the reaction solvent is miscible with water, the solvents may be removed by concentration in vacuum and the residue taken up in a mixture of ethyl acetate and water. Chloroform is sometimes superior to ethyl acetate for dissolving the product.

When the product is a peptide acid, it will appear as the sodium salt in the aqueous sodium bicarbonate, which may be extracted with ethyl ether and acidified with hydrochloric acid to precipitate the product.

If the reaction did not proceed in nearly quantitative yield, the  $\alpha$ -acylamino acid starting material will precipitate with the product. Sometimes purification by recrystallization is satisfactory; in other cases it is not at all practical. This must be determined experimentally. If a carbobenzyloxyglycyl-DL-amino acid proves to be easy to purify, it does not follow that the carbobenzyloxyglycyl-L-amino acid may also be readily purified. Countercurrent distribution or fractional extraction may be necessary. Aqueous ethanol as well as ethyl acetate-petroleum ether are commonly used to recrystallize acylamino peptides.

## 4.5. Experimental Procedures

### 4.5.1. Ethyl Carbobenzyloxy-S-benzyl-L-cysteinyl-S-benzyl-L-cysteinate<sup>170</sup>

A solution of 346 g. of carbobenzyloxy-S-benzyl-L-cysteine and 139 ml. of triethylamine in 3 l. of toluene was chilled to  $-5^{\circ}$  and treated with 131 ml. of isobutyl chloroformate. After 10 minutes a cold solution of 276 g. of S-benzyl-L-cysteine ethyl ester hydrochloride and 139 ml. of triethylamine in 2 l. of chloroform was added, and the mixture allowed to stand overnight at  $25^{\circ}$ . One additional liter of chloroform was added, and the mixture was washed successively with water, aqueous bicarbonate, and water, and finally dried over anhydrous sodium sulfate. The filtrate was concentrated in vacuum to a small volume, and triturated with petroleum ether. The precipitated carbobenzyloxy-S-benzyl-L-cysteinyl-S-benzyl-L-cysteine ethyl ester was collected and recrystallized from ethanol. The yield was 382 g. (67%) of product, m.p.  $105^{\circ}$  (cor.).

### 4.5.2. CarbobenzyloxyL-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine<sup>84</sup>

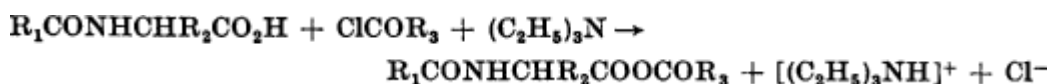
To a solution of 4.0 g. of carbobenzyloxy-L-glutamine in 60 ml. of tetrahydrofuran and 60 ml. of dioxane at  $-5^{\circ}$  were added 2.0 ml. of triethylamine and 1.35 ml. of ethyl chloroformate. A solution of asparaginyl-S-benzyl L-cysteine (prepared from 5.9 g. of the N-carbobenzyloxy derivative) in 20 ml. of water and sufficient 2N sodium hydroxide to bring the pH to 7.5 was then added to the solution of the anhydride. The reaction mixture was stirred for 3 hours, while being maintained at pH 7.5 by the addition of 4N sodium hydroxide as needed. After the addition of 350 ml. of ether the precipitate was collected, air-dried, dissolved in 70 ml. of water, and the solution brought to pH 2 with hydrochloric acid. The precipitate was again collected, air-dried, stirred for 1 hour at  $20^{\circ}$  with ethyl acetate, and finally collected to give 4.8 g. (64%) of carbobenzyloxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine, m.p.  $90^{\circ}$ .

### 4.5.3. Benzyl Carbobenzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanylglycyl-L-prolinate<sup>124</sup>

A solution of 1.30 g. (2 mmoles) of carbobenzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanylglycine and 0.40 g. (4 mmoles) of triethylamine in 25 ml. of dimethylformamide was cooled to  $-5^{\circ}$  and 0.31 g. (10% excess) of isobutyl chloroformate was added with stirring. After 10 minutes at this temperature, a solution of 0.48 g. (2 mmoles) of benzyl L-prolinate hydrochloride in 20 ml. of dimethylformamide was added and the mixture heated rapidly to about  $70^{\circ}$ , then immediately cooled. On addition of an excess of water, the product precipitated as a colorless solid. Two recrystallizations of this material from 40-ml. portions of 50% acetic acid gave 1.00 g. (60%) of product as colorless, microcrystalline prisms, m.p.  $210-212^{\circ}$ ,  $[\alpha]_D^{22} + 53.5 \pm 0.3^{\circ}$  ( $c = 2.1\%$ , glacial acetic acid).

## 5. $\alpha$ -Acylamino Acid Carboxylic Acid Anhydrides

The reaction of the salt of an  $\alpha$ -acylamino acid with an organic acid halide leads to the formation of an  $\alpha$ -acylamino acid carboxylic acid anhydride as shown in the accompanying equation. The mixed anhydride may be used for peptide synthesis.



Curtius<sup>171</sup> used a mixed anhydride of this kind for a peptide bond synthesis as early as 1881. The reaction of benzoyl chloride with silver glycinate gave some benzoylglycylglycine. Curtius correctly assumed that the benzoylglycine initially formed would react further with benzoyl chloride to form a mixed anhydride; he was wrong in assuming that the mixed anhydride would be formed by displacement of benzoic acid to give hippuryl chloride rather than by displacement of the chlorine to give hippuryl benzoate. The correct course of the reaction was recently clarified.<sup>172</sup>

Although a method for the preparation of mixed carboxylic acid anhydrides was described in 1900,<sup>79</sup> this reaction was not used for peptide synthesis until recent years. In 1948 penicillin acetic anhydride was prepared in good yield by treatment of sodium penicillin in dimethylformamide at  $5^{\circ}$  with acetyl chloride.<sup>173</sup> It underwent the normal anhydride reactions and reacted preferentially at the penicillin carbonyl group to give the corresponding amides. By this method penicillin was coupled to amino acids. Besides acetyl chloride, other acid halides up to octadecanoyl were employed to form similar mixed anhydrides.<sup>174, 175</sup> Diphenylacetyl chloride and isobutyryl chloride appear to be preferable to other acid chlorides in this reaction.

The first application of a mixed anhydride of an  $\alpha$ -acylamino acid and a carboxylic acid for peptide bond formation was reported in 1950.<sup>172</sup> The method stemmed from an attempt to synthesize azlactones<sup>176</sup> when it became apparent that a mixed anhydride could be an intermediate in azlactone formation. In an effort to prepare and isolate such a mixed anhydride, the silver salt of carbobenzyloxyglycine was treated with acetyl chloride in ether. A low-melting crystalline mixed anhydride resulted. Recrystallization from benzene and petroleum ether resulted in disproportionation. Treatment of the mixed anhydride with aniline and hydroxylamine gave carbobenzyloxyglycine anilide and hydroxamate, respectively.<sup>177, 178</sup>

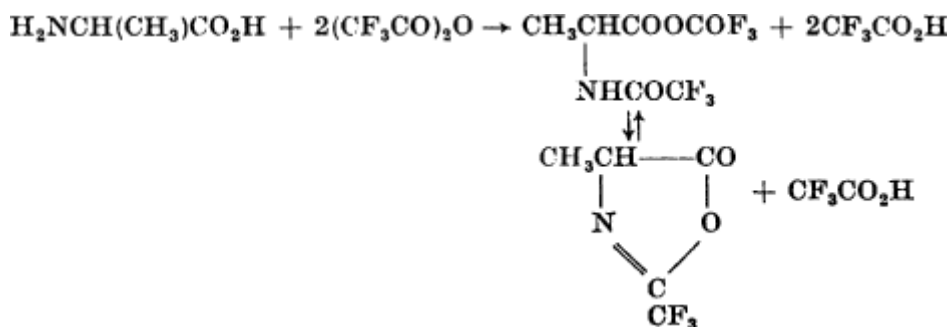
### 5.1. Mechanism

Mixed anhydrides of  $\alpha$ -acylamino acids with carboxylic acids contain the grouping  $R_1CONHCHR_2COOCOR_3$ , and the comments previously made on p. 163 apply here. The mechanism of



acylation reactions of mixed anhydrides has also been discussed by Tedder.<sup>179</sup> A number of mixed anhydrides have been allowed to react with hydroxylamine and the ratio of hydroxamic acids determined.<sup>179a</sup> With hippuric acetic anhydride, hippurylation predominated over acetylation by a ratio of 3:1. With hippuric benzoic anhydride the ratio of hippurylation rose to 21:1. These results indicated liberation of the weaker acid. The previously mentioned role of the solvent (see p. 163) in reversing or altering the normal course of the reaction should be kept in mind.

Anhydrides of carboxylic acids and trifluoroacetic acid react with primary amines to give mixtures of amides in which the trifluoroacetamide usually predominates.<sup>180</sup> However, when the carboxylic acid is an  $\alpha$ -amino acid, the trifluoroacetamide acid amide is the main or exclusive product.<sup>181</sup> Furthermore, trifluoroacetyl-L-alanine is racemized in the formation of the trifluoroacetic acid mixed anhydride. These results suggest that the reaction proceeds by way of an azlactone.



Trifluoroacetyl-L-proline trifluoroacetic anhydride disproportionates to trifluoroacetyl-L-proline anhydride, which has been used to acylate ethyl glycinate in 47% yield.<sup>182</sup>

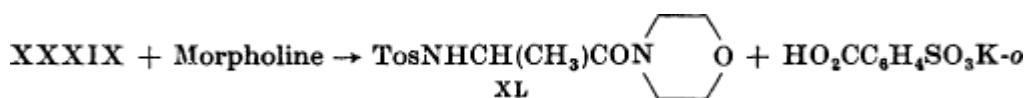
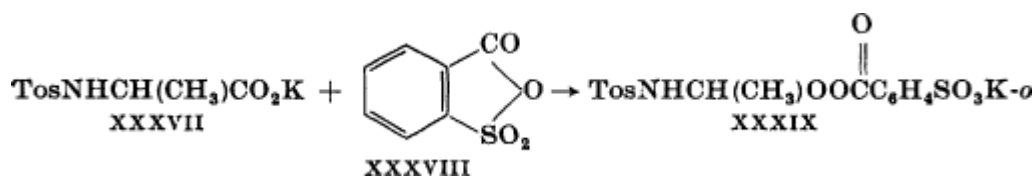
## 5.2. Scope and Limitations

### 5.2.1. Carboxylic Acids Used in Anhydride Formation

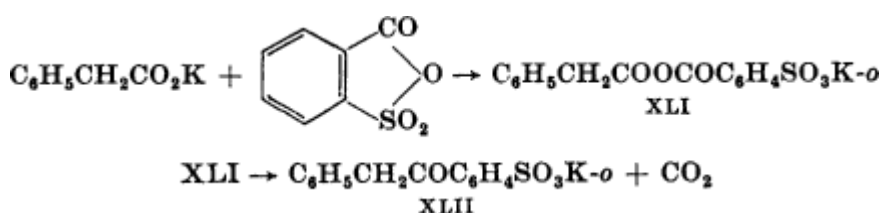
Initial work with acetyl chloride and benzoyl chloride<sup>172, 176</sup> showed that the benzoic acid mixed anhydride gave less disproportionation than the acetic acid mixed anhydride. In a systematic study mixed anhydrides of carbobenzyloxyglycine and a number of carboxylic acids were prepared and allowed to react with aniline, the yields and melting points of the products being noted. Since anhydrous media were used, the results could be correlated with the prediction of Emery and Gold<sup>3, 4</sup> that, in anhydrous solvents, attack by the amine should occur at the carbonyl carbon atom having the lower electron density. The results confirmed the superiority of the mixed anhydride of benzoic acid over that of acetic acid. However, the  $\alpha$  and  $\beta$  branched-chain acids were found to be better than any of the aromatic acids. In these branched-chain acids both the inductive and the steric effects of the alkyl groups operate to increase the attack by the amine at the amino acid carbonyl group. The aromatic acids, having relatively unfavorable electronic and inductive effects, generally gave lower yields of less pure product.<sup>8</sup>

The reactions of some cyclic mixed anhydrides of carboxylic and sulfonic acids with acylamino acids have been studied. Potassium tosyl-DL-alaninate (XXXVII) reacts with *o*-sulfobenzoic anhydride (XXXVIII) in dimethylformamide to give an acyclic mixed anhydride from which a 59% yield of tosyl-DL-alanine morpholide (XL) was obtained.<sup>183</sup> The reaction presumably proceeds as shown in the accompanying equations, although the structure of the intermediate anhydride was not determined.

Potassium tosyl-DL-alaninate gave a 45% yield of the morpholide starting with 3,5-dibromo-2-sulfobenzoic anhydride and an 8% yield with  $\beta$ -sulfopropionic anhydride.



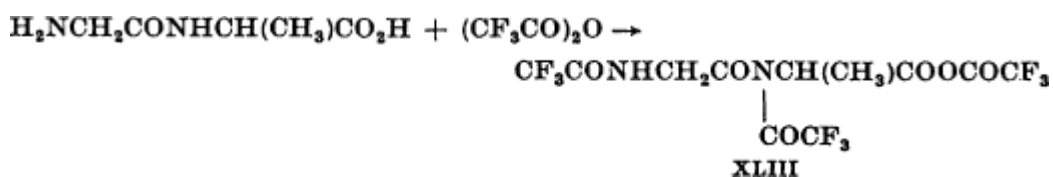
In a model experiment, dry potassium phenylacetate dissolved immediately in dimethylformamide upon addition of o-sulfobenzoyl anhydride, but introduction of excess aniline gave only a 50% yield of anilide. The authors concluded that either the mixed anhydride disproportionated or, more probably, the amine attacked at both carbonyl positions.<sup>183</sup> An alternative explanation is that the intermediate mixed anhydride XLI undergoes a Perkin reaction to give the ketone XLII.

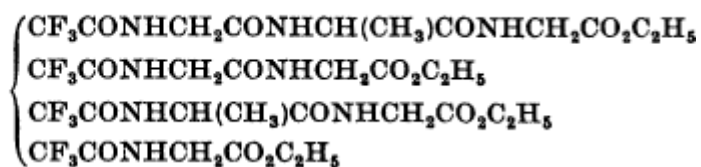


The mixed cyclic anhydrides of sulfocarboxylic acids have not been used with acylamino acids to form peptides, although the synthesis of tosylalanine morpholide indicates that it should be possible to do so.

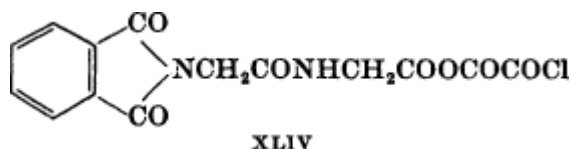
An investigation of the use of the trifluoroacetyl group as an amine blocking group,<sup>184, 185</sup> showed that the addition of 1 mole of amino acid to 1 mole of trifluoroacetic anhydride gave crystalline trifluoroacetyl amino acids but that excess anhydride gave other products. DL-Alanine and DL-valine gave liquids (boiling at 36° and 45°, respectively, at 0.02 mm.) that were formulated as mixed anhydrides although in each case the carbon, hydrogen, and nitrogen values fell between those calculated for the mixed anhydride and those calculated for the oxazolone or for the symmetrical trifluoroacetyl amino acid anhydride. Later it was shown that heating trifluoroacetic anhydride with trifluoroacetyl-DL-alanine to 140° gave 2-trifluoromethyl-4-methyl-5-oxazolone contaminated with trifluoroacetic acid.<sup>186</sup> The symmetrical trifluoroacetyl-DL-alanine anhydride gave the oxazolone on heating.

The use of the mixed anhydrides of trifluoroacetic acid and an α-acylamino acid for peptide synthesis suffers a serious disadvantage in that racemization is observed even at relatively low temperatures. A second disadvantage is that excess trifluoroacetic anhydride acylates the peptide nitrogen atom. Subsequent treatment with the ester of an amino acid will result in the cleavage of some peptide bonds. For example, the anhydride prepared from glycyl-DL-alanine and an excess of trifluoroacetic anhydride reacts with ethyl glycinate to give a mixture of trifluoroacetyl-glycyl-DL-alanyl-glycine ester, trifluoroacetyl-glycyl-glycine ester, trifluoroacetyl-DL-alanyl-glycine ester, and trifluoroacetyl-glycine ester.<sup>187</sup>





Heating phthaloylglycine with oxalyl chloride for 48 hours in benzene gave phthaloylglycine anhydride in 99% yield. The same reactants heated for 6 hours gave the mixed anhydride XLIV,<sup>136</sup> which was not used for peptide synthesis, and would appear not to be suitable for this purpose since 2 moles of amino acid ester or peptide ester would be required per mole of mixed anhydride.



In spite of the considerable number of mixed anhydrides of  $\alpha$ -acylamino acids and carboxylic acids that have been prepared, peptide bond formation has actually been attempted with only a few, namely the anhydrides of acylamino acids with benzoic, isovaleric, and trifluoroacetic acids. Ethyl carbobenzyloxyglycyl-DL-phenylalaninate has been prepared using the mixed anhydrides of carbobenzyloxyglycyl-DL-phenylalanine and trimethylacetic and diethylacetic acids.<sup>8</sup>

### 5.2.2. $\alpha$ -Acylamino Acids Used in Anhydride Formation

Anhydrides prepared from isovaleryl chloride and acyl derivatives of glycine, alanine, leucine, norleucine, proline, phenylalanine, asparagine, and lysine have been employed for the synthesis of peptides. The use of anhydrides derived from isovaleryl chloride and sarcosine, D-isoleucine and D-isoleucyl-L-proline have been reported but with no details.<sup>188</sup> Dehydration of the amido group of asparagine to the nitrile, observed when the pyrophosphite or carbodiimide method is used, does not occur when the anhydride derived from isovaleryl chloride and carbobenzoyl-L-asparagine is coupled with S-benzyl-L-cysteine.<sup>87</sup> Low yields (10–30%) were obtained in the acylation of allothreonine with the anhydrides prepared from the carbobenzyloxy derivatives of alanine, norleucine, and phenylalanine.<sup>189</sup>

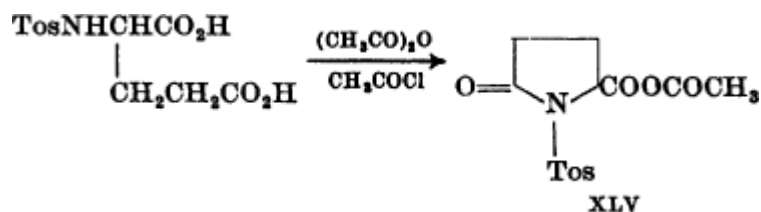
The anhydride derived from benzoyl chloride was used to prepare an extensive series of lysine peptide intermediates.<sup>190, 191</sup> This procedure was reported to be simpler experimentally and to give purer products than the azide method. These results represent the only reported experiments in which mixed anhydrides of optically active acylamino polypeptides and carboxylic acids have been used. Racemization was not a problem even though a lysine pentapeptide derivative was synthesized by the addition of one lysine ester group at a time to a percarbobenzyloxylysine polypeptide. Mixed anhydrides of benzoic acid and N-formyl-O-acetyl-L-tyrosine, N-carbobenzyloxy-O-acetyl-L-tyrosine, carbobenzyloxy- and phthaloyl-glycine, carbobenzyloxy-DL-alanine, carbobenzyloxyglycylglycine, and carbobenzyloxy-DL-alanyl-DL-alanine have also been prepared.

The mixed anhydride of trifluoroacetyl-glycine and trifluoroacetic acid reacts with ethyl glycinate to give more than 60% of ethyl trifluoroacetyl-glycylglycinate. Reaction of ethyl glycinate with the anhydride of trifluoroacetyl-DL-alanine and trifluoroacetic acid gave ethyl trifluoroacetyl-DL-alanyl-glycinate in 55% yield. Glutamic acid reacts with trifluoroacetic anhydride to give the anhydride of N-trifluoroacetyl-L-glutamic acid.<sup>181</sup>

No information is available on the possible use of mixed anhydrides of the hydroxy amino acids such as serine and threonine. Pantotheine, however, has been prepared in 38% yield from the mixed anhydride of

benzoic acid and pantothenic acid which contains two hydroxyl groups.<sup>75</sup>

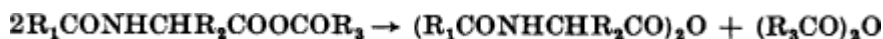
Acylglutamic acids in which the acyl group is acetyl, carbobenzyloxy, phthaloyl, 4-nitrobenzoyl, or phenacetyl react with acetic anhydride or thionyl chloride to form acylaminoglutaric anhydrides.<sup>192</sup> The same type of reaction would be likely to occur in an attempt to prepare mixed anhydrides of other carboxylic acids. When the acyl group of the amino acids is tosyl, the reaction takes a different course. Acetic anhydride or acetyl chloride leads to the formation of 1-tosylpyroglutamyl acetate (XLV).<sup>193</sup> Treatment of the anhydride XLV with ammonia leads to less than a 50% yield of 1-tosylpyroglutamic acid amide, presumably because fission occurs at both carbonyl groups.<sup>192</sup>



1-Tosylpyroglutamyl chloride<sup>107, 194, 195</sup> will probably prove as useful as any mixed anhydride of 1-tosylpyroglutamic acid and a carboxylic acid.

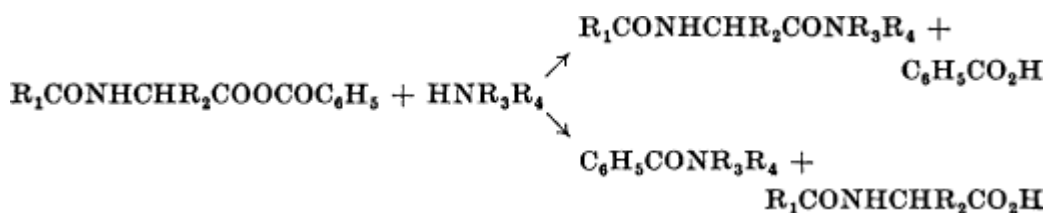
### 5.3. Side Reactions

The principal side reaction observed in the use of mixed anhydrides of  $\alpha$ -acylamino acids and carboxylic acids has been disproportionation.



The mixed anhydrides with benzoic acid are less prone to this reaction than those with acetic acid, but upon warming they too disproportionate.<sup>176</sup> Carbobenzyloxy-DL-alanine benzoate when warmed just above its melting point for 10 minutes gave benzoic anhydride and carbobenzyloxy-DL-alanine anhydride in good yield. Silver carbobenzyloxyglycylglycinate and benzoyl chloride in benzonitrile gave a mixture of carbobenzyloxyglycylglycyl benzoate and carbobenzyloxyglycylglycine anhydride.<sup>176</sup>

Although mixed anhydrides of  $\alpha$ -acylamino acids and benzoic acid can react at either carbonyl groups, no benzamide has been observed as a by-product in this type of peptide synthesis except when the amine-protecting group is trifluoroacetyl.<sup>196</sup> However, this side reaction may contribute to lowered yields even when the substituted benzamides do not interfere with the purification of the desired products.<sup>8</sup> The mixed anhydrides of trifluoroacetyl amino acids and acetic or benzoic acid react with aniline to give mixtures of anilides difficult to separate. Trifluoroacetyl-DL-alanyl acetate gave only a 6% yield of trifluoroacetyl-DL-alanyl anilide.<sup>196</sup>

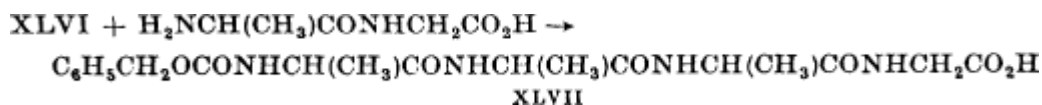
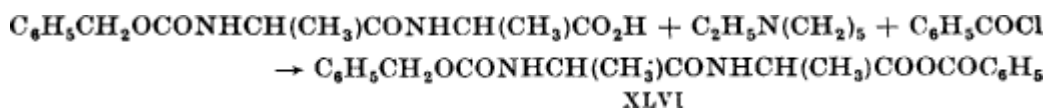


## 5.4. Experimental Conditions

The preparation of an  $\alpha$ -acylamino acid carboxylic acid mixed anhydride involves reaction of an  $\alpha$ -acylamino acid salt with a carboxylic acid chloride or, for mixed anhydrides of trifluoroacetic acid, trifluoroacetic anhydride.

In earlier work the silver salt of the  $\alpha$ -acylamino acid in ether or benzonitrile<sup>176, 197</sup> was employed. The latter solvent is especially suitable. Silver chloride was removed by centrifugation. The sodium salts were found to react more slowly than the silver salts, but the sodium salt of benzylpenicillin reacts rapidly with acetyl chloride in dimethylacetamide.<sup>173</sup> N-Ethylpiperidine<sup>172</sup> or triethylamine<sup>8</sup> is convenient for the preparation of the salts of an acylamino acid. Pyridine is usually less satisfactory, and dimethylaniline is generally unsuitable because of its lower basicity.<sup>172</sup> Toluene, benzene, tetrahydrofuran and other inert solvents may be used.

The mixed anhydride is usually prepared between  $-5^\circ$  and  $5^\circ$  in order to minimize disproportionation. For the same reason it is advisable to use the mixed anhydride without isolation.<sup>172</sup> The mixed anhydride may be prepared in a water-immiscible solvent such as benzene and then treated, with vigorous stirring, with an aqueous solution of the sodium salt of the amino acid or peptide to be acylated. In this manner, carbobenzyloxy-DL-alanyl-DL-alanyl-DL-alanylglycine (XLVII) was prepared in 80% yield.<sup>172</sup>



The benzoic acid formed as a by-product may be removed by extraction with petroleum ether or by steam distillation.<sup>172, 197</sup>

The yields are generally higher if dry solvents are employed. The mixed anhydrides of carbobenzyloxyglycine and trimethylacetic acid, dimethylacetic acid, and isovaleric acid reacted with ethyl DL-phenylalaninate to give ethyl carbobenzyloxyglycyl-DL-phenylalaninate in 81, 84, and 86% yields, respectively, in anhydrous solvents but 58, 67, and 55% yields in wet solvents.

Although mixed anhydrides derived from benzoyl chloride have been used as frequently as those from isovaleryl chloride to synthesize peptides, the latter acyl halide in toluene with the triethylammonium salt of an acylamino acid appears to be preferable. About 1 or 2 hours are usually allowed for anhydride formation.<sup>8, 198</sup> However, when the mixed anhydride from dicarbobenzyloxy-L-lysine and benzoyl chloride was allowed to stand for only 2 minutes at  $0^\circ$  before adding L-tyrosinamide, the dipeptide amide was isolated in 70% yield.

Once the mixed anhydride has been prepared, the amide-forming step and the isolation of the product are essentially the same as for the acylamino alkyl carbonates already described (p. 194).

## 5.5. Experimental Procedures

### 5.5.1. Ethyl Carbobenzyloxy-L-prolyl-L-leucylglycinate (Use of Isovaleryl Chloride)<sup>199</sup>

A solution of 69.5 g. of carbobenzyloxy-L-proline and 28.2 g. of triethylamine in a mixture of 335 ml. of dry toluene and 335 ml. of dry chloroform was cooled to  $-5^{\circ}$  and 33.8 g. of isovaleryl chloride added. After  $\frac{11}{2}$  hours a cooled solution of ethyl N-leucylglycinate hydrochloride (from 100 g. of ethyl carbobenzyloxy-L-leucylglycinate) and 28.2 g. of triethylamine in 700 ml. of chloroform was added and the reaction mixture left overnight at  $5^{\circ}$ . The solution was then washed with water and 3% aqueous sodium bicarbonate, and concentrated under reduced pressure to a volume of approximately 500 ml. Dilution of the solution with hexane caused 120 g. of white crystalline product, m.p.  $145-146^{\circ}$ , to separate. One recrystallization from aqueous ethanol gave 115.5 g. (92%) of the carbobenzyloxytripeptide ester, m.p.  $148-149^{\circ}$  [ $\alpha$ ]<sub>D</sub><sup>25</sup>  $-79.8^{\circ}$  (c = 2.5%, ethanol).

### 5.5.2. Methyl Tetra-(N-carbobenzyloxy)-L-lysyl-L-lysyl-L-lysinate (Use of Benzoyl Chloride)<sup>190</sup>

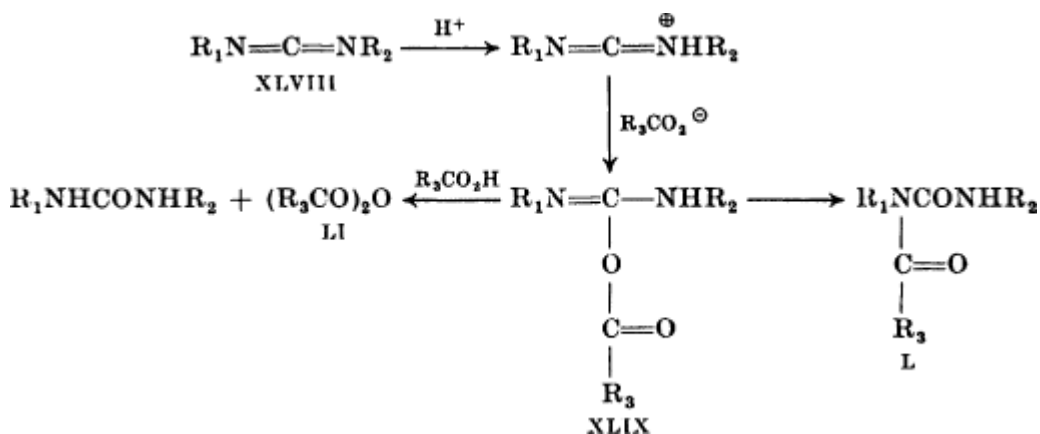
A solution of 11.1 g. of tricarbobenzyloxy-L-lysyl-L-lysine in 30 ml. of tetrahydrofuran containing 2.22 ml. of N-ethyl-piperidine was treated at  $0^{\circ}$  with 18.8 ml. of benzoyl chloride and the mixture added to 7.1 g. of  $\epsilon$ -carbobenzyloxy-L-lysine methyl ester in 90 ml. of ethyl acetate and 30 ml. of 1.4N aqueous potassium bicarbonate. The reaction mixture was vigorously stirred at  $0^{\circ}$  for 45 minutes, the precipitate collected and recrystallized from methanol to give 9.1 g. (58%) of product, m.p.  $164-165.5^{\circ}$ . When the reaction was conducted in benzonitrile, a less pure product was obtained.

## 6. Carbodiimides

Carbodiimides, ketenimines, isocyanates, and ketenes all possess a central carbon atom having twinned double bonds, and all add carboxylic acids by 1,2 addition to give intermediates from which amides may be obtained.

### 6.1. Mechanism

The addition of carboxylic acids to carbodiimides has been studied in detail, and the course of the reaction has been shown to involve addition of a proton to the carbodiimide (XLVIII) followed by attack of the acid anion. The relevant literature has been reviewed.<sup>200-202</sup>





The intermediate adduct XLIX can either rearrange to an acylurea L or react with a second mole of acid to give a symmetrical anhydride LI and the urea. The adduct XLIX will be recognized as a nitrogen analog of an acyl alkyl carbonate mixed anhydride: two oxygen atoms have been replaced by nitrogen. The adduct is sensitive to base<sup>203</sup> and will react with an amino acid (or peptide) ester as shown in the accompanying equation. This reaction provides a versatile and convenient peptide synthesis.<sup>201, 204, 204a</sup>



## 6.2. Scope and Limitations

All the common amino acids have been used as the acylating species in peptide bond formation with N,N $\epsilon$ -dicyclohexylcarbodiimide. The complete synthesis of oxytocin<sup>205, 206</sup> and a tyrosine homolog<sup>207</sup> using the carbodiimide method as the sole means of peptide bond formation has been described. The carbodiimide procedure was also employed extensively in synthesizing an ACTH-like peptide of twenty amino acids.<sup>208</sup> The synthesis of phenoxypenicillin was accomplished using N,N $\epsilon$ -dicyclohexylcarbodiimide to close the  $\beta$ -lactam ring,<sup>209</sup> and the same carbodiimide served to prepare dimethylpyruvoyl-L-phenylalanine methyl ester in 86% yield.<sup>120</sup>

Trityl-Y-alkyl-L-glutamate,<sup>103</sup> ditrityl-L-histidine, trityl DL-methionine, and trityl-DL-tryptophan<sup>11</sup> may be used for formation of peptides. These reactions are of special interest because the same substituted amino acids in the form of their mixed anhydrides with carbonic acid failed to undergo coupling reactions. This effect was ascribed to steric hindrance;<sup>10</sup> either no anhydride is formed or the anhydride reacts to form the carbonate.<sup>210</sup> An alternative explanation is that the anhydride step becomes sufficiently slow that the reaction of the alkyl chloroformate with the triethylamine predominates. This complicating side reaction is impossible with the carbodiimides, and peptides are formed.

N,N $\epsilon$ -Dicyclohexylcarbodiimide has been used to prepare polypeptides with average molecular weights as high as 1,000,000 from lower-molecular-weight polypeptides.<sup>211</sup>

N-Acetyl-DL-penicillamine is rapidly converted at room temperature to the  $\beta$ -thiolactone by N,N $\epsilon$ -dicyclohexylcarbodiimide.<sup>72</sup>

O-Seryl derivatives have been prepared from N-benzoylserylglycine using N,N $\epsilon$ -dicyclohexylcarbodiimide in pyridine. In a similar manner O-carbobenzyloxyaminoacyl-N-benzoylserylglycine<sup>212</sup> was prepared from carbobenzyloxy-leucine and carbobenzyloxyphenylalanine in yields of 84% and 82%, respectively. The optical configurations were presumably L.

### 6.2.1. Hydroxy Amino Acids

The successful use of carbobenzyloxy-L-serine,<sup>213-216</sup> carbobenzyloxy-L-hydroxyproline<sup>213, 217</sup> and phthaloyl-L-threonine<sup>213, 217</sup> with the hydroxyl groups unprotected is noteworthy. Phthaloyl-L-threonyl-L-phenylalanine ethyl ester (96%), phthaloyl-L-threonyl-L-phenylalanyl-L-phenylalanine methyl ester (92%), and phthaloyl-L-threonyl-L-phenylalanylglycine ethyl ester (94%) were synthesized using N,N $\epsilon$ -dicyclohexylcarbodiimide in methylene chloride at room temperature.<sup>213</sup> Likewise, methyl L-isoleucinate was acylated by N-carbobenzyloxy-L-tyrosine in 94% yield,<sup>218</sup> and by N-formyl-L-tyrosine in 74% yield.<sup>43</sup> Satisfactory results were obtained in the acylation of the methyl esters of L-tyrosine, L-tryptophan, and L-serine by carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine.<sup>219</sup>

The reaction with hydroxyproline and allohydroxyproline very probably proceeds at least in part through the lactone, since N,N $\epsilon$ -dicyclohexylcarbodiimide converts N-carbobenzyloxy-L-allohydroxyproline to its lactone, which reacts with glycine ester to give the dipeptide derivative.[220](#)

### 6.2.2. Acidic Amino Acids

The ability of N,N $\epsilon$ -dicyclohexylcarbodiimide to promote the formation of amide bonds in aqueous media is illustrated by the synthesis of L-glutamine from L-glutamic acid.[221](#) The copper salt was used to protect the  $\alpha$ -amino and adjacent carboxyl groups while the  $\gamma$  carboxyl group was converted to the amide. This method should be applicable to the preparation of  $\gamma$ -glutamyl peptides.

Although N-trityl-L-asparagine reacted with methyl L-tyrosinate in the presence of N,N $\epsilon$ -dicyclohexylcarbodiimide to give, after saponification of the intermediate, 50% of N-trityl-L-asparaginyl-L-tyrosine,[222](#) asparagine itself gave generally disappointing results, owing possibly to partial dehydration of the amide to the nitrile.[223](#) However, the readily accessible carbobenzyloxy- $\beta$ -cyano-L-alanine does form a peptide bond with the aid of N,N $\epsilon$ -dicyclohexylcarbodiimide.[224](#)

The condensation of carbobenzyloxy-L-asparagine with methyl S-benzyl-L-cysteinate in tetrahydrofuran by means of N,N $\epsilon$ -dicyclohexylcarbodiimide gave 39% of methyl carbobenzyloxy-L-asparaginyl-S-benzyl-L-cysteinate, and 26% of the nitrile.[87](#), [223](#) When carbobenzyloxyglutamine was substituted for asparagine in this reaction, a 76% yield of peptide resulted and no nitrile was isolated.[223](#) While yields of 20–30% were obtained in the coupling of equimolar amounts of N-trityl-L-asparagine with amino acid esters at room temperature, the use of excess trityl-L-asparagine at  $-10^\circ$  gave yields of 82–96%.[225](#)

### 6.2.3. Basic Amino Acids

N,N $\epsilon$ -Dicyclohexylcarbodiimide gives satisfactory results with lysine, histidine, and arginine. Ditrityl-L-lysine,[12](#) ditrityl-L-histidine,[11](#), [45](#) dicarbobenzyloxy-L-histidine,[89](#), [226](#) dicarbocyclopentyloxy-L-histidine,[15](#) carbobenzyloxy-im-benzyl-L-histidine,[227-229](#) carbobenzyloxy-L-arginine,[45](#), [208](#) and carbobenzyloxy nitro-L-arginine[216](#) have been employed for the synthesis of dipeptide intermediates. The scope of the reaction with basic amino acids is better shown by the coupling of carbobenzyloxy-L-arginyl-L-arginine with methyl L-prolyl-L-valinate in 57% yield,[208](#) of carbobenzyloxy-L-histidyl-L-phenylalanyl-L-nitroarginine with benzyl-L-tryptophylglycinate in 86% yield,[44](#) and of carbobenzyloxy-L-asparaginyl nitro-L-arginine with methyl L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucinate in 70% yield.[230](#) Lactam formation has been observed with carbobenzyloxynitro-L-arginine in the presence of N,N $\epsilon$ -dicyclohexylcarbodiimide.[230a](#)

### 6.2.4. Racemization

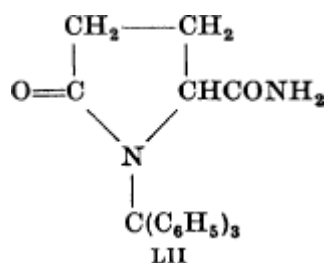
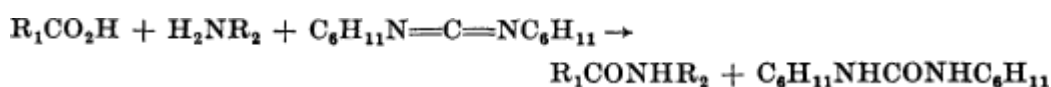
From 40% to 100% retention of configuration in peptide synthesis has been the experience with N,N $\epsilon$ -dicyclohexylcarbodiimide as a reagent. In three experiments in which carbobenzyloxyglycyl-L-phenylalanine was coupled with ethyl glycinate in tetrahydrofuran at room temperature, the DL mixture was obtained in yields of 6.6, 7.6, and 8.2%, respectively. At  $-5^\circ$ , only 0.5% of DL mixture was isolated, whereas in methylene dichloride at room temperature 12% was obtained.[231](#)



## 6.3. Experimental Conditions

Warning: Cases of dermatitis in several laboratories have been ascribed to N,N $\phi$ -dicyclohexylcarbodiimide; most chemists are not susceptible.

Unlike most other mixed anhydride reactions, the preparation of the anhydride and the formation of the peptide bond are not done separately. Instead, the  $\alpha$ -acylamino acid (or peptide) and the amino acid (or peptide) ester are treated with a slight excess of N,N $\phi$ -dicyclohexylcarbodiimide in a solvent such as acetonitrile. An exothermic reaction occurs. After 4 hours at room temperature, excess carbodiimide is destroyed by the addition of a small amount of acetic acid, the N,N $\phi$ -dicyclohexylurea removed by filtration, and the acyl peptide ester isolated in the usual fashion. (Compare the isolation of products from acylaminoalkyl carbonates, p. 194.) An excess of the acylating species is used with tritylasparagine, tritylglutamine, or tritylisoglutamine, and the reaction in methylene dichloride is allowed to proceed for 13 to 45 hours at  $-10^\circ$ . Some of the tritylisoglutamine is cyclized to the tritylpyrrolidone LII.



The reaction may be carried out in the presence of water, although better yields usually result in anhydrous solvents such as methylene dichloride or acetonitrile.<sup>213</sup> For example, phthaloyl-L-phenylalanine was coupled with ethyl glycinate in 92% yield in methylene dichloride and in 72% yield in aqueous tetrahydrofuran.<sup>204</sup> Carbobenzyloxy-L-serine was coupled with ethyl glycinate in 59% yield in tetrahydrofuran;<sup>204</sup> it was later reported that higher yields were obtained in acetonitrile or methylene dichloride.<sup>213</sup> Khorana used dioxane, tetrahydrofuran, chloroform, and ether as solvents and always obtained acylureas as by-products.<sup>201</sup> With phthaloyl-L-threonine, acylurea formation was observed in dioxane and in tetrahydrofuran, but not in methylene dichloride or acetonitrile.<sup>217</sup> Pyridine and dimethylformamide have also been used as solvents. Low temperatures suppress acylurea formation.<sup>232</sup>

Carbodiimides vary in reactivity and in stability<sup>202</sup> and not all are suitable for peptide synthesis. Although ease of preparation, commercial availability, and stability of N,N $\phi$ -dicyclohexylcarbodiimide have made it the carbodiimide of choice for peptide synthesis, there are some situations in which the dicyclohexylurea produced as a by-product may not be readily separable from the desired peptide intermediate. In these cases N,N $\phi$ -dicyclohexylcarbodiimide has been replaced by carbodiimides with solubilizing groups.<sup>213, 233</sup> Of these, 1-cyclohexyl-3-[2-morpholinyl-(4)-ethyl]carbodiimide (LIII) and its metho-p-toluenesulfonate are most convenient since they are readily prepared from commercially available chemicals. The acylurea derived from the former carbodiimide is soluble in dilute acids, and that from the latter is soluble in water. Basic carbodiimides such as LIII can be used directly with the amino acid ester hydrochloride in dioxane. Acetonitrile is the preferred solvent for carbodiimides having a quaternary nitrogen atom. If the hydrohalide salt of an amino acid ester is used, an equivalent amount of triethylamine is added. Carbodiimides having a quaternary nitrogen atom require about 2 days at room temperature for completion of the reaction and tend to give lower yields of product than do the carbodiimides bearing tertiary amine substituents.<sup>233</sup>



## 6.4. Experimental Procedures

### 6.4.1. N,N $\zeta$ -Dicyclohexylcarbodiimide<sup>237</sup>

#### 6.4.1.1. A. Preparation of N,N $\zeta$ -Dicyclohexylurea

A mixture of 60 g. of urea and 240 g. of cyclohexylamine is heated under reflux for 20 hours in 480 ml. of isoamyl alcohol. The solution is cooled, the solid collected, washed with diethyl ether, and dried to give 200 g. (89%) of product, m.p. 234°.

With n-amyl alcohol as a solvent, yields of 94% of N,N $\zeta$ -dicyclohexylurea were obtained.

#### 6.4.1.2. B. Preparation of N,N $\zeta$ -Dicyclohexylcarbodiimide

A solution of 200 g. of N,N $\zeta$ -dicyclohexylurea and 300 g. of p-toluenesulfonyl chloride in 600 ml. of pyridine is stirred at 70° for 1 hour and then poured onto 1.5 kg. of ice. The product is taken up in ether. Some insoluble material often is formed at this point; it is probably 1,3-dicyclohexyl-2,4-bis(cyclohexylimino)uretidine. The ether extracts, filtered if necessary, are washed with water, dried, concentrated, and distilled to give 152 g. (82%) of N,N $\zeta$ -dicyclohexylcarbodiimide, b.p. 148–152°/11 mm. The product crystallizes readily, m.p. 35°.

### 6.4.2. Ethyl Carbobenzyloxyglycyl-L-phenylalanylglycinate<sup>204</sup>

To a solution of equimolar quantities of carbobenzyloxyglycyl-L-phenylalanine and ethyl glycinate in tetrahydrofuran is added slightly more than one mole equivalent of N,N $\zeta$ -dicyclohexylcarbodiimide. The solution is allowed to stand at room temperature for 4 hours, treated with a small amount of acetic acid to decompose the excess reagent, the insoluble urea removed, and the solvent replaced by ethyl acetate. The ethyl acetate solution is washed with dilute hydrochloric acid and with aqueous potassium bicarbonate, and petroleum ether added. Chilling affords an 87% yield of carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester; m.p. 118–119°;  $[\alpha]_D^{27} -13.5^\circ$  (in ethanol).

### 6.4.3. L-Histidyl-L-leucine<sup>11</sup>

To a solution of 1.69 g. of methyl L-leucinate in methylene dichloride is added a solution of 2.5 g. of N,N $\zeta$ -dicyclohexylcarbodiimide in 5 ml. of the same solvent. The solution is cooled to 0°, and 6.4 g. of N,N $\zeta$ -ditrityl-L-histidine is added with stirring. The reaction mixture is allowed to stand overnight at room temperature, 0.5 ml. of acetic acid added to destroy the excess carbodiimide, and the dicyclohexylurea which precipitates (2.5 g.) is removed by filtration. The filtrate is washed with 5N aqueous ammonia and with water, dried, and concentrated to give crude ditrityl-L-histidyl-L-leucine ester which is saponified by refluxing it for 5 minutes with 8 ml. of 20% methanolic potassium hydroxide and 2 ml. of water. The solution is diluted with 30 ml. of water, cooled, and acidified with acetic acid to precipitate the crude acid

which, after drying at 100°, weighs 6.5 g. (86%).

The trityl groups are removed by warming the ditrityl peptide for 15 minutes on a water bath with 50% aqueous acetic acid. The solution is then diluted with an equal volume of water, cooled, the triphenylcarbinol removed by filtration, and the solution concentrated. Crystallization is induced by the addition of ethanol. After crystallization from dilute ethanol and drying at 110°, L-histidyl-L-leucine is obtained in 93% yield, m.p. 245° dec.;  $[\alpha]_{D+13}^{\circ} \pm 1$  (c = 2%, N HCl);  $[\alpha]_{D-41.5}^{\circ} \pm 2$  (c = 1%, 0.1N NaOH).

#### 6.4.4. Cyclo-glycyl-L-leucylglycylglycyl-L-leucylglycyl<sup>242</sup>

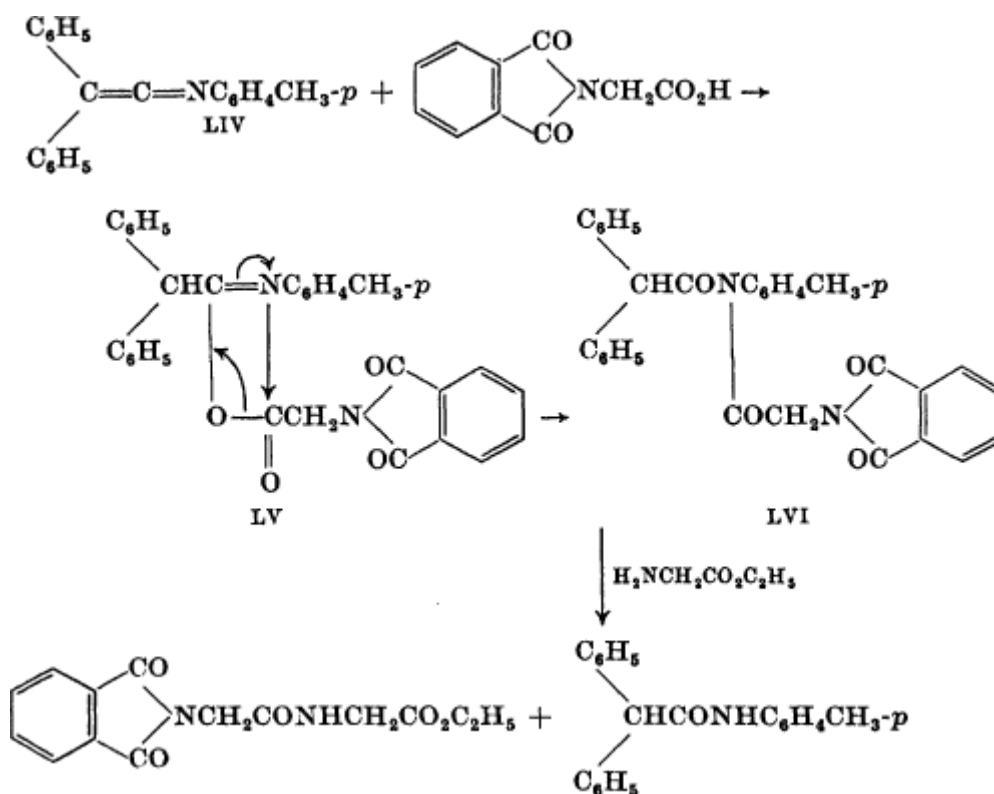
A solution of 500 mg. of glycyl-L-leucylglycylglycyl-L-leucylglycine in a mixture of 100 ml. of water and 400 ml. of methanol is cooled to -3° and 2 g. of N,N'-dicyclohexylcarbodiimide is added. The reaction mixture is allowed to stand for 3 days at -3° and then for 3 days at room temperature. The methanol is removed in vacuum and the excess carbodiimide converted to N,N'-dicyclohexylurea by the addition of 5 ml. of glacial acetic acid. The urea is removed, and the solution is concentrated to about 20 ml. The solution deposits white crystals upon standing. These are collected and recrystallized from hot water to give 190 mg. (47%) of the cyclohexapeptide monohydrate melting with decomposition above 320°.

## 7. Ketenimines

### 7.1. Mechanism

Ketenimines resemble carbodiimides. An acid will add to a ketenimine LIV to give an isoimide LV which rearranges to a diacylimide LVI.<sup>243-245</sup>

Both the isoimide LV and the diacylimide LVI are acylating agents. Thus N-phthaloylglycyldiphenylacetic acid p-toluide (LVI) reacts with ethyl glycinate to give ethyl phthaloylglycylglycinate and N-(p-tolyl)diphenylacetamide. Other adducts of  $\alpha$ -acylamino acids and diphenyl-ketene-p-tolyimine (LIV) behave in the same fashion; the reverse cleavage to give a diphenylacetyl amino acid ester has not been observed.<sup>246</sup> If the ketenimine is added to a mixture of the acid and amine, some of the acylation undoubtedly proceeds via the isoimide.<sup>243, 244, 246</sup>



## 7.2. Scope and Limitations

The principal difference between the carbodiimide and the ketenimine method is the stability of the intermediate acylating species. Adducts of diphenylketene-p-tolylimine with phthaloylglycine, carbobenzyloxyglycine, phthaloyl- $\beta$ -alanine, and phthaloyl-DL-methionine have been isolated, purified, and stored.<sup>244</sup> No evidence of disproportionation has been observed.<sup>246</sup> N-Carbobenzyloxy-S-benzyl-L-cysteine and N-carbobenzyloxy-L-asparagine have been used for peptide synthesis without isolation of the adducts.<sup>244</sup> Phenoxypenicillin has been synthesized by closing the  $\beta$ -lactam ring with pentamethyleneketene cyclohexylimine.<sup>209</sup>

Amine components for peptide synthesis have been ethyl glycinate, ethyl glycyglycinate, ethyl L-leucinate, methyl L-tyrosinate, methyl S-benzyl-L-cysteinate, ethyl p-aminobenzoate,<sup>244</sup> and ethyl DL-threonate.<sup>246, 247</sup> The use of sodium salts of amino acids or peptides as the amine component has not been reported, but yields below the 45–77% obtained with esters of the amino acids and peptides in inert solvents would be expected. The presence of water or ethanol has been found to reduce yields because it interferes with the initial addition reaction.<sup>244, 246</sup> The effect of water on the amide-forming step has not been determined.

The extent to which racemization may occur is not known.

The separation of the N-(p-tolyl)diphenylacetamide from the acylamino peptide ester may present problems. With methyl N-carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosinate the difficulty was overcome by saponifying the peptide ester. The ester group of ethyl phthaloylglycyl-L-leucinate was removed by acid hydrolysis.<sup>244</sup> Structural modification of the diphenylketene-p-tolylimine by introduction of solubilizing groups should eliminate some purification problems, as it has with the carbodiimides.<sup>213, 233</sup>

Acylated piperazinediones also possess a diacylimide structure. 1,4-Diacetyl-2,5-piperazinedione reacts with methyl and ethyl glycinate to give the corresponding aceturic esters;<sup>248</sup> the corresponding 1,4-bis-(N-phthaloylglycyl)-2,5-piperazinedione<sup>136</sup> has not been used for peptide synthesis.



from ethanol.

### 7.3.3. Amide Formation

A solution of one equivalent of ketenimine with one equivalent of an  $\alpha$ -acylamino acid or of the preformed adduct prepared from them is treated with one equivalent of amino acid or peptide ester in a solvent such as benzene, methylene dichloride, or tetrahydrofuran. The hydrochloride of the amino acid ester may be used if at least one equivalent of triethylamine is added. The reaction is usually complete after heating under reflux for 2 or 3 hours. However, with ethyl *p*-aminobenzoate a reaction time of 44 hours was necessary.<sup>244, 247</sup> If the  $\alpha$ -acylamino peptide ester precipitates from the reaction mixture it may be recovered by filtration and washed with water to remove triethylamine hydrochloride, if present. If the product does not precipitate, transfer to another solvent may be attempted or the crude reaction mixture may be employed in the next step.

## 7.4. Experimental Procedures

### 7.4.1. N-Phthaloylglycyldiphenylacetic Acid *p*-Toluide<sup>244</sup>

A solution of 2.0 g. (7.1 mmoles) of diphenylketene-*p*-tolylimine and 1.5 g. (7.1 mmoles) of phthaloylglycine in 35 ml. of benzene is heated under reflux until the yellow ketenimine color is discharged. The solution is then evaporated to dryness in vacuum and the solid residue, m.p. 168–170°, is recrystallized from hexane-acetone to yield 3.2 g. (92%) of adduct, m.p. 179.5–180.5°.

### 7.4.2. Ethyl Phthaloylglycylglycylglycinate<sup>244</sup>

To a solution of 1.0 g. (2.1 mmoles) of N-phthaloylglycyldiphenylacetic acid *p*-toluide in 10 ml. of methylene dichloride is added, with stirring, 0.4 g. (2.1 mmoles) of glycylglycine ethyl ester hydrochloride and 0.5 ml. (3.3 mmoles) of triethylamine. The mixture is stirred and heated for 9 hours, during which time the amount of suspended solid increases. The white solid is then separated by filtration, washed with water, and dried to give 0.35 g. (49%) of the tripeptide, m.p. 221–222°. Recrystallization from water raises the melting point to 225–226°.

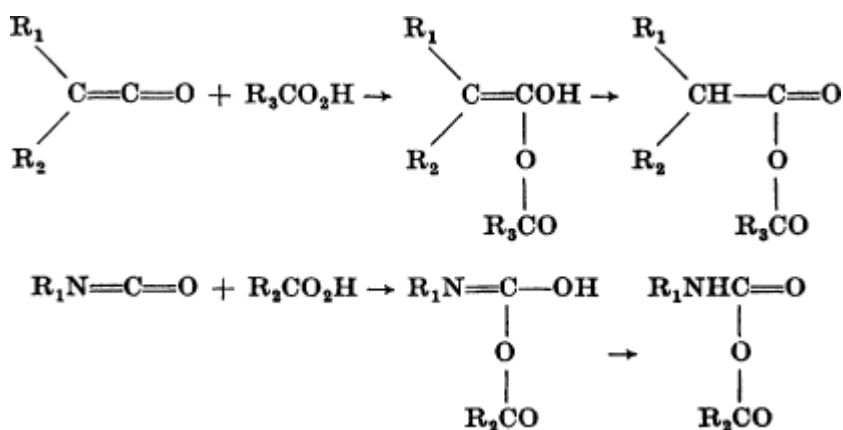
### 7.4.3. Ethyl Phthaloylglycyl-*p*-aminobenzoate<sup>244</sup>

To 15 ml. of methylene dichloride are added 1.09 g. (3.5 mmoles) of diphenylketene-*p*-tolylimine, 0.8 g. (3.9 mmoles) of phthaloylglycine and 0.6 g. (3.6 mmoles) of ethyl *p*-aminobenzoate. The mixture is heated under reflux for one hour and forty minutes, although the yellow ketenimine color is completely discharged after fifteen minutes. The solution is evaporated to dryness in vacuum and the solid residue recrystallized from benzene to give 0.95 g. (77%) of dipeptide, m.p. 204.0–205.5°.

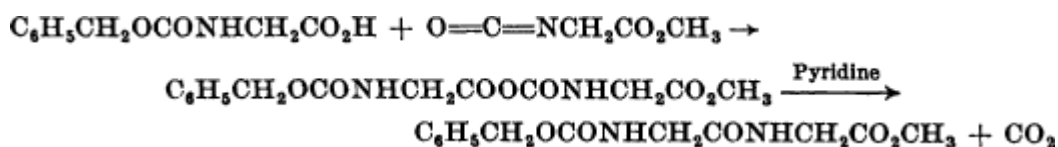
## 8. Ketenes and Isocyanates



Both ketenes and isocyanates react with carboxylic acids by 1,2 addition followed by rearrangement to mixed anhydrides.<sup>200</sup> However, these mixed anhydrides have not yet been used for peptide synthesis. With ketene the mixed anhydride is the same as that obtained from the more readily accessible acetyl chloride, and with diphenylketene the anhydride is that obtained more conveniently from diphenylacetyl chloride.

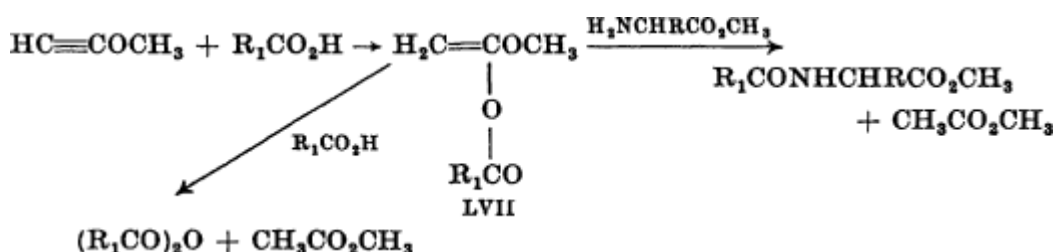


Acyl carbamates derived from isocyanates have been used for the synthesis of amides but not of peptides.<sup>251</sup> A useful peptide synthesis has been developed using certain isocyanates obtained from esters of amino acids. An acylamino acid and such an isocyanate react to give an anhydride which rearranges to a peptide.<sup>117, 252</sup> The rearrangement is base catalyzed.



## 9. Acetylenic Ethers

Organic acids add to acetylenic ethers to give intermediates LVII which behave as mixed anhydrides, for a second mole of acid may be added to give an anhydride and an alkyl acetate. The same products would result if the acid anion attacked the carbonyl group of the adduct.<sup>253, 254</sup>



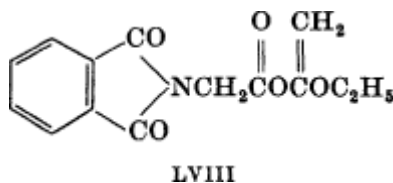
An amide would be expected as the product from the reaction of the adduct with an amine. Arens realized this expectation by preparing peptides from methyl ethynyl ether with esters of amino acids.<sup>255, 256</sup> The by-product is methyl acetate.

The method has been used to prepare di- and tri-peptides in which the acylating species have been glycine, alanine,  $\beta$ -alanine, valine, leucine, isoleucine, proline, S-benzylcysteine, phenylalanine,



tryptophan, tyrosine, lysine, and glutamic acid. Yields have ranged from 34% to 100%. No pure products could be isolated in attempts to prepare ethyl carbobenzyloxy-DL-serylglycinate or ethyl carbobenzyloxy-L-tryptophylglycinate.[257](#)

Phthaloylglycine reacts with glycine ester in water in the presence of ethyl ethynyl ether to give ethyl phthaloylglycylglycinate and a neutral product assigned structure LVIII. The latter product reacts with ethyl glycinate in dioxane at 50° to give 80% of ethyl phthaloylglycylglycinate.[258](#)



Although mercuric salts accelerate peptide synthesis with acetylenic ethers, less pure products are obtained than in their absence.[257](#)

In the synthesis of peptides by this method, racemization has been encountered but can be decreased considerably by the selection of suitable reaction conditions.[259](#) Carbobenzyloxyglycyl-L-phenylalanine reacts with ethyl glycinate hydrochloride in the presence of ethyl ethynyl ether in boiling ethyl acetate to give a product which is racemized to the extent of 45%. When ethyl glycinate is substituted for the hydrochloride, no racemization is observed in the product. However, the recovered carbobenzyloxyglycyl-L-phenylalanine is racemized to a slight extent. Carbobenzyloxyglycyl-L-phenylalanine and carbobenzyloxyglycyl-L-leucine are racemized by refluxing with ethyl ethynyl ether in ethyl acetate.[257](#)

Carbodiimides, ketenimines, and acetylenic ethers have all been used in the total synthesis of penicillin V. The carbodiimide method gave the best yield.[209](#) N,N'-Dicyclohexylcarbodiimide is commercially available and ketenimines are readily prepared by newly developed methods, but acetylenic ethers are not so accessible. The method of preparation of ethyl ethynyl ether appearing in Organic Syntheses[260](#) involves the reaction of sodium amide with chloroacetal. The reaction has been characterized as hazardous unless the directions are closely followed,[254](#) and it does not always give reproducible results. More satisfactory routes for the synthesis of ethyl ethynyl ether appear to be the treatment of chloroacetal with potassium persulfate and then potassium hydroxide,[261](#), [262](#) or the bromination of ethyl vinyl ether followed by dehydrobromination.[263](#), [264](#)

## 9.1. Experimental Conditions

Three general procedures for peptide synthesis with acetylenic ethers have been developed. In the first, an amino acid ester is powdered with a 5–10% excess of an  $\alpha$ -acylamino acid and four or five molar equivalents of an acetylenic ether added. If a spontaneous reaction does not occur, a drop of water or of N hydrochloric acid is added to initiate the reaction. This procedure is rapid, but it does not give the best yields.[257](#)

The second method differs only in that a solvent is employed. Ethyl acetate containing 0.5% water is greatly superior[257](#) to other solvents such as diethyl ether, chloroform, methylene dichloride, dimethylformamide, dioxane, nitromethane, and ethanol,[265](#), [266](#) which have been used. Acetonitrile is sometimes a good solvent. Anhydrous ethyl acetate requires longer heating than moist ethyl acetate and the products are less pure. The reaction mixture is heated under refluxing conditions until solution occurs, but not longer than 3 hours. Closed reaction vessels have been used in some instances because of the low boiling point of the acetylenic ether.

When racemization is a problem, a third method is employed. The free amino acid ester is heated under

reflux with a slight excess of  $\alpha$ -acylamino acid and four to five equivalents of ethyl ethynyl ether in moist ethyl acetate for  $\frac{11}{2}$  to 2 hours.

## 9.2. Experimental Procedures

### 9.2.1. Benzyl Carbobenzyloxy-L-valyl-L-tyrosyl-L-prolinate<sup>257</sup>

A mixture of 10.4 g. of carbobenzyloxy-L-valyl-L-tyrosine, 5.8 g. of L-proline benzyl ester hydrochloride, and 7 g. of ethyl ethynyl ether in 200 ml. of moist ethyl acetate (5% water) was heated under reflux for  $\frac{21}{2}$  hours. The mixture was cooled for 18 hours and filtered to give 8.9 g. (61%) of carbobenzyloxytripeptide ester, m.p. 186–188°,  $[\alpha]_D^{21.5} -40.6^\circ$  (c = 1%, pyridine).

### 9.2.2. Ethyl N-Carbobenzyloxy-S-benzyl-L-cysteinylglycinate<sup>266</sup>

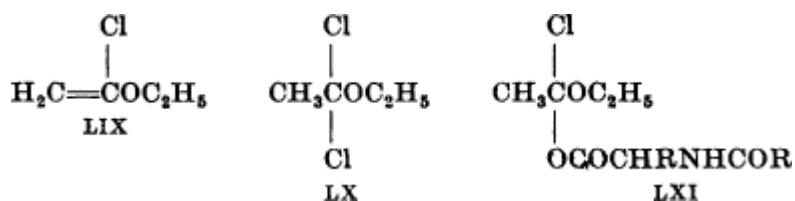
An ethyl acetate solution of N-carbobenzyloxy-S-benzyl-L-cysteine, ethyl glycinate, and ethyl ethynyl ether in the molar ratio of 1:1:2 was heated at 60° for 3 hours. The reaction mixture was then washed successively with 2N hydrochloric acid, water, 2N sodium carbonate, and water. The ethyl acetate solution was dried and concentrated under reduced pressure, and the residue crystallized from ethyl acetate and petroleum ether to give 90% of product, m.p. 98°,  $[\alpha]_D^{20} -26.5^\circ$  (c = 6%, glacial acetic acid).

### 9.2.3. Cyclo-glycyl-L-leucylglycylglycyl-L-leucylglycyl<sup>242</sup>

To a solution of 500 mg. of glycyl-L-leucylglycylglycyl-L-leucylglycine in 500 ml. of methanol at 20° was added 1.75 ml. of ethyl ethynyl ether. The reaction mixture was allowed to stand for 1 week at room temperature and was then heated and stirred for 3 hours at 40–45°. The methanol solution was concentrated in vacuum to a small volume and diluted with 15 ml. of water. The white crystalline precipitate that separated on standing was collected and recrystallized from hot water to give 52 mg. of material, dec. > 320°. It was insoluble in 2N hydrochloric acid or sodium hydroxide as well as in most organic solvents, and it gave a negative ninhydrin test. The yield of cyclohexapeptide monohydrate was 11.2%.

## 10. Ethyl $\alpha$ -Chlorovinyl Ether and $\alpha,\alpha$ -Dichlorodiethyl Ether

An  $\alpha$ -acylamino acid and the ester of an amino acid hydrochloride will react in the presence of ethyl  $\alpha$ -chlorovinyl ether (LIX) or  $\alpha,\alpha$ -dichlorodiethyl ether (LX) to give an acyldipeptide ester, hydrogen chloride, and ethyl acetate.<sup>267</sup>



The reaction is believed to proceed through the hypothetical intermediate LXI which decomposes to give the  $\alpha$ -acylamino acid chloride, the active acylating species. The acid chloride may be isolated if the amino acid ester hydrochloride is not added to the reaction mixture.

The requisite  $\alpha$ -chloro ethers LIX and LX are obtained by addition of one or two equivalents of hydrogen chloride, respectively, to ethyl ethynyl ether. In general, better yields result and shorter reaction times are required with the dichloro ether LX than with the monochloro ether LIX. When using the monochloro ether superior results are obtained if the reaction mixture is allowed to stand at room temperature overnight before heating under reflux. For example, ethyl carbobenzyloxyglycylglycinate was prepared in 60% yield when the reactants were heated immediately after mixing, and in 91% yield when they were allowed to stand at room temperature before heating. At room temperature the hydrogen chloride liberated during peptide synthesis probably converts some of the  $\alpha$ -chlorovinyl ether to the dichloro ether, so that part of the reaction then proceeds via the dichloro ether. The correlation between reaction time and refractive index of the ether supports this proposition.

## 10.1. Scope and Limitations

Both the carbobenzyloxy and phthaloyl derivatives of glycine, L-alanine, L-leucine, L-phenylalanine, and carbobenzyloxy-L-valine have been used as the acid component. The amine component has been ethyl glycinate, ethyl L-phenylalaninate, and ethyl glycylglycinate. Satisfactory yields with carbobenzyloxy amino acids were obtained even though their acid chlorides decompose when heated. It is unlikely, however, that either carbo-t-butoxy or trityl amino acids will survive an attempt at peptide synthesis using the  $\alpha$ -chloro ether method.

The reaction of an  $\alpha$ -acylamino acid chloride with the ester of an amino acid hydrochloride by heating under refluxing conditions in ethyl acetate appears to be general.<sup>267</sup>

Although optically pure carbobenzyloxy and phthaloyl dipeptide esters were prepared by the  $\alpha$ -chloro ether procedure, racemization would probably be encountered if an acyldipeptide were used as the acid component.

## 10.2. Experimental Conditions

A suspension of one equivalent of the ester of an amino acid hydrochloride in ethyl acetate is allowed to react with 1.3 molar equivalents of the carbobenzyloxy- or phthaloyl-amino acid and three to four molar equivalents of ethyl  $\alpha$ -chlorovinyl ether for 12 to 24 hours at room temperature, and is then heated under refluxing conditions. Generally completion of the reaction is indicated by formation of a clear solution. If solution does not occur after 9 hours, the reaction is stopped.

The procedure using  $\alpha,\alpha$ -dichlorodiethyl ether differs only in the shorter reaction time,  $\frac{1}{2}$  to  $\frac{11}{2}$  hours.

The reaction may be conducted without a solvent by intimately mixing equivalent amounts of the acid and amino acid ester hydrochloride, adding three to four equivalents of  $\alpha$ -chlorovinyl ether and heating to

80–110° for 10 to 20 minutes. A vigorous reaction occurs. Ethyl acetate is then added and the mixture heated under refluxing conditions for  $\frac{1}{2}$  to 1 hour.

The product is isolated by washing the reaction mixture with water and with aqueous potassium carbonate, drying, diluting with hexane, and chilling.

## 11. $\alpha$ -Acylamino Acid Phenolic Esters

Several phenolic esters of phthaloylglycine have been condensed with ethyl glycinate in boiling benzene to give ethyl phthaloylglycylglycinate.[268](#)

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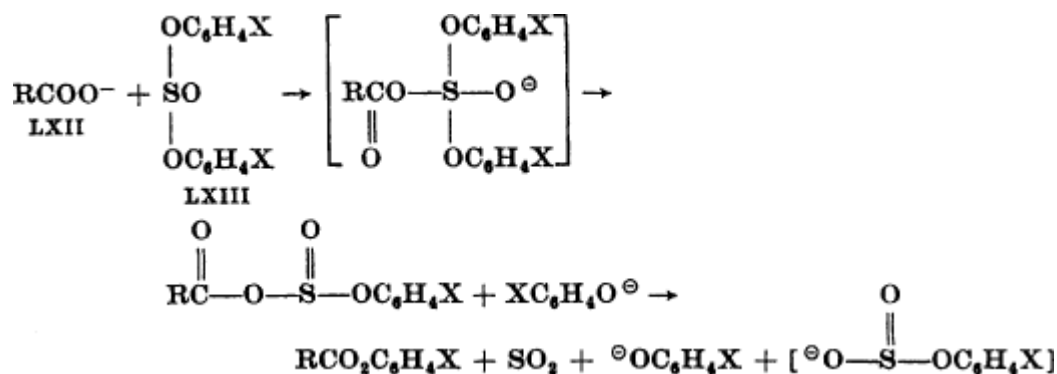
### 11.1. Scope and Limitations

Two methods of synthesis of phenyl esters of  $\alpha$ -acylamino acids have been used, namely the reaction of a mixed anhydride of an  $\alpha$ -acylamino acid with a phenol and the reaction of an  $\alpha$ -acylamino acid with an acylated phenol. The first procedure adds an extra step since the  $\alpha$ -acylamino acid anhydride could itself be used as an acylating agent.

Acid chlorides,[269](#), [270](#) sulfuric acid anhydrides,[38](#) mixed carbonates,[269](#) phosphorus oxychloride,[37](#) thioglycolic esters,[271](#) and dicyclohexylcarbodiimide[272](#), [273](#) have been used to couple the  $\alpha$ -acylamino acid and phenol. However, an attempt to condense an  $\alpha$ -acylamino acid with salicylamide using dicyclohexylcarbodiimide failed.[274](#) There are several advantages in the use of phenolic esters for forming peptide bonds: (1) the phenolic esters, particularly the p-nitrophenyl esters, are stable crystalline compounds which may be stored until needed; (2) the phenyl esters permit the use of the free amino acid rather than its ester and thus eliminate the need for purification of the product by countercurrent distribution; and (3) the group protecting the  $\alpha$ -amino function can be removed from the peptide without affecting the phenolic ester. The last advantage is especially useful in the synthesis of cyclic peptides. The conversion of  $\alpha$ -acylamino acids to phenolic esters with carbodiimides avoids contamination of the final peptide with the N-acylurea which might be formed if the carbodiimide were used directly for peptide synthesis.[272](#)

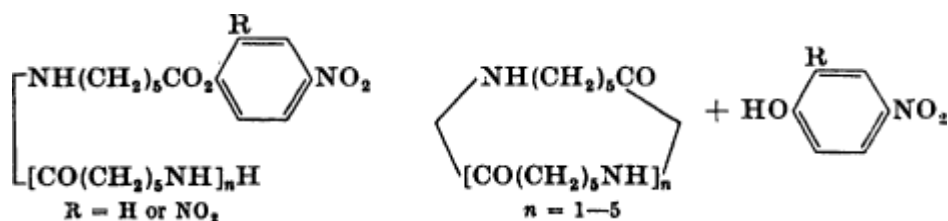
The  $\alpha$ -acylamino acid may be converted to a phenolic ester in one step by reaction with a triaryl phosphite[275](#), [276](#) or a diaryl sulfite.[276-278](#) It is believed that the reaction between an acid such as LXII and diphenyl sulfite LXIII proceeds as shown. This formulation accommodates the observation that carbobenzyloxyglycine and diphenyl sulfite in the presence of a five-fold excess of p-nitrophenol in pyridine give 83% of p-nitrophenyl carbobenzyloxyglycinate and 8% of phenyl carbobenzyloxyglycinate.[276](#) In the accompanying formulas (see equation at top of p. 224) X is preferably a para nitro group, but it may be a methylsulfonyl, cyano, or other negative substituent.

Negatively substituted symmetrical triaryl phosphites react with two moles of an  $\alpha$ -acylamino acid to give the acyl ester and presumably a monoaryl phosphorous ester.[276](#)



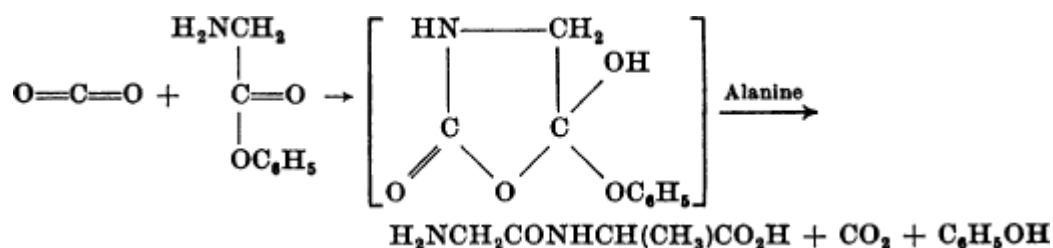
It was noted previously (p. 223) that phenolic esters are particularly useful for the synthesis of cyclic peptides. Gramicidin S was synthesized from trityl-L-valyl-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolyl-L-valyl-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline by conversion to the p-nitrophenyl ester with di-p-nitrophenyl sulfite, detritylation with trifluoroacetic acid, cyclization in hot pyridine, and detosylation with sodium in liquid ammonia.<sup>278-281</sup> A number of cyclohexapeptides have been similarly prepared.<sup>146, 149</sup> The tendency of peptides having an odd number of amino acids to double on cyclization was utilized in synthesizing ditosyl gramicidin S in 31% yield from L-valyl-S-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline p-nitrophenyl ester.<sup>282</sup>

A series of cyclopolycaprolactams was prepared from the nitrophenyl and dinitrophenyl esters of the peptides by warming them in dimethylformamide or in pyridine.<sup>273</sup>



Carbobenzyloxy-S-benzyl-L-cysteine p-nitrophenyl ester reacts with L-tyrosine in aqueous tetrahydrofuran to give 9% of acyldipeptide, whereas the reaction with ethyl L-tyrosinate followed by hydrolysis gives the same acyl dipeptide in 83% yield. Phthaloylglycine p-nitrophenyl ester reacts with glycine in aqueous dimethylformamide to give 74% of phthaloylglycylglycine; this is more typical of the yields ordinarily obtained.<sup>269</sup> Substitution of glycine amide for glycine in the above reaction leads to a 75–80% yield of phthaloylglycylglycylamide.<sup>283</sup>

Glycine phenyl ester reacts with alanine (configuration not specified) in the presence of bicarbonate, but not in the presence of pyridine. An oxazolidone intermediate was postulated to explain these results.<sup>270</sup>



The formation of 2,4-dinitrophenylamino acids from 2,4-dinitrofluorobenzene and the amino acid in aqueous ethanol in the presence of sodium bicarbonate is accompanied by 2,4-dinitrophenyl dimers and higher polymers as by-products.<sup>284</sup> These results suggest that the 2,4-dinitrophenylamino acids LXIV form with 2,4-dinitrofluorobenzene a mixed anhydride LXV which reacts further with another molecule of amino acid. With  $\epsilon$ -aminocaproic acid, evidence for the formation of a dinitrophenyl pentapeptide was





## 11.3. Experimental Procedures

### 11.3.1. p-Nitrophenyl Carbobenzyloxyglycinate<sup>276</sup>

A solution of 209 mg. (1 mmole) of carbobenzyloxyglycine in 2 ml. of ethyl acetate and 0.61 ml. (2 mmoles) of pyridine was treated with 324 mg. (1 mmole) of di-p-nitrophenyl sulfite. The solution was held at 50° for 3 hours, cooled to 0°, washed with 2N HCl, saturated aqueous sodium bicarbonate, and water, dried, and the solvent evaporated to give a crystalline residue (328 mg., m.p. 119–121°) which was recrystallized from ethanol to give 315 mg. (95%) of the ester, m.p. 124–125°.

### 11.3.2. Cyclo-glycylglycyl-DL-phenylalanyl-glycylglycyl-DL-phenylalanyl<sup>149</sup>

A solution of 4.1 g. of the p-methanesulfonylphenyl ester of glycylglycyl-DL-phenylalanyl-glycylglycyl-DL-phenylalanine hydrochloride in 80 ml. of dimethylformamide and 4 ml. of acetic acid was added dropwise to 820 ml. of pyridine at 95° during 5 hours. The reaction mixture was stirred for an additional 2 hours at the same temperature and the solvents were then removed in vacuum. The residue was dissolved in 1:1 methanol-water and passed through strongly acidic and basic ion exchange resins. The columns were washed with the same solvent, and the combined eluates and washings were concentrated in vacuum to dryness. The residue was triturated with acetone and filtered to give 380 mg. (13%) of product. The crude product was dissolved in a large volume of aqueous methanol, concentrated, and allowed to crystallize. It was recrystallized from a small volume of acetic acid to give colorless needles, m.p. about 300° with decomposition.

### 11.3.3. N-Carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine<sup>269</sup>

To a solution of 0.47 g. (0.001 mole) of the p-nitrophenyl ester of N-carbobenzyloxy-S-benzyl-L-cysteine in 3 ml. of tetrahydrofuran were added 0.25 g. (0.011 mole) of ethyl L-tyrosinate hydrochloride and 0.15 ml. of triethylamine. The solution soon became yellow. On the next day, 20 ml. of water was added. The oil that precipitated was dissolved in 1 ml. of 2N aqueous sodium hydroxide and 1 ml. of methanol and acidified with N hydrochloric acid after 1 hour. The precipitate was dissolved in aqueous sodium bicarbonate, filtered, and again acidified with N hydrochloric acid. The product, 0.43 g. (84.5%), m.p. 196–198°, was recrystallized from ethanol to give 60% over-all of the acyl peptide, m.p. 197–200°; [ $\alpha$ ]<sub>D</sub>-6.4[c = 1.4% (0.5 N-KHCO<sub>3</sub>)].

### 11.3.4. Phthaloylglycylglycinamide<sup>283</sup>

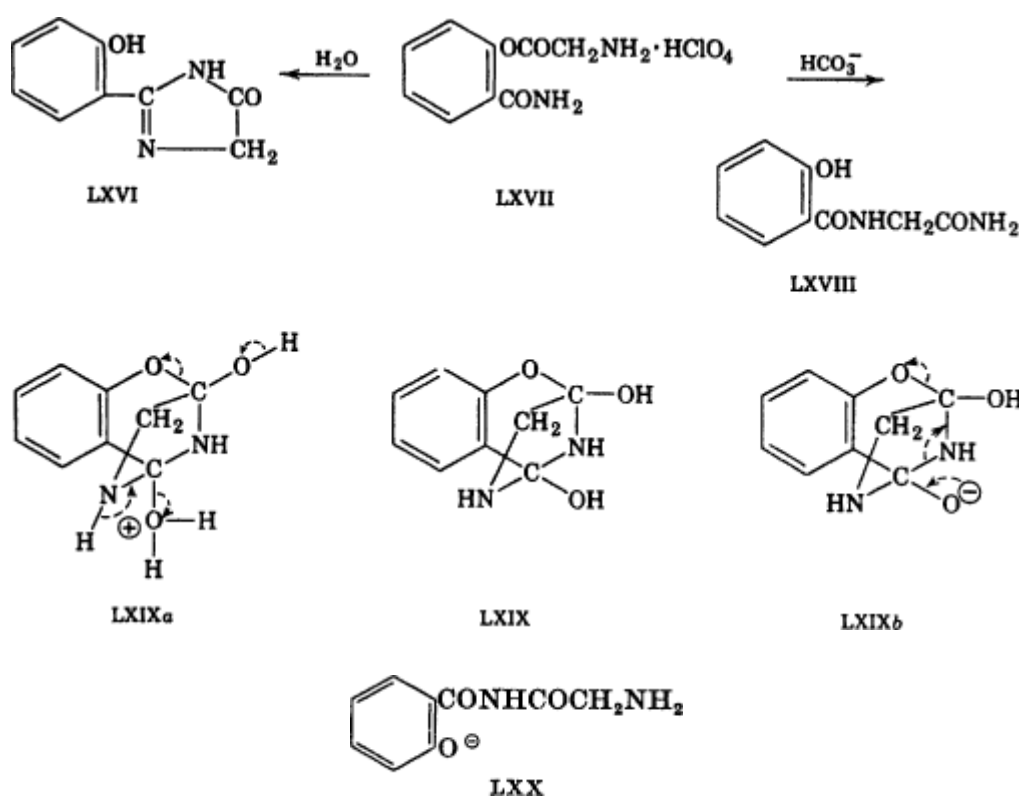
To a solution of 1.63 g. (0.005 mole) of p-nitrophenyl phthaloylglycinate in 10 ml. of dimethylformamide were added 0.7 ml. (0.005 mole) of triethylamine and 0.55 g. (0.005 mole) of glycylglycinamide hydrochloride. The mixture was heated for 50 minutes on a steam bath, cooled, and 30 ml. of water was added to precipitate the product which was collected, washed with water, and dried to give 0.95 g. (75%) of acyldipeptide amide, m.p. 235° with decomposition. Recrystallization of 0.15 g. of this material from 45 ml. of ethanol gave 0.12 g. of amide, m.p. 250–252°.

# 12. Brenner's Method

An interesting method of forming peptide bonds was described by Brenner in 1955,[285-287](#) and a summary of the work has appeared.[288](#) (See also ref. [149a](#), pp. 157–261.)

The perchlorate of O-glycylsalicylamide (LXVII) rearranges in aqueous potassium bicarbonate to salicylglycinamide (LXVIII). The same perchlorate LXVII on solution in water rearranges to the imidazolone LXVI. To account for these results, the very plausible assumption was made that the amino groups reacted with sterically adjacent carbonyl groups to give a tricyclic intermediate LXIX.

The rearrangement in basic solution may proceed via bicyclic intermediates.[141](#), [289](#) Ring closure between the amide nitrogen and ester carbonyl components of LXVII followed by scission of the labile phenolic oxygen bond would lead to a diacylimide LXX, a type which Wieland<sup>290</sup> has shown rearranges further to give, in this case, the observed salicylglycinamide. Later work has given results difficult to reconcile with this proposed mechanism.[288](#), [291](#)

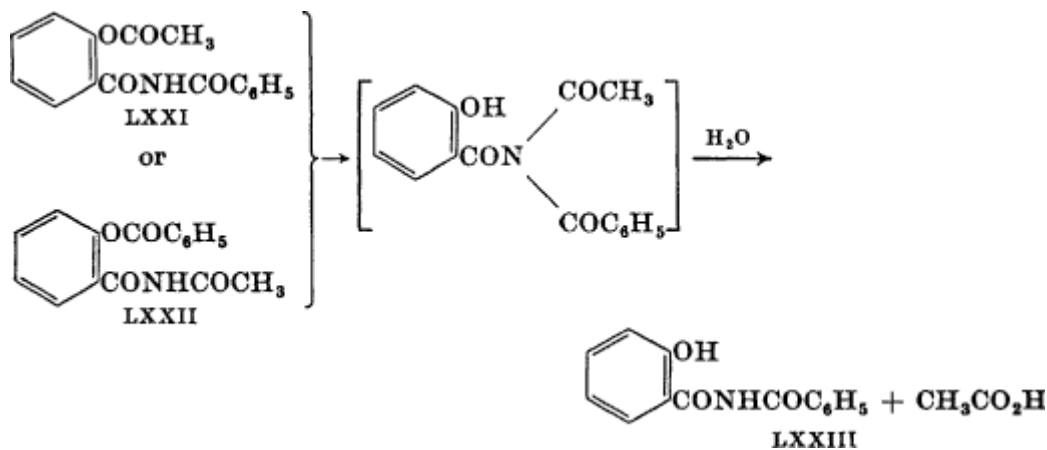


A related rearrangement is that of O-acetyl-N-benzoylsalicylamide (LXXI) and O-benzoyl-N-acetylsalicylamide (LXXII) to N-benzoylsalicylamide (LXXII) on treatment with aqueous base.[292](#) (Equations on p. 229.)

## 12.1. Scope and Limitations

The most serious limitations of the Brenner method for synthesizing peptides is the difficulty of removing the salicyloyl group from the peptide. It has been accomplished by treatment with sodium in liquid ammonia, but the yields, presumably low, were not recorded.[293-295](#)



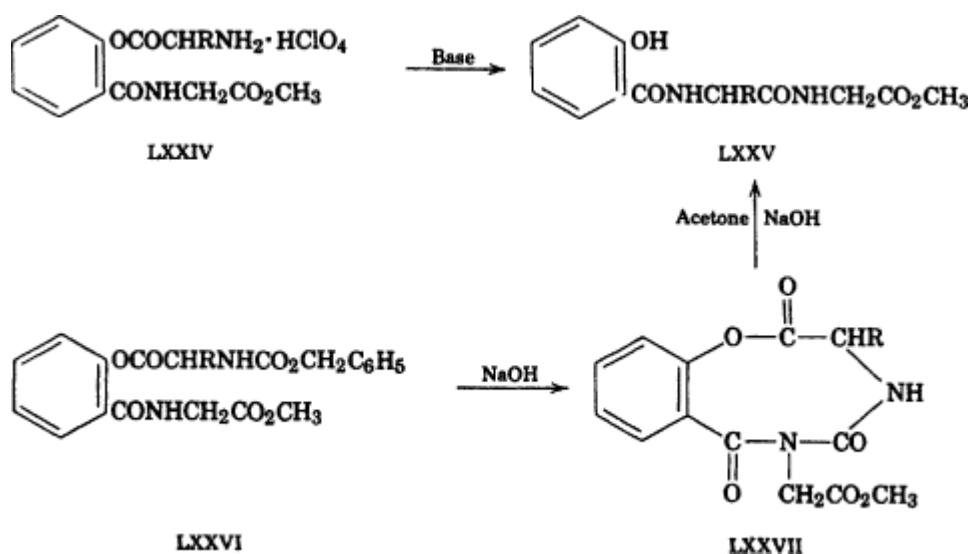


The reaction appears to be general for O-aminoacylsalicylic acids. The presence of the benzene ring is necessary to bring the reacting groups into spatial proximity so that reaction will occur under mild conditions. The reaction failed with  $\beta$ -hydroxybutyric acid, serine, and cysteine derivatives. However, the use of potassium t-butoxide led to successful rearrangement of derivatives of serine and threonine.[296](#)

The rearrangement may be repeated to lengthen the peptide chain by one amino acid residue at a time. Optically active methyl salicylglycyl-L-phenylalanyl-glycinate was prepared in this way.[293](#), [294](#), [297](#)

O- $\alpha$ -Aminoacylsalicylic acids can be employed in place of salicylamides. Thus O-glycylsalicylic acid[298](#), [299](#) and O-L-phenylalanylsalicylic acid[298](#) rearrange in neutral or weakly acid media at room temperature to give the salicyloylamino acid. Since no racemization occurred with L-phenylalanine, it was concluded that an oxazolone was not an intermediate. In contrast to the salicylic acid and amide derivatives, the ester derivatives do not undergo the desired rearrangement. Thus methyl O-glycylsalicylate does not rearrange to salicyloylglycine but, instead, gives a diketopiperazine.

If, in place of an O-aminoacylsalicyloylamide LXXIV the corresponding carbobenzyloxy derivative LXXVI is employed, rearrangement proceeds by way of a nine-membered cyclic acylurea LXXVII. The urea is formed in variable yield by treatment of the carbobenzyloxy derivative LXXVI with aqueous alkali in the presence of ethyl acetate. The yield would probably be improved if sodium ethoxide were used for the cyclization reaction. The cyclic urea LXXVII reacts with aqueous sodium hydroxide in acetone at room temperature to give the salicyloyl dipeptide ester LXXV. When R is benzyl, the urea LXXVII gives 97% of salicyloyl-DL-phenylalanyl-glycine methyl ester (LXXV).[293](#), [294](#)



Imidazolones become the major product from O-aminoacylsalicyloylamides below pH 8. The tendency toward imidazolone formation decreases with O-aminoacylsalicyloylamino acid esters and is less with O-aminoacylsalicyloyl dipeptides.[288](#)

## 12.2. Experimental Conditions

The rearrangement of an O-aminoacylsalicyloylamino acid ester LXXIV to the salicyloyl peptide ester LXXV is brought about by bases such as sodium bicarbonate, sodium carbonate, or sodium hydroxide in water, alcohol, or phenol, or by tertiary organic bases such as triethylamine, N-alkylpiperidine, or pyridine preferably in solvents such as chloroform, dioxane, tetrahydrofuran or dimethylformamide. Triethylamine is commonly used and gives satisfactory results in water, methanol, or chloroform.<sup>293, 294</sup> However, triethylamine in tetrahydrofuran leads to the formation of imidazolones as by-products.<sup>288</sup>

The reaction is usually conducted at room temperature for 1 to 14 hours. The reaction mixture is then evaporated to dryness in vacuum and the residue partitioned between ethyl acetate and dilute hydrochloric acid. The ethyl acetate layer is washed with dilute aqueous potassium bicarbonate, dried, filtered, and evaporated to give the salicyloyl dipeptide ester.

The free peptide may be obtained from the salicyloyl peptide in unstated yields by treatment with sodium in liquid ammonia. Thus salicyloylglycyl-DL-phenylalanyl-glycine gave glycyl-DL-phenylalanyl-glycine, and DL-phenylalanyl-glycine was obtained from its salicyloyl derivative.<sup>293, 294</sup>

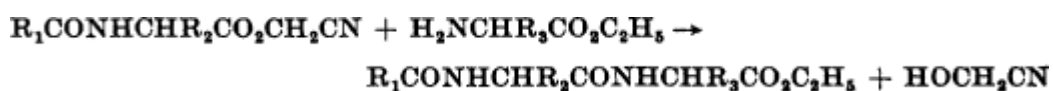
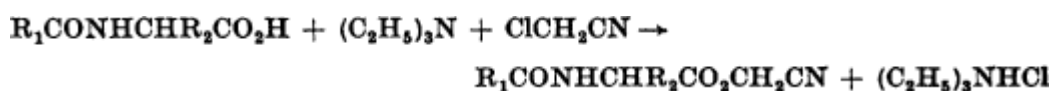
The requisite starting materials are prepared by converting salicylic acid hydrazide to the azide, coupling with an amino acid, and esterifying with methanol and hydrogen chloride to give the salicyloylamino acid ester. This product is then acylated on oxygen with a carbobenzyloxyamino acid chloride.<sup>293</sup> Use of a carbobenzyloxyaminoacyl alkyl carbonate results in a competing reaction between the phenolic hydroxyl and the alcoholic hydroxyl derived from the mixed carbonate. This side reaction is not entirely suppressed by the addition of excess tertiary base. The mixed anhydride derived from phosgene and a carbobenzyloxyamino acid proved satisfactory for acylation of the phenolic hydroxyl at  $-70^\circ$ ,<sup>53</sup> and dicyclohexylcarbodiimide was used to couple carbobenzyloxyphenylalanine with salicylic acid amide in 85% yield.<sup>212</sup> The optical configuration was not specified.

The removal of the carbobenzyloxy group has been accomplished by hydrogenolysis with a palladium catalyst. Phosphonium iodide has been used to decarboxylate thiosalicylic acid derivatives.<sup>293</sup> In both cases anhydrous hydrogen bromide in acetic acid should be equally satisfactory.<sup>26</sup>

## 13. Cyanomethyl Esters

In addition to phenolic esters, others commonly referred to as activated esters have been used in peptide synthesis. Of these, the cyanomethyl esters are by far the most useful.

The reactions involved in the preparation of an activated ester and its use in the formation of a dipeptide are illustrated below for the cyanomethyl ester of an  $\alpha$ -acylamino acid.



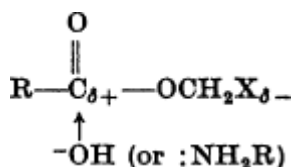
Curtius prepared carboxymethyl hippurate in 1888,<sup>300</sup> but the first use of activated esters in peptide synthesis was described in a series of papers beginning in 1954 by Schwyzer, Iselin, Feurer, and

co-workers.

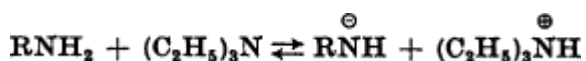
## 13.1. Mechanism

Since aminolysis or basic hydrolysis of esters involves nucleophilic attack by an amino or hydroxyl group at the carbonyl carbon atom, factors which tend to make this carbon atom more positive will favor such attack.

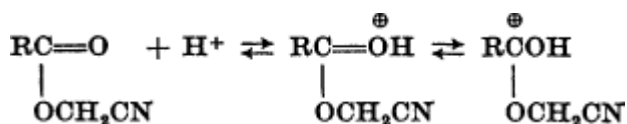
The synthesis of penicillin initiated research in this area, and seven classes of activated esters of the type  $\text{RCO}_2\text{CH}_2\text{X}$  where X is acyl, carbamyl, acyloxy, carbalkoxy, cyano, alkoxy, or acyloxy were described.<sup>301</sup> These esters were studied because of their ease of hydrolysis but were not used for aminolysis. The presence of X favors nucleophilic attack and helps to stabilize the anion  $\text{O}^-\text{CH}_2\text{X}$  which is formed in the reaction.<sup>302</sup>



Studies of the rate of ammonolysis of methyl phenylacetate led to the conclusion that two reactions occurred, an uncatalyzed reaction of ester and ammonia and a base-catalyzed reaction of ester with amide ion.<sup>303</sup> These results suggested that the addition of a strong base to the activated ester and amine would catalyze the formation of the amide bond by increasing the concentration of amide ions.<sup>304</sup> This supposition was confirmed when triethylamine was used to catalyze the reaction between cyanomethyl hippurate and aniline, a relatively weak base; the yield of amide was improved. Triethylamine was without effect when diethylamine, a much stronger base, was substituted for aniline. Sodium methoxide resulted in trans-esterification.



Addition reactions to a carbonyl group may also be acid catalyzed, since the proton on oxygen increases the positive charge on the carbon atom.<sup>305</sup>



Acetic acid catalyzes the reaction between amines and activated esters,<sup>304</sup> and acetic acid was employed as a catalyst in much of the later work on the synthesis of peptide intermediates.

Cyanomethyl hippurate is hydrolyzed 6.8 times as fast as the methyl ester but is aminolyzed by benzylamine 740 times as fast.<sup>306</sup>

## 13.2. Scope and Limitations

### 13.2.1. Nature of the Ester

The most reactive esters studied are those derived from chloroacetonitrile or bromomalonic ester. The difference in reaction rate between a methyl ester and a cyanomethyl ester is considerable; methyl hippurate reacts with benzylamine to give only a 16% yield of amide after 11 days, but under the same conditions the cyanomethyl ester gives an 82% yield in half an hour.[302](#)

The cyanomethyl ester was preferred to all others investigated.[307](#), [308](#) Amide formation was slower with carbobenzyloxyamino acid esters derived from methyl or ethyl chloroacetate or p-nitrobenzyl chloride. The carboxymethyl ester gave good results at high concentrations of reactants, but was less satisfactory than the cyanomethyl ester in more dilute solutions.[302](#) The preparation of the dicarbethoxymethyl ester was unsatisfactory because of the formation of ethylenetetracarboxylic ester as a major by-product. The methoxymethyl ester could be prepared only in poor yield, and the methoxymethyl alcohol liberated during aminolysis reacted quantitatively with one equivalent of the amine. The relatively poor results observed in the reaction of the acetyl ester with amines was probably due to some Schiff base formation. The p-nitrobenzyl ester reacted rather slowly with benzylamine, and a satisfactory yield of amide (65%) could be obtained only by heating the reaction mixture for 2 hours at 77°.  $\beta$ -Diethylaminoethyl hippurate methobromide was rapidly aminolyzed, but the ester is difficult to prepare.[302](#) Tetrahydropyranyl esters were less active than cyanomethyl esters and tended to decompose on standing. Moreover, an additional asymmetric center is created upon the formation of a tetrahydropyranyl ester. Reaction of the tetrahydropyranyl ester with an amine liberates a mole of 5-hydroxypentanal, which combines with one equivalent of amine.[309](#)

Propargyl phthaloylglycinate has been condensed with ethyl glycinate.[310](#)

### 13.2.2. Nature of the Amine

The reaction of the activated ester with an amine to form an amide is dependent not only upon the nature of the ester, including the component acylamino acid, but also upon the nature of the amine. Primary aliphatic amines react with cyanomethyl esters at room temperature, aromatic primary amines require a higher temperature, and secondary aliphatic amines react with difficulty.[304](#), [307](#) Although the yields are generally quite good, the reaction may be slow with the more complex amines. Glycine cyanomethyl ester reacts with amino acid esters in 1 to 5 hours,[307](#) whereas some amino and peptide cyanomethyl esters are allowed to react for 4 days.[311](#) In the synthesis of peptides the amine component was usually an ester of glycine, leucine, isoleucine, or tyrosine[211](#), [304](#) and yields were generally 70%. Where the amine component was a peptide ester, yields of 43% to 96% were obtained.[311](#)

The amine function may be part of the same peptide bearing the cyanomethyl group, thus permitting the synthesis of cyclic peptides. Trityldiglycylglycine was converted to the cyanomethyl ester in 84% yield. After detritylation with hydrogen chloride the cyanomethyl ester of triglycine hydrochloride was dissolved in dimethylformamide and the solution added during a period of 5 hours to pyridine at 95° to give 36% of cyclohexaglycyl. Under similar conditions the cyanomethyl ester of tetraglycine gave 12.5% of cyclotetraglycyl.[312](#), [313](#) The cyanomethyl ester of glycyl-DL-phenylalanyl-glycine was converted to cyclo-glycylglycyl-DL-phenylalanyl-glycylglycyl-DL-phenylalanyl in 20% yield.[149](#)

The removal of a carbobenzyloxy group from carbobenzyloxylated tripeptide cyanomethyl esters with hydrogen bromide in glacial acetic acid, without the expected conversion of the nitrile to an amide,[315](#) has been reported.[314](#)

### 13.2.3. Nature of the $\alpha$ -Acylamino Acid

Limited data are available concerning the  $\alpha$ -acylamino acids. Cyanomethyl carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosinate (in which the phenolic group on the tyrosine residue was not protected) reacted with ethyl L-isoleucinate to give 58% of the acylated peptide.<sup>306, 311</sup> Even more noteworthy is the coupling of cyanomethyl tosyl-L-glutamate with ethyl glycinate in 90% yield;<sup>304</sup> in a patent application the same reaction is reported to give a 72% yield based on the cyanomethyl ester or a 49% yield based on tosyl-L-glutamine.<sup>316</sup> Cyanomethyl phthaloylglycinate is noticeably less reactive than cyanomethyl carbobenzyloxyglycinate.<sup>317</sup>

### 13.2.4. Racemization

Cyanomethyl carbobenzyloxy-L-leucinate was coupled with ethyl glycinate, and the product decarbobenzoylated to give ethyl L-leucylglycinate. This, in turn, was coupled with cyanomethyl hippurate to give ethyl hippuryl-L-leucylglycinate. After hydrolysis the leucine was isolated as its naphthalene  $\beta$ -sulfonate with no evidence of racemization.<sup>318</sup> No racemization, however, should have been expected in this reaction.

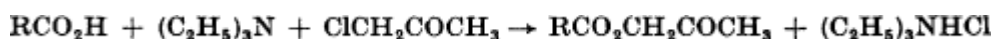
Carbobenzyloxy-S-benzyl-L-cysteine, triethylamine, and chloroacetonitrile at room temperature gave 82% of the optically active ester. However, at higher temperatures partial or complete racemization was noticed.<sup>311</sup> Since the optically active esters show no tendency to racemize on recrystallization, it was concluded that the reaction temperature was responsible for the racemization.

## 13.3. Experimental Conditions

The cyanomethyl esters have a distinct superiority over other activated esters for peptide synthesis.

### 13.3.1. Preparation of the Ester

The salt is prepared in situ by the addition of trimethylamine to a solution of the  $\alpha$ -acylamino acid and then allowed to react with a halide such as chloroacetone, ethyl chloroacetate, chloroacetonitrile, phenacyl bromide, or p-nitrobenzyl bromide,<sup>319</sup> to give the ester.



Trifluoroethoxy trifluoroacetylglucinate, prepared from trifluoroacetylglucyl chloride and 2,2,2-trifluoroethoxymagnesium iodide, reacted with ethyl glycinate to give 94% of ethyl trifluoroacetylglucylglycinate.<sup>320</sup>

Cyanomethyl carbobenzyloxyglycinate has been prepared by two methods.<sup>321</sup> In the first, carbobenzyloxyglycine was heated under reflux in ethyl acetate with one equivalent of triethylamine and a 50% excess of chloroacetonitrile for 3 hours to give 83% of the ester. Cyanomethyl hippurate was prepared in other solvents in a similar fashion; the yield was 80% in ethyl acetate, 83% in acetone, 80% in benzene, 70% in acetonitrile, and 75% in dimethylformamide.<sup>316</sup> The second method consisted in

covering the carbobenzyloxyglycine with a 50% excess of triethylamine and three equivalents of chloroacetonitrile. After the initial exothermic reaction had subsided, the mixture was heated at 70° for  $\frac{1}{2}$  hour. This procedure gave a 94% yield.[321](#) The ester was isolated by removing the solvent in vacuum, taking up the residue in ethyl acetate, and washing the solution with dilute hydrochloric acid, aqueous sodium bicarbonate, and water. Removal of the solvent left the ester, which is readily recrystallized.

In general, the cyanomethyl esters of  $\alpha$ -acylamino acids may be prepared in yields of 60–95% under mild conditions, and the removal of by-products is a simple matter. Solid cyanomethyl esters usually crystallize well;[307](#), [308](#), [316](#) the liquid esters are distillable.[302](#), [316](#), [321](#) The esters can be stored until needed.[308](#)

The reaction of 2-phenyl-4-bromo-5-oxazolone with ethyl glycolate gave (after treatment with water to replace bromine by hydroxyl) the carbethoxymethyl ester of  $\alpha$ -hydroxyhippuric acid. The activated ester reacted with ethyl glycinate and with ethyl phenylalaninate to form the peptide derivatives.[322](#)

### 13.3.2. Formation of the Amide Bond

The best solvent for amide bond formation is absolute ethyl acetate. Hydroxylated solvents give low yields, and the reaction is relatively slow in benzene, chloroform, dioxane, and acetonitrile. Ethylene glycol, which normally catalyzes the aminolysis of an ester, decreases the aminolysis rate of cyanomethyl hippurate.[302](#) Under otherwise identical conditions, N-benzylhippuramide was prepared from cyanomethyl hippurate in 82% yield in ethyl acetate, 60% yield in methanol, 56% yield in 1:1 ethanol-water, and 74% yield in 2:3 dimethylformamide-water.[316](#)

Better results are obtained when concentrated solutions are used for peptide bond formation.[302](#) For example, cyanomethyl hippurate reacted with an equivalent amount of benzylamine in ethyl acetate in  $\frac{1}{2}$  hour at room temperature to give 82% of amide when the cyanomethyl ester was present in a concentration of 0.5 mole per liter, and only 51% when the concentration was 0.1 mole per liter. The use of a 100% excess of benzylamine increased the yield to 96% (calculation based on the ester).[316](#) The peptide bond has also been formed by heating an N-trifluoroacetyl amino acid with the ester of an amino acid without a solvent, but experimental details are lacking.[323](#)

The by-product cyanomethanol has not been observed to react with the amine component.

Yields are improved by carrying out the reaction in the presence of 5–10 mole per cent of acetic acid as a catalyst.[306](#)

A reaction time of 4 days at room temperature has been commonly used for peptide synthesis,[311](#) although a glycine ester may be acylated in a few hours.[324](#) Amino acid esters with bulky side chains require longer time for acylation.[304](#)

## 13.4. Experimental Procedures

### 13.4.1. Cyanomethyl Hippurate[316](#)

To 3.58 g. of hippuric acid (0.02 mole) and 3.03 g. of triethylamine (0.03 mole) in 30 ml. of ethyl acetate was added 2.27 g. of chloroacetonitrile (0.03 mole) and the mixture was heated under reflux for 3 hours. It was then cooled, freed from the solid triethylamine hydrochloride, and the ethyl acetate solution washed with dilute aqueous sodium bicarbonate and water, dried, and evaporated. The residue crystallized on



addition of ethyl ether to give 3.47 g. (80%) of hippuric acid cyanomethyl ester, m.p. 97–99°. Recrystallization from acetone-ether raised the melting point to 99–100°.

### 13.4.2. *p*-Nitrobenzyl Hippurate<sup>316</sup>

The method is analogous to that described above except that *p*-nitrobenzyl chloride is used in place of chloroacetonitrile and heating is continued for 15 hours. The ester, m.p. 134–135°, after recrystallization from ethanol, was obtained in 82% yield.

### 13.4.3. Cyanomethyl Carbobenzyloxyglycyl-DL-alanylglycinate<sup>316</sup>

A solution of 0.44 g. of carbobenzyloxyglycyl-DL-alanylglycine and 0.2 g. of triethylamine in 1 ml. of chloroacetonitrile was heated for  $\frac{1}{2}$  hour at 80°. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate, and the solution washed with aqueous sodium bicarbonate and water. The dried solution was evaporated to give 490 mg. of crystalline ester. Recrystallization from acetone gave colorless crystals of product, m.p. 145–145.5°. The yield was 470 mg. (95%).

### 13.4.4. Ethyl Trifluoroacetylglycylglycylglycinate<sup>320</sup>

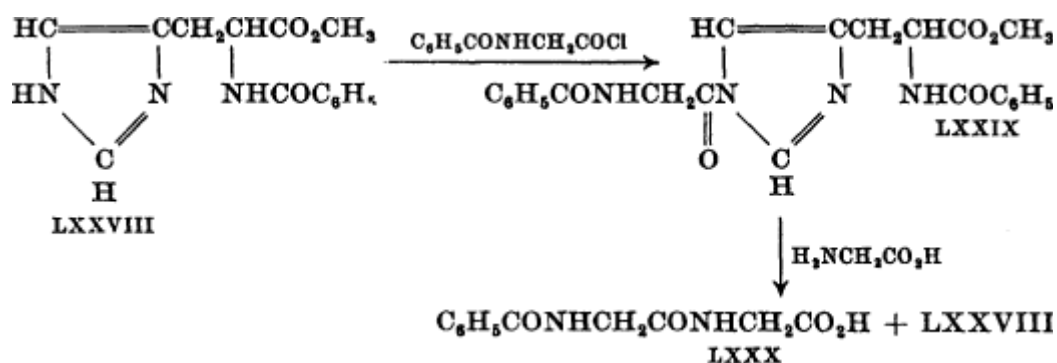
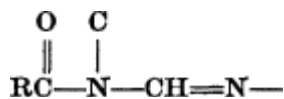
A solution of 1.60 g. of cyanomethyl trifluoroacetylglycylglycinate and 0.742 g. of ethyl glycinate in 5 ml. of ethyl acetate was heated at 110° for 90 minutes, evaporated in a high vacuum, and the residue sublimed at a bath temperature of 180–190° to give 1.71 g. (91%) of product, m.p. 232–234°.

### 13.4.5. Ethyl (N-Carbobenzyloxy-S-benzyl-L-cysteinyl)-O-tetrahydropyranyl-L-tyrosyl-L-isoleucinate<sup>311</sup>

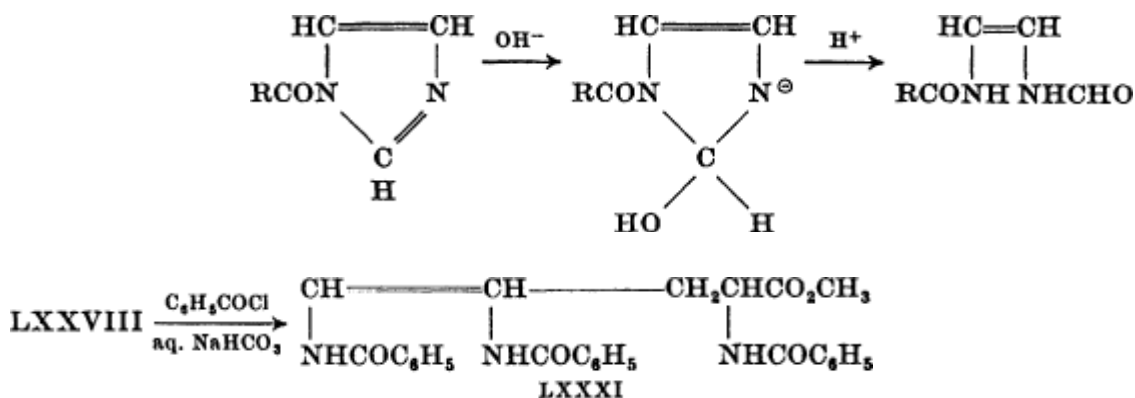
To a solution of 5.76 g. (0.015 mole) of cyanomethyl N-carbobenzyloxy-S-benzyl-L-cysteinate and 5.80 g. (ca. 0.014 mole) of crude O-tetrahydropyranyl-L-tyrosyl-L-isoleucine ethyl ester in 6.5 ml. of dry ethyl acetate was added 30 mg. of acetic acid as a catalyst. The product gradually separated as a gelatinous precipitate. The reaction mixture was allowed to stand for 4 days at room temperature, then triturated with ethyl ether and filtered to give 8.9 g. of product, m.p. about 90°. Two recrystallizations from acetone-ether gave 6.73 g. (65% based on the tetrahydropyranyl ester) of fine needles, m.p. 143–145°,  $[\alpha]_D^{23} -46^\circ \pm 1^\circ$  ( $c = 3.92\%$  in  $\text{CHCl}_3$ ). Further recrystallization from methanol or ethanol did not change the melting point.

## 14. Acylimidazoles

The ammono anhydride resulting from the replacement of one carbonyl oxygen atom and the central oxygen atom of an anhydride with nitrogen will react with amines at the carbonyl carbon atom to form amides. Thus benzoyl-L-histidine methyl ester (LXXVIII) reacts with hippuryl chloride to give im-hippuryl-N-benzoyl-L-histidine methyl ester\* (LXXIX), which in turn reacts with sodium glycinate to give benzoylglycylglycine (LXXX) in 35% yield.<sup>325</sup>



The ready cleavage of the imidazole ring under Schotten-Baumann reaction conditions has been known for a long time.<sup>326</sup> Thus the reaction of benzoyl-L-histidine methyl ester (LXXVIII) with benzoyl chloride in aqueous sodium bicarbonate leads to a tribenzoyl derivative LXXXI presumably by way of an intermediate formyl derivative.<sup>327</sup>



The mixed ammonio anhydride, im-N-bis(carbobenzyloxyglycyl)-histidine methyl ester obtained in 16% yield from carbobenzyloxyglycyl ethyl carbonate and L-histidine methyl ester in benzene<sup>229</sup> reacts with methyl alaninate to give, after saponification, a 30% yield of carbobenzyloxyglycylalanine.

Dicarbobenzyloxy-L-histidine reacts with methyl glycinate to give methyl carbobenzyloxyglycinate and carbobenzyloxyhistidine.<sup>226</sup> Benzoyl theobromine and sodium glycinate give hippuric acid and theobromine.<sup>325</sup> An  $\alpha$ -acylaminoacyl theobromine has not been used for peptide synthesis.

N,N $\zeta$ -Carbonyldiimidazole (LXXXII) reacts readily with  $\alpha$ -acylamino carboxylic acids to form  $\alpha$ -acylaminoacylimidazoles. This reaction provides a practical peptide synthesis.<sup>328-330</sup> Thus carbobenzyloxyglycinimidazole (LXXXIII), prepared from carbobenzyloxyglycine and N,N $\zeta$ -carbonyldiimidazole (LXXXII), reacts with ethyl L-tyrosinate to give ethyl carbobenzyloxyglycyl-L-tyrosinate in 83% over-all yield. The intermediate LXXXIII was also used to acylate sodium L-phenylalaninate in aqueous solution to give 40% of carbobenzyloxyglycyl-L-phenylalanine. DL-Phenylalanine is not polymerized by N,N $\zeta$ -carbonyldiimidazole, but yields N,N $\zeta$ -carbonyl-bis-DL-phenylalanine.<sup>331</sup>







The thiol esters are relatively stable toward hot water and dilute acid but are slowly attacked by base.<sup>336</sup> Aminolysis generally occurs readily, but the rate depends upon a number of factors discussed more fully below.

Thiol esters possess certain advantages over most other mixed anhydrides as a result of their stability toward weak bases, anhydrous acids, and heat. The coupling of an  $\alpha$ -acylamino acid thiol ester with the sodium salt of an amino acid will lead usually to a pure dipeptide derivative.<sup>336</sup> For example, in the coupling of carbobenzyloxyglycine thiophenyl ester with phenylalanine in basic solution to give carbobenzyloxyglycylphenylalanine and thiophenol, extraction of the reaction mixture with ether will remove unreacted carbobenzyloxyglycine thiophenyl ester and thiophenol. Acidification then precipitates only the product. With most other mixed anhydrides, acidification would precipitate unreacted carbobenzyloxyglycine with the product.

A further advantage of thiol esters is that a carbobenzyloxy, a carbo-t-butoxy, or a carbocyclopentyloxy protecting group is readily removed from a peptide thiol ester with anhydrous hydrogen bromide without affecting the thiol ester group. The less convenient phosphonium iodide may also be used for removal of the carbobenzyloxy group from a peptide thiophenyl ester.<sup>337</sup> The resulting intermediates are of interest, both for the preparation of polymers in which two or more amino acids are repeated in known sequence, and for the preparation of cyclic peptides. Thus triglycylthioglycolic ester in dimethylformamide was added to pyridine at 60° over a 10-hour period to give a 69% yield of cyclohexaglycyl.<sup>312</sup>

$\alpha$ -Amino acid thiophenyl esters have been coupled with acyldipeptides in good yield via the mixed carbonic anhydride. This lengthens the peptide chain and forms an acyltripeptide thiophenyl ester ready to undergo further coupling. Alternatively, the thiol ester group may be removed by hydrogen peroxide in acetic acid.<sup>15</sup>

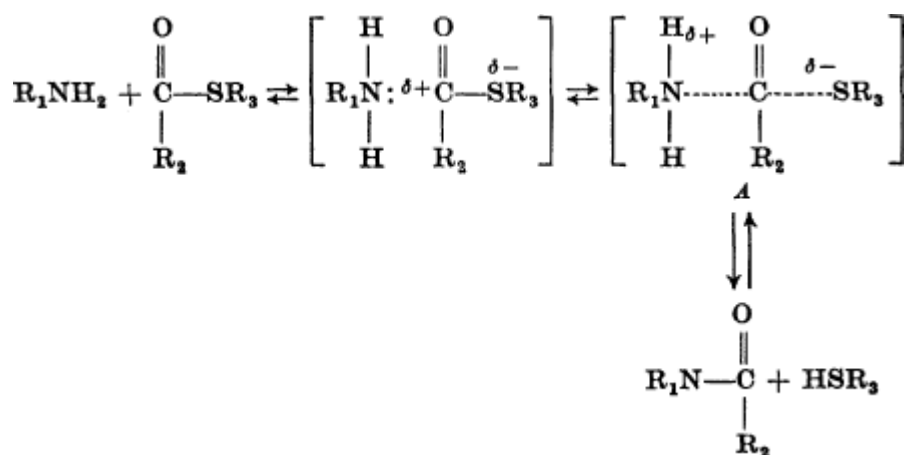
The stability of thiol esters is indicated by the fact that initially odorless crystals of the thiophenyl esters of carbobenzyloxyglycine and carbobenzyloxytryptophan developed only a slight odor after 1 year.<sup>338</sup>

The pioneering work of Wieland suggested that reaction of mixed anhydrides of  $\alpha$ -acylamino acids with hydrogen sulfide would lead to  $\alpha$ -acylamino thioacids. Reaction of phthaloylglycine with ethyl chloroformate and then with hydrogen sulfide gave phthaloyl thioglycinate in 61% yield.<sup>339</sup> The same product was obtained in good yield from phthaloylglycyl chloride and sodium hydrosulfide. Methyl phthaloylglycylglycinate was obtained in unstated yield from phthaloylthioglycinate and methyl glycinate. In similar manner thiolhippuric acid and phthaloylthioglycine were prepared as were thiolacetic acid, thiolbenzoic acid, and p-phenylthiolbenzoic acid.<sup>340</sup> The mixed anhydride of carbobenzyloxyglycine and isobutyl carbonate was converted to the thiol acid and the thiol acid converted to the anilide in 24% over-all yield.<sup>15</sup> The  $\alpha$ -acylaminothiol acids generally offer no advantage in peptide synthesis over the thiol esters and indeed require an additional step.

## 16.2. Mechanism

The reaction between thiol esters and amines is considered to be a bimolecular nucleophilic substitution.<sup>341, 342</sup>

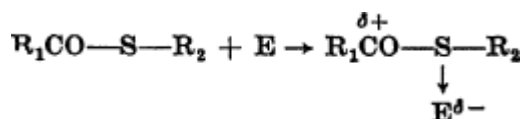
The weak permanent polarization of the C single bond S bond in the thiol ester is supplemented by the larger polarization induced by the approach of the amine. Sufficiently close approach of the amine leads to the transition state A and to the amide and thiol.



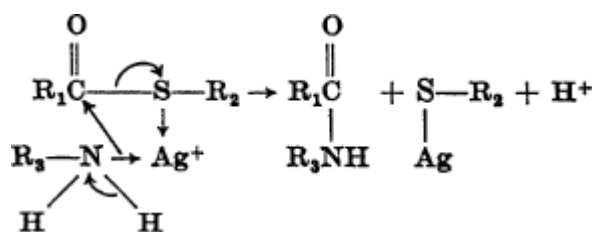
This mechanism suggests that changes in R<sub>3</sub> which will increase the polarization of the C single bond S bond will favor amide bond formation. This has been verified. For example, p-nitrothiophenyl carbobenzyloxyglycinate reacted with alanine in aqueous dioxan 140 times as fast as the thiophenyl ester.<sup>335</sup> The carbobenzyloxy thiol esters of acylamino acids<sup>343</sup> are especially useful for peptide syntheses.<sup>344</sup>

The maximum yields of anilide obtained in the reaction of various thiol esters of acetic, benzoic, and hippuric acid with aniline in 1% aqueous solution were in the order; single bond SC<sub>2</sub>H<sub>5</sub> < single bond SC<sub>6</sub>H<sub>5</sub> < single bond SCH<sub>2</sub>CH<sub>2</sub>NHCOCH<sub>3</sub> < single bond SCH<sub>2</sub>CH(NHCOCH<sub>3</sub>)CO<sub>2</sub>H < single bond SCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H < single bond SCH<sub>2</sub>CO<sub>2</sub>H.

Another method of increasing the C single bond S bond polarization would be to form a bond between an electrophilic reagent, E, and the sulfur through the 3p electrons of the latter. The catalysis by aminoacylase of the reaction between benzoyl coenzyme A and glycine to give hippuric acid may be an instance of this type of polarization.<sup>341</sup>

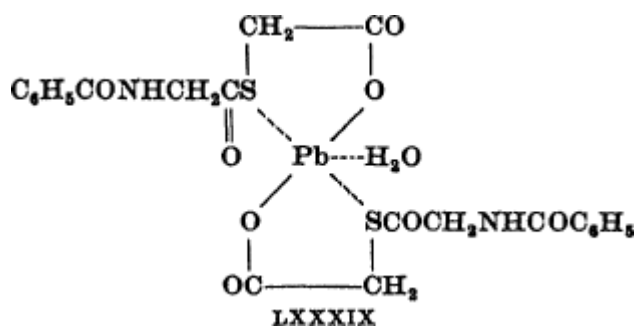


A more practical application to peptide synthesis is the use of metal ions as the electrophilic reagent E. Catalysis by silver ion is explained on the basis of a complex of the thiol ester, silver ion, and amine.

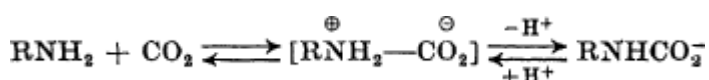


The varying degrees of effectiveness of different metal ions may be due to the difference in their ability to coordinate with the amine.<sup>341</sup>

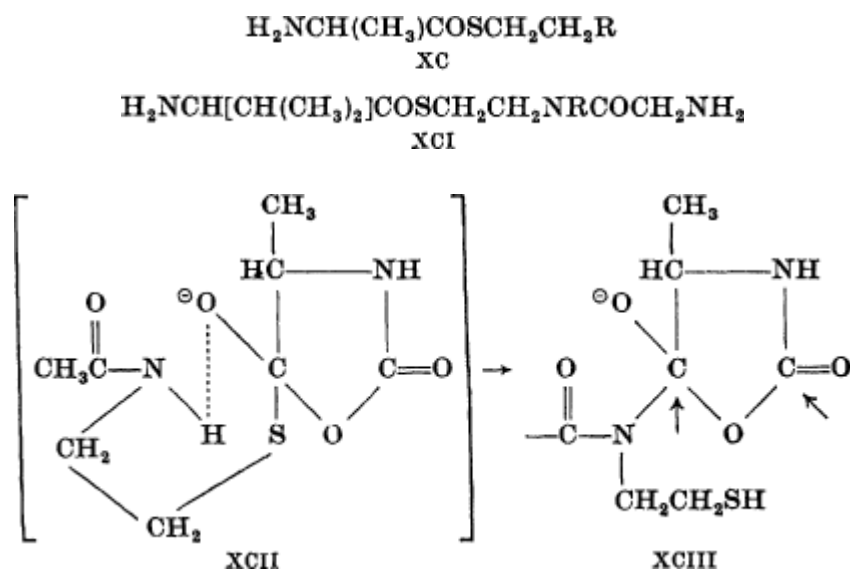
In the reaction between hippuryl thioglycolic acid and glycine with lead acetate as catalyst, the lead salt of hippurylthioglycolic acid was isolated as an intermediate. The structure LXXXIX was proposed for this intermediate to explain the catalytic effects of the lead ion.



Aqueous bicarbonate will catalyze the cleavage (either hydrolysis or aminolysis) of  $\alpha$ -aminoacyl thiols, but the ions  $\text{HPO}_4^{-2}$ ,  $\text{SO}_4^{-2}$ ,  $\text{HSO}_3^-$ , and  $\text{HCO}_2^-$  do not.<sup>345</sup> The initial step may involve reaction of the amine and carbon dioxide or bicarbonate ion with the loss of a proton.



The acetamidoethyl ester  $\text{XC}$  ( $\text{R} = \text{CH}_3\text{CONH}-$ ) was aminolyzed or hydrolyzed more rapidly than the ethyl ester ( $\text{R} = \text{H}$ ) and the same reactions involving the amide  $\text{XCI}$  proceeded more rapidly when  $\text{R} = \text{H}$  than when  $\text{R} = \text{CH}_3$ . These results obtained in the presence of aqueous bicarbonate were interpreted as indicating cyclization of the carbonate of  $\text{XC}$  to  $\text{XCII}$ , followed by rearrangement to the diacylimide  $\text{XCIII}$ . The latter compound can undergo ring opening via aminolysis or hydrolysis at either of the acyl groups.



The “bicarbonate effect” has been used to synthesize alanylglycine from thiolalanine and glycine. Peptide formation did not take place in the absence of aqueous sodium bicarbonate.<sup>346</sup>

## 16.3. Scope and Limitations

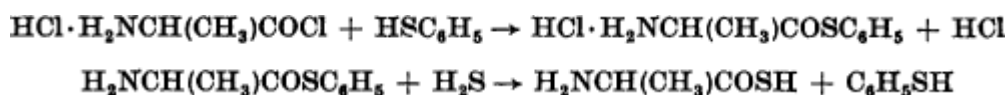
Comparatively few peptides have been prepared from  $\alpha$ -acylamino acid thiol esters. Acyl derivatives of glycine, phenylalanine,<sup>335, 336</sup>  $\beta$ -alanine,<sup>336, 347</sup> S-benzyl-L-cysteine,<sup>348</sup> and tryptophan<sup>338</sup> have been used as acidic components in peptide synthesis. When the amine component is proline, acylation with carbobenzyloxyglycine thiophenyl ester or carbobenzyloxyglycylglycine thiophenyl ester proceeds in

yields of about 80%, whereas with the mixed carbonic anhydrides of the acylated amino acid or dipeptide yields are 20% or less.[59](#) A series of cyclopolycaprolactams ranging from the cyclo-dipeptide to the cyclohexapeptide has been prepared.[273](#)

The common practice of preparing the  $\alpha$ -acylamino acid thiol ester from a mixed anhydride of the  $\alpha$ -acylamino acid limits the utility of this method because of the extra step. In general, the use of tri-*p*-nitrothiophenyl phosphite for the synthesis of the  $\alpha$ -acylamino thiol esters[335](#) obviates this disadvantage. Attempts to prepare the *p*-nitrothiophenyl ester of carbobenzyloxy-L-leucylglycyl-L-leucylglycyl-L-leucylglycyl-L-leucylglycine failed, presumably because of the insolubility of the acylpeptide.[349](#)

It would be of interest to extend the tri-*p*-nitrothiophenyl phosphite method to acyl derivatives of the hydroxy amino acids. If it functions satisfactorily, the scope of the acylaminoacyl thiol ester and the activated ester procedure would be similar.

Hydrogen sulfide reacts with amino acid thiophenyl esters to give the aminothiols and thiophenol.[350-352](#) The thiophenyl esters may be prepared from the amino acid chloride hydrochloride and thiophenol. These reactions follow the typical pattern of an anhydride and an acid giving a new anhydride with liberation of the stronger acid as shown in the accompanying equations.



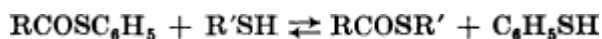
Actually the aminothiols were shown to exist as zwitter ions. They failed to acylate ammonia or amino acids.[346](#), [351](#) If the amino group was further separated from the thiol acid group, reactivity increased; thio- $\beta$ -alanine, for example, polymerized on heating at 100° for 48 hours.[352](#)

Treatment of benzylpenicillin with ethyl chloroformate and triethylamine in chloroform followed by reaction with hydrogen sulfide gave the symmetrical benzylpenicillanic thiol anhydride as a crystalline solid.[353](#) Unlike the oxygen anhydrides which can acylate only 1 mole of amine, thiol anhydrides can acylate 2 moles. However, benzylpenicillanic thiol anhydride gave with cyclohexylamine only a 42% yield of benzylpenicillin cyclohexylamide. Thiol anhydrides of other acylamino acids have not been prepared.

The  $\alpha$ - and  $\gamma$ -thiophenyl esters of carbobenzyloxyglutamic acid reacted with ammonia to give homogeneous products.[354](#) However, the corresponding  $\alpha$ - and  $\gamma$ -carbobenzyloxythiolglutamic acids always gave a mixture of S- $\alpha$ - and S- $\gamma$ -glutamylglutathione from pure starting materials. The latter result may probably be ascribed to the use of base in the synthesis rather than to the use of thiol acid in place of a thiophenyl ester. The interconversion of  $\alpha$  and  $\gamma$  isomers of glutamic acid is known to occur with ease.[97](#), [98](#), [101](#), [106](#), [355](#)

Although S-valylcysteamine was prepared by fusion of valyl chloride and cysteamine hydrochloride,[356](#) this reaction failed when cysteine was used in place of cysteamine.[290](#)

The exchange reaction between thiophenyl esters and hydrogen sulfide was employed to prepare S-leucyl-, S-valyl-, and S-methionyl-glutathiones,[290](#) but these thiol esters proved unsatisfactory for peptide synthesis. S-Methionylglutathione reacts in aqueous trimethylamine to give oligopeptides of methionine as shown by paper chromatography. S-Alanyl- and S-acetylglycyl-glutathione have also been prepared.[357](#)



The reaction of alanine thiophenyl ester hydrochloride with coenzyme A gave S-alanyl-coenzyme A hydrochloride, isolated by electrophoresis. When this compound was treated with glutamic acid in a solution buffered at pH 8, the product was reported to be alanylglutamic acid on the basis of an



electropherogram.[358](#)

Tritylglycylglycine could not be converted to the azide via the hydrazide, but it was converted to the thiophenyl or thio benzyl ester via the alkyl carbonate mixed anhydride.[9](#) Acylpenicillamines react with isobutyl chloroformate and triethylamine to give  $\alpha$ -acylamino- $\beta$ -propiothiolactones[359](#) which have been used for peptide synthesis. L- $\alpha$ -Phthalimido- $\beta$ -propiothiolactone reacts with L-methionine ethyl ester to give a 31% yield of crude N-phthaloyl-L-cysteinyl-L-methionine ethyl ester.[360](#)

Basic German patents have been issued to cover peptide bond formation from amino acids or peptides or their esters and  $\alpha$ -acylaminothiol esters NHR(X)CHCOSA, where R is an alkyl, aralkyl, acyl, or other amine-protecting group, X is a residue as found in amino acids and peptides, and A is an alkyl, aryl, aralkyl, or similar residue.[347](#), [361](#), [362](#)

French patents[343](#), [344](#) claim the preparation and use of compounds differing from those described in the German patents in the nature of the thiol portion of the molecule. They may be represented as NHR(X)CHCOSYZ, where Y is methylene, ethylene, propylene, or phenylene, and Z represents an electron-acceptor group such as carboxyl, sulfonyl, or nitro. The examples refer to the use of thioglycolic and thiosalicylic acids which should give the most reactive intermediates. Separation of the thiol and electron-accepting group by a propylene chain partially nullifies the advantage of having the electron-accepting group in the molecule. Thioglycolic acid combines the advantages of a thiol ester with those of an activated ester in respect to reactivity.

Patents also claim the use of metal salts such as silver nitrate or lead acetate to increase the yield of amide obtained from thiol esters.[363](#) In some reactions the catalytic effect is quite marked, as in the reaction of benzoylpantethein with glycine to give an 80% yield of hippuric acid in the presence, but not in the absence, of silver ion.

## 16.4. Racemization

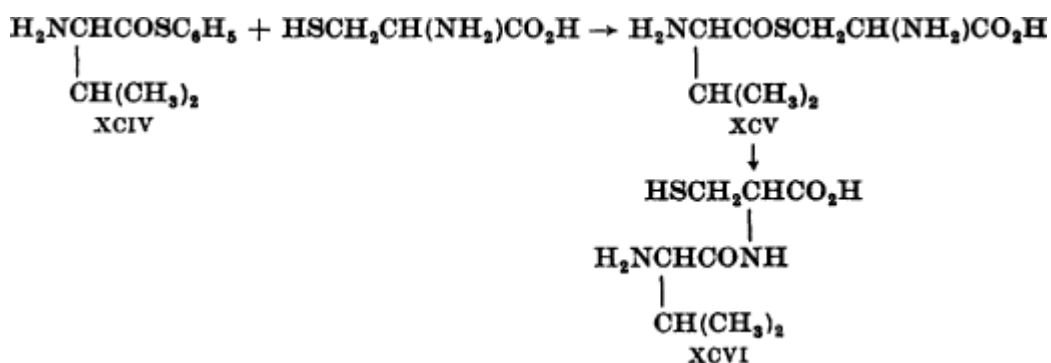
Preliminary results with tri-p-nitrothiophenyl phosphite for peptide synthesis indicate that the intermediates are obtained with higher optical purity than by some other methods of synthesis.[335](#) Thus the reaction of the lithium salt of carbobenzyloxyglycyl-L-phenylalanine with tri-p-nitrothiophenyl phosphite in dimethylformamide at 18° gave a 99% yield of carbobenzyloxyglycyl-L-phenylalanyl-p-nitrothiophenyl ester with a rotation of  $-67^\circ$ . The same thiol ester, prepared from the same lithium salt with sulfur trioxide in dimethylformamide, gave a 67% yield of product with a rotation of  $-36^\circ$ . The thiol ester, prepared from the mixed anhydride of ethyl chloroformate and carbobenzyloxyglycyl-L-phenylalanine followed by reaction with p-nitrothiophenol in dimethyl formamide, was optically inactive. Carbobenzyloxyglycyl-L-phenylalanine p-nitrothiophenyl ester is reported to give a quantitative yield of carbobenzyloxyglycyl-L-phenylalanylglycine and equally good results in other amide syntheses.[335](#)

The use of nitrophenyl thiol esters may sometimes result in racemization.[141](#) The reaction of the thiol ester of carbobenzyloxyglycyl-L-alanine with L-phenylalanylglycine gave almost half as much DL isomer as LL isomer.[38](#) p-Nitrophenyl thiol esters with a terminal glycine residue may help to avoid the substantial risk of racemization.[349](#)

The  $\alpha$ - and  $\gamma$ -thiophenyl esters of  $\alpha$ -N-acylglutamic acids have been synthesized from an  $\alpha$ -N-acyl-L-glutamic acid anhydride and thiophenol under a variety of experimental conditions.[99](#), [354](#) In weakly polar media in the presence of a weak base the optically active  $\alpha$ -thiophenyl ester is the major product.[99](#) The use of triethylamine increases the proportion of the  $\gamma$ -ester (especially in the case of  $\alpha$ -N-phthaloyl-L-glutamic acid anhydride) without causing racemization. However, in strongly polar solvents, the use of triethylamine gives almost exclusively the  $\gamma$ -ester with racemization.

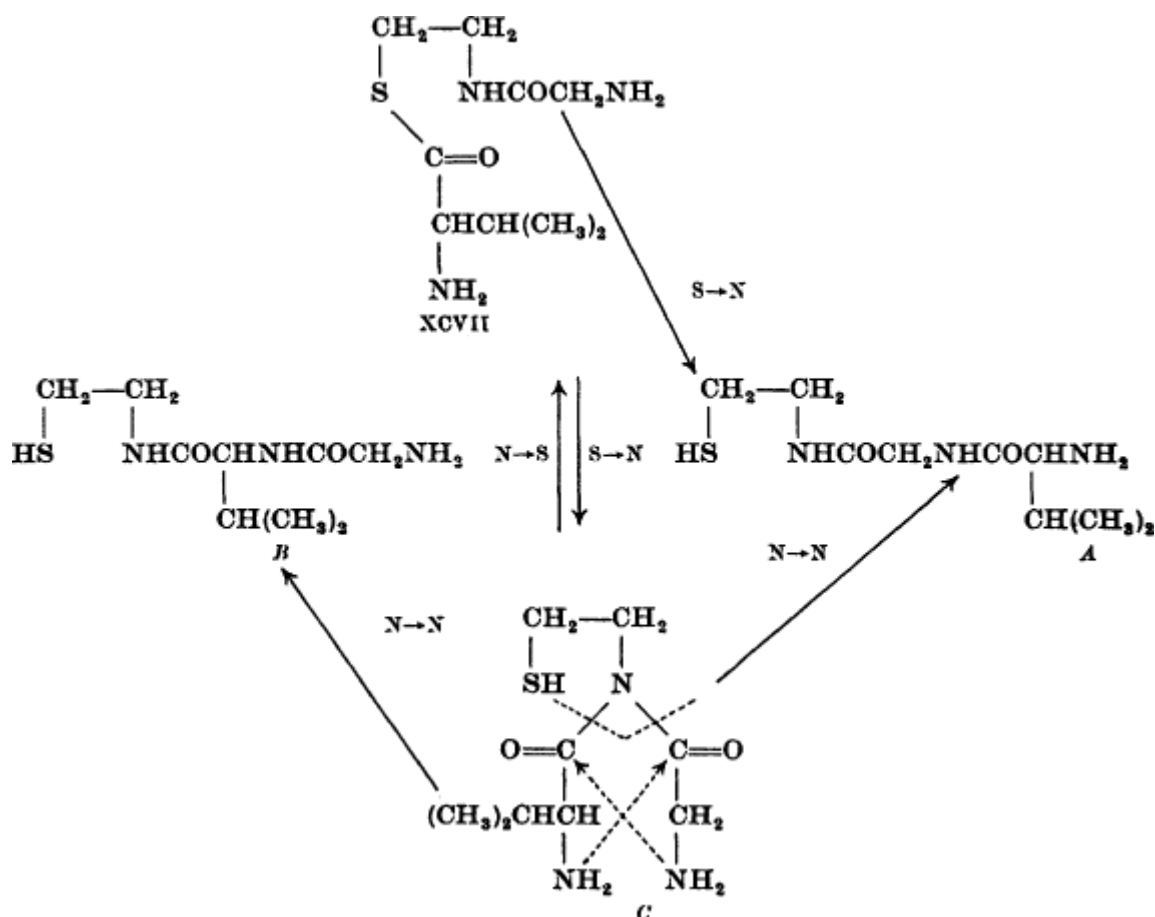
## 16.5. Intramolecular Aminoacyl Migration\*

An  $\alpha$ -aminoacyl group on a sulfur atom will migrate to a nitrogen atom in a sterically favorable position. Thus thiophenyl valinate (XCIV) and cysteine give S-valylcysteine (XCV), which rearranges rapidly to N-valylcysteine (XCVI). The reaction was allowed to proceed for two minutes at pH 7.5, stopped by the addition of acid, and the final product was identified by chromatography. Under the same conditions, substitution of glycine for cysteine gave only a trace of valylglycine, and other aliphatic amino acids gave no valyl peptides, thus suggesting that the reaction occurs first at the thiol group. Histidine gave valylhistidine, an indication that the initial reaction was probably at the ring nitrogen.



Somewhat unexpected was the further observation that thiophenyl esters will acylate a neighboring amide group.<sup>290</sup> S-Valyl-N-glycylcysteamine (XCVII) dihydrochloride was treated with base and the product chromatographed. Since N-valylglycylcysteamine (A) and N-glycylvalylcysteamine (B) could not be separated from each other by this means, the mixture was treated with S-methyl isothiurea and hydrolyzed. The presence of small amounts of  $\alpha$ -guanidoacetic acid together with large amounts of  $\alpha$ -guanidoisovaleric acid showed that some of the glycine was in the terminal position. This led to the deduction that a bis(aminoacyl) imide C, a new form of mixed anhydride, may have been the intermediate. The postulated reactions are shown below.

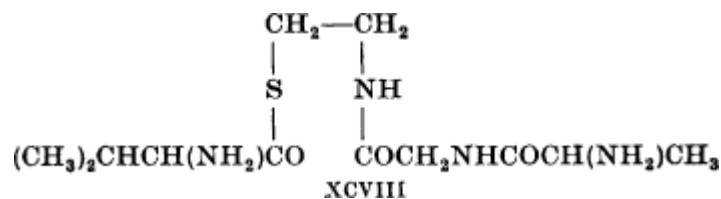




Experimental support for this reaction scheme was subsequently obtained from the observation that diglycylimide underwent an N to N migration at pH  $\geq 5$  to give diglycinamide.[364](#)

It is possible that the same sort of transformation might occur with glutathione in dilute solution. A reactive amino acid intermediate would be expected to react first with the thiol group to give a thiol ester. An S to N migration to the glycine nitrogen via a six-membered cyclic intermediate followed by an N to N migration of the cysteine moiety via a five-membered cyclic intermediate would lead to insertion of the amino acid into glutathione between the cysteine and glycine residues. The process could be repeated. A peptide synthesis has not been achieved with S-methionylglutathione, but the objective of previous studies was merely the use of S-amino acid glutathione derivatives for acylation of other amino acids rather than for insertion of the amino acids into the glutathione chain.

Reaction of S-valyl-N-alanyl-L-cysteamine (XCVIII) with aqueous calcium carbonate gave a mixture of peptide derivatives. The presence of N-alanylvalyl-L-cysteamine among the products can be explained by assuming that the valyl group first migrates from sulfur to the neighboring amide nitrogen. An N to N migration can then place either valine or alanine in the penultimate position.[289](#)



## 16.6. Experimental Conditions

### 16.6.1. Preparation of Thiol Esters and Thiol Acids

Although a variety of  $\alpha$ -acylamino acid mixed anhydrides could serve as starting materials for the synthesis of thiol esters or thiol acids, the mixed alkyl carbonic anhydride has been most commonly used. The  $\alpha$ -acylamino acid or peptide alkyl carbonate is prepared in an indifferent solvent, and the mercaptan is then added to the solution of the mixed anhydride. The subsequent procedure is similar to that used in the coupling of alkyl carbonic mixed anhydrides with amino acids or esters.

Thiosalicylic or thioglycolic acid is customarily dissolved in ethyl acetate containing an equivalent of triethylamine and added to the solution of the  $\alpha$ -acylaminoacyl alkyl carbonate.[343](#), [365](#), [365a](#) After  $\frac{1}{2}$  to 4 hours at room temperature, the mixture is washed with water and dilute hydrochloric acid, and concentrated to give the thiol ester. With thiophenol, a bicarbonate wash is also used. If the solvent is miscible with water, it is removed in vacuum and the residue taken up in ethyl acetate (or other water-immiscible solvent) before washing with acid and bicarbonate.

In the preparation of thiol acids, the solution of mixed carbonic anhydride is saturated with hydrogen sulfide at room temperature in the presence of one equivalent of triethylamine. After the solution has stood overnight, the solvent is removed in vacuum, the residue taken up in water and acidified with dilute hydrochloric acid.[339](#), [340](#), [351](#)

When dicyclohexylcarbodiimide is used to form the acyl peptide thiophenyl ester, equivalent amounts of acyl peptide and thiophenol dissolved in a solvent such as tetrahydrofuran are treated with a 10% excess of dicyclohexylcarbodiimide. After 4 or more hours, the dicyclohexylurea is removed by filtration and the product isolated by concentrating the filtrate.[273](#) By this procedure, carbobenzyloxy- $\epsilon$ -aminocaproyl- $\epsilon$ -aminocaproic acid was converted to the thiophenyl ester in 89% yield.

When amino acid thiophenyl esters are employed, polymerization of the amine component is possible as it is liberated from its salt.[163](#), [366](#), [367](#) This is especially true of the p-nitrothiophenyl derivative.[37](#) To minimize this reaction, one equivalent of triethylamine is added to the mixed carbonic anhydride followed by one equivalent of the desired amino acid thiophenyl ester hydrobromide. The latter may be dissolved in chloroform or other suitable solvent. After 2 to 4 hours the product is isolated in the same manner as an  $\alpha$ -acylamino peptide ester. Mixed anhydrides of  $\alpha$ -carbobenzyloxyamino acids and dichlorophosphoric acid react with thiophenol and p-nitrothiophenol to give the thiophenyl esters. The best yields are obtained if the  $\alpha$ -carbobenzyloxyamino acid, thiophenol, and phosphorus oxychloride are dissolved in tetrahydrofuran, cooled to  $-15^\circ$ , and pyridine is then added. The reaction is complete after 1 hour at room temperature.[37](#)

Amino acid thiol esters are prepared by warming amino acid chloride hydrochlorides with excess thiophenol to  $70^\circ$  for 15 minutes and cooling, or by allowing the reaction to proceed several days at room temperature.[367](#) The addition of glycyl chloride hydrochloride to thioglycolic acid resulted in a spontaneous reaction. The mixture was then heated for 30 minutes at  $70^\circ$  and 20 minutes at  $90^\circ$ . Ethanol was added to give a clear solution. Introduction of acetone caused precipitation of S-glycylthioglycolic acid hydrochloride in 80% yield.[343](#)

When L-valine chloride hydrochloride was heated with one equivalent of thiophenol in benzene for 1 hour at  $80^\circ$  the reaction product contained diketopiperazine, dipeptide thiophenyl ester hydrochloride, and some thiophenyl esters of higher oligopeptides.[368](#) The use of excess thiophenol with the acid chloride hydrochloride at room temperature has been applied to the preparation of several peptides; glycyl-DL-valine, glycyl-DL-leucine, and glycyl-DL-valyl-DL-isoleucine were converted to thiophenyl ester hydrochlorides in yields of 42, 40, and 80%, respectively.[368](#)

Phthaloylglycyl chloride was converted to phthaloylthioglycine in good yield by reaction with sodium hydrogen sulfide in dimethylformamide.[339](#)

Exchange reactions between amino acid thiophenyl esters and other thiols are conducted in aqueous or

ethanolic solution at weakly acid pH with excess thiol ester.[290](#)

p-Nitrothiophenyl carbobenzyloxyglycyl-L-phenylalaninate was prepared in 99% yield by treating lithium carbobenzyloxyglycyl-L-phenylalaninate with tri-p-nitrothiophenyl phosphite in dimethylformamide at 18°. [335](#) p-Nitrothiophenyl esters may also be prepared by reaction of tri-p-nitrothiophenyl phosphite with an equivalent amount of carboxylic acid in dimethylformamide at 85° for 20 minutes. Pyridine may be substituted for dimethylformamide if the mixture is heated to 60° for 5 minutes and then left overnight at 18°. [38](#) Yields are generally high for both acylamino acid and acyl peptides.

The mixed sulfuric anhydrides of carbobenzyloxyglycine and of carbobenzyloxyglycyl-L-phenylalanine were used for preparation of the p-nitrothiophenyl esters in 70% and 58% yields, respectively. [38](#)

## 16.6.2. Amide Bond Formation

Although acyl thiols react with amines in the absence of a solvent, the use of water, alcohols, dimethylformamide, tetrahydrofuran, or mixtures of these solvents is more usual. Concentrations are preferably one molar or more for the two reactants, [344](#) but reactions catalyzed by metal ions may be carried out in dilute aqueous solutions. [363](#) It is preferable to carry out syntheses of more complex peptides at room temperature, but the reaction of an S-acylthioglycolic or thiosalicylic acid or their esters with the sodium salt of an amino acid may be completed by warming at 80–85° or by heating under reflux in methanol for 1 hour. The solvent is removed in vacuum, the residue taken up in water, and the product precipitated by acidification. [336](#) This procedure, with the thiophenyl ester, gave 90% of analytically pure carbobenzyloxyglycylalanine. Methanol generally gives better yields than aqueous solvents. Reaction of a thiol ester with an amino acid in neutral solution fails because the reaction produces an acid which reduces the concentration of uncharged amino groups and stops the reaction. Pyridine may be used as a buffer with the result that good yields may be obtained in 1 hour of heating under refluxing conditions. [336](#)

Better results have been obtained when coupling has been conducted in the presence of sodium bicarbonate rather than sodium hydroxide. For example, carbobenzyloxy- $\beta$ -alanine thiophenyl ester gave a 70% yield of pure carbobenzyloxy- $\beta$ -alanyl- $\beta$ -alanine when concentrated sodium bicarbonate solution was employed, but only a 50% yield of crude material with N sodium hydroxide. [336](#)

S-Acylthioglycolates and thiosalicylates have been used only when the acyl group was benzoylglycine or carbobenzyloxyglycine. They were coupled with the sodium salts of amino acids and dipeptides in yields varying from 45% to 80%.

Several workers have noted that control of pH may be advisable. In the reaction of carbobenzyloxyglycylthioglycolic acid with aniline in buffered dimethylformamide solutions, yields increased from 14.5% to 66% as the pH was increased from 2 to 4 but then decreased as the pH was increased beyond pH 4. The optimum pH was found to vary with the amine. Benzylamine reacts with S-hippurylthioglycolic acid at pH 8 to give 43% and at pH 9 to give 73% of the amide. [344](#) The reaction of p-nitrothiophenyl esters with amino acids in dioxane solution at 18° for 18 hours gave excellent yields when buffered at an apparent pH 6.8 with excess solid magnesium carbonate. [335](#)

Peptide bond formation that is catalyzed by metal ions (silver, lead, copper, or mercury) requires control of the pH to obtain optimum yields. Best results are usually obtained at pH 6 to 8. S-Hippurylthioglycolic acid reacts with glycine in the presence of silver nitrate to give the maximum yield, 85%, of hippurylglycine at pH 6; the yield was only 30% at pH 8.1. However, the same components react in the presence of lead acetate to give an 80% yield at pH 8 and a 9% yield at pH 7. [363](#) The reaction is normally carried out by dissolving the  $\alpha$ -acylamino acid thiol ester and the amino acid to be acylated in an aqueous medium and adding dropwise N aqueous sodium hydroxide and a solution of the metal salt (silver nitrate is best) either simultaneously or alternately to maintain the pH at the desired value. Buffered solutions have also been employed. The reaction mixture is allowed to stand at room temperature for about 15 hours to

complete the reaction. If the metal has precipitated as a salt (e.g., silver thioglycolate), it is removed by filtration. Otherwise the metal catalyst is precipitated with hydrogen sulfide and removed before isolating the peptide intermediate.

## 16.7. Experimental Procedures

### 16.7.1. Thiophenyl Carbobenzyloxy- $\beta$ -alaninate (Preparation of a Thiophenyl Ester via the Mixed Carbonic anhydride)[336](#)

A solution of 3 g. of carbobenzyloxy- $\beta$ -alanine and 1.53 g. of N-ethylpiperidine in 13.5 ml. of tetrahydrofuran was cooled to 0° and 1.5 g. of ethyl chloroformate added dropwise. N-Ethylpiperidinium chloride precipitated at once. When the odor of the acid chloride had disappeared (10–15 minutes), 1.52 g. of thiophenol was added and the mixture allowed to stand 4 hours at room temperature. The solvent was removed under reduced pressure and the residual syrup triturated with water to induce crystallization. Recrystallization from water gave 3.7 g. (90%) of product, m.p. 70°.

### 16.7.2. p-Nitrothiophenyl Carbobenzyloxyglycyl-L-phenylalaninate (Preparation of a Thiophenyl Ester via Tri-p-nitrothiophenyl Phosphite)[38](#)

A solution of 1.78 g. (5 mmoles) of carbobenzyloxyglycyl-L-phenylalanine in 65 ml. of dimethylformamide was neutralized with methanolic lithium methoxide and then concentrated to 50 ml. at 50° and 11 mm. under a six-inch column of steel gauze rings. The solution was cooled to 20° and treated with 1.70 g. (5 mmoles) of tri-p-nitrothiophenyl phosphite, which dissolved on shaking. The solution was kept overnight and then poured onto water. The product was extracted with ethyl acetate and washed successively with N sulfuric acid, water, sodium bicarbonate solution (twice), and water. The ethyl acetate was combined with ethyl acetate extracts of the aqueous washings and the combined extracts evaporated to dryness. The residue was recrystallized from methanol to give 79% of the thiol ester, colorless needles, m.p. 154–155°;  $[\alpha]_D^{16} -67^\circ \pm 0.4^\circ$  (c = 4.6%, dioxane).

### 16.7.3. Carbobenzyloxyglycyl-DL-alanine (Amide Formation in Absolute Methanol)[336](#)

A solution of 1.78 g. of thiophenyl carbobenzyloxyglycinate in 16 ml. of methanol containing 128 mg. of sodium and 0.5 g. of DL-alanine was heated under reflux for 4 hours. The solvent was removed under reduced pressure and the residue taken up in a small amount of water. Acidification of the solution to Congo red with dilute hydrochloric acid precipitated 1.4 g. (90%) of analytically pure carbobenzyloxydipeptide, m.p. 177°.

In aqueous tetrahydrofuran (4 hours at 60°) the same compound was obtained, 75% yield.

### 16.7.4. Hippurylglycine (Amide Formation Catalyzed by Metal Ions)[363](#)

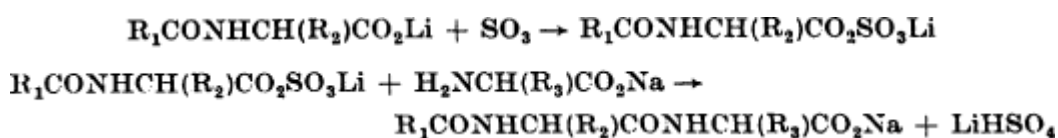
To a solution of 0.243 g. of S-hippurylthioglycolic acid and 0.10 g. of glycine in 7 ml. of water was added

dropwise and alternately a solution of 0.170 g. of silver nitrate in 3 ml. of water and N aqueous sodium hydroxide so as to maintain the pH at 6.0. The solution was diluted to 14 ml. with water and allowed to stand 15 hours at 40°. The silver thioglycolate was removed by filtration, the filtrate concentrated under reduced pressure, the residue taken up in a small amount of water and acidified to pH 2. There was obtained after recrystallization from water and washing with absolute ethanol 0.193 g. (85%) of hippurylglycine, m.p. 206–206.5°.

In the absence of silver nitrate, the yield of hippurylglycine was 46%.

## 17. $\alpha$ -Acylaminoacyl Sulfates

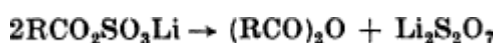
Sulfuric acid anhydrides were introduced in peptide synthesis early in 1951.<sup>369</sup> The method consists of the reaction of the salt of an  $\alpha$ -acylamino acid with sulfur trioxide to give a mixed anhydride. To this anhydride is added the sodium salt of an amino acid to give an acyl dipeptide as illustrated in the accompanying equations.



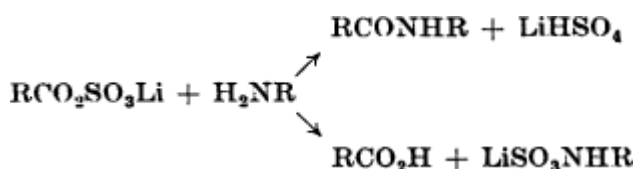
The dibasicity of sulfuric acid makes it possible to obtain the mixed anhydride in the form of a water-soluble salt. Thus acylation of the sodium salt of an amino acid can be achieved in a single-phase reaction.

The peptide-forming step involves the usual attack on the carbonyl carbon by the amine. Kenner<sup>5</sup> has suggested that by-products may arise because of moisture, disproportionation of the mixed anhydride, or by attack of the amine on sulfur as well as on carbon.

Disproportionation:



Attack on S and C:



### 17.1. Scope and Limitations

Acyl derivatives of glycine, alanine, cystine, cysteine, tyrosine, tryptophan, and phenylalanine have been used as the  $\alpha$ -acylamino components. The hydroxyl group of tyrosine must be protected.<sup>370</sup> Yields of acyl di- and tri-peptides have generally been about 60–80%. Amides of lysergic acid were also prepared.<sup>371</sup>

For satisfactory results alkali metal salts of the  $\alpha$ -acylamino acid or acyl peptide must be employed.

4-Methylmorpholine salts gave very poor yields.<sup>183</sup> Commercially available trimethyl- and triethyl-amine sulfur trioxide complexes are unsatisfactory because they are too stable.<sup>5</sup>

Less than 5% of racemization was observed when the mixed anhydride of carbobenzyloxyglycyl-L-phenylalanine and sulfuric acid was coupled with glycine at pH 7.4, but considerable racemization was observed at pH 9. Earlier experiments had indicated that racemization was caused by aqueous alkali and not during the anhydride-forming step.<sup>183</sup> Coupling the anhydride of sulfuric acid and carbobenzyloxyglycyl-L-alanine with L-phenylalanyl-glycine at pH 7.4 gave a ratio of LL to DL tetrapeptide of 6.2:1. The products were separated by countercurrent distribution.<sup>5</sup> It was suggested that formation of the tetrapeptide was a slower reaction than that of the tripeptide, so that more racemization and hydrolysis occurred with the former. The tetrapeptide was formed in 60% yield, the carbobenzyloxyglycyl-L-phenylalanyl-glycine in 83% yield. Subsequent work showed that, if the pH was kept below 6.8 by powdered magnesium carbonate, less than 1% of the tetrapeptide was racemized.<sup>370</sup>

When esters were substituted for the sodium salts of amino acids and the reactions carried out in dry dimethylformamide, no racemization was observed,<sup>5, 370</sup> The use of esters in inert solvents obviates the necessity for control of pH; a mole of triethylamine is merely added to the reaction mixture.

The sulfuric acid mixed anhydride will not acylate an amide even intramolecularly.<sup>5</sup> This observation may prove of some value in the synthesis of peptides of asparagine or glutamine.

The sulfuric acid anhydride procedure has been extended to cyclic anhydrides of sulfonic and carboxylic acids (pp. 198–199). However, relatively poor results were obtained with *o*-sulfobenzoic anhydride, 3,5-dibromo-2-sulfobenzoic anhydride, and  $\beta$ -sulfopropionic anhydride in model experiments with *p*-toluenesulfonyl-DL-alanine and morpholine.<sup>183</sup> Furthermore, the intermediates are probably carboxylic acid mixed anhydrides and not sulfonic acid mixed anhydrides. Propane 1,3-disulfonic anhydride gave only a 27% yield of *p*-toluenesulfonyl-DL-alanine morpholide.<sup>183</sup> The mixed anhydrides of  $\alpha$ -acylamino acids prepared from these cyclic sulfonic anhydrides probably disproportionate readily or, more likely, are attacked at both points by the amine.

The mixed anhydride prepared from carbobenzyloxyglycine and sulfuryl chloride, when treated with sodium glycinate in tetrahydrofuran at 0° in the presence of *N*-ethylpiperidine, gave carbobenzyloxyglycyl-glycine in only 30% yield.<sup>48</sup> Probably disproportionation caused the low yield. Substitution of thionyl chloride for sulfuryl chloride served to increase the yield of product to 35%.

The sulfuric anhydride method is patented.<sup>372-376</sup>

## 17.2. Experimental Conditions

The mixed anhydride is prepared by adding sulfur trioxide in the form of its crystalline dimethylformamide complex to the alkali metal salt of the  $\alpha$ -acylamino acid or peptide in dimethylformamide, a particularly useful solvent for this reaction.

Alternatively, a solution of known normality of the sulfur trioxide-dimethylformamide complex in dimethylformamide may be introduced into the cold solution of the salt of the  $\alpha$ -acylamino acid or peptide.

Sulfur trioxide was formerly prepared from sulfur dioxide and oxygen in the presence of a platinum catalyst at 650° and distilled twice before conversion to the dimethylformamide complex. Sulfur trioxide prepared from oleum usually contained traces of moisture and gave lower yields than that prepared from sulfur dioxide unless the dimethylformamide complex was purified by recrystallization.<sup>5</sup> The complex may be stored for several months in a refrigerator.<sup>183, 370</sup> Sulfur trioxide-dioxane or sulfur trioxide-pyridine complexes do not give satisfactory results.



The salt of the  $\alpha$ -acylamino acid or peptide is prepared by exact neutralization of the acid in dimethylformamide with potassium methoxide or with phenyltrimethylammonium methoxide in methanol followed by removal of the methanol in vacuum at 50°. [369](#), [372](#), [373](#) On drying the phenyltrimethylammonium salts, some decomposition to dimethylaniline and the methyl ester of the carboxylic acid was observed. [370](#) Lithium methoxide is now favored for neutralization [5](#), [36](#), [370](#) because of the relatively high solubility of lithium salts of  $\alpha$ -acylamino acids or peptides in organic solvents. [375](#)

The reaction of the sulfur trioxide-dimethylformamide complex with the potassium or lithium salt of the  $\alpha$ -acylamino acid in dimethylformamide is complete within 1 minute at 0°. The stability of the mixed anhydride with respect to disproportionation was investigated by the preparation of tosyl-DL-alanyl-cyclohexylamide. Quantitative yields of amide were obtained when the mixed anhydride was allowed to stand for 3 to 130 minutes before the addition of the amine. [183](#)

The mixed  $\alpha$ -acylamino sulfuric anhydrides are fairly stable at pH 7, but not at higher pH. For example, the half-life of carbobenzyloxyglycyl lithium sulfate in 40% dimethylformamide containing potassium phosphate varied from 10.5 hours at pH 6 to about 1 hour at pH 9 and about 0.1 hour at pH 10. [5](#) During the reaction of the mixed anhydride with the aqueous amino acid solution the pH is controlled either by the use of a buffer such as powdered magnesium carbonate, or by the addition of alkali to maintain the pH between 7.4 and 8.5, using phenol red as an indicator. [370](#) When magnesium carbonate is used, stirring is continued for 15 hours. Excess magnesium carbonate is then dissolved with hydrochloric acid. When sodium hydroxide is employed, the reaction mixture may be worked up 15 minutes after the addition of the anhydride. In reactions in anhydrous dimethylformamide, the reaction is allowed to proceed for 1 hour at 20°.

In most cases in which sulfuric acid mixed anhydrides have been employed for peptide synthesis, coupling has been between an  $\alpha$ -acylamino acid or acyl peptide and an amino acid sodium salt so that purification has necessitated the use of countercurrent distribution. An eleven or twenty-two transfer distribution between ethyl acetate and molar phosphate buffer has proved satisfactory. [183](#), [369](#), [372](#), [373](#)

## 17.3. Experimental Procedures

### 17.3.1. Sulfur Trioxide-Dimethylformamide Complex [183](#)

Sulfur trioxide is distilled directly onto the surface of dimethylformamide which is stirred and cooled in an ice bath. When crystals start to separate, distillation is stopped and dimethylformamide added to give a clear solution which is standardized by titration with aqueous alkali.

### 17.3.2. Preparation of Anhydrous Salts of $\alpha$ -Acylamino Acids [183](#)

Two to ten millimoles of the  $\alpha$ -acylamino acid is dissolved in 30 to 50 ml. of dimethylformamide and the solution neutralized with methanolic potassium methoxide or lithium methoxide. About half of the solvent is removed by distillation at 50°/15 mm. through a 15-cm. packed column.

Phenyltrimethylammonium salts may also be used. They are prepared by neutralizing the  $\alpha$ -acylamino acid with the filtrate from the reaction of phenyltrimethylammonium p-toluenesulfonate with methanolic sodium methoxide.

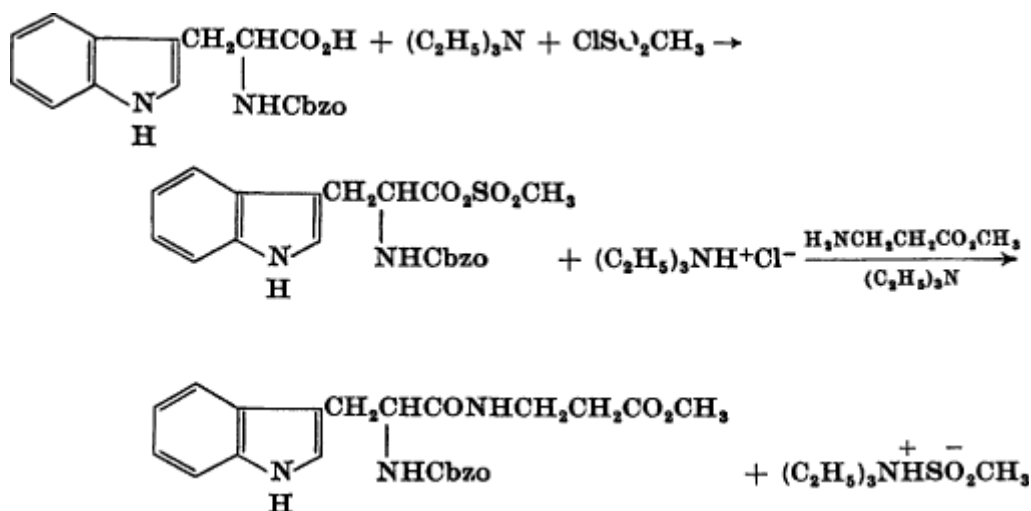
### 17.3.3. Carbobenzyloxyglycyl-DL-phenylalanine<sup>183, 372, 373</sup>

A solution of 10 mmoles (6.6 ml.) of the sulfur trioxide-dimethylformamide complex in excess dimethylformamide was added to 10 mmoles of potassium carbobenzyloxyglycinate in dimethylformamide and the reaction mixture shaken at 20° for 5 minutes before it was cooled in an ice-salt bath. A solution of 1.98 g. (12 mmoles) of DL-phenylalanine in 10 ml. of water and 12 ml. of aqueous sodium hydroxide containing phenolphthalein was then added with stirring in one portion to the solution of the mixed anhydride. Sufficient 0.5N aqueous sodium hydroxide was then rapidly added to restore and maintain the pink color. After 10 minutes the solution was neutralized with 3N sulfuric acid and evaporated under reduced pressure to a syrup which was taken up in 12 ml. of 3N sulfuric acid and 50 ml. of ethyl acetate. The layers were separated and the aqueous layer extracted four times with ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to give 5.15 g. of pale yellow oil. An eleven-transfer distribution between ethyl acetate and M phosphate buffer (7 moles of potassium dihydrogen phosphate to 3 moles of dipotassium hydrogen phosphate) gave 2.5 g. (70%) of product and 0.7 g. (3 mmoles) of carbobenzyloxyglycine. Recrystallization of the product from ethyl acetate gave colorless needles, m.p. 162°.

The use of phenol red rather than phenolphthalein to control the pH gives better results with optically active amino acids.<sup>370</sup>

## 18. $\alpha$ -Acylaminoacyl Alkyl and Aryl Sulfonates

Although it has been reported that benzene- or p-toluene-sulfonyl chloride cannot be used for the synthesis of peptides,<sup>48</sup> these chlorides have been successfully used in such syntheses.<sup>377</sup> Methanesulfonyl chloride is equally satisfactory, but sulfenyl and sulfinyl chlorides gave poor results. The synthesis of methyl carbobenzyloxy-DL-tryptophyl- $\beta$ -alaninate is illustrated in the accompanying equations. The two-step reaction, which is carried out without isolation of the mixed anhydride, requires a mole of base for each step.



The isolation of a crude mixed anhydride<sup>15</sup> affords partial support of the postulated course of reaction. The reaction has also been conducted by adding benzenesulfonyl chloride to a mixture of the  $\alpha$ -acylamino acid and amino acid ester in pyridine;<sup>378</sup> the reaction is assumed to proceed by way of the symmetrical anhydride.

### 18.1. Scope and Limitations



Both the scope of and the yields obtained with the sulfonyl chloride procedure appear to be comparable to those with the chloroformate procedure. Reaction of L-proline in aqueous acetone with p-toluenesulfonyl chloride in the presence of sodium bicarbonate gave, in addition to a 77% yield of p-toluenesulfonyl-L-proline, a 6% yield of p-toluenesulfonyl-L-prolyl-L-proline.<sup>379</sup> A mixed anhydride between p-toluenesulfonyl-L-proline and p-toluenesulfonic acid was presumably formed in the aqueous solution.

The modification employing pyridine as a solvent<sup>378</sup> failed with hippuric acid and gave side reactions with carbobenzyloxyamino acids, but phthaloyl and tosyl dipeptide esters were obtained in 50% to 90% yield.

## 18.2. Experimental Conditions

A solution of the  $\alpha$ -acylamino acid and one equivalent of triethylamine in an inert solvent such as acetone or toluene is cooled normally at  $-10^\circ$  with methanesulfonyl chloride and to  $0^\circ$  with p-toluenesulfonyl chloride or benzenesulfonyl chloride. The reaction mixture is then stirred for 3 to 30 minutes, and the amine to be acylated is added, usually in solution in a suitable solvent such as acetone, water, or chloroform. An additional mole of triethylamine is also added. If an amino acid ester hydrochloride is used, two additional moles of triethylamine are used.

The amide-forming step is allowed to proceed for 2 hours at room temperature, or the reaction mixture is warmed to  $65-70^\circ$  for 5 minutes, cooled, and worked up. The isolation procedure is the same as for the products formed by the mixed alkyl carbonate method.

The reaction also proceeds satisfactorily when the  $\alpha$ -acylamino acid and amino acid ester are dissolved in dry pyridine and one equivalent of benzenesulfonyl chloride is added. The product is isolated by diluting the reaction mixture with water after 1 to 20 hours at room temperature.<sup>378</sup>

## 18.3. Experimental Procedures

### 18.3.1. Methyl Carbobenzyloxy-L-leucyl-L-leucinate<sup>377</sup>

A solution of 25 g. of carbobenzyloxy-L-leucine and 13.2 ml. of triethylamine in 200 ml. of acetone was cooled to  $-10^\circ$  and treated with 7.2 ml. of methanesulfonyl chloride. The mixture was stirred for 4 minutes at  $-10^\circ$  to form the mixed anhydride. To this solution were added 17.2 g. of methyl L-leucinate hydrochloride and 26.4 ml. of triethylamine in 75 ml. of chloroform, and the mixture was allowed to warm to room temperature. Stirring was continued for 2 hours, the mixture was filtered, the solvent removed by distillation, and the residue taken up in ethyl acetate. The ethyl acetate solution was washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and again with water. The ethyl acetate layer was dried and concentrated and the residue recrystallized from ethyl acetate-n-hexane to give 26.8 g. (73%) of methyl carbobenzyloxy-L-leucyl-L-leucinate, m.p.  $73-81^\circ$ ;  $[\alpha]_D^{25} -35.8 \pm 0.2^\circ$  (c = 1%, ethanol).

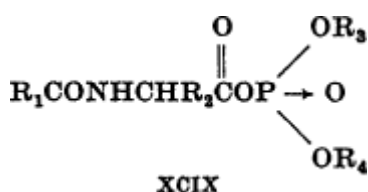
### 18.3.2. Ethyl Carbobenzyloxyglycyl-L-leucyl-D-tryptophanate<sup>15</sup>

To a solution of 8.1 g. of carbobenzyloxyglycyl-L-leucine and 7 ml. of triethylamine in 70 ml. of toluene, cooled to  $0^\circ$ , was added 4.8 g. of p-toluenesulfonyl chloride and the mixture was stirred for 30 minutes. To

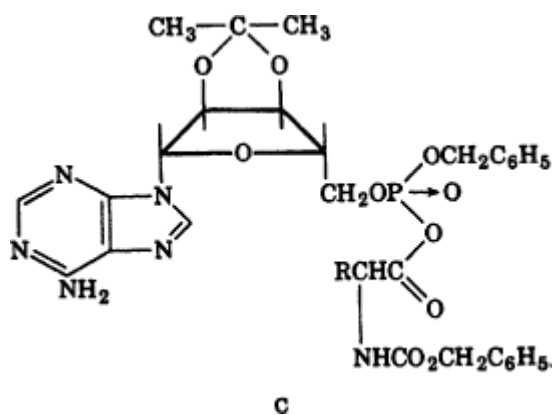
the solution of the mixed anhydride was added a solution of 6.6 g. of ethyl D-tryptophanate in 40 ml. of warm toluene. The mixture was heated rapidly to 65°, kept at this temperature for 5 minutes, and then cooled. The solution was successively washed with water, dilute hydrochloric acid, and aqueous sodium bicarbonate and the solvent removed to give 7.1 g. of product, m.p. 127–130°.

## 19. $\alpha$ -Acylaminoacyl Phosphates

The  $\alpha$ -acylaminoacyl phosphates that have been used for peptide synthesis have the general formula XCIX, where  $R_1\text{CONHCHR}_2\text{CO}$  is an acylated amino acid and  $R_3$  and  $R_4$  are both ethyl, phenyl, or benzyl, or one is silver and one is phenyl. Mixed anhydrides of 2 $\phi$ -3 $\phi$ -isopropylideneadenosine-5 $\phi$ -benzylphosphoric acid with carbobenzyloxyamino acids such as C have also been used.[380](#)



Although the  $\alpha$ -acylaminoacyl phosphates are of interest biochemically, they have not proved to be of practical utility in the synthesis of peptides. In general, anhydrides of phosphoric acid or its mono- or di-alkyl derivatives with  $\alpha$ -acylamino acids are not so readily prepared as a number of other mixed anhydrides. Furthermore, the necessary phosphate must itself be synthesized before it can be converted to the  $\alpha$ -acylaminoacyl phosphate, and the use of the  $\alpha$ -acylaminoacyl chloride for the preparation of the aminoacyl phosphate adds an additional step. The use of esters of the enol phosphate of malonic acid to synthesize  $\alpha$ -acylaminoacyl phosphates[381-383](#) might increase the utility of phosphate anhydrides.



### 19.1. Scope and Limitations

#### 19.1.1. Use of an $\alpha$ -Acylamino Acid Mixed Anhydride and a Phosphate Salt

The use of  $\alpha$ -acylaminoacyl phosphates was designed to test the suggestions of Lipmann[384](#) that acyl phosphates supplied the energy necessary for peptide bond formation in vivo. Except for the use of enol phosphates, the work has been largely limited to model experiments with carbobenzyloxy- and phthaloyl-glycine.

Carbobenzyloxyglycyl chloride reacts with disilver phenyl phosphate to give silver phenyl carbobenzyloxyglycyl phosphate.<sup>22, 385</sup> This anhydride is fairly stable for several hours in aqueous solution at pH 7.4 at 37° but reacts rapidly with glycine to give carbobenzyloxyglycylglycine in high yield. The reaction was carried out on a very small scale, and the products were identified by paper chromatography.

Hydrogenolysis of silver phenyl carbobenzyloxyglycyl phosphate at pH 7.4 resulted in a mixture of dipeptide and diketopiperazine; at pH 3.0 it gave phenyl glycyl phosphate as shown by reaction of the product with hydroxylamine.

Phthaloylglycyl chloride reacts with silver dibenzyl phosphate to give dibenzyl phthaloylglycyl phosphate. This mixed anhydride in benzene readily disproportionates when heated or upon long standing. The addition of triethylamine caused rapid disproportionation.<sup>386</sup>

Dibenzyl phthaloylglycyl phosphate reacts rapidly and exothermically with aniline to give phthaloylglycylanilide in 91% yield.<sup>386</sup> There was no evidence that the mixed anhydride had reacted to give N-(dibenzylphosphoryl)aniline. Dibenzyl phthaloylglycyl phosphate also acylates DL-phenylalanine and glycine to give the phthaloyldipeptides in 83% and 91% yields, respectively.

The reaction of phthaloylglycyl chloride with triethylammonium dibenzyl phosphate gave only the symmetrical anhydrides.<sup>386</sup>

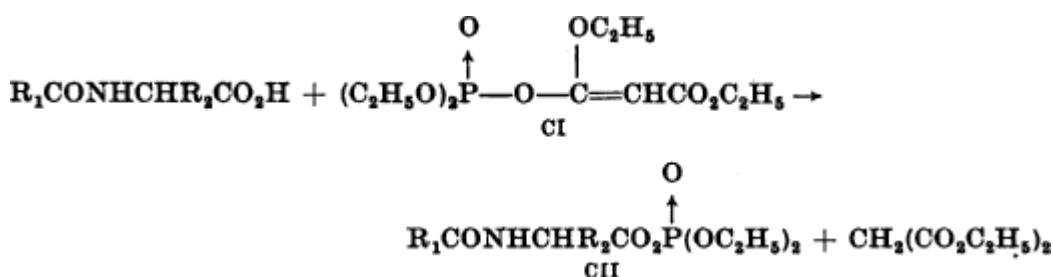
Carbethoxyglycyl phosphate was prepared from carbethoxyglycyl ethyl carbonate and phosphoric acid, but no amides were prepared from this mixed anhydride.<sup>387</sup>  $\alpha$ -Azidoamino acid chlorides react with silver dibenzyl phosphate to give nearly quantitative yields of the mixed anhydrides of the glycine, DL-alanine, and DL-phenylalanine analogs.<sup>388</sup> Hydrogenation in the presence of Raney nickel reduced the  $\alpha$ -azido group and further reduction with a palladium catalyst removed the benzyl groups. The mixed anhydrides were isolated as the disilver and also as the neutral barium salts in about 50% yield.

The mixed adenylic acid DL-valine anhydride (valyl AMP) has been prepared in 10–20% yield by warming the sodium salt of adenosine-5 $\phi$ -phosphoric acid with thiophenyl-DL-valinate hydrochloride in dimethylformamide for half an hour at 120°. <sup>389</sup> The synthesis of L-leucyl adenosine-S-phosphate was achieved in 9% yield from L-leucyl chloride hydrochloride and disilver adenosine monophosphate in acetic acid.<sup>390</sup>

### 19.1.2. Use of an $\alpha$ -Acylamino Acid Salt and a Phosphate Mixed Anhydride

The conversion of an  $\alpha$ -acylamino acid directly to a phosphate anhydride without the prior formation of an intermediate acylamino acid anhydride is a prerequisite for any practical phosphate mixed anhydride synthesis. The use of an enol phosphate of malonic ester achieves this.

An  $\alpha$ -acylamino acid will react with  $\alpha$ -ethoxy- $\beta$ -carbethoxyvinyl diethyl phosphate (CI) to give an  $\alpha$ -acylaminoacyl diethyl phosphate CII and diethyl malonate.<sup>381, 382, 391</sup>



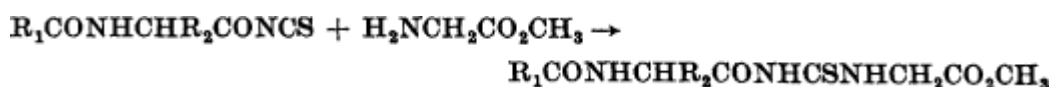
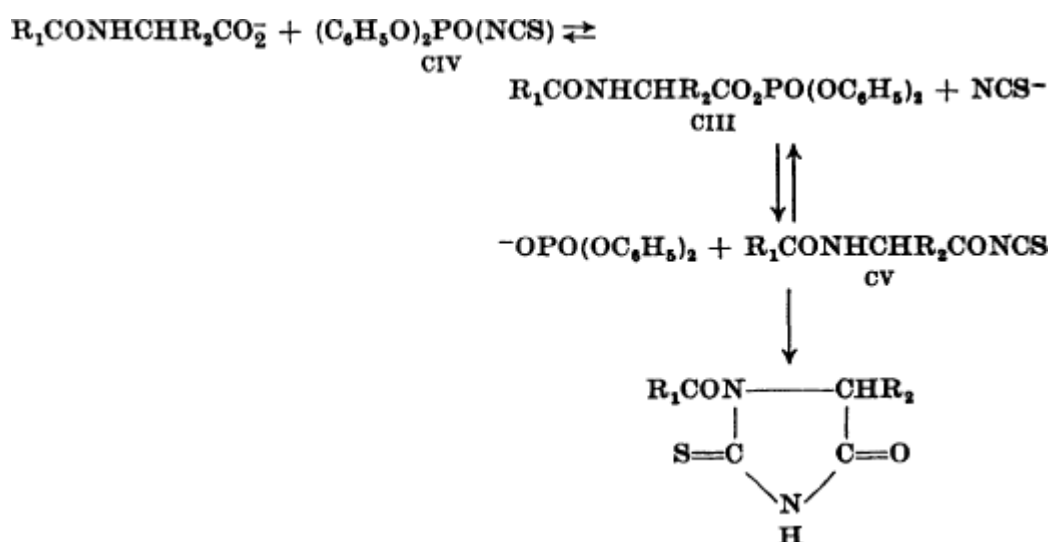
Carbobenzyloxy derivatives of glycine, DL-alanine, and L-leucine have been converted to diethyl phosphate mixed anhydrides and used to acylate the esters or sodium salts of amino acids and peptides. Over-all yields of product varied from 61% to 87%. This method would be expected to be accompanied by racemization when it is possible.

The enol phosphate CI can be prepared from triethyl phosphite and bromomalonic ester and stored.<sup>383</sup> This is the only feasible method so far developed for the synthesis of  $\alpha$ -acylaminoacyl phosphates.

Silver carbobenzyloxy-L-leucinate reacts with 2*φ*,3*φ*-isopropylideneadenosine-5*φ*-benzyl chlorophosphate in a mixture of benzene, acetonitrile, and dioxane to give the mixed anhydride C[R = (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>] as an oil. This oil acylated methyl glycinate to give methyl carbobenzyloxy-L-leucylglycinate. Methyl carbobenzyloxyglycyl-L-phenylalaninate was similarly prepared from silver carbobenzyloxyglycinate and methyl L-phenylalaninate.<sup>380</sup>

An attempt to prepare dibenzyl phthaloylglycyl phosphate from silver phthaloylglycinate and dibenzyl chlorophosphate was unsuccessful;<sup>386</sup> the more reactive diphenyl carbobenzyloxyglycyl phosphate was successfully prepared from the N-ethylpiperidinium salt of carbobenzyloxyglycine and diphenyl chlorophosphate in tetrahydrofuran.<sup>48</sup> The anhydride was not isolated but was treated with sodium glycinate to give carbobenzyloxyglycylglycine in 10% yield. The low yield was attributed to the difficulty of separating the product from diphenylphosphoric acid. If an ester instead of the sodium salt of the amino acid were used this difficulty might be avoided, but disproportionation might then lead to a low yield of product.

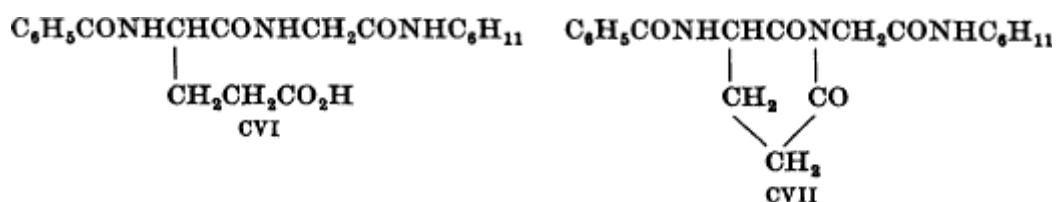
The intermediate formation of acylpeptide diphenyl phosphates such as CIII has been postulated in the reaction of acylpeptide anions with diphenyl isothiocyano-phosphate (CIV).<sup>19</sup> The acyl diphenyl phosphate reacts with isothiocyanate ion to give a new anhydride CV which cyclizes. Actually, the direct preparation of the acyl isothiocyanate CV from the acylpeptide and diphenyl isothiocyano-phosphate (CIV) might well be the principal reaction. This synthesis of a diphenyl acylpeptide phosphate was designed to be used in peptide degradation rather than synthesis. While the slowness of the cyclization step would permit an amino acid ester to react with the various anhydrides in solution, the acyl isothiocyanate CV would be expected to add rather than acylate the first mole of amine.



The possibility of an  $\alpha$ -acylamino acid reacting with a tetraalkyl pyrophosphate to give an  $\alpha$ -acylaminoacyl phosphate ester that could be employed in peptide synthesis was investigated (unpublished work, but see ref. 19). However, tetrabenzyl-, tetraphenyl-, and tetra-p-nitrophenyl-pyrophosphates gave

disappointing results with tosylalanine and cyclohexylamine in model experiments. The authors state that “presumably in the basic medium the acyl phosphates are rapidly brought into equilibrium with the two symmetrical anhydrides.” If this is the reason for the poor results, the symmetrical  $\alpha$ -acylamino acid anhydride should give a 50% yield of amide plus a 50% recovery of the  $\alpha$ -acylamino acid. The acid could then react with more tetraphenyl pyrophosphate to give ultimately another 50% yield of amide. If, however, the amine reacts with either the mixed anhydride or the pyrophosphate to give a diester phosphate amide, no further peptide bond formation would occur.<sup>392</sup>

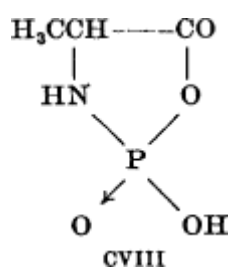
The reaction of benzoyl-DL- $\alpha$ -glutamylglycine cyclohexylamide (CVI) with one equivalent of tetraethyl pyrophosphate gave a 67% yield of the imide CVII. The use of two equivalents of tetraethyl pyrophosphate increased the yield of imide to 89%, but the recovery of the product was complicated by the presence of excess pyrophosphate.<sup>393</sup> The same product, CVII, was obtained in 99% yield with thionyl chloride in pyridine, in 95% yield with ethyl chloroformate, in 76% yield with excess cold acetic anhydride, and in only 6% yield with the sulfur trioxidedimethyl-formamide complex. The yield of product CVII exceeds 50% when tetramethyl pyrophosphate is used, although no amine is present to remove the phosphate as a diester phosphate amide. It is not yet understood why the use of tetraalkyl pyrophosphates gives poor results in peptide synthesis.



$\alpha$ -Acylamino acid anhydrides of phosphoric acid rather than its esters have been prepared, but these anhydrides have not been used for the controlled synthesis of peptides. Phthaloylglycyl chloride and alanyl chloride\* react with monosilver phosphate to give phthaloylglycyl and alanyl phosphates.<sup>394</sup> Phosphate anhydrides of glycine,<sup>395</sup> alanine,<sup>395</sup> and leucine,<sup>395</sup>, <sup>396</sup> and the  $\beta$ - and  $\gamma$ -phosphate anhydrides of L-aspartic and L-glutamic acids<sup>396</sup> have been prepared from the silver salt of the carbobenzyloxyamino acid and dibenzyl chlorophosphate; the three benzyl groups are removed from the intermediate dibenzyl carbobenzyloxyaminoacyl phosphates with anhydrous hydrogen bromide in carbon tetrachloride. In neutral aqueous solution the monoamino monocarboxylic acid phosphates are rapidly hydrolyzed and polymerized, whereas L- $\beta$ -aspartyl phosphate and L- $\gamma$ -glutamyl phosphate do not polymerize readily. The results are in marked contrast to those obtained with amino thiol acids.  $\alpha$ -Amino thiol acids ( $^-\text{H}_3\text{NCHRCOS}^-$ ), existing in the zwitter ion form, are unreactive toward ammonia or other amino acids.<sup>351</sup>

The work of Chantrenne<sup>22</sup> suggests that amino acid phosphates<sup>395</sup>, <sup>396</sup> might react faster with peptides than with themselves, but a controlled peptide synthesis still would not be feasible.

Alanine phosphate\* was partly converted to the cyclic anhydride CVIII on drying in vacuum.



L- $\beta$ -Aspartyl phosphate and L- $\gamma$ -glutamyl phosphate react with aqueous ammonia to give L-asparagine and L-glutamine, respectively, in 90% yield, so that it is reasonable to assume that these anhydrides could be

used for the preparation of L- $\beta$ -aspartyl or L- $\gamma$ -glutamyl peptides. Contamination of the product with some of the  $\alpha$ -isomer might occur under some conditions since the reaction could proceed at least in part through the amino acid anhydride.

## 19.2. Experimental Conditions

### 19.2.1. Preparation of the Mixed Anhydride

Carbobenzyloxyamino acids react with  $\alpha$ -ethoxy- $\beta$ -carbethoxyvinyl diethyl phosphate in warm dry acetone to give nearly quantitative yields of diethyl carbobenzyloxyamino acid phosphate. The reaction may also be conducted in dimethylformamide at 40° for 24 hours or at 70° for 1 hour.[381](#)

Phthaloyl- or carbobenzyloxy-glycyl chloride reacts with silver phosphates in ether or benzene when shaken for a few hours at room temperature. Shaking carbobenzyloxyglycyl chloride with disilver phenyl phosphate[397](#) for 2 hours in ether gives silver phenyl carbobenzyloxyglycyl phosphate.[22](#) When equimolar amounts of phthaloylglycyl chloride and silver dibenzyl phosphate were shaken in benzene for 4 hours, a 25% molar excess of the silver salt added, and the mixture shaken for an additional 2 hours, crystalline dibenzyl phthaloylglycyl phosphate was obtained in 91% yield.[386](#) The azido acid chlorides corresponding to glycine, DL-alanine, and DL-phenylalanine gave nearly quantitative yields of the mixed anhydrides when the chlorides were shaken with silver dibenzyl phosphate in benzene for three days at room temperature.[388](#) The reaction of phthaloylglycyl chloride with triethylammonium dibenzyl phosphate in benzene gave a 58% yield of phthaloylglycine anhydride based upon the chloride. A 71% yield of tetrabenzyl pyrophosphate was also isolated.[386](#) Carbobenzyloxyglycyl chloride reacted with pulverized silver dibenzyl phosphate at 4° overnight (shaking for the first half hour) to give a 50% yield of crystalline carbobenzyloxyglycyl dibenzyl phosphate.[386](#) Carbethoxyglycyl phosphate was prepared via the mixed carbonic anhydride.[387](#) The addition of diphenyl chlorophosphonate to a cold (0°) solution of carbobenzyloxyglycine in tetrahydrofuran containing one equivalent of N-ethylpiperidine gave a solution of diphenyl carbobenzyloxyglycyl phosphate which can be used as such.[48](#)

### 19.2.2. Preparation of Amide

The amide-forming step is conducted by mixing solutions of the  $\alpha$ -acylaminoacyl phosphate and the salt of an amino acid at room temperature. The latter solution is preferably buffered at pH 7.4. Dibenzyl phthaloylglycyl phosphate in dioxane was allowed to stand for 16 hours with two equivalents of glycine in a boric acid-borax buffer of pH 7.4. Removal of the solvent and recrystallization from ethanol afforded a 78% yield of pure phthaloylglycylglycine. In similar manner, crude phthaloylglycyl-DL-phenylalanine was obtained from dibenzyl phthaloylglycyl phosphate and DL-phenylalanine in 83% yield. Here again a 100% excess of amino acid was employed.

Silver phenyl carbobenzyloxyglycyl phosphate reacts rapidly with glycine, tryptophan,<sup>\*</sup> and glycytryptophan at 37° in dilute aqueous solution of pH 7.4.[22](#) These reactions were performed with milligram quantities and the products were not isolated; with larger quantities, countercurrent distribution would probably be needed to obtain pure products. At a pH of 6–8, the yields were 90% in a solution 0.01 M with respect to the amino acid or peptide, and nearly 100% at 0.1 M. These do not represent yields of isolated products, however.

Carbobenzyloxyamino acids react with  $\alpha$ -ethoxy- $\beta$ -carbethoxyvinyl diethyl phosphate to give a nearly quantitative yield of diethyl carbobenzyloxyamino acid phosphate when warmed in dry acetone or



dimethylformamide at 40° for 24 hours or at 70° for 1 hour.[381](#)

## 19.3. Experimental Procedures

### 19.3.1. Dibenzyl Phthaloylglycyl Phosphate[386](#)

A solution of 2.73 g. (12 mmoles) of phthaloylglycyl chloride in 100 ml. of dry benzene was shaken with 4.65 g. (12 mmoles) of silver dibenzyl phosphate for 4 hours at room temperature. A second portion of the silver salt (1.16 g., 25% molar excess) was added and the suspension was shaken for two additional hours. The benzene solution was filtered through Celite to remove silver salts and the filtrate concentrated by freeze-drying. The residue crystallized on seeding. (A previous experiment gave a crystalline product after 4 days at room temperature.) The product was triturated with 20 ml. of dry ether, then with 20 ml. of dry ether containing 5 ml. of dry benzene, and finally with 20 ml. of dry ether. Dibenzyl phthaloylglycyl phosphate (5.11 g., 91%) was obtained as small needles, m.p. 63–65°.

### 19.3.2. Phthaloylglycylglycine[386](#)

A solution of 1.09 g. (2.34 mmoles) of dibenzyl phthaloylglycyl phosphate in 10 ml. of dioxane was added to a solution of 0.353 g. (4.7 mmoles) of glycine in 10 ml. of a boric acid-borax buffer (prepared by adding 0.05M borax to 0.2M boric acid to pH 7.4). About 5 ml. of dioxane was added to effect solution. The mixture was allowed to stand for 16 hours, concentrated under reduced pressure, and the residue recrystallized from ethanol to give 0.51 g. (83%) of crude product, m.p. 180–190°. Recrystallization from ethanol yielded 0.478 g. (78%) of phthaloylglycylglycine, m.p. 229–231°. The mother liquor yielded additional product which, after recrystallization, weighed 0.08 g. (13%), m.p. 227–230°.

### 19.3.3. Diethyl $\alpha$ -Ethoxy- $\beta$ -carbethoxyvinyl Phosphate[383](#)

An ice-cold solution of 6.2 g. of triethyl phosphite in two volumes of ethyl ether was added dropwise with stirring to an ice-cold solution of 9 g. of diethyl bromomalonate in two volumes of ether. The reaction mixture should be colorless at the end of the addition; the use of impure starting materials or too rapid addition of the triethyl phosphite produces a yellow color. The ether was removed under reduced pressure and the residue distilled with caution because of initial foaming. The main fraction distilled at 124–126°/0.05 mm.;  $n_D^{25} = 1.4513$ . The yield was 9 g. (82%).

### 19.3.4. Carbobenzyloxyglycyl-DL-phenylalanine[381](#)

A solution of 1.04 g. of carbobenzyloxyglycine and 1.48 g. of diethyl  $\alpha$ -ethoxy- $\beta$ -carbethoxyvinyl phosphate in 2 ml. of acetone was heated at 70° for 1 hour. The reaction mixture was cooled, diluted with 2 ml. of benzene, and dropped slowly into a solution of 0.82 g. of DL-phenylalanine and 0.2 g. of sodium hydroxide in 2 ml. of water containing phenolphthalein. The solution was kept basic by the addition of 2N sodium hydroxide as needed. The benzene layer was separated, the aqueous layer acidified with concentrated hydrochloric acid, and the precipitated carbobenzyloxy peptide recrystallized from water. The yield was 1.05 g. (61%) of material, m.p. 160°.

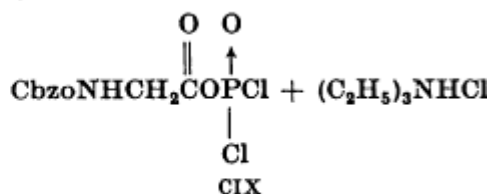
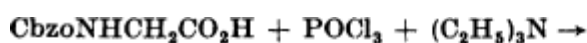
## 20. $\alpha$ -Acylaminoacyl Dichlorophosphates

The reaction of two moles of carbobenzyloxyglycine with phenyl dichlorophosphate in the presence of a tertiary base gave bis-carbobenzyloxyglycyl phenyl phosphate.<sup>48</sup> This mixed anhydride reacts with sodium glycinate to give carbobenzyloxyglycylglycine in the low yield of 30%, which was interpreted as an indication of rapid disproportionation.

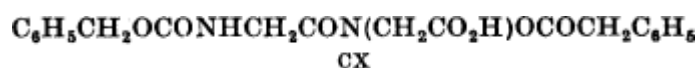
Carbobenzyloxyglycine, when treated with N-ethylpiperidine and phosphorus oxychloride in tetrahydrofuran, failed to react with sodium glycinate.<sup>48</sup> A reinvestigation of the use of phosphorus oxychloride with non-aqueous solvents, employing amino acid esters rather than free amino acids, showed that peptide synthesis was possible. Fifteen peptide intermediates were prepared in yields of 62% to 95%.<sup>130</sup> Of special interest is the preparation of carbobenzyloxy-L-hydroxypropyl-L-tryptophan methyl ester. While this compound was obtained as a glass in 75% yield, saponification and hydrogenolysis gave crystalline L-hydroxypropyl-L-tryptophan. Apparently sulfhydryl groups are oxidized with phosphorus oxychloride in the presence of a tertiary amine, thus preventing a compound like methyl cysteinate from being satisfactorily acylated by  $\alpha$ -aminoacyl dichlorophosphates.

The reaction of phosphorus oxychloride with a mixture of the  $\alpha$ -acylamino acid and the  $\alpha$ -amino acid ester proceeds via the  $\alpha$ -acylaminoacyl dichlorophosphate and not via a derivative of the  $\alpha$ -amino group.<sup>130</sup> The latter type of compound has been shown to give tris-amido compounds which react very slowly with  $\alpha$ -acylamino acids.<sup>117</sup>

One mole of phosphorus oxychloride per mole of  $\alpha$ -acylamino acid gives the maximum yield of product, showing that only one chlorine atom participates in the synthesis of the anhydride. The equations for the preparation of methyl carbobenzyloxyglycylglycinate are therefore the following.



The mixed anhydride CIX will acylate the nitrogen atom of carbobenzyloxyglycine to give N,N $\zeta$ -dicarbobenzyloxyglycine (CX). This reaction has been observed only with glycine,<sup>130</sup> presumably because of the lack of steric hindrance with this amino acid.



Pyruvic acid forms a mixed anhydride with phosphorus oxychloride which permits the preparation of pyruvoylamino acid esters.<sup>119, 398</sup>

### 20.1. Experimental Conditions

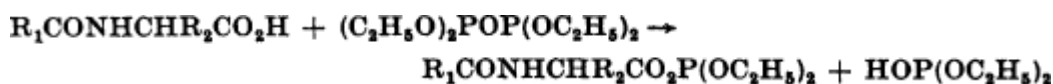
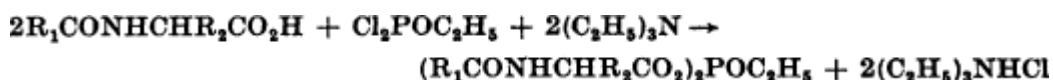
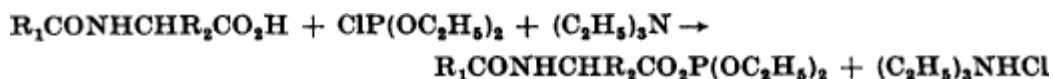
Three procedures have been employed for the synthesis of peptides with phosphorus oxychloride.<sup>130</sup> The preferred procedure follows: to a cooled solution,  $-15^\circ$ , of 0.01 mole of  $\alpha$ -acylamino acid and 0.01 mole



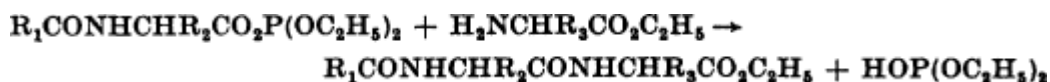
of amino acid ester in 50 ml. of tetrahydrofuran is added with shaking 0.01 mole of phosphorus oxychloride followed immediately by 0.02 mole of triethylamine. One hour is allowed for completion of the reaction. Pyridine may be used in place of triethylamine, sometimes with improved yields.[37](#)

## 21. $\alpha$ -Acylaminoacyl Phosphites

The reaction of a mono- or di-halophosphite or a tetraalkyl pyrophosphite with an  $\alpha$ -acylamino acid leads to an  $\alpha$ -acylaminoacyl phosphite.



These phosphite mixed anhydrides react with amines to form amides.



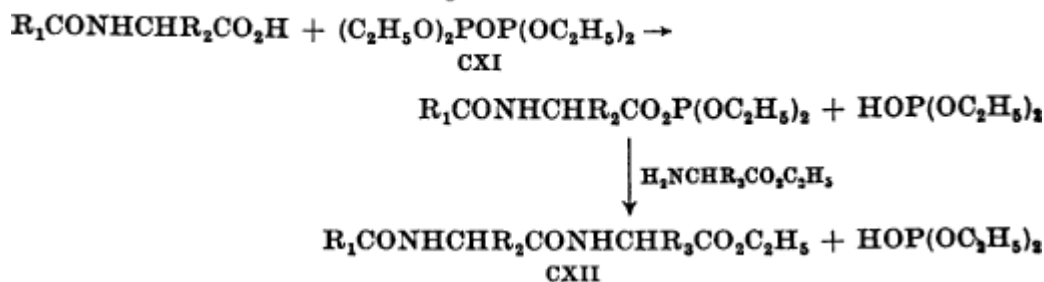
The method was developed by Young[399-408](#) and Anderson[42, 409-411](#) and co-workers.

The structure of the intermediate phosphorus compounds has not been rigorously established. None of the mixed  $\alpha$ -acylaminoacyl phosphite anhydrides has been obtained in crystalline form, and attempted distillation of even the simpler mixed anhydrides leads to decomposition.[42](#) However, similar anhydrides from organic acids such as butyric acid and tetraethyl pyrophosphite have been distilled.[412](#) The molecular refractivity for butyric acid diethyl phosphite was 49.3 as compared with a theoretical value of 49.6.[400](#) Although the proposed structures depend for the most part on analogies, there is little doubt about their correctness.

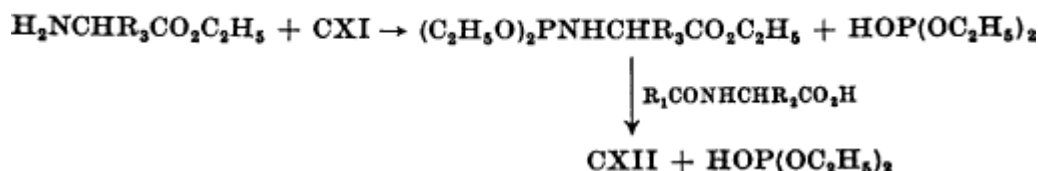
### 21.1. Mechanism

The phosphite method of peptide synthesis differs from most other methods in that the reagent will react with either the carboxylic acid or the amine function to give a useful reactive intermediate. The nature of the intermediate depends upon the order of mixing the reactants, and the methods have been referred to as the anhydride procedure, the amide procedure, and the standard procedure.[410](#) The course of the reactions using tetraethyl pyrophosphite (CXI) is indicated in the accompanying equations. Similar reactions occur when halophosphites are used in place of the pyrophosphite.[42, 392](#)

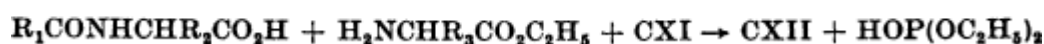
*Anhydride Procedure*



*Amide Procedure*



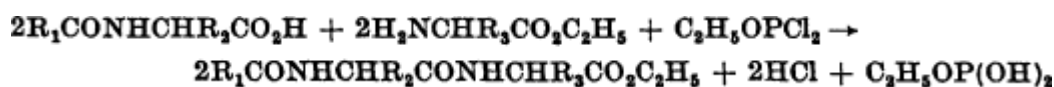
*Standard Procedure*

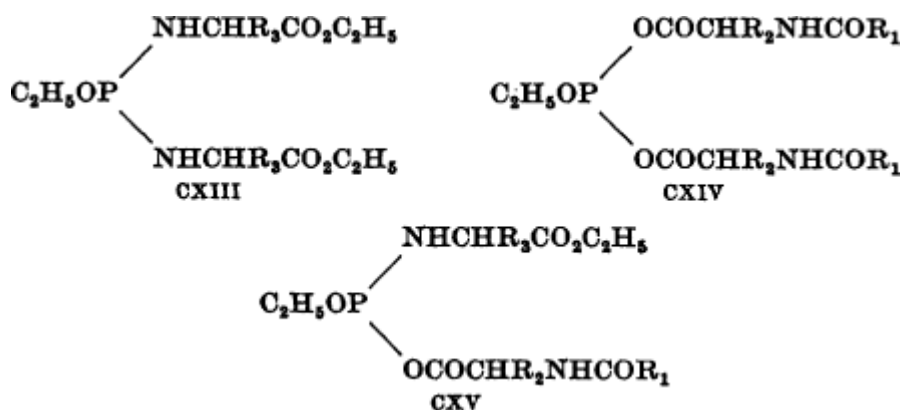


These reactions indicate that disproportionation of mixed phosphite anhydrides, unlike most other mixed anhydrides, will not necessarily lower the yields of products. Disproportionation merely produces more tetraalkyl pyrophosphite which can react with either the amine component or the acid component to give additional active intermediate.

The amide procedure, although very useful, is not within the scope of this chapter. In the standard procedure, the reagent is added to a mixture of the amine and acid. Since the addition of phosphorus trichloride to an acid and an amine leads to a reaction, proceeding by way of a phosphorazo compound and not via an acid chloride,<sup>413</sup> it is believed that the standard procedure also proceeds primarily via the phosphite amide and not via the mixed anhydride. However, in the preparation of intermediates for the synthesis of oxytocin, the addition of diethyl chlorophosphite to a pyridine solution of carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine and methyl L-isoleucinate according to the general procedure used in the phosphorazo peptide synthesis<sup>414</sup> led to a partially racemized product. This could be avoided by allowing the chlorophosphite to react first with the isoleucine ester, using the amide procedure,<sup>392, 411</sup> These results suggest that the standard procedure proceeds, at least in part, via the mixed anhydride and not exclusively via the phosphite amide.

The reaction of an acid and an amine in the presence of dihalophosphite such as ethyl dichlorophosphite proceeds as shown in the accompanying equation.<sup>403, 407, 408</sup> The nature of the intermediate has not been established, but three possibilities have been suggested, namely structures CXIII, CXIV, and CXV. It is probable that the order of addition is the principal factor determining the particular intermediate obtained and that appreciable amounts of the mixed anhydride CXIV can be obtained only if the amine component is added last.





## 21.2. Scope and Limitations

Phosphite mixed anhydrides have been used to prepare peptides of glycine, DL-alanine, DL-valine, L-leucine, L-phenylalanine, L-tyrosine, and L-lysine. The method should be as applicable as the alkyl carbonate mixed anhydride procedure. Lower than average yields may be anticipated with L-serine, L-threonine, L-asparagine, and L-glutamine derivatives. However, merely reversing the order of addition of the reactants so that the phosphite amide is formed rather than the mixed anhydride should obviate this difficulty. L-Asparagine peptides have been prepared by the amide procedure.[66](#), [415](#), [416](#) This method has also been used to synthesize a peptide of L-arginine[23](#), [406](#) and key intermediates of oxytocin[417](#), [418](#) and arginine vasopressin.[86](#)

Diethyl benzoyl phosphite and ethanol give benzoic acid and triethyl phosphite.[412](#) Whether a reaction of this type will interfere with the acylation of a serine ester by an acylaminoacyl phosphite is not known.

The phosphite mixed anhydrides are relatively stable to disproportionation. The mixed anhydride formed between *o*-phenylene chlorophosphite and phthaloylglycine deposited only 20% of the symmetrical phthaloylglycine anhydride on standing for 2 days at 30°.[42](#)

No racemization was observed when carbobenzyloxy- or phthaloylamino acids were used.[410](#) When the acid component was an acyldipeptide, the extent of racemization depended upon the reaction conditions. The anhydride method resulted in more racemization than the amide method. Final addition of tetraethyl pyrophosphite gave results essentially the same as those obtained by the amide procedure, thus substantiating the view that both proceed via the amide. Substitution of ethyl glycinate hydrochloride and triethylamine for ethyl glycinate as the amine component increased racemization with each of the three methods, but the increase was most pronounced with the anhydride procedure. The use of hydrocarbon solvents such as benzene or toluene tends to minimize racemization, presumably by removing triethylammonium chloride from solution. In these solvents no racemization was observed when carbobenzyloxyglycyl-L-leucyl-*o*-phenylene phosphite or carbobenzyloxyglycyl-L-phenylalanyl-*o*-phenylene phosphite was coupled with glycine ester.[42](#), [399](#) Racemization does not occur in the absence of the anhydride-forming reagent. On the basis of these facts it has been suggested that racemization is due to the formation of an oxazolonium salt.[406](#)

## 21.3. Experimental Conditions

### 21.3.1. Preparation of the Phosphite

Diethyl chlorophosphite, which is frequently employed, is readily prepared in about 50% yield from phosphorus trichloride, ethanol, and diethylaniline in ether.<sup>419</sup> *o*-Phenylene chlorophosphite, which can be prepared from catechol and phosphorus trichloride in 94% yield, offers some advantages in stability.<sup>392, 420, 421</sup> It has been reported<sup>66</sup> that diethyl chlorophosphite will sometimes suddenly decompose on vacuum distillation with liberation of an inflammable gaseous by-product whereas *o*-phenylene chlorophosphite has never given any evidence of decomposition. Ethyl dichlorophosphite is prepared in 40–50% yields from ethanol and phosphorus trichloride,<sup>422</sup> and tetraethyl pyrophosphite is prepared from diethyl phosphite and ethyl chlorophosphite in benzene in the presence of triethylamine.<sup>410, 423-426</sup> A similar method of synthesis is used for the preparation of diethyl ethylenepyrophosphite.<sup>427</sup> Diethylene pyrophosphite has been prepared from ethylene chlorophosphite and water in the presence of triethylamine.<sup>427</sup> The refractive index has been used as a criterion of purity of tetraethyl pyrophosphite.<sup>410</sup> Bis-*o*-phenylene pyrophosphite may be prepared in 87% yield from *o*-phenylene chlorophosphite and water.<sup>421</sup>

### 21.3.2. Preparation of the $\alpha$ -Acylaminoacyl Phosphite

When a dialkyl chlorophosphite is employed to prepare the mixed anhydride, it is added to the solution of the  $\alpha$ -acylamino acid in an inert solvent in the presence of a base such as triethylamine. The silver salt of carbobenzyloxyglycine has been used in chloroform to prepare the mixed anhydride with diethyl chlorophosphite, but the over-all yield of carbobenzyloxyglycine anilide was only 22% as compared with an 88% yield when the triethylammonium salt in benzene was used.<sup>399</sup> The mixed anhydride is formed rapidly at the usual reaction temperature of 15° to 25°. Young<sup>399</sup> reports that chlorinated hydrocarbons, aliphatic ethers, and dioxane are useful solvents, although aromatic hydrocarbons such as benzene and toluene are preferred.<sup>42</sup> Aliphatic ketones and esters give less satisfactory results. The presence of thiophene in toluene used as a solvent is claimed to lower the yields when the phosphite amide procedure is used.<sup>66</sup> It is not known whether this observation can be extrapolated to the mixed anhydride procedure. In any event, this observation is sufficiently unusual to warrant confirmation. If true, poor results might be obtained with cysteine and methionine peptides.

The triethylamine hydrochloride, formed in quantitative yield, is removed by filtration to give a solution of the mixed anhydride which is normally used without isolation.

The use of dihalophosphite, preferably ethyl dichlorophosphite, involves no change in experimental procedure except that 1 mole of dichlorophosphite is used for 2 moles of acid and 2 moles of amine.<sup>403, 406-408</sup>

Tetraethyl pyrophosphite may be employed in excess without added solvent.<sup>410</sup> Trialkyl phosphites have been recommended as acid acceptors with alkyl dichlorophosphites or tetraalkyl pyrophosphites.<sup>428</sup> In the preparation of the mixed anhydride by the pyrophosphite procedure, the  $\alpha$ -acylamino acid or acylpeptide is warmed with the tetraethyl pyrophosphite for 2 minutes, and the amine to be acylated is then added.<sup>410</sup> Tetrahydrofuran has been suggested as a solvent for peptide synthesis with tetraethyl pyrophosphite.<sup>429</sup>

### 21.3.3. Formation of the Amide Bond

The mixed anhydride in solution reacts with an  $\alpha$ -amino acid ester or peptide ester. The  $\alpha$ -amino acid ester hydrochloride may be used and a mole of triethylamine added to liberate the amine, but better results are usually obtained if the base is used directly. The solution may be warmed for 15 minutes on the steam bath,<sup>42, 406</sup> or allowed to stand for 12 hours at room temperature<sup>399</sup> to complete the reaction. Heating the reaction mixture gives better yields,<sup>410</sup> but room temperature is preferable if ammonium salts are present.<sup>406</sup> Reactions carried out in water-immiscible solvents are worked up by washing with water,

aqueous sodium bicarbonate, and again with water. In many cases an acid wash would also be advisable. After drying, the solvent is removed to give the  $\alpha$ -acylpeptide ester. Yields generally range from 50% to 92%. With water-miscible solvents the product may usually be precipitated by addition of water. The addition of 5% aqueous sodium bicarbonate to dissolve unreacted  $\alpha$ -acylamino acid frequently causes oily products to crystallize.<sup>410</sup> The crude products are recrystallized from aqueous ethanol, ethyl acetate-hexane, or other suitable solvents.

## 21.4. Experimental Procedures

### 21.4.1. Ethyl Carbobenzyloxyglycyl-L-phenylalanyl-glycinate (Use of a Dialkyl Chlorophosphite)<sup>42</sup>

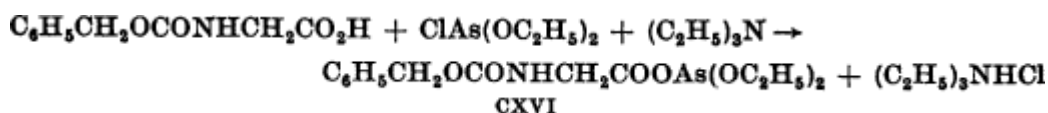
To a solution of 1.789 g. of carbobenzyloxyglycyl-L-phenylalanine in 50 ml. of benzene containing 0.6 g. of triethylamine was added 0.88 g. of *o*-phenylene chlorophosphite. The solution was filtered and the filtrate heated to boiling for 15 minutes with 0.5 g. of distilled ethyl glycinate. The solution was cooled and 25 ml. of ethyl acetate added to facilitate separation of two phases. The organic layer was washed with water, aqueous sodium bicarbonate, and water. Removal of the solvent left an oil which rapidly crystallized upon the addition of 10 ml. of anhydrous ethyl ether. The product weighed 2.03 g. (92.5%), m.p. 115–118°,  $[\alpha]_D^{25} -11.5^\circ$  (c = 2%, ethanol). Recrystallization from 20 ml. of ethyl acetate-petroleum ether gave 1.85 g. (89%) of product, m.p. 116–118°;  $[\alpha]_D^{25} -12.0^\circ$ .

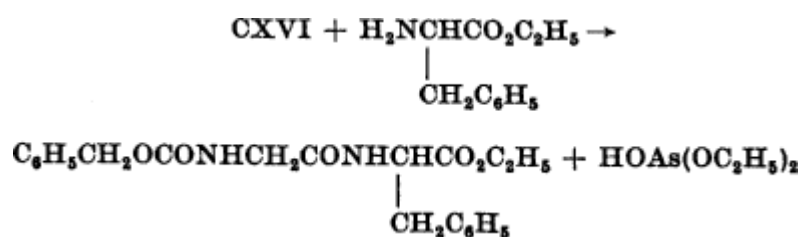
### 21.4.2. Methyl Carbobenzyloxyglycyl-L-leucyl-L-leucinate (Use of an Alkyl Dichlorophosphite)<sup>406</sup>

To a solution of 3.2 g. (0.01 mole) of carbobenzyloxyglycyl-L-leucine in 30 ml. of benzene containing 1.09 (0.01 mole) of triethylamine was added 0.74 g. (0.005 mole) of ethyl dichlorophosphite in 10 ml. of benzene. The amine hydrochloride was removed by filtration, 1.5 g. (0.01 mole) of distilled methyl L-leucinate added to the filtrate, and the solution held under reflux for 15 minutes. The cooled reaction mixture was washed with 10 ml. of water and 15 ml. of saturated aqueous sodium bicarbonate. The benzene solution was dried and concentrated under reduced pressure and the residue recrystallized from ethyl acetate-petroleum ether to give a 60% yield of product, m.p. 133–134°;  $[\alpha]_D^{25} -47.4^\circ$  (c = 2%, methanol).

## 22. $\alpha$ -Acylaminoacyl Arsenites

The properties of diethyl chloroarsenite are very similar to those of diethyl chlorophosphite. The reagent is readily prepared from arsenic trichloride and ethanol<sup>430</sup> and is relatively stable. The arsenite mixed anhydride is prepared from the  $\alpha$ -acylamino acid and diethyl chloroarsenite in an inert solvent such as toluene in the presence of triethylamine.<sup>431, 432</sup> The triethylamine hydrochloride is removed by filtration, and the mixed anhydride in solution is used directly for reaction with an amino acid ester. Heating under reflux for 1 hour completes the reaction.





This method has been used to prepare ethyl carbobenzyloxyglycyl-DL-phenylalaninate (52%), ethyl carbobenzyloxy-DL-alanyl-DL-phenylalaninate (60%), ethyl carbobenzyloxy-L-leucyl-DL-phenylalaninate (74%), and ethyl carbobenzyloxyglycylglycyl-DL-phenylalaninate (30%).

The diethyl chloroarsenite may also be initially added to the amino acid or peptide ester to form the arsenite amide.<sup>433</sup> The amide is then allowed to react with an  $\alpha$ -acylamino acid.<sup>434, 435</sup> This procedure has given slightly better yields than the anhydride method in the two cases where the same compound was prepared by both procedures.

## 23. Tabular Survey

In the following tables are listed peptide intermediates prepared by the use of mixed anhydrides. Each table, which deals with a single mixed anhydride, is arranged according to the increasing number of amino acid residues in the product. Peptides with the same number of residues are arranged according to increasing number of residues in the acylating species. Further subdivision depends upon the particular amino acid which forms the anhydride; aliphatic, aromatic, acidic, basic, and unnatural amino acids appear in that order.

A dash in the solvent or yield column indicates that the solvent or yield was not reported.

The literature was surveyed through the March 25, 1959, issue of Chemical Abstracts. Abstracts were relied upon only in those few cases in which it was impossible to secure a copy or photostat of the original. Those peptide intermediates appearing in the patent literature which most probably have never been made have been omitted from the tables.

The amino acid residues, single bond HNCHRCO single bond, are abbreviated according to the system developed by Erlanger and Brand<sup>436</sup> in which the first three letters of the name represent the particular residue. For those not familiar with peptide chemistry, abbreviations are listed below.

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Table I. Anhydride Formation with Phosgene

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Table II. Anhydride Formation with Ethyl Chloroformate

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Table III. Anhydride Formation with sec-Butyl Chloroformate

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Table IV. Anhydride Formation with Isobutyl Chloroformate

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Table V. Anhydride Formation with Miscellaneous Chloroformates, ClCO<sub>2</sub>R

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Table VI. Anhydride Formation with Isovaleryl Chloride

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Table VII. Anhydride Formation with Trimethylacetyl and Diethylacetyl Chlorides

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Table VIII. Anhydride Formation with Benzoyl Chloride

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Table IX. Anhydride Formation with N,N $\epsilon$ -Dicyclohexylcarbodiimide

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Table X. Anhydride Formation with Miscellaneous Carbodiimides

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Table XI. Anhydride Formation with Ketenimines

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Table XII. Anhydride Formation with Acetylenic Ethers

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Table XIII. Anhydride Formation with Ethyl  $\alpha$ -Chlorovinyl Ether and with  $\alpha,\alpha\text{-}\phi$ -Dichloroethyl Ether

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Table XIV. Anhydride Formation with p-Nitrophenol

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Table XV. Anhydride Formation with Miscellaneous Phenols

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Table XVI. Brenner's Method

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Table XVII. Anhydride Formation with Chloroacetonitrile

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Table XVIII. Anhydride Formation with Miscellaneous Esters

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Table XIX. Anhydride Formation with Acylimidazoles im-Acyl-L-Histidine Methyl Ester

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Table XX. Anhydride Formation with N,N $\phi$ -Carbonyldiimidazole



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Table XXI. Anhydride Formation with 3,5-Dimethylpyrazole

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Table XXII. Anhydride Formation with Thiophenyl Esters

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Table XXIII. Anhydride Formation with Miscellaneous Thiol Compounds

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Table XXIV. Anhydride Formation with Sulfuric Acid

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Table XXV. Anhydride Formation with Benzenesulfonyl Chloride

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Table XXVI. Anhydride Formation with Phosphorus Oxychloride

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Table XXVII. Anhydride Formation with Diethyl  $\alpha$ -Ethoxy- $\beta$ -Carbomethoxyvinyl Phosphate

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Table XXVIII. Anhydride Formation with Miscellaneous Phosphates

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Table XXIX. Anhydride Formation with Phosphites

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Table XXX. Anhydride Formation with Diethyl Chloroarsenite

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#### End Notes

- \*  
The prefix im indicates substitution on the imidazole ring. The convention follows the nomenclature suggested by Wieland in ref. [229](#) (see p. 208).
  
- \*  
The phosphorazo method was developed by Goldschmidt and co-workers. See *Angew. Chem.*, 62, 538 (1950); *Ann.*, 580, 68 (1953).
  
- \*  
The prefix “im” is used to indicate substitution on the imidazole ring. See ref. [229](#).
  
- \*  
The optical configurations of the amino acids used in the migration studies, while not specified, were presumably L.
  
- \*  
The optical configuration was not specified for alanine or leucine.
  
- \*  
The tryptophan was of unspecified optical configuration.

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TABLE I  
ANHYDRIDE FORMATION WITH PHOSGENE

Acid	Amine	Solvent	Yield, %	Reference
<i>o</i> -HOC <sub>6</sub> H <sub>4</sub> CO.L.Phe.OH	H.Gly.OCH <sub>3</sub>	Toluene-THF*	50	53

\* THF is tetrahydrofuran.

TABLE II  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
HCO.Gly.OH	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Acetone	47	13
CH <sub>3</sub> CO.Gly.OH	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Dioxane	52	13
	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	52	13
Cbzo.Gly.OH	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF*	73	37
	H.Leu.OCH <sub>3</sub>	Chloroform	89	314
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Toluene	—	437
	H.L.Leu.SC <sub>6</sub> H <sub>5</sub>	THF	70	37
	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	Chloroform	54	348
	H.S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform	53	348
	H.L.Pro.OH	—	20	59
	H.DL.Pro.OH	—	18	59
	H.DL.Ser.OH	DMF†	88	69
	H.DL.Ser.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	72	69
	H.L.Asp(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	79	415
	NH <sub>2</sub>   H.L.Asp.OH	Dioxane	—	66
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	76	317
	H.L.Lys.OCu/2	THF	50	61
	H.NO <sub>2</sub> .L.Arg.OCH <sub>3</sub>	Dioxane	54‡	438, 439
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	—	440
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Chloroform	70	441
	[SCH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> H] <sub>2</sub>	—	61	442
<i>p</i> -NO <sub>2</sub> Cbzo.Gly.OH	H.L.Glu(OCH <sub>3</sub> ) <sub>2</sub>	Chloroform	51	317
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	57	317
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	72 crude	317
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCO.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	43	443, 444
Phth.Gly.OH	H.Gly.OH	Chloroform	62	125, 152
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	70	54, 125
	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	—	67	348
	H.DL.Ser.OH	Dioxane	61	445
	H.DL.Ser.OCH <sub>3</sub>	Dioxane	62	445
	NH <sub>2</sub>   H.L.Asp.OH	Dioxane	72	66
	H.L.Glu(OCH <sub>3</sub> ) <sub>2</sub>	Chloroform	79 crude	317
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	77 crude	317
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	86 crude	317
	H.DL.Phe.OH	Dioxane	72	54
	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Dioxane	65	13

Note: References 437 to 538 are on pp. 353–355.

\* THF is tetrahydrofuran.

† DMF is dimethylformamide.

‡ This is the yield after saponification.

ORGANIC REACTIONS

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES

TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Phth.Gly.OH ( <i>continued</i> )	$  \begin{array}{c}  \text{(L) } \text{H}_3\text{C} \text{---} \text{CHCO}_2\text{CH}_3 \\    \qquad \quad   \\  \text{S} \qquad \quad \text{NH} \\  \diagdown \quad / \\  \text{C} \\  / \quad \backslash \\  \text{H}_3\text{C} \quad \text{CH}_3  \end{array}  $	Methylene dichloride	41	32
(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> .Gly.OH	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	Chloroform	92	446, 447
	D.DL.Ser.OC <sub>2</sub> H <sub>5</sub>	Chloroform	95	446, 447
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	98	446, 447
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	90	446, 447
	H.DL.Try.OCH <sub>3</sub>	Chloroform	77	446, 447
Tri.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	63-90	9, 10, 448, 449
	H.DL.Met.OH	Benzene	—	9, 10
	H. <i>im</i> .C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	60	227
	H. <i>im</i> .C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>3</sub>	—	—	450
	$  \begin{array}{c}  \text{Cbzo} \\    \\  \text{H.L.Lys.OCH}_3  \end{array}  $	THF	88	45
	H.DL.Try.OCH <sub>3</sub>	Chloroform	90	10, 448, 449
Stearoylglycine	H.Gly.OH	THF	75-80	451
	H.β.Ala.OH	THF	75-80	451
	NH <sub>2</sub>			
	$  \begin{array}{c}    \\  \text{H.Asp.OH}  \end{array}  $	THF	70-75	451
	H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> SO <sub>3</sub> H	THF	80-90 crude	451
Cbzo.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	80	452
Cbzo.DL.Ala.OH	H.Gly.OC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - <i>p</i>	THF	67	37
	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	70	37
Cbzo.L.Ala.OH	H.L.Ala.NHC <sub>18</sub> H <sub>37</sub> - <i>n</i>	THF	80§	451
Cbzo.DL.Ala.OH	H.β.Ala.OH	THF	64	453
Cbzo.L.Ala.OH	H.L.Ser.OCH <sub>3</sub>	Chloroform	51	454-456
	OH			
	$  \begin{array}{c}    \\  \text{H.L.Glu.OCH}_2\text{C}_6\text{H}_5  \end{array}  $	Dioxane	45	97
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	70	96
	H.NO <sub>2</sub> .L.Arg.OCH <sub>3</sub>	Dioxane	66‡	438, 439
Cbzo.DL.Ala.OH	<i>i</i> -C <sub>3</sub> H <sub>7</sub> CHOHCH(NH <sub>2</sub> )CO <sub>2</sub> H	THF	46§	457
	NH <sub>2</sub>			
	$  \begin{array}{c}    \\  \text{H.L.Asp.OH}  \end{array}  $	Dioxane	—	66
Phth.L.Ala.OH				
	NH <sub>2</sub>			
	$  \begin{array}{c}    \\  \text{H.L.Asp.OH}  \end{array}  $	Dioxane	50	66
Phth.DL.Ala.OH				

Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield after saponification.

§ This is the yield after hydrogenolysis.

|| Other optical isomers were prepared.

TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> .DL.Ala.OH	H.DL.Try.OCH <sub>3</sub>	Chloroform	90	446, 447
	DL-C <sub>2</sub> H <sub>5</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	80	446, 447
Tri.DL.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	80-88	10, 448, 449
	H.DL.Ser.OC <sub>2</sub> H <sub>5</sub>	Chloroform	68	10, 448, 449
	H.DL.Try.OCH <sub>3</sub>	Chloroform	90	10, 448, 449
Stearoylalanine	H.Ala.OH	THF	—	451
Cbzo.β.Ala.OH	H.DL.Ala.OH	THF	87	453
	H.β.Ala.NHC <sub>18</sub> H <sub>37-n</sub>	THF	—	451
	H.DL.Ser.OH	DMF	48	122
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	100	458
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	96	458
	DL-CH <sub>2</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	96	453
	DL- <i>i</i> -C <sub>2</sub> H <sub>5</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	91	453
	DL-CH <sub>2</sub> SCH <sub>2</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	28	453
Stearoyl-β-alanine	H.Gly.OH	THF	75	451
	H.β.Ala.OH	THF	71	451
	H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> SO <sub>3</sub> H	THF	78	451
Cbzo.DL.Ser.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	50	69
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Dioxane	55¶	70
Cbzo.L.Pro.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	88	459
Cbzo.DL.Pro.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	94 crude	59
Cbzo.L.Pro.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	98 crude	59
	H.L.Val.OCH <sub>3</sub>	THF	81	45
	H.NO <sub>2</sub> .L.Arg.OCH <sub>2</sub>	Dioxane	60‡	438, 439
	H.L.Phe.OCH <sub>3</sub>	THF	71**	460
Cbzo.Pro.OH	H.L.Phe.OCH <sub>3</sub>	THF	—	461
HCO.DL.Val.OH	H.DL.Phe.OH	Dioxane	32	133
	H.DL.Phe.OCH <sub>3</sub>	Dioxane	35	133
Cbzo.DL.Val.OH	H.Gly.OH	Dioxane	62	20
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	83	20
	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	69	37
	H.DL.Ala.OH	Dioxane	71	20
	H.DL.Ala.OC <sub>2</sub> H <sub>5</sub>	Ether	86	20
	H.DL.Val.OH	Dioxane	80	20
	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	Ether	80	20
	H.DL.Leu.OH	Dioxane	56	20
	H.DL.Leu.OC <sub>2</sub> H <sub>5</sub>	Ether	75	20
	H.DL.Nleu.OH	Dioxane	76	20
	H.DL.Nleu.OC <sub>2</sub> H <sub>5</sub>	Ether	69	20
Cbzo.L.Val.OH	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	Chloroform	76	452, 454
Cbzo.DL.Val.OH	H.DL.Asp(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Ether	76	20
	H.L.Glu(OH) <sub>2</sub>	Dioxane	58	20
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Ether	45	20
	Tos   H.L.Orn.OH	Dioxane	48	131

Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield after saponification.

¶ The product is benzyl carbobenzyloxy-D-seryl-L-leucinate. See Fölsch, *Acta Chem. Scand.*, **13**, 1422 (1959).

\*\* This is the yield after saponification and hydrogenolysis.



TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Bis-(carbobenzyloxy)-L-cystine	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	57	459
Bis-( <i>p</i> -nitrocarbobenzyloxy)-L-cystine	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	75	468
Cbzo.L.Met.OH	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	THF	81	468
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	77	469
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	82	469, 470
Phth.L.Met.OH	OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>   H.L.Glu.OH	THF	42††	471
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	50	133
HCO.L.Phe.OH	H.Gly.NHC <sub>6</sub> H <sub>5</sub>	Methylene dichloride	56	133
Cbzo.DL.Phe.OH	H.Gly.OCH <sub>3</sub>	Dioxane	80	288, 314
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	87	157, 440
	H.DL.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	80	472
Cbzo.L.Phe.OH	H.L.Lys.OCu/2	THF	52	61
	H.L.His.OCH <sub>3</sub>	Chloroform	80	18
	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>3</sub>	Chloroform	70	227, 450
	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	61	227
	H.NO <sub>2</sub> .L.Arg.OCH <sub>3</sub>	Dioxane	70	438, 439, 473
	H.DL.Phe.OH	Dioxane	31	472
Cbzo.DL.Phe.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Dioxane	74	472

ORGANIC REACTIONS

Phth.L.Phe.OH	(L) $\begin{array}{c} \text{H}_2\text{C} \cdots \text{CHCO}_2\text{CH}_3 \\   \quad   \\ \text{S} \quad \text{NH} \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	Methylene dichloride-dioxane	24	32
Cbzo.O.CH <sub>3</sub> .L.Tyr.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-DMF	73	123
Cbzo.DL.Try.OH	H.Gly.OH	THF	70	459
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	09	459
$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{C}_6\text{H}_5\text{CO.DL.Asp.OH} \end{array}$	H.Gly.NHC <sub>6</sub> H <sub>13-n</sub>	Chloroform-dioxane	80	101, 473a
$\begin{array}{c} \text{OH} \\   \\ \text{C}_6\text{H}_5\text{CO.DL.Asp.OC}_2\text{H}_5 \end{array}$	H.Gly.NHC <sub>6</sub> H <sub>13-n</sub>	Chloroform-dioxane	60	101
$\begin{array}{c} \text{OCH}_3 \\   \\ \text{Cbzo.L.Asp.OH} \end{array}$	H.NO <sub>2</sub> .L.Arg.OH	THF	51	460
$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{Cbzo.L.Asp.OH} \end{array}$	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	50	416
	$\begin{array}{c} \text{H} \\   \\ \text{H.Tos.L.Lys.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Chloroform	57	474

Note: References 437 to 538 are on pp. 353-355.

†† This is the yield after removal of the phthaloyl group.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES

TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
$\begin{array}{c} \text{OH} \\   \\ \text{Cbzo.L.Asph.OCH}_2\text{C}_6\text{H}_5 \end{array}$	$\begin{array}{c} \text{H} \\   \\ \text{H.Tos.L.Lys.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Chloroform	—	474
$\begin{array}{c} \text{OH} \\   \\ \text{Phth.DL.Asph.OCH}_3 \end{array}$	$p\text{-H}_2\text{NC}_6\text{H}_4\text{CO}_2\text{H}$	Dioxane	66	445
	$p\text{-H}_2\text{NC}_6\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$	Dioxane	87	445
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Asph.OH} \end{array}$	H.L.Ser.OCH <sub>3</sub>	Chloroform	22	110
$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{C}_6\text{H}_5\text{CO.DL.Glu.OH} \end{array}$	H.Gly.NHC <sub>6</sub> H <sub>13-7</sub>	Chloroform-dioxane	84	101
$\begin{array}{c} \text{OCH}_3 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	72	317
	H.L.Ala.OH	—	—	474a
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	68	317
	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.L.Glu.OH} \end{array}$	—	37	475
$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	70	96
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	70	96
$\begin{array}{c} \text{OH} \\   \\ \text{Cbzo.L.Glu.OCH}_2\text{C}_6\text{H}_5 \end{array}$	H.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	70	96
	$\begin{array}{c} \text{OH} \\   \\ \text{H.L.Glu.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Dioxane	35	97
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	70	96
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.S.Bz.L.Cys.OCH <sub>3</sub>	THF-dioxane	56	83
(Cbzo) <sub>2</sub> .DL.Lys.OH	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	THF	>35	455
	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	THF	62	462
(Cbzo) <sub>2</sub> .L.Lys.OH	H.DL.Val.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	60	462
	H.L.Lys.OCu/2	THF	50	61
	H.NO <sub>2</sub> .L.Arg.OCH <sub>3</sub>	Dioxane	64	438, 439
$\begin{array}{c} \text{Cbzo} \\   \\ \text{Tos.Lys.OH} \end{array}$	$p\text{-H}_2\text{NC}_6\text{H}_4\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$	THF	21	160
		Dioxane	14	
(Cbzo) <sub>3</sub> .L.Arg.OH	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform	11	
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	—	—	93
		Chloroform	75	93, 94

Note: References 437 to 538 are on pp. 353–355.

|| Other optical isomers were prepared.



TABLE II—Continued  
 ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
(Cbzo) <sub>2</sub> .L.Arg.OH ( <i>continued</i> )	$\begin{array}{c} \text{Cbzo} \\   \\ \text{H.L.Arg.OCH}_3 \end{array}$	Chloroform	52	94
Cbzo.NO <sub>2</sub> .L.Arg.OH	N.Cbzo.L.Arg.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform	73	94, 476
	H.Gly.OCH <sub>3</sub>	Dioxane	44	438, 439
	H.L.Ala.OCH <sub>3</sub>	Dioxane	46	91, 438, 439
	H.L.Leu.OCH <sub>3</sub>	Dioxane	60	438, 439
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	52	438, 439
	H.L.Phe.OCH <sub>3</sub>	Dioxane	65	91, 438, 439
<i>p</i> -NO <sub>2</sub> Cbzo.NO <sub>2</sub> .L.Arg.OH	H.L.Tyr.OCH <sub>3</sub>	Dioxane	66	91, 438, 439
	H.L.Tyr.OCH <sub>3</sub>	Dioxane	48	438, 439
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	51	92
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	THF	71	92
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	THF	61	92
	H.L.Phe.OH	THF	—	92
Cbzo-L-NHCH(C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> H	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	THF	69	92
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	70	92
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	61	477
	DL-(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> NCH(C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> H	Chloroform	70	446, 447
C <sub>6</sub> H <sub>5</sub> SCONH(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	H.DL.Try.OCH <sub>3</sub>	Chloroform	68	446, 447
	DL-C <sub>2</sub> H <sub>5</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	79	446, 447
	H.DL.Ala.OCH <sub>3</sub>	—	75	478

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DL- <i>i</i> -C <sub>3</sub> H <sub>7</sub> CH(NHCbzo)CH <sub>2</sub> CO <sub>2</sub> H	DL-H <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	74	453
<i>i</i> -C <sub>3</sub> H <sub>7</sub> CHOHCH(NHCbzo)CO <sub>2</sub> H	DL- <i>i</i> -C <sub>3</sub> H <sub>7</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	90	453
Cbzo-DL-NH(CH <sub>2</sub> ) <sub>3</sub> CH(NHCbzo)CH <sub>2</sub> CO <sub>2</sub> H	H.Ala.OH	THF	56§	457
Dicarbobenzyloxy-3,3'-( <i>p</i> -phenylene)di-alanine	DL- <i>i</i> -C <sub>3</sub> H <sub>7</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H	THF	92	453
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	79	479
(L) $\begin{array}{c} \text{H}_2\text{C} \text{---} \text{CHCO}_2\text{H} \\   \quad \quad   \\ \text{S} \quad \quad \text{NCHO} \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	H.Gly.OCH <sub>3</sub>	Chloroform	30	31
	H.Gly.OCH <sub>3</sub>	Methylene dichloride-dioxane	89	32
Cbzo.Gly.OH	H.DL.Ala.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	63	37
	H.L.Pro.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	90 crude	59
	H.DL.Pro.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	80 crude	59
Cbzo.DL.Ala.OH	H.Gly.Gly.OH	THF	58	337
	OH			
Cbzo.L.Pro.OH	H.L.Glu.L.Ala.OH	Dioxane	55	97
	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	87 crude	59
	H.L.Leu.Gly.NH <sub>2</sub>	THF	66	84, 463
Cbzo.DL.Val.OH	H.Gly.Gly.OH	Dioxane	60	20
	OH			
Cbzo.L.Val.OH	H.L.Glu.L.Val.OH	Toluene	58	480

Note: References 437 to 538 are on pp. 353-355.

§ This is the yield after hydrogenolysis.

|| Other optical isomers were prepared.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES

TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.Leu.OH	H.S.Bz.L.Cys.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	50	454
	H.S.Bz.L.Cys.L.Tyr.NH <sub>2</sub>	Chloroform	90	466
Cbzo.S.Bz.L.Cys.OH	OH   H.L.Glu.L.Leu.OH	Toluene	43	480
	H.Gly.Gly.OCH <sub>3</sub>	Chloroform	21	348
	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	86	348
	H.L.Ala.L.Ser.OCH <sub>3</sub>	Chloroform	—	454-456
Cbzo.Phe.OH	H.Gly.Val.OCH <sub>3</sub>	Chloroform	87	481
Cbzo.DL.Phe.OH	H.DL.Glu.DL.Phe.OH	Dioxane	51	472
Cbzo.L.Asp.OH	NH <sub>2</sub>   H.L.Ser.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	9	110
	H   C <sub>2</sub> H <sub>5</sub> O <sub>2</sub> C.DL.Ileu.L.Lys.OCH <sub>3</sub>	Chloroform	25	467
Cbzo.L.Glu.OH	Tos.DL.Ileu   H.L.Lys.OCH <sub>3</sub>	Chloroform	17	467
	OCH <sub>3</sub>   H.Gly.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	75	317
Cbzo.L.Glu.OH	OCH <sub>3</sub>   H.L.Glu.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	70	317
	NH <sub>2</sub> NH <sub>2</sub>     H.L.Glu.L.Glu.OH	—	53	475
Cbzo.L.Glu.OH	OC <sub>2</sub> H <sub>5</sub>   H.Gly.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	58	317
Cbzo.DL.Glu.OH	OH   H.DL.Glu.DL.Phe.OH	Dioxane	40	472
Cbzo.L.Glu.OH	NH <sub>2</sub>   H.L.Asp.S.Bz.L.Cys.OH	THF-dioxane	64	84
	NH <sub>2</sub>   H.L.Asp.S.Bz.L.Cys.OCH <sub>3</sub>	THF-dioxane	72	84, 463
(Cbzo) <sub>2</sub> .DL.Lys.OH	NH <sub>2</sub>   H.L.Glu.S.Bz.L.Cys.OCH <sub>3</sub>	THF-dioxane	63	83
	H.DL.Val.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	THF	79	462
p-NO <sub>2</sub> Cbzo.NO <sub>2</sub> .L.Arg.OH	H.β.Phe.L.Ser.OC <sub>2</sub> H <sub>5</sub>	THF	65	92
ClCH <sub>2</sub> CO.Gly.Gly.OH	H.Gly.OH	Dioxane	40	482
Cbzo.Gly.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	59	348
	OC <sub>2</sub> H <sub>5</sub>   H.L.Glu.OH	Chloroform	24	101

Note: References 437 to 538 are on pp. 353-355.

TABLE II—Continued  
 ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Tri.Gly.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Benzene	46	9, 10
Cbzo.DL.Ala.Gly.OH	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	68	37
Cbzo.Ph <sup>o</sup> .Gly.OH	H.Leu.OCH <sub>3</sub>	Chloroform	76	314
Cbzo.Gly.Ala.OH	H.S.Bz.L.Cys.OH	THF	72	290
Cbzo.Gly.DL.Val.OH	H.Gly.OH	THF	86	483
	H.DL.Ala.SC <sub>6</sub> H <sub>5</sub>	THF	70	37
	H.DL.Leu.SC <sub>6</sub> H <sub>5</sub>	THF	65	37
	H.DL.Ileu.SC <sub>6</sub> H <sub>5</sub>	THF	40	37
Cbzo.DL.Val.DL.Val.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	72	20
	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	Ether	48	20
Cbzo.L.Leu.L.Val.OH	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	THF	44	464
Cbzo.Gly.Leu.OH	H.Gly.OCH <sub>3</sub>	Chloroform	84	242
	H.Phe.OCH <sub>3</sub>	Chloroform	55	314
Cbzo.DL.Val.DL.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	66	20
Cbzo.DL.Val.DL.Nleu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	69	20
Cbzo.Gly.Phe.OH	H.Leu.OCH <sub>3</sub>	Chloroform	64	314
Cbzo.Gly.DL.Phe.OH	H.DL.Ser.OCH <sub>3</sub>	THF	74	484
Cbzo.DL.Val.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	73	20
	H.DL.Leu.OC <sub>2</sub> H <sub>5</sub>	Ether	59	20
Cbzo.L.Leu.D.Phe.OH	H.L.Pro.OCH <sub>3</sub>	Chloroform	78	153
Cbzo.DL.Phe.DL.Phe.OH	H.DL.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	75	472
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	35	472
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Val.OCH <sub>3</sub>	THF	74	83, 463
	H.L.Leu.OCH <sub>3</sub>	THF	61	83
	H.L.Ileu.OCH <sub>3</sub>	THF	60	84
	H.L.Phe.OCH <sub>3</sub>	THF	63	83
(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> .DL.Ala.DL.Try.OH	DL-C <sub>2</sub> H <sub>5</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	60	446, 447

Cbzo.L.Ala.L.Glu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	70	97
Cbzo.L.Glu.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	70	97
Tri.Gly. <i>im</i> .C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OH	H.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Dioxane	70	97
Cbzo.L.Phe.NO <sub>2</sub> .L.Arg.OH	H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	—	450
Cbzo.Gly.OH	H.L.Try.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	—	439, 473
Cbzo.S.Bz.L.Cys.OH	H.L.Leu.S.Bz.L.Cys.L.Tyr.NH <sub>2</sub>	Chloroform	70	466
	H.Gly.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	75	348
Cbzo.L.Glu.OH	H.L.His.L.Phe.NO <sub>2</sub> .L.Arg.OH	Dioxane	57	485
Cbzo.Gly.Gly.OH	H.Gly.L.Pro.OC <sub>2</sub> H <sub>5</sub>	Chloroform	14§	59
Cbzo.L.Ala.Gly.OH	H.L.Val.S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform	64	452
Phth.Gly.DL.Phe.OH	H.Gly.L.Leu.OH	Dioxane	67	54
Cbzo.L.Ala.L.Phe.OH	H.L.Pro.L.Leu.OCH <sub>3</sub>	—	79	60
Cbzo.Gly.Gly.Gly.OH	H.L.Pro.OC <sub>2</sub> H <sub>5</sub>	Chloroform	10§	59
Cbzo.Gly.Gly.L.Glu.OH	H.Gly.NHC <sub>6</sub> H <sub>13</sub> <sup>n</sup>	Dioxane-toluene	76	101
Phth.Gly.Gly.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Water-nitro-benzene	50	125

Note: References 437 to 538 are on pp. 353–355.

§ This is the yield after hydrogenolysis.

|| Other optical isomers were prepared.

TABLE II—Continued  
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Ref.
Cbzo.Gly.Leu.OH	H.Gly.Leu.Gly.OCH <sub>3</sub>	Chloroform	66	242
Cbzo.L.Leu.S.Bz.L.Cys.OH	H.L.Leu.L.Val.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Methylene dichloride	20	465
Cbzo.Gly.DL.Val.Gly.OH	H.Gly.DL.Val.Gly.OH	THF	44	483
Cbzo.Gly.DL.Val.DL.Ala.OH	H.Gly.DL.Val.DL.Ala.SC <sub>6</sub> H <sub>5</sub>	THF	76	37
Cbzo.Gly.Gly.DL.Phe.OH	H.Gly.Gly.DL.Phe.OCH <sub>3</sub>	DMF	66	149
Cbzo.L.Ala.L.Phe.L.Pro.L.Leu.OH	$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{H.L.Glu.L.Phe.OCH}_3 \end{array}$	—	39	60
$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{H.L.Ala.L.Phe.L.Pro.L.Leu.L.Glu.L.Phe.OCH}_3 \end{array}$	—	36	60
$\begin{array}{c} \text{OCH}_3 \\   \\ \text{Cbzo.L.Asp.NO}_2\text{.L.Arg.OH} \end{array}$	H.L.Val.L.Tyr.L.Ileu.L.His.L.Pro.L.Phe.OCH <sub>3</sub>	Dioxane	36	460
Cbzo.[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> .OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>6</sub> .OCH <sub>3</sub>	—	—	486
$\begin{array}{c} \text{Cbzo} \\   \\ \text{Cbzo.S.Bz.L.Cys.Gly.Gly.DL.Lys.OH} \end{array}$	$\begin{array}{c} \text{CO}_2\text{,cyclohexyl} \\   \\ \text{H.Gly.Gly.DL.Lys.S.Bz.L.Cys.OCH}_3 \end{array}$	—	—	487
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>3</sub> .OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>6</sub> .OCH <sub>3</sub>	—	—	486

Note: References 437 to 538 are on pp. 353–355.

TABLE III  
ANHYDRIDE FORMATION WITH *sec*-BUTYL CHLOROFORMATE

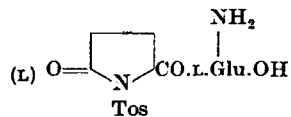
Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Val.OH	Toluene	49	21, 56
	H.DL.Phe.OH	Chloroform-toluene	63	56
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	71	21, 150, 151
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	51	21
Phth.Gly.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Toluene	67	21, 56
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	58	21
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF*	50	488
CH <sub>3</sub> CO.DL.Ala.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	50	21, 56
Cbzo.DL.Ala.OH	H.DL.Phe.OH	Toluene	41	21
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	86	169
Cbzo.L.Pro.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Chloroform	65	21
Cbzo.DL.Val.OH	H.DL.Ala.OC <sub>2</sub> H <sub>5</sub>	Toluene	68	21
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Toluene	47	21
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene		
	Cbzo 			
Phth.L.Val.OH	H.L.Orn.OCH <sub>3</sub>	THF	83 crude	97
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	86	21, 150, 151, 169
	H.L.Leu.OCH <sub>3</sub>	Toluene	64	21, 150, 151
Phth.DL.Leu.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	63	21, 56, 198
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	55	21
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	46	21, 150, 151
Cbzo.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	64	21, 150, 151
(Cbzo) <sub>2</sub> .L.Lys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene		

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 301

TABLE III—Continued  
ANHYDRIDE FORMATION WITH *sec*-BUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	References
Tos.   Cbzo   Lys.OH	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	6	160
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	74	489
DL-CbzoNHCH <sub>2</sub> CH(NHCbzo)CO <sub>2</sub> H	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	59†	490
Cbzo.DL.S.Bz.homo.Cys.OH	H.L.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	79	169
Cbzo.L.Pro.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	67	21, 56, 150, 151, 198
Phth.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	76	21
Cbzo.Gly.DL.Phe.OH	H.L.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF‡	85	491
(L) 	H.L.Pro.L.Leu.Gly.NH <sub>2</sub>	Chloroform	80	169
Cbzo.S.Bz.L.Cys.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	65	21, 150, 151
Cbzo.Gly.DL.Phe.OH	H.DL.Val.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	36	21
Cbzo.DL.Ala.DL.Phe.OH	H.DL.Phe.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	59	21, 56, 150
Cbzo.Gly.DL.Phe.OH				
	Cbzo 			
Phth.L.Val.L.Orn.OH	H.L.Leu.D.Phe.L.Pro.OCH <sub>3</sub>	THF	63	153

Note: References 437 to 538 are on pp. 353-355.

† Other optical isomers were prepared.

‡ DMF is dimethylformamide.

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TABLE IV  
ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
(CH <sub>3</sub> ) <sub>2</sub> CHOCO.Gly.OH	H.DL.Phe.OCH <sub>3</sub>	Acetone	95	65
(CH <sub>3</sub> ) <sub>3</sub> COCO.Gly.OH	H.DL.Phe.OCH <sub>3</sub>	Acetone	78	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.Gly.OH	H.Gly.OCH <sub>3</sub>	Acetone	62	28
	H.DL.Phe.OCH <sub>3</sub>	Acetone	61	28
Cbzo.Gly.OH	H.Gly.OCH <sub>3</sub>	Acetone	71	65
	H.DL.Phe.OH	Toluene	63	21
	H.DL.Phe.OCH <sub>3</sub>	Acetone	81	65
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	64	21
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	68	21, 56, 150, 151
	Cbzo 			
	H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Ethyl acetate	70	132
	H.NO <sub>3</sub> .L.Arg.OH	Toluene	49	492
Phth.Gly.OH	H.Gly.OH	Chloroform	73	152
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	85	152
	H.DL.Ala.OH	Chloroform	62	152
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Toluene	57	21
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	58	21
(CH <sub>3</sub> ) <sub>3</sub> COCO.DL.Ala.OH	H.Gly.OCH <sub>3</sub>	Acetone	50	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.DL.Ala.OH	H.Gly.OCH <sub>3</sub>	Acetone	68	28
Cbzo.DL.Ala.OH	H.Gly.OCH <sub>3</sub>	Acetone	68	65
Cbzo.D.Ala.OH	H.L.Ala.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	Low	67

Note: References 437 to 538 are on pp. 353-355.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 303

TABLE IV—Continued  
ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.β.Ala.OH	H.DL.Phe.OCH <sub>3</sub>	Acetone	90	65
	H.Glu(OH) <sub>2</sub>	DMF*	55	122
	DL-3-(2-Thienyl)alanine	Acetone	75	493
	Tos 			
Cbzo.L.Pro.OH	H.L.Lys.OH	THF†	47	494
Cbzo.allo.HO.L.Pro.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	—	495
(CH <sub>3</sub> ) <sub>3</sub> COCO.DL.Val.OH	H.Gly.OCH <sub>3</sub>	Acetone	72	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.L.Val.OH	H.Gly.OCH <sub>3</sub>	Acetone	68	28
	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	77	28
	H.L.Ser.OCH <sub>3</sub>	Acetone	44	28
Cbzo.DL.Val.OH	H.Gly.OCH <sub>3</sub>	Acetone	92	65
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.DL.Nval.OH	H.Gly.OCH <sub>3</sub>	Acetone	66	28
	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	63	28
(CH <sub>3</sub> ) <sub>3</sub> COCO.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Acetone	80	28
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Acetone	48	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.L.Leu.OH	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	70	28
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Acetone	64	28
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	53	21
	H.L.Ala.OH	THF	62	124
	H.L.Leu.OCH <sub>3</sub>	Toluene	71	21
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	83	496
	H.L.Tyr.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	80	496
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.L.Ileu.OH	H.Gly.OCH <sub>3</sub>	Acetone	52	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.DL.Ileu.OH	H.DL.Val.OCH <sub>3</sub>	Acetone	61	28
	H.DL.Ser.OCH <sub>3</sub>	Acetone	63	28

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$(\text{CH}_2)_4\text{CHOCO.L.Ileu.OH}$	H.L.His.OCH <sub>3</sub>	Acetone	44	28
$(\text{CH}_2)_4\text{CHOCO.DL.Nleu.OH}$	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	69	28
$\text{Cbzo.S.Bz.L.Cys.OH}$	H.L.Cys.OH	THF	45	452
	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	67†	170
$\text{Phth.S.Bz.Cys.OH (DL + L)}$	H.Gly.OH	—	70	497
$(\text{CH}_2)_4\text{CHOCO.DL.Met.OH}$	H.Gly.OCH <sub>3</sub>	Acetone	71	28
$\text{Cbzo.DL.Met.OH}$	H.Gly.OCH <sub>3</sub>	Acetone	78	65
$(\text{CH}_2)_2\text{COCO.DL.Phe.OH}$	H.Gly.OCH <sub>3</sub>	Acetone	45	28
	H.β.Ala.OC <sub>2</sub> H <sub>5</sub>	Acetone	35	28
$(\text{CH}_2)_5\text{CHOCO.DL.Phe.OH}$	H.Gly.OCH <sub>3</sub>	Acetone	71	28
$\text{Cbzo.L.Phe.OH}$	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	72	40
	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Toluene	48	57
	H.NO <sub>2</sub> .L.Arg.OH	Toluene	50	492
$(\text{CH}_2)_4\text{CHOCO.O.Ac.L.Tyr.OH}$	H.Gly.OCH <sub>3</sub>	Acetone	57	28
$\text{Cbzo.L.Try.OH}$	H.Gly.NH <sub>2</sub>	Dioxane	55	498
	Cbzo 			
	H.L.Lys.OH	THF	37	124
$(\text{CH}_2)_4\text{CHOCO.L.Asp.OH}$	H.L.Glu[OCH(CH <sub>2</sub> ) <sub>4</sub> ] <sub>2</sub>	Acetone	20	28
	OH 			
$\text{Cbzo.L.Asp.NH}_2$	H.S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	82	499

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

† THF is tetrahydrofuran.

‡ Other optical isomers were prepared.

TABLE IV—Continued  
ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
$\text{Cbzo.L.Glu.NH}_2$	H.L.Asp.OH	THF	41	500
$(\text{Cbzo})_2\text{.L.Lys.OH}$	H.Gly.OCH <sub>3</sub>	Ethyl acetate	32	132
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	64	21
	H.L.Val.OH	THF	65	57
	H.L.Val.OC <sub>2</sub> H <sub>5</sub>	Toluene	81	57
	Cbzo 			
$\text{Cbzo.NO}_2\text{.L.Arg.OH}$	H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Ethyl acetate	89	132
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	28	492, 501
	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	58	492, 501
	H.L.Leu.OCH <sub>3</sub>	THF	53	492, 501
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	THF	41	492, 501
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	60	492
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	THF	62	492, 501
	H.Gly.OH	Chloroform	0	31
	H.Gly.OCH <sub>3</sub>	Chloroform	67	31
	H.Gly.NH <sub>2</sub>	Dioxane	90	497
$(\text{L}) \begin{array}{c} \text{H}_2\text{C} \quad \text{CHCO}_2\text{H} \\   \quad \quad   \\ \text{S} \quad \quad \text{NCHO} \\ \diagdown \quad \diagup \\ \text{C} \\ / \quad \backslash \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	H.Gly.OCH <sub>3</sub>	Toluene	47	490
$\text{Cbzo.DL.S.Bz.homo.Cys.OH}$	H.D.Val.OH	THF	31	490
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	33	490
$(\text{CH}_2)_4\text{CHOCNH}(\text{CH}_2)_6\text{CO}_2\text{H}$	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	76	28

CbzoNH(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	H <sub>2</sub> N(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	THF	83	273
(CH <sub>2</sub> ) <sub>4</sub> CHOC(=O)NHCH(C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> H	H.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	84	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.Gly.OH	H.L.Leu.Gly.OCH(CH <sub>2</sub> ) <sub>4</sub>	Acetone	63	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.Gly.OH	H.L.Leu.Gly.OCH <sub>3</sub>	Acetone	—	28
(CH <sub>2</sub> ) <sub>4</sub> CHOCO.L.Val.OH	H.L.Leu.Gly.OCH <sub>3</sub>	Acetone	88	28
Cbzo.L.Val.OH	H.L.Phe.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	65	57
OH   Cbzo.L.Asp.OC <sub>2</sub> H <sub>5</sub>	H.S.Bz.DL.homo.Cys.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	71	502
OC <sub>2</sub> H <sub>5</sub>   Cbzo.L.Glu.OH	H.S.Bz.DL.homo.Cys.Gly.OCH <sub>3</sub>	Dioxane	34	502
OH   Phth.L.Glu.OCH <sub>3</sub>	H.S.Bz.DL.homo.Cys.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	67	502
NH <sub>2</sub>   Cbzo.L.Glu.OH	(L) H <sub>2</sub> C—CHCONHCH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>           S       NH C H <sub>2</sub> C   CH <sub>3</sub>	Chloroform	—	497
NH <sub>2</sub>   Cbzo.L.Glu.OH	NH <sub>2</sub>   H.L.Asp.S.Bz.L.Cys.OCH <sub>3</sub>	THF	81	87
Cbzo.NH(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> SC <sub>4</sub> H <sub>9</sub>	THF	87	273
Cbzo.Gly.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Toluene	60	40
Cbzo.Gly.L.Phe.OH	H.Gly.OH	THF	39	57
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene-dioxane	77	40

Note: References 437 to 538 are on pp. 353-355.

TABLE IV—Continued  
ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.Gly.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	83	21, 56, 150, 151
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	H <sub>2</sub> N(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	THF	76	273
O,N-(Cbzo) <sub>2</sub> .L.Tyr.OH	NH <sub>2</sub> NH <sub>2</sub>           H.L.Phe.L.Glu.L.Asp.OH	THF	71	82
N-Cbzo-O-Tos.L.Tyr.OH	NH <sub>2</sub> NH <sub>2</sub>           H.L.Phe.L.Glu.L.Asp.OH	THF	79	81
(Cbzo) <sub>2</sub> .L.Lys.OH	H.L.Val.L.Phe.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	70	57
Cbzo.Gly.Gly.OH	Cbzo   H.Gly.L.Lys.OCH <sub>3</sub>	THF	67	503
(Cbzo) <sub>2</sub> .L.Lys.L.Val.OH	H.L.Phe.Gly.OH	THF	29	57
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	H.L.Phe.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	54	57
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	—	—	273
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> SC <sub>4</sub> H <sub>9</sub>	DMF	64	273
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	H <sub>2</sub> N(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	DMF	83 crude	273
Cbzo.S.Bz.L.Cys.OH	NH <sub>2</sub> NH <sub>2</sub>           H.L.Tyr.L.Phe.L.Glu.L.Asp.OH	THF	87 crude	82
	NH <sub>2</sub> NH <sub>2</sub>           H.O-Tos.L.Tyr.L.Phe.L.Glu.L.Asp.OH	THF	83	81



Cbzo.L.Leu.L.Ala.OH	H.L.Val.L.Phe.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	70	124
Cbzo.S.Bz.L.Cys.L.Phe.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{H.L.Ileu.L.Glu.L.Asp.OH} \end{array}$	—	—	504
Cbzo.S.Bz.L.Cys.L.Tyr.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{H.L.Phe.L.Glu.L.Asp.OH} \end{array}$	THF	64 crude	82, 86
Tos.S.Bz.L.Cys.L.Tyr.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{H.L.Phe.L.Glu.L.Asp.OH} \end{array}$	THF	62	85, 505
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>3</sub> OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> OH	DMF	68	273
	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>2</sub> SC <sub>6</sub> H <sub>5</sub>	DMF	—	273
Cbzo.L.Pro.OH	$\begin{array}{c} \text{Tos} \\   \\ \text{H.L.Val.L.Orn.L.Leu.D.Tyr.L.Pro.OCH}_3 \end{array}$	THF	72	496
N.Tos.S.Bz.L.Cys.L.Tyr.L.Phe.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{H.L.Glu.L.Asp.S.Bz.L.Cys.OH} \end{array}$	THF-DMF	59	87
Cbzo[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>3</sub> OH	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>3</sub> OH	DMF	64	273
	H[NH(CH <sub>2</sub> ) <sub>5</sub> CO] <sub>3</sub> SC <sub>6</sub> H <sub>5</sub>	DMF	59	273
Cbzo.L.Leu.L.Ala.L.Val.L.Phe.Gly.OH	H.L.Pro.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	60	124
$\begin{array}{c} \text{Cbzo} \\   \\ \text{Cbzo.L.Tyr.L.Lys.OH} \end{array}$	H.L.Leu.L.Ala.L.Val.L.Phe.Gly.L.Pro.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	31	124

Note: References 437 to 538 are on pp. 353-355.

TABLE V  
ANHYDRIDE FORMATION WITH MISCELLANEOUS CHLOROFORMATES, ClCO<sub>2</sub>R

R	Acid	Amine	Solvent	Yield, %	Refs.
CH <sub>3</sub>	Cbzo.Gly.OH	H.Gly.OH	THF*	Poor	48
C <sub>2</sub> H <sub>5</sub> -i	$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.L.Glu.OH	Acetone	42	491
	$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.L.Ala.OCH <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Acetone	82	401
	$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.L.Glu.L.Ala.OH} \end{array}$	Acetone	89	491
C <sub>4</sub> H <sub>9</sub> -n	$\begin{array}{c} \text{OC}_2\text{H}_5 \quad \text{OC}_2\text{H}_5 \\   \quad / \\ \text{Cbzo.L.Glu.L.Glu.OH} \\ \text{(L) } \begin{array}{c} \text{H}_2\text{C} \quad \text{CHCO}_2\text{H} \\   \quad   \\ \text{S} \quad \text{NCHO} \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array} \end{array}$	$\begin{array}{c} \text{OC}_2\text{H}_5 \\   \\ \text{H.L.Glu.OH} \\ \text{H.Gly.OH} \end{array}$	THF Chloroform	51 0	491 31
	$\begin{array}{c} \text{(L) } \begin{array}{c} \text{H}_2\text{C} \quad \text{CHCO}_2\text{H} \\   \quad   \\ \text{S} \quad \text{NCHO} \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array} \end{array}$	H.Gly.OCH <sub>2</sub>	Chloroform	66	31
CH <sub>3</sub> C <sub>2</sub> H <sub>5</sub>	Cbzo.Gly.OH	L-CbzoNHCH <sub>2</sub> CH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	80	154
	Cbzo.L.Leu.OH	L-CbzoNHCH <sub>2</sub> CH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	63	154
	Cbzo-L-NHCH <sub>2</sub> CH <sub>2</sub> CH(NHCbzo)CO <sub>2</sub> H	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Chloroform	40	154
	Cbzo-L-NHCH <sub>2</sub> CH <sub>2</sub> CH(NHCbzo)CO <sub>2</sub> H	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	70	154
	Cbzo-L-NHCH <sub>2</sub> CH <sub>2</sub> CH(NHCbzo)CO <sub>2</sub> H	L-CbzoNHCH <sub>2</sub> CH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	56	154
	Cbzo.Gly.Gly.OH	H.Ala.OH	Acetone	57	111
C <sub>8</sub> H <sub>17</sub> -n	(C <sub>2</sub> H <sub>5</sub> S) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> CH(NHCOCH <sub>2</sub> Cl)CO <sub>2</sub> H	H.Gly.OH	THF	30	14, 506
	Cbzo.Gly.Gly.Gly.OH	H.Gly.OH	THF	68	177, 197, 507, 508
	Cbzo.Gly.Gly.Ala.OH	H.Gly.Gly.OH	Acetone-dioxane	68	111
	Cbzo.DL.Ala.Gly.Gly.OH	H.DL.Ala.Gly.Gly.OH	THF	40	337
	Cbzo.Gly.Gly.Ala.OH	H.Gly.Gly.Ala.OH	Acetone-dioxane	25	111, 509
	Cbzo.Gly.Gly.Ala.Gly.Gly.OH	H.Ala.Gly.OH	DEF†	36	111
	Cbzo.Gly.Gly.Ala.Gly.Gly.OH	H.Ala.Gly.Gly.OH	DEF	24	111

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

† DEF is diethyl formamide.

TABLE VI

## ANHYDRIDE FORMATION WITH ISOVALERYL CHLORIDE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.Gly.OH	Dioxane	52	189
	H.DL.Phe.OH	Toluene	—	198, 510
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	86	8, 198, 510
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Toluene	77	8, 198, 510
C <sub>6</sub> H <sub>5</sub> SCO.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	36	444
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	62	8
Phth.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	68	8, 198, 510
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	60	8, 198
Cbzo.D.Alc.OH	H.L.Alc.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	87	67
Cbzo.L.Alc.OH	L-H <sub>2</sub> NCH(C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	>65	67
Cbzo.D.Alc.OH	L-H <sub>2</sub> NCH(C <sub>2</sub> H <sub>5</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	>65	67
Cbzo.L.Alc.OH	H.L.Nval.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	>65	67
Cbzo.D.Alc.OH	H.L.Nval.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	>65	67
Cbzo.L.Alc.OH	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	—	67
Cbzo.D.Alc.OH	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	—	67
Cbzo.DL.Alc.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	48	8, 198, 510
Cbzo.Alc.OH	H.allo.Thr.OH	Dioxane	20	189
n-C <sub>4</sub> H <sub>9</sub> SCO.DL.Alc.OH	H.Gly.OH	THF*	33	444
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	74 crude	444
Phth.DL.Alc.OH	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	40	8
Cbzo.L.Pro.OH	H.L.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	92	199
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	70	8, 198, 199, 510
	H.L.Leu.OCH <sub>3</sub>	Chloroform-toluene	29	8, 198, 510
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	38	8
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	52	8, 198
Cbzo.Nleu.OH	H.allo.Thr.OH	Dioxane	20	189

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Cbzo.Phe.OH	H.allo.Thr.OH	Dioxane	30	189
n-C <sub>4</sub> H <sub>9</sub> SCO.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Toluene	70	444
Cbzo.L.Asp.OH	H.S.Bz.L.Cys.OCH <sub>3</sub>	THF	58	87, 223
		Chloroform-toluene	58	8, 198, 510
(Cbzo) <sub>2</sub> .L.Lys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	92	511
Cbzo.L.Pro.OH	H.L.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	—	100 crude	511
Cbzo.Gly.L.Pro.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	THF	86	8, 198, 510
Cbzo.Gly.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform-toluene	86	8, 198, 510

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES

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TABLE VII  
ANHYDRIDE FORMATION WITH TRIMETHYLACETYL AND DIETHYLACETYL CHLORIDES

Acid Chloride	Acid	Amine	Solvent	Yield, %	References
$(\text{CH}_3)_3\text{CCOCl}$	Cbzo.Gly.OH	H.DL.Phe.O $\text{C}_2\text{H}_5$	Toluene	81	8, 198
$(\text{C}_2\text{H}_5)_2\text{CHCOCl}$	Cbzo.Gly.OH	H.DL.Phe.O $\text{C}_2\text{H}_5$	Toluene	84	8, 198

*Note:* References 437 to 538 are on pp. 353-355.

TABLE VIII

## ANHYDRIDE FORMATION WITH BENZOYL CHLORIDE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Ala.OH	Benzonitrile	71	177, 197, 507, 508, 538
Phth.Gly.OH	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Benzonitrile	69	178, 512
	H.Gly.OCH <sub>3</sub>	Ether	—	177, 197, 507, 508, 538
Cbzo.DL.Ala.OH	H.Ala.OH	Benzonitrile	83*	172
	H.DL.Phe.OH	Benzonitrile	67*	177, 197, 507, 508, 538
Dicarbobenzyloxy-L-cystine	H.S.Bz.L.Cys.OH	Benzonitrile	47	348
N.Cbzo.O-CH <sub>3</sub> CO.L.Tyr.OH	H.L.Leu.OCH <sub>3</sub>	THF†	76	191
	H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	61	191
(Cbzo) <sub>1</sub> .L.Lys.OH	Cbzo   H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	48	191
	H.L.Tyr.OCH <sub>3</sub>	THF	73	191
	H.L.Tyr.NH <sub>2</sub>	THF	70	191
Cbzo.Gly.OH	Cbzo   H.L.Lys.OCH <sub>3</sub>	Benzonitrile	62	190
	Cbzo   H.L.Lys.OC <sub>2</sub> H <sub>5</sub>	THF	71	191
	H.DL.Ala.Gly.OH	Benzonitrile	72	177, 197, 507, 538
(Cbzo) <sub>2</sub> .L.Lys.OH	H.L.Tyr.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	65	191
Cbzo.Gly.Gly.OH	Cbzo   H.L.Tyr.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	55	191
	H.DL.Phe.OH	Benzonitrile	64*	177, 197, 507, 508, 538
(Cbzo) <sub>1</sub> .L.Lys.L.Lys.OH	H.L.Tyr.NH <sub>2</sub>	THF	58	191
Cbzo.DL.Ala.DL.Ala.OH	Cbzo   H.L.Lys.OCH <sub>2</sub>	THF	58	190
	Cbzo   H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	50	190
	H.DL.Ala.Gly.OH	Benzonitrile	80	177, 197, 507, 538
(Cbzo) <sub>2</sub> .L.Lys.L.Lys.L.Lys.OH	Cbzo Cbzo     H.L.Lys.OCH <sub>3</sub>	THF	62	190
	Cbzo   H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	48	190
Cbzo(L.Lys) <sub>4</sub> OH	Cbzo   H.L.Lys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Benzonitrile	33	190

Note: References 437 to 538 are on pp. 353-355.

\* This yield is based upon the mixed anhydride.

† THF is tetrahydrofuran.

TABLE IX  
ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.Gly.OH	H.DL.Ser.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF*	69	69
	H.O-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .DL.Ser.OC <sub>2</sub> H <sub>5</sub>	Chloroform	88	513
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF†	—	514
	H.NO <sub>2</sub> .L.Arg.OC <sub>2</sub> H <sub>5</sub>	THF-methylene dichloride	59-71	216
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCO.Gly.OH	H.L.Arg.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Acetonitrile-ethanol	66	515
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	53, 74	443, 444
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform	50, 70	443, 444
Tri.Gly.OH	Tri   H.L.Lys.OCH <sub>3</sub>	Chloroform	68‡	12
	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	60	227
Cbzo.DL.Ala.OH	H.NO <sub>2</sub> .L.Arg.OC <sub>2</sub> H <sub>5</sub>	THF-methylene dichloride	—	216
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	37	443, 444
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCO.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	73	443, 444
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCO.DL.Ala.OH	H.L.Pro.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	74	204
Phth.L.Ala.OH	H.L.Tyr.OCH <sub>3</sub>	THF-water	40	516
N-CH <sub>3</sub> CO.DL.Ser.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	59	204
Cbzo.L.Ser.OH	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	72	69
Cbzo.DL.Ser.OH	H.L.Tyr.OCH <sub>3</sub>	Acetonitrile-dioxane	68	471
Cbzo.L.Ser.OH	H.L.His.OCH <sub>3</sub>	THF	49	464
	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	57	227
	H.NO <sub>2</sub> .L.Arg.OC <sub>2</sub> H <sub>5</sub>	THF-methylene dichloride	—	216
Cbzo.O-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Ser.OH	H.NO <sub>2</sub> .L.Arg.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF-methylene dichloride	61	216
	H.L.His.OCH <sub>3</sub>	—	—	513
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	—	214
	H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	—	214
Phth.O-CH <sub>3</sub> CO.L.Ser.OH	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	89	213, 214, 217
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	60	214
Phth.L.Thr.OH	H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Acetonitrile	60, 89	214, 217
	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	91	217
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	96	213, 214
Cbzo.L.Thr.OH	H.L.His.OCH <sub>3</sub>	Methylene dichloride	95	517
	H.L.Val.OCH <sub>2</sub>	THF	81	45
Cbzo.L.Pro.OH	H.L.His.OCH <sub>3</sub>	THF	> 64	518
	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	86	213, 217
Cbzo.HO.L.Pro.OH	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	72	133
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane-methylene dichloride	—	—
Cbzo.L.Val.OH	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	65	133
	H.L.Tyr.OCH <sub>3</sub>	THF	81	461
	H.L.Glu(OCH <sub>3</sub> ) <sub>2</sub>	Dioxane	80	226
Phth.L.Val.OH	H.L.Val.OCH <sub>3</sub>	Methylene dichloride	—§	46
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	75	511
Cbzo.L.Leu.OH	H.L.Val.OCH <sub>3</sub>	THF	> 65	234
	H.S.Bz.L.Cys.OCH <sub>3</sub>	Methylene dichloride	55	465
Phth.L.Leu.OH	H.L.Leu.OCH <sub>3</sub>	Methylene dichloride	80	46

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

† THF is tetrahydrofuran.

‡ This is the yield of product after saponification.

§ All the optical isomers were prepared.

TABLE IX—Continued  
 ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Tri.L.Leu.OH	H.L.Tyr.OCH <sub>3</sub>	Methylene dichloride	>70	222
Cbzo.L.Ileu.OH	H.O-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Tyr.OCH <sub>3</sub>	Methylene dichloride	>77	222
	H.L.His.OCH <sub>3</sub>	Acetonitrile-ethyl acetate	77	461
Cbzo.S.Bz.L.Cys.OH	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	70	227
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	71	459
	H.L.Phe.OCH <sub>3</sub>	—	—	504
S,N-(Tri) <sub>2</sub> .L.Cys.OH	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>3</sub>	Methylene dichloride	64	465
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	85	519
	H.L.Pro.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	>74	205
Tos.S.Bz.L.Cys.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	83	205
N.C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> .S.Bz.L.Cys.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	86	85
	H.L.Tyr.OCH <sub>3</sub>	THF	—	463
Phth.L.Met.OH	$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{H.L.Glu.OH} \end{array}$	—	26	208
		—	26	208
Tri.DL.Met.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	71	11
HCO.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane-methylene dichloride	85	133
CH <sub>3</sub> C(NHCOCH <sub>3</sub> ) <sub>2</sub> CO.L.Phe.OH	H.L.Pro.OCH <sub>3</sub>	Methylene dichloride	83	120
(CH <sub>3</sub> ) <sub>2</sub> CHCOCO.L.Phe.OH	H.L.Pro.OCH <sub>3</sub>	Methylene dichloride	90	120
Cbzo.L.Phe.OH	H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	70	227
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	92	204
Phth.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Aq.THf	72	
		Dioxane or THF	33-56	201
Phth.L.Phe.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	—	91	204
Tos.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	—	—	201
Tos.L.Phe.OH	H.L.Arg.OCH <sub>3</sub>	DMF	66	45
Cbzo.L.Tyr.OH	H.L.Ser.OCH <sub>3</sub>	Acetonitrile	70, 81	208, 471
		Acetonitrile	94	218
(Cbzo) <sub>2</sub> .L.Tyr.OH	H.L.Ileu.OCH <sub>3</sub>	Acetonitrile	80	218
Cbzo.L.Try.OH	H.Gly.OCH <sub>3</sub>	Dioxane	59	44
Tri.DL.Try.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	80	11
Tri.L.Asp.OH	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.Gly.OCH}_2\text{C}_6\text{H}_5 \\ \text{H.L.Leu.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Methylene dichloride	82	225
		Methylene dichloride	>85	225
Cbzo.L.Asp.OH	H.S.Bz.L.Cys.OCH <sub>3</sub>	DMF-THF	39¶	87, 223
Tri.L.Asp.OH	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.L.Tyr.OCH}_3 \end{array}$	Methylene dichloride	50‡	222
		Methylene dichloride	50‡	222
Cbzo.L.Glu.OH	$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{H} \\   \\ \text{Tos.L.Lys.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Methylene dichloride	67	520
		Methylene dichloride	67	520
Tri.L.Glu.OH	$\begin{array}{c} \text{OCH}_3 \\   \\ \text{H.L.Asp.OCH}_2\text{C}_6\text{H}_5 \end{array}$	Methylene dichloride	>80	205
		Methylene dichloride	>80	205

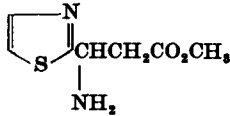
Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield of product after saponification.

|| This is the yield after removal of the phthaloyl group.

¶ A 26% yield of the corresponding nitrile was obtained.

TABLE IX—Continued  
ANHYDRIDE FORMATION WITH *N,N'*-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.S.Bz.L.Cys.OCH <sub>3</sub>	THF	76	87, 223
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Tri.L.Glu.OH} \end{array}$	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Methylene dichloride Methylene dichloride	>70 >70	225 225
$\begin{array}{c} \text{NH}_2 \\   \\ (\text{Tri})_2\text{L.Lys.OH} \end{array}$	H.L.Asp.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.Gly.OC <sub>2</sub> H <sub>5</sub> H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Methylene dichloride Methylene dichloride Methylene dichloride	>70 92‡ 63‡	225 12 12
$\begin{array}{c} \text{Tri} \\   \\ (\text{Cbzo})_2\text{L.His.OH} \end{array}$	H.L.Lys.OCH <sub>3</sub> H.Gly.OCH <sub>3</sub> H.O-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Ser.OCH <sub>3</sub> H.L.Thr.OCH <sub>3</sub> H.L.Leu.OCH <sub>3</sub> H.L.Met.OCH <sub>3</sub> H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Methylene dichloride Chloroform Chloroform Chloroform Chloroform Chloroform	— 68 81 78 68 85, 90 70	12 226 89, 226 89, 226 89, 226 89, 226
$\text{Cbzo.im.C}_6\text{H}_5\text{CH}_2\text{L.His.OH}$	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.L.Ser.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.L.Leu.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> H.im.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF DMF DMF DMF DMF Methylene dichloride	40 60 65 50 54, 65	227 227 228 227 227, 228
$(\text{Tri})_2\text{L.His.OH}$	H.Gly.OC <sub>2</sub> H <sub>5</sub> H.L.Leu.OCH <sub>3</sub> H.L.Phe.OCH <sub>3</sub>	Methylene dichloride Methylene dichloride Pyridine-acetonitrile	80‡ 86‡ 86	11 11 45
$\text{Cbzo.L.Arg.OH}$	H.L.Try.OCH <sub>3</sub> H.L.Arg.OCH <sub>3</sub>	DMF DMF	80, 84 58	45, 208 208
$\text{Tri.L.Arg.OH}$	H.L.Try.OCH <sub>3</sub>	Pyridine	92	45
$\begin{array}{c} \text{NO}_2 \\   \\ \text{Cbzo.L.Arg.OH} \end{array}$	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.DL.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> H.DL.Ser.OC <sub>2</sub> H <sub>5</sub> H.DL.Ser.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF-methylene dichloride THF-methylene dichloride THF-methylene dichloride THF-methylene dichloride	54 53 35 58	216 216 216 216
$\text{L-NCCH}_2\text{CH}(\text{NHCbzo})\text{CO}_2\text{H}$	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	—	—	224
$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{CH}(\text{NHCOCH}_3)\text{CO}_2\text{H}$		THF	1	521
$p\text{-(ClCH}_2\text{CH}_2)_2\text{NC}_6\text{H}_4\text{CH}_2\text{CH}(\text{NHCHO})\text{CO}_2\text{H}$	H.Gly.OC <sub>2</sub> H <sub>5</sub> H.β.Ala.OC <sub>2</sub> H <sub>5</sub> H.Val.OC <sub>2</sub> H <sub>5</sub> H.Leu.OC <sub>2</sub> H <sub>5</sub>	Chloroform Chloroform Chloroform Chloroform	100 57 69 40	522 523 523 523

Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield of product after saponification.



TABLE IX—Continued  
ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
<i>p</i> -(ClCH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH(NHCHO)CO <sub>2</sub> H (continued)				
	H.Met.OC <sub>2</sub> H <sub>5</sub>	Chloroform	70	522
	H.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform	73	523
	H.Try.OCH <sub>3</sub>	Chloroform	47	523
	ClCH <sub>2</sub> CH <sub>2</sub> SCH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	40	522
	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCH <sub>2</sub> CH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Chloroform	100	522
	Tri 			
Tri.Gly.OH	H.L.Lys.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Chloroform	46†	12
Cbzo.L.Ser.OH	H.Gly.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform-acetonitrile	56	215
	H.L.Tyr.L.Ser.OCH <sub>3</sub>	DMF	56, 75	208, 471
Cbzo.L.Thr.OH	H.L.Val.L.Glu(OCH <sub>3</sub> ) <sub>2</sub>	Chloroform	72	226
Cbzo.L.Try.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	—	514
Tri.L.Glu(OH) <sub>2</sub> **	H.S.Tri.L.Cys.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	75†	519
	NH <sub>2</sub> 			
Cbzo.L.Glu.OH	H.L.Asp.S.Bz.L.Cys.OCH <sub>3</sub>	THF	78	87
	NH <sub>2</sub> 			
Tos.L.Glu.OH	S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>   H.L.Asp.NH <sub>2</sub>	Dioxane	86	499
N-[4-(4'-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> N=N)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OCO]-N <sup>ω</sup> -Tos.L.Arg.OH	H.L.Try.Gly.OCH <sub>3</sub>	—	—	47
Cbzo.Gly.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Acetonitrile	86	149
Cbzo.Val.Gly.OH	N <sup>6</sup> -Phenylalanyl-3-β-d-tetraacetyl- glucopyranosylcytosine	Dioxane	38	524
Cbzo.Gly.DL.Ser.OH	H.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	65	69
Cbzo.Gly.L.Pro.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	THF	100 crude	511
S,N-(Tri) <sub>2</sub> .L.Cys.L.Pro.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	—	100	205
Phth.L.Val.L.Val.OH	H.D.Val.OCH <sub>3</sub>	Methylene dichloride	66§	46
Cbzo.L.Leu.L.Val.OH	H.L.Phe.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Methylene dichloride	79	465
	H.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	THF	68	234, 465
	H.L.Glu(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Methylene dichloride	64	465
Cbzo.Val.Leu.OH	N <sup>6</sup> -Phenylalanyl-3-β-tetraacetyl- glucopyranosylcytosine	Dioxane	32	524
Phth.L.Leu.L.Leu.OH	H.L.Leu.OCH <sub>3</sub>	Methylene dichloride	83	46
Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	87	204, 231
Phth.L.Thr.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	94	213
	H.L.Phe.OCH <sub>3</sub>	Methylene dichloride	92	213, 217
HCO.L.Val.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane-methylene dichloride	40	133
Cbzo.Val.Phe.OH	N <sup>6</sup> -Phenylalanyl-3-β-tetraacetyl- glucopyranosylcytosine	Dioxane	46	524
Cbzo.Gly.L.Try.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	—	514
Cbzo.L.Ser.L.Tyr.OH	H.L.Ser.OCH <sub>3</sub>	Chloroform-acetonitrile	78	471
Cbzo.L.Val.L.Tyr.OH	H.L.Val.OCH <sub>3</sub>	—	75	230
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Ileu.OCH <sub>3</sub>	THF	66	500
S,N(Tri) <sub>2</sub> .L.Cys.L.Tyr.OH	H.L.Ileu.OCH <sub>3</sub>	—	62†	205
S.Bz.N.Tos.L.Cys.L.Tyr.OH	H.L.Ileu.OCH <sub>3</sub>	THF	78	525
	H.L.Phe.OCH <sub>3</sub>	THF	94	87

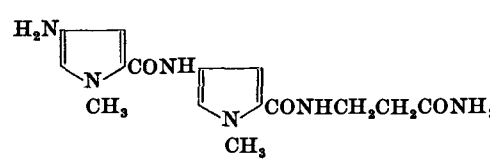
Note. References 437 to 538 are on pp. 353–355.

† This is the yield of product after saponification.

§ All the optical isomers were prepared.

\*\* Only the γ-carboxyl group reacts.

TABLE IX—Continued  
ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{Tos.L.Glu.L.Asp.OH} \end{array}$	H.S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	40††	87, 223
$\begin{array}{c} \text{Cbzo} \\   \\ \text{Tri.Gly.L.Lys.OH} \end{array}$	$\begin{array}{c} \text{Cbzo} \\   \\ \text{H.L.Lys.OCH}_3 \end{array}$	THF	—	208
Cbzo.O.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Ser.L.His.OH	H.L.Leu.OCH <sub>3</sub>	Dioxane	68	513
Cbzo.L.Phe. <i>im</i> .C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OH	H.L.Leu.OCH <sub>3</sub>	DMF	50‡	227
	H.L.Asp(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	DMF	74	227
Cbzo.L.Ser.OH	H.L.Leu.L.Val.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Methylene dichloride	57	465
Cbzo.S.Bz.L.Cys.OH	$\begin{array}{c} \text{Tos} \\   \\ \text{H.L.Pro.L.Lys.Gly.OC}_2\text{H}_5 \end{array}$	THF	81	494, 505
4-(4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> N=N)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OCO.L.Phe.OH	H(N <sup>o</sup> -Tos).L.Arg.L.Try.Gly.OCH <sub>3</sub>	—	—	47
(Cbzo) <sub>2</sub> .L.His.OH	H.L.Thr.L.Val.L.Glu(OCH <sub>3</sub> ) <sub>2</sub>	DMF	90	226
$\begin{array}{c} \text{NH} \\    \\ \text{H}_2\text{NCNHCH}_2\text{CO}_2\text{H} \end{array}$		—	30	95
Cbzo.L.Pro.L.Phe.OH	H.L.His.L.Leu.OCH <sub>3</sub>	Ethyl acetate-acetonitrile	61	230
(Tri) <sub>2</sub> .L.His.L.Phe.OH	H.L.Arg.L.Try.OCH <sub>3</sub>	DMF	69, 89	45, 208
Tri.L.Leu.O.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Tyr.OH	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.L.Glu.L.Leu.OCH}_3 \end{array}$	DMF	76	222
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Tyr.L.Ileu.OCH <sub>3</sub>	DMF-acetonitrile	65	218
$\begin{array}{c} \text{Cbzo} \\   \\ \text{Tri.Gly.L.Lys.OH} \end{array}$	H.L.Pro.L.Val.OCH <sub>3</sub>	THF	93	45, 208
$\begin{array}{c} \text{NH}_2 \quad \text{NO}_2 \\   \quad   \\ \text{Cbzo.L.Asp.L.Arg.OH} \end{array}$	H.L.Val.L.Tyr.OCH <sub>3</sub>	DMF	33	461
Cbzo.L.Arg.L.Arg.OH	H.L.Pro.L.Val.OCH <sub>3</sub>	—	57	208
S,N-(Tri) <sub>2</sub> .L.Cys.L.Pro.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Methylene dichloride	68	205
Phth.L.Leu.L.Leu.L.Leu.OH	H.L.Leu.OCH <sub>3</sub>	Methylene dichloride	86	46
Tri.L.Asp.OH	H.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH <sub>3</sub>	Methylene dichloride	96	225
N <sup>o</sup> -[4-(4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> N=N)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OCO]-N <sup>im</sup> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.His.OH	H.L.Phe(N <sup>o</sup> -Tos).L.Arg.L.Try.Gly.OCH <sub>3</sub>	—	—	47
Cbzo.O.C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> .L.Ser.L.His.OH	H.L.Leu.L.Val.L.Glu(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Dioxane	82	234

Note: References 437 to 538 are on pp. 353–355.

‡ This is the yield after saponification

†† A 15% yield of "anhydro" compound was obtained, presumably due to dehydration of the asparagine amide group.

TABLE IX—Continued  
 ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.His.L.Phe.L.Arg.OH $\begin{array}{c} \text{NO}_2 \\   \\ \text{C}_6\text{H}_4 \end{array}$	H.L.Try.Gly.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	DMF	86††	44
Tri.L.Glu.OH $\begin{array}{c} \text{NH}_2 \\   \\ \text{C}_6\text{H}_5 \end{array}$	H.L.Asp.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH <sub>3</sub> $\begin{array}{c} \text{NH}_2 \\   \\ \text{C}_6\text{H}_5 \end{array}$	Methylene dichloride	72	225
Cbzo.L.Val.L.Tyr.OH	H.L.Val.L.His.L.Pro.L.Phe.OCH <sub>3</sub>	Ethyl acetate	74	526
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Ileu.L.Glu.L.Asp.S.Bz.L.Cys.NH <sub>2</sub> $\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	—	—	527
Tri.L.Glu.L.Asp.OH $\begin{array}{c} \text{OCH}_3 \quad \text{OCH}_3 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	H.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH <sub>3</sub>	Methylene dichloride	72	205
Cbzo.Gly.Gly.DL.Phe.OH	H.Gly.Gly.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	DMF	<66	149
H.Gly.DL.Val.Gly.Gly.DL.Val.Gly.OH§§		Methanol-water	45	483
H.Gly.Leu.Gly.Gly.Leu.Gly.OH§§		Methanol-water	47	242
Tri.Gly.L.Lys.L.Lys.OH $\begin{array}{c} \text{Cbzo} \quad \text{Cbzo} \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	H.L.Arg.L.Arg.L.Pro.L.Val.OCH <sub>3</sub>	DMF	45	208
Cbzo.L.Asp.L.Arg.OH $\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	H.L.Val.L.Tyr.L.Val.L.His.L.Pro.L.Phe.OCH <sub>3</sub> $\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	DMF	61	526
(Tri) <sub>2</sub> .L.His.L.Phe.L.Arg.L.Try.OH	H.Gly.L.Lys.L.Pro.L.Val.NH <sub>2</sub> $\begin{array}{c} \text{Cbzo} \\   \\ \text{C}_6\text{H}_5 \end{array}$	DMF-acetonitrile	83	45
Cbzo.L.Val.L.Tyr.L.Val.L.His.OH	H.L.Pro.L.Phe.L.His.L.Leu.OCH <sub>3</sub>	DMF	51	230
Cbzo.L.His.L.Phe.L.Arg.L.Try.Gly.OH $\begin{array}{c} \text{NO}_2 \\   \\ \text{C}_6\text{H}_4 \end{array}$	H.L.Lys.L.Pro.L.Val.NH <sub>2</sub> $\begin{array}{c} \text{Tos} \\   \\ \text{C}_6\text{H}_4 \end{array}$	—	—	528
Tos.S.Bz.L.Cys.L.Tyr.L.Phe.L.Glu.L.Asp.OH $\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	H.S.Bz.L.Cys.L.Pro.L.Lys.NH <sub>2</sub> $\begin{array}{c} \text{Tos} \\   \\ \text{C}_6\text{H}_4 \end{array}$	THF	42	85, 505
Cbzo.S.Bz.L.Cys.L.Tyr.L.Val.OH	H.L.Glu.L.Asp.S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH <sub>2</sub> $\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	DMF	—	463
Cbzo.S.Bz.L.Cys.L.Tyr.L.Ileu.OH	L.Asp.S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH <sub>2</sub> $\begin{array}{c} \text{NH}_2 \\   \\ \text{C}_6\text{H}_5 \end{array}$	THF	64	500
	H.L.Glu.L.Asp.NH <sub>2</sub> $\begin{array}{c} \text{NH}_2 \quad \text{S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH}_2 \\   \quad   \\ \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \end{array}$	THF-water	73	499

Note: References 437 to 538 are on pp. 353–355.

†† The product was partially racemized; a 19% yield of the L isomer was obtained.

§§ The product is the cyclohexapeptide.

TABLE IX—Continued  
ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
S,N-(Tri) <sub>2</sub> .L.Cys.L.Tyr.L.Ileu.OH	$\begin{array}{c} \text{OCH}_3 \text{ OCH}_3 \\   \quad   \\ \text{H.L.Glu.L.Asp.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH}_3 \end{array}$	Methylene dichloride	75	205
Cbzo.S.Bz.L.Cys.L.Phe.L.Ileu.L.Glu.L.Asp.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{H.S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH}_2 \end{array}$	—	—	504
Cbzo.L.Asp.L.Arg.OH	$\begin{array}{c} \text{NH}_2 \quad \text{NO}_2 \\   \quad   \\ \text{H.L.Val.L.Tyr.L.Val.L.His.L.Pro.L.Phe.L.His.L.Leu.OCH}_3 \end{array}$	—	70	230
Tri.L.Val.L.Lys.L.Leu.D.Phe.L.Pro.OH	$\begin{array}{c} \text{Tos} \\   \\ \text{H.L.Val.L.Lys.L.Leu.D.Phe.L.Pro.OCH}_3 \end{array}$	Acetonitrile	95	529
Tri.Gly.L.Lys.L.Pro.L.Val.OH	$\begin{array}{c} \text{Cbzo} \quad \text{Cbzo} \\   \quad   \\ \text{H.Gly.L.Lys.L.Lys.L.Arg.L.Arg.L.Pro.L.Val.OCH}_3 \end{array}$	DMF	49	208
(Tri) <sub>2</sub> .L.His.L.Phe.L.Arg.L.Try.OH	$\begin{array}{c} \text{Cbzo} \quad \text{Cbzo} \quad \text{Cbzo} \\   \quad   \quad   \\ \text{H.Gly.L.Lys.L.Pro.L.Val.Gly.L.Lys.L.Lys.L.Arg.L.Arg.L.Pro.L.Val.OCH}_3 \end{array}$	DMF	73	208
Cbzo.L.Ser.L.Tyr.L.Ser.L.Met.L.Glu.OH	$\begin{array}{c} \text{OCH}_2\text{C}_3\text{H}_5 \\   \\ \text{H.L.His.L.Phe.L.Arg.L.Try.Gly.L.Lys.L.Pro.L.Val.Gly.L.Lys.L.Lys.L.Arg.L.Arg.L.Pro.L.Val.OCH}_3 \end{array}$	DMF	77	208

Note: References 437 to 538 are on pp. 353-355.

TABLE X  
ANHYDRIDE FORMATION WITH MISCELLANEOUS CARBODIIMIDES

Acid	Amine	Solvent	Yield, %	Ref.
	<i>A. 1-Cyclohexyl-3-(2-diethylaminoethyl)carbodiimide</i>			
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	20	233
	<i>B. 1-Cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide Metho-p-toluenesulfonate</i>			
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Water	75	233
	<i>C. 1-Cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide Metho-p-toluenesulfonate</i>			
Phth.L.Phe.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Acetonitrile	80	233
(L) H <sub>2</sub> C—CHCO <sub>2</sub> H            S        NCHO C H <sub>3</sub> C    CH <sub>3</sub>	H.Gly.OCH <sub>3</sub>	Methylene dichloride	63	32
Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Acetonitrile	63	233
	<i>D. 1-Cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide</i>			
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	90	233
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane-water (3:1)	71	233
Phth.L.Phe.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Dioxane	87	233
Phth.L.Phe.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Dioxane-water (5:2)	50	233
Phth.L.Phe.OH	H.L.Phe.OCH <sub>3</sub>	Dioxane	88	233
Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	81	233

Note: References 437 to 538 are on pp. 353-355.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 329

TABLE X—Continued  
ANHYDRIDE FORMATION WITH MISCELLANEOUS CARBODIIMIDES

Acid	Amine	Solvent	Yield, %	Ref.
	<i>E. 1-Cyclohexyl-3-[2-morpholinyl-(4)-ethyl]carbodiimide</i>			
Cbzo.L.Val.OH	H.L.His.OCH <sub>3</sub>	Acetonitrile	77	230
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	81	233
Cbzo.L.Val.L.Tyr.OH	H.L.Val.L.His.OCH <sub>3</sub>	Acetonitrile	65	230
Cbzo.L.Val.L.Tyr.L.Val.OH	H.L.His.OCH <sub>3</sub>	THF*	50	230
Cbzo.L.Val.L.Tyr.L.Val.L.His.OH	H.L.Pro.L.Phe.OCH <sub>3</sub>	DMF†	58	526
Cbzo.L.Asp.L.Arg.L.Val.L.Tyr.OH	H.L.Ileu.L.His.L.Pro.L.Phe.OCH <sub>3</sub>	DMF	22	461
Tri.L.Val.L.Orn.L.Leu.D.Phe.L.Pro.OH	H.L.Val.L.Orn.L.Leu.D.Phe.L.Pro.OCH <sub>3</sub>	Ethyl acetate	80	280

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

† DMF is dimethylformamide.

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TABLE XI  
ANHYDRIDE FORMATION WITH KETENIMINES

Acid	Amine	Solvent	Yield, %	References
<i>A. Diphenylketene-p-tolylimine</i>				
Cbzo.Gly.OH	H.DL.Thr.OC <sub>2</sub> H <sub>5</sub>	Benzene	—	247
	H.L.Try.OCH <sub>3</sub>	Benzene	—	247
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	54	244, 246, 247
	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Benzene	28*	244, 247
Phth.β.Ala.OH	<i>p</i> -H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Methylene dichloride	77	244, 246, 247
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	—	247
Cbzo.S.Bz.L.Cys.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	32†	244, 246
Phth.L.Phe.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Benzene	—	247
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Asp.OH} \end{array}$	H.S.Bz.L.Cys.OCH <sub>3</sub>	THF‡	45	244
	Phth.Gly.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene-methylene dichloride	45
<i>B. Ethyl-n-butylketene-n-butylimine</i>				
Cbzo.Gly.OH	H.Met.OC <sub>2</sub> H <sub>5</sub>	Methylene dichloride	—	247
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene or ethanol-water	—	247

Note: References 437 to 538 are on pp. 353–355.

\* This is the yield of acyl peptide.

† This is the yield of product obtained upon saponification.

‡ THF is tetrahydrofuran.

TABLE XII  
ANHYDRIDE FORMATION WITH ACETYLENIC ETHERS

Acid	Amine	Solvent	Yield, %	References
<i>A. Methyl Ethinyl Ether</i>				
Cbzo.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Nitromethane	75	255, 265, 266
	H.L.Phe.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Ethyl acetate	90	265, 266, 530
(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> .Gly.OH	H.DL.Ser.OC <sub>2</sub> H <sub>5</sub>	DMF*	60	265, 266, 530
Phth.L.Ala.OH	H.L.Pro.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Methylene dichloride	—	265, 266, 530
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	None	70	255, 265, 266, 530
Tos.L.Ileu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ether	60	265, 266, 530
OH 				
Cbzo.L.Glu.OC <sub>2</sub> H <sub>5</sub>	H.S.Bz.L.Cys.Gly.OC <sub>2</sub> H <sub>5</sub>	None	70	265, 266, 530
<i>B. Ethyl Ethinyl Ether</i>				
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Dioxane	80†	258
Tri.DL.Ala.OH	H.DL.Try.OCH <sub>3</sub>	None	80	265, 266, 530, 531
Cbzo.S.Bz.L.Cys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	90	265, 266, 530
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Chloroform	60	258
Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	None	49	258
H.Gly.Leu.Gly.Gly.Leu.Gly.OH‡		Methanol	11	242

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

† The yield is based on the adduct of phthaloylglycine with ethoxyacetylene.

‡ The product was a cyclo-hexapeptide.

TABLE XIII  
 ANHYDRIDE FORMATION WITH ETHYL  $\alpha$ -CHLOROVINYL ETHER AND WITH  $\alpha,\alpha'$ -DICHLOROETHYL ETHER

Acid	Amine	Solvent	Yield, %	References
<i>A. Ethyl <math>\alpha</math>-Chlorovinyl Ether</i>				
Cbzo.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	01	267
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	85	267
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	42	267
Cbzo.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	54	267
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	51	267
Phth.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	67	267
Cbzo.L.Val.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	20	267
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	60	267
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	51	267
Phth.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	None	75	267
Cbzo.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	83	267
Phth.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	70	267
Cbzo.Gly.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	25	267
Phth.Gly.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	None	56	267
<i>B. <math>\alpha,\alpha'</math>-Dichloroethyl Ether</i>				
Cbzo.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	71	267
Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	None	90	267
	H.S.Bz.L.Cys.OH	Ethyl acetate	92	267
Cbzo.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	61	267
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	53	267
Cbzo.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	61	267
Phth.Gly.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	None	64	267
Phth.L.Ala.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	None	38	267

*Note:* References 437 to 538 are on pp. 353-355.



TABLE XIV  
ANHYDRIDE FORMATION WITH *p*-NITROPHENOL  
(All yields are based upon the *p*-nitrophenyl ester.)

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.Gly.OH	Ethanol-water	90	38
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethanol	94	38
	H.L.Phe.OH	Dioxane-water	32	38
Phth.Gly.OH	H.Gly.OH	DMF-water*	72	269
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	96†	283
	H.L.Ala.OC <sub>2</sub> H <sub>5</sub>	THF‡	43	269
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	71	269
Cbzo.L.Val.OH	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H.L.Asph.OH} \end{array}$	Dioxane-water	64	283
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	67	230
	H.O.C <sub>6</sub> H <sub>5</sub> CO.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	95	230
Cbzo.L.Leu.OH	$\begin{array}{c} \text{Tos} \\   \\ \text{H.L.Lys.OCH}_3 \end{array}$	—	67	529
	$\begin{array}{c} \text{Tos} \\   \\ \text{H.L.Orn.OCH}_3 \end{array}$	THF	67	280
	H.D.Phe.OC <sub>2</sub> H <sub>5</sub>	THF	96	280
Phth.D.Leu.OH	H.Gly.NH <sub>2</sub>	DMF	93	283
Cbzo.S.Bz.L.Cys.OH	H.L.Phe.OCH <sub>3</sub>	—	—	504
	H.L.Tyr.OH	THF-water	9	269
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	83§	269, 532
Cbzo.L.Asp.OH	$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{H.L.Arg.OH} \end{array}$	—	—	272
Cbzo.L.Asp.L.Arg.OH	$\begin{array}{c} \text{OCH}_2\text{C}_6\text{H}_5 \\   \\ \text{H.L.Val.OH} \end{array}$	—	—	272
Cbzo.S.Bz.L.Cys.OH	H.L.Pro.L.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	—	283
Cbzo.L.Val.L.Tyr.L.Val.OH	H.L.His.OH	—	—	272
H.Gly.L.Leu.Gly.OH		DMF-pyridine	20	146
H.Gly.DL.Phe.Gly.OH		DMF-pyridine	29-38	149
H(Gly.L.Leu.Gly) <sub>2</sub> OH		DMF-pyridine	68	146
H(L.Val.L.Lys.L.Leu.D.Phe.L.Pro) <sub>2</sub> OH¶	$\begin{array}{c} \text{Tos} \\   \\ \text{H(L.Val.L.Lys.L.Leu.D.Phe.L.Pro)}_2\text{OH}\¶ \end{array}$	DMF-pyridine	21	148, 281, 529
Tri(L.Val.L.Orn.L.Leu.D.Phe.L.Pro) <sub>2</sub> OH¶¶	$\begin{array}{c} \text{Tos} \\   \\ \text{Tri(L.Val.L.Orn.L.Leu.D.Phe.L.Pro)}_2\text{OH}\¶\¶ \end{array}$	DMF-pyridine	28**	148, 278-280

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

† Lower yields were obtained in other solvents.

‡ THF is tetrahydrofuran.

§ This is the yield after hydrolysis.

|| The product is a cyclo-hexapeptide.

¶ The product is a ditosyl cyclo-decapeptide.

\*\* This is the over-all yield of ditosyl Gramicidin S.

TABLE XV  
ANHYDRIDE FORMATION WITH MISCELLANEOUS PHENOLS  
(All yields are based upon the phenyl ester.)

Phenol	Acid	Amine	Solvent	Yield, %	Reference
$\text{HOC}_6\text{H}_5$	Phth.Gly.OH	H.Gly. $\text{OC}_2\text{H}_5$	Benzene	3	268
$\text{HOC}_6\text{H}_4\text{NO}_2$ - <i>m</i>	Phth.Gly.OH	H.Gly. $\text{OC}_2\text{H}_5$	Benzene	86	269
	Cbzo.S.Bz.L.Cys.OH	H.L.Tyr. $\text{OC}_2\text{H}_5$	THF*	74†	269
$\text{HOC}_6\text{H}_3(\text{NO}_2)_2$ -2,4	Phth.Gly.OH	H.Gly. $\text{OC}_2\text{H}_5$	Dioxane	60	269
$\text{HOC}_6\text{H}_4\text{SO}_2\text{CH}_3$ - <i>p</i>	H.Gly.DL.Phe.Gly.OH‡		DMF-pyridine§	40-46	149
	H.Gly.Gly.DL.Phe.OH‡		DMF-pyridine	25	149
	H(Gly.Gly.DL.Phe) <sub>2</sub> .OH‡		DMF-pyridine	13	149

Note: References 437 to 538 are on pp. 353-355.

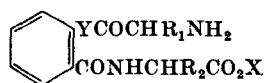
\* THF is tetrahydrofuran.

† This is the yield after hydrolysis.

‡ DMF is dimethylformamide.

§ The product is the cyclo-hexapeptide.

TABLE XVI  
BRENNER'S METHOD



Y	$\text{H}_2\text{NCHR}_1\text{CO}_2\text{H}$	$\text{H}_2\text{NCHR}_2\text{CO}_2\text{X}$	Solvent	Yield, %	References
O	H.Gly.OH	H.L.Phe.OCH <sub>3</sub>	Chloroform	Moderate	293-295
O	H.L.Phe.OH	H.Gly.OCH <sub>3</sub>	Chloroform	100	293, 294
O	H.DL.Phe.OH	H.Gly.OCH <sub>3</sub>	THF-methanol*	95	288, 293-295
O	H.Gly.OH	H.L.Phe.Gly.OCH <sub>3</sub>	Methanol	100	293, 294
O	H.Gly.OH	H.DL.Phe.Gly.OCH <sub>3</sub>	Methanol	95	288, 293-295
O	H.DL.Phe.OH	H.DL.Phe.Gly.OCH <sub>3</sub>	Various	—	293-295
S	H.DL.Phe.OH	H.Gly.NHC <sub>6</sub> H <sub>5</sub>	Chloroform	—	293, 295

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.



TABLE XVIII  
ANHYDRIDE FORMATION WITH MISCELLANEOUS ESTERS

Reagent	Acid	Amine	Solvent	Yield, %	Reference
$\text{BrCH}_2\text{CO}_2\text{C}_2\text{H}_5$	Cbzo.Gly.OH	H.Gly.Gly.OH	Acetonitrile-water	40	316
	$\text{C}_6\text{H}_5\text{CONHCHOHCO}_2\text{H}$	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Acetonitrile	56	322
$\text{BrCH}(\text{CO}_2\text{C}_2\text{H}_5)_2$	$\text{C}_6\text{H}_5\text{CO.Gly.OH}$	H.O.C <sub>6</sub> H <sub>5</sub> CO.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	65	316
$\text{BrCH}_2\text{C}\equiv\text{CH}$	Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	—	310
$\text{IMgOCH}_2\text{CH}_3$	$\text{F}_3\text{CCO.Gly.OH}$	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Ethyl acetate	94	320

Note: References 437 to 538 are on pp. 353-355.

TABLE XIX  
ANHYDRIDE FORMATION WITH ACYLMIDAZOLES (*im*-ACYL-L-HISTIDINE METHYL ESTER)

Starting Compound	Amine	Product	Yield, %	Reference
<i>im</i> -Hippuryl-N-benzoyl-L.His.OCH <sub>3</sub>	H.Gly.OH	C <sub>6</sub> H <sub>5</sub> CO.Gly.Gly.OH	35	325
<i>im</i> -N-(Cbzo.Gly) <sub>2</sub> -L.His.OCH <sub>3</sub>	H.Ala.OCH <sub>3</sub>	Cbzo.Gly.Ala.OCH <sub>3</sub>	30	229

*Note:* References 437 to 538 are on pp. 353-355.

TABLE XX  
ANHYDRIDE FORMATION WITH N,N'-CARBONYLDIIMIDAZOLE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo.Gly.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	THF*	> 68	328
	H.L.Phe.OH	THF	40	328
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	83	328
Cbzo.L.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	65	328
(CH <sub>3</sub> ) <sub>3</sub> COCO.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	78	328
Cbzo.Gly.L.Phe.OH	H.L.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF†	87	328

*Note:* References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

† DMF is dimethylformamide.

TABLE XXI  
ANHYDRIDE FORMATION WITH 3,5-DIMETHYLPYRAZOLE

Acylpyrazole	Amine	Solvent	Yield, %	Reference
Tos.Gly.OH	H.DL.Al <sub>a</sub> .OC <sub>2</sub> H <sub>5</sub>	None	80	332
Tos.DL.Al <sub>a</sub> .OH	H.DL.Al <sub>a</sub> .OC <sub>2</sub> H <sub>5</sub>	None	75	332
Tos.Gly.DL.Al <sub>a</sub> .OH	H.DL.Val.OC <sub>2</sub> H <sub>5</sub>	—	56	332

*Note:* References 437 to 538 are on pp. 353-355.



TABLE XXII  
ANHYDRIDE FORMATION WITH THIOPHENYL ESTERS

Acid	Amine	Solvent	Yield, %	References
<i>A. Thiophenyl Esters</i>				
F <sub>3</sub> CCO.Gly.OH	H.DL.Phe.OH	THF-water*	14	533
Cbzo.Gly.OH	H.Gly.OH	—	75	338
	H.DL.Ala.OH	Methanol	90	336, 347, 361
	H.DL.Ala.OH	THF-water	75	336
	H.L.Pro.OH	THF-methanol-water	68 crude	59
	H.DL.Pro.OH	THF-methanol-water	80	59
	H.S.Bz.L.Cys.OH	THF-water	—	348
	H.DL.Phe.OH	THF-water	75	336
Cbzo.β.Ala.OH	H.β.Ala.OH	Methanol-water	70	336
Cbzo.S.Bz.L.Cys.OH	H.Gly.OH	THF-water	69	348
	H.S.Bz.L.Cys.OH	THF-water	100	348
Cbzo.DL.Try.OH	H.Gly.OH	—	75	338
Tos.β.Ala.OH	H.β.Ala.β.Ala.OH	Methanol-water	—	347
Cbzo.S.Bz.L.Cys.OH	H.Gly.Gly.OH	THF-water	31	348
Cbzo.Gly.Gly.OH	H.L.Pro.OH	THF-methanol-water	82 crude	59
	H.S.Bz.L.Cys.OH	THF-water	78	348
Cbzo.S.Bz.L.Cys.Gly.OH	H.S.Bz.L.Cys.OH	THF-water	21	348
Cbzo.Gly.L.Leu.OH	H.Gly.OH	THF-methanol-water	70	37
Cbzo.Gly.DL.Phe.OH	H.DL.Ala.OH	THF-water	70	336
Cbzo.Gly.Gly.OH	H.Gly.L.Pro.OH	THF-methanol-water	100 crude	59
H.Gly.DL.Val.DL.Ala.Gly.DL.Val.DL.Ala.OH†		DMF-pyridine‡	18	37
<i>B. p-Nitrothiophenyl Esters</i>				
Cbzo.Gly.OH	H.L.Phe.OH	Dioxane-water	93	38
	H.DL.Phe.OH	Dioxane-water	90	38

Cbzo.L.Leu.OH	H.Gly.OH	THF-water	98	38, cf. 349
Cbzo.Gly.OH	H.L.Leu.Gly.OH	THF-water	93	38
Cbzo.Gly.L.Phe.OH	H.Gly.OH	Dioxane-water	100	38, 335
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	96	38
Cbzo.Gly.L.Ala.OH	H.L.Phe.Gly.OH	Dioxane-water	55 LL	38
			24 DL	
Cbzo.Gly.L.Leu.Gly.OH	H.L.Leu.Gly.OH	THF	93 crude	38, cf. 349
H.Gly.L.Leu.Gly.L.Leu.Gly.OH§		Water	41-44	334, 349
Cbzo.Gly.L.Leu.Gly.OH¶		Water	11.5	349
	H.Gly.L.Leu.Gly.OH	THF	—	349
Cbzo.Gly.L.Leu.Gly.Gly.L.Leu.Gly.OH¶		Water	20	349

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

† The product was a cyclo-hexapeptide.

‡ DMF is dimethylformamide.

§ The product was a cyclo-peptide.

¶ A cyclo-hexapeptide was formed upon hydrogenolysis.

TABLE XXIII  
ANHYDRIDE FORMATION WITH MISCELLANEOUS THIOL COMPOUNDS

Thiol	Acid	Amine	Solvent	Yield, %	References
H <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub> CO.Gly.OH	H.DL.Ala.OH	DMF*	70	340
	Phth.Gly.OH	H.Gly.OCH <sub>3</sub>	Methylene dichloride	—	339
	Benzalglycine	H.Gly.OH	Water	20	346
HSCH <sub>3</sub>	Cbzo.Gly.OH	H.DL.Val.OH	Methylene dichloride	—	347, 301
HSCH <sub>2</sub> CO <sub>2</sub> H	C <sub>6</sub> H <sub>5</sub> CO.Gly.OH	H.Gly.OH	—	46†	271, 344, 363
	Cbzo.Gly.OH	H.Gly.OH	—	70	271, 344
	Cbzo.Gly.OH	H.DL.Met.OH	—	60	271, 344
	Cbzo.Gly.OH	H.Gly.Gly.OH	—	79	271, 344
	Cbzo.Gly.OH	H.DL.Ala.Gly.OH	—	73	271, 344
	H.Gly.Gly.Gly.OH‡		Pyridine	13	312
	H.Gly.Gly.Gly.OH‡		DMF-pyridine	69	312
	Cbzo.Gly.OH	H.Gly.OH	—	49	271, 344
o-HSC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	C <sub>6</sub> H <sub>5</sub> CO.Gly.OH	H.Gly.OH	—	80	271, 344
	Cbzo.Gly.OH	H.Gly.Gly.OH	—	52	271, 244

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

† With metal catalysts yields up to 80% were obtained.

‡ The product was a cyclo-tetrapeptide.

TABLE XXIV  
ANHYDRIDE FORMATION WITH SULFURIC ACID

Acid	Amine	Solvent	Yield, %	References
C <sub>6</sub> H <sub>5</sub> CO.Gly.OH	H.DL.Ser.OCH	DMF*	70	370
Cbzo.Gly.OH	H.Gly.OH	DMF	81	370
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	85	370
	H.L.Ala.OH	DMF	87	370
	H.DL.Ala.OH	DMF	75	370
	H.L.Phe.OH	DMF	86	370
	H.DL.Phe.OH	DMF	70	183, 372-375
	H.L.Phe.OC <sub>2</sub> H <sub>5</sub>	DMF	48	183
Tos.Gly.OH	H.L.Phe.OH	DMF	86	5, 370, 375
	H.DL.Phe.OH	DMF	—	370
Cbzo.DL.Ala.OH	H.Gly.OH	—	60	183
Cbzo.L.Ala.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	DMF	87	370
Tos.DL.Ala.OH	H.Gly.OH	DMF	80	183
Cbzo.L.Leu.OH	H.Gly.OH	DMF	64	370
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	85	370
Cbzo.DL.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	87	370
CH <sub>3</sub> CO.S.Bz.L.Cys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	73	370
(Cbzo) <sub>2</sub> .L.cystine	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	81	370
Cbzo.L.Phe.OH	H.Gly.OH	DMF	25, 92	183, 370
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	83	370
Cbzo.L.Try.OH	H.Ala.OH	DMF	74, 78	370, 375
Cbzo.Gly.OH	H.Gly.Gly.OH	DMF	75	375
	H.L.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	78	370
	H.DL.Leu.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	> 60	370

Note: References 437 to 538 are on pp. 353-355.

\* DMF is dimethylformamide.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 345

TABLE XXIV—Continued  
ANHYDRIDE FORMATION WITH SULFURIC ACID

Acid	Amine	Solvent	Yield, %	References
Tos.Gly.OH	H.DL.Phe.Gly.OH	DMF	92	5, 370, 375
Cbzo.Gly.Gly.OH	H.Gly.OH	DMF	84	370
Cbzo.Gly.L.Phe.OH	H.Gly.OH	DMF	52	183, 372-375
			83	5, 370
Cbzo.Gly.DL.Phe.OH	H.Gly.OH	DMF	72	183, 372-375
Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	81	370
Cbzo.L.Ala.O-CH <sub>3</sub> CO.L.Tyr.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	DMF	62	370
Cbzo.Gly.L.Ala.OH	H.L.Phe.Gly.OH	DMF	36, 78	370, 375
	OH			
Tos.Gly.L.Phe.OH	H.L.Glu.Gly.NHCH(CH <sub>2</sub> ) <sub>5</sub>	DMF	71	375
Cbzo.Gly.L.Leu.Gly.OH	H.L.Leu.Gly.OH	—	—	334

Note: References 437 to 538 are on pp. 353-355.

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TABLE XXV  
ANHYDRIDE FORMATION WITH BENZENESULFONYL CHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Phth.Gly.OH	H.Gly.OCH <sub>3</sub>	Pyridine	79	378
	H.DL.Phe.OCH <sub>3</sub>	Pyridine	86	378
Tos.Gly.OH	H.Gly.OCH <sub>3</sub>	Pyridine	58	378
Phth.DL.Phe.OH	H.Gly.OCH <sub>3</sub>	Pyridine	90	378
O,N-(Tos) <sub>2</sub> .L.Tyr.OH	H.Gly.OCH <sub>3</sub>	Pyridine	95	378

*Note:* References 437 to 538 are on pp. 353-355.

TABLE XXVI  
ANHYDRIDE FORMATION WITH PHOSPHORUS OXYCHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo.Gly.OH	H.Gly.OCH <sub>3</sub>	THF*	70	130
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	80	130
	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	65	37
	H.DL.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	70	130
	H.DL.Ala.SC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - <i>p</i>	THF	56	37
	H.DL.Val.SC <sub>6</sub> H <sub>5</sub>	THF	74	37
	H.DL.Leu.OC <sub>2</sub> H <sub>5</sub>	THF	76	130
	H.L.Leu.SC <sub>6</sub> H <sub>5</sub>	THF	87	37
	H.DL.Met.OCH <sub>3</sub>	THF	95	130
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	THF	90	130
	Cbzo.DL.Ala.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	80
H.Gly.OC <sub>2</sub> H <sub>4</sub> NO <sub>2</sub> - <i>p</i>		THF	70	37
H.Gly.SC <sub>6</sub> H <sub>5</sub>		THF	67	37
H.DL.Thr.OCH <sub>3</sub>		THF	67	130
Cbzo.HO.L.Pro.OH	H.L.Try.OCH <sub>3</sub>	THF	75 crude	130
Cbzo.DL.Val.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	88	130
	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	70	37
Cbzo.DL.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	60	130
Cbzo.S.Bz.L.Cys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	THF	81	130
	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	Chloroform	52	454
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	THF	35	454
	H.S.Bz.L.Cys.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Chloroform	33	454

Note: References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 347

TABLE XXVI—Continued  
ANHYDRIDE FORMATION WITH PHOSPHORUS OXYCHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo.Gly.OH	H.DL.Ala.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	65	37
Cbzo.S.Bz.L.Cys.OH	H.Gly.DL.Ala.OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	THF	70	130
Cbzo.L.Phe.OH	H.Gly.L.Ala.OC <sub>2</sub> H <sub>5</sub>	THF	53-58†	534
	H.Gly.L.Val.OC <sub>2</sub> H <sub>5</sub>	THF	50	534
Cbzo.D.Phe.OH	H.Gly.D.Val.OC <sub>2</sub> H <sub>5</sub>	THF	50	534
$\begin{array}{c} \text{NH}_2 \\   \\ \text{Cbzo.L.Glu.OH} \end{array}$	H.S.Bz.L.Cys.S.Bz.L.Cys.OC <sub>2</sub> H <sub>5</sub>	THF	94	454
Cbzo.DL.Ala.Gly.OH	H.Gly.SC <sub>6</sub> H <sub>5</sub>	THF	56	37
Cbzo.Gly.DL.Val.OH	H.DL.Ala.SC <sub>6</sub> H <sub>5</sub>	THF	54	37
	H.DL.Leu.SC <sub>6</sub> H <sub>5</sub>	THF	63	37
	H.DL.Ileu.SC <sub>6</sub> H <sub>5</sub>	THF	33	37
Cbzo.Gly.DL.Leu.OH	H.DL.Val.OCH <sub>3</sub>	THF	77	130

Note: References 437 to 538 are on pp. 353-355.

† All the optical isomers were prepared.

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TABLE XXVII  
 ANHYDRIDE FORMATION WITH DIETHYL  $\alpha$ -ETHOXY- $\beta$ -CARBETHOXYVINYL PHOSPHATE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.Gly.OH	Acetone	82	381, 391
	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Acetone	74	381
	H.DL.Ala.OC <sub>2</sub> H <sub>5</sub>	Acetone	67	381, 391
	H.DL.Phe.OH	Acetone	61	381, 391
	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Acetone	80	381, 391
Cbzo.DL.Ala.OH	H.DL.Ala.OH	Acetone	76	381, 391
	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Acetone	68	381
Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Acetone	63	381, 391
Cbzo.Gly.OH	H.Gly.Gly.OH	Acetone	87	381, 391
	H.Gly.Gly.Gly.OH	Acetone	81	381, 391

Note: References 437 to 538 are on pp. 353-355.

TABLE XXVIII  
ANHYDRIDE FORMATION WITH MISCELLANEOUS PHOSPHATES

Phosphate	Acid	Amine	Solvent	Yield, %	Reference
Silver dibenzyl phosphate	Phth.Gly.OH	H.Gly.OH	Benzene	78	386
	Phth.Gly.OH	H.DL.Phe.OH	Benzene	83 crude	386
Disilver phenyl phosphate	Cbzo.Gly.Cl	H.Gly.OH	Ether	—	22
	Cbzo.Gly.Cl	H.Try.OH	Ether	—	22
	Cbzo.Gly.Cl	H.Gly.Try.OH	Ether	—	22
Diphenyl chlorophosphate	Cbzo.Gly.OH	H.Gly.OH	THF*	10	48
Phenyl dichlorophosphate	Cbzo.Gly.OH	H.Gly.OH	THF	30	48
2',3'-Isopropylideneadenosine-5'-benzylphosphoric acid	Cbzo.Gly.OH	H.Phe.OCH <sub>3</sub>	—	—	380
	Cbzo.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Benzene-acetonitrile-dioxane	—	380

*Note:* References 437 to 538 are on pp. 353-355.

\* THF is tetrahydrofuran.

TABLE XXIX  
ANHYDRIDE FORMATION WITH PHOSPHITES

Phosphite	Acid	Amine	Solvent	Yield, %	References
Diethyl chlorophosphite	Cbzo.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	92	399, 401, 402, 404, 411
	Cbzo.DL.Ala.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	88	399, 401, 402, 404
	(Cbzo) <sub>2</sub> .L.Lys.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	92	399, 401, 402, 404, 411
Ethylene chlorophosphite	Cbzo.Gly.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	43	399, 401, 402, 404
	Phth.Gly.DL.Ala.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	71	399-402, 404, 411
	Cbzo.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Diethyl phosphite	91	406
	Cbzo.Gly.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Diethyl phosphite	79	406
	Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Diethyl phosphite	52 L 14 DL	406
Ethyl dichlorophosphite	Cbzo.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Benzene	91	403, 405-408
	Cbzo.Gly.OH	H.L.Tyr.OC <sub>2</sub> H <sub>5</sub>	Benzene	44	403, 405-408
	Phth.Gly.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	62	403, 405-408
	Phth.Gly.OH	H.L.Leu.OC <sub>2</sub> H <sub>5</sub>	Benzene	91	403, 405-408
	Cbzo.DL.Val.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	86	406
	Cbzo.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Benzene	40	406
	Cbzo.L.Leu.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	42	406
	Cbzo.L.Leu.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	—	403, 405, 407, 408
	Cbzo.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	65	406
	Cbzo.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	—	403, 407, 408
	Cbzo.Gly.L.Leu.OH	H.Gly.OCH <sub>3</sub>	Benzene	64	406
	Cbzo.Gly.L.Leu.OH	H.L.Leu.OCH <sub>3</sub>	Benzene	60	406
	Cbzo.Gly.L.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	71	406
	Cbzo.Gly.DL.Phe.OH	H.Gly.OC <sub>2</sub> H <sub>5</sub>	Benzene	75-78	403, 405-408

Note: References 437 to 538 are on pp. 353-355.

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES 351

TABLE XXIX—Continued

ANHYDRIDE FORMATION WITH PHOSPHITES

Phosphite	Acid	Amine	Solvent	Yield, %	References
Tetraethyl pyrophosphite	Cbzo.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	None	—	407, 408, 535
	Cbzo.L.Tyr.OH	H.Gly.Gly.OC <sub>2</sub> H <sub>5</sub>	Diethyl phosphite	—	407, 408, 535

Note: References 437 to 538 are on pp. 353-355.

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TABLE XXX  
ANHYDRIDE FORMATION WITH DIETHYL CHLOROARSENITE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Chloroform	52	434, 536, 537
Cbzo.DL.Ala.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	60	434, 536, 537
Cbzo.L.Leu.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	74	434, 536, 537
Cbzo.Gly.Gly.OH	H.DL.Phe.OC <sub>2</sub> H <sub>5</sub>	Toluene	30	434, 536, 537

*Note:* References 437 to 538 are on pp. 353-355.

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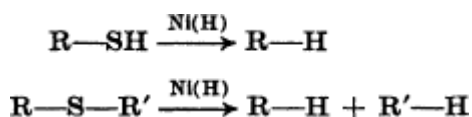
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# Desulfurization with Raney Nickel

## 1. Introduction

The first example of the desulfurization of an organic compound by means of Raney nickel was reported by Bougault in 1940.<sup>1</sup> Since that time the reaction has been used with much success both for synthesis and the determination of structure. In general, a Raney nickel desulfurization involves the breaking of a carbon-sulfur bond in an organic substance and, usually, the formation of at least one new carbon-hydrogen bond. The oxidation state of the sulfur that is removed may vary from two to six. Although the hydrogenolysis of organic compounds containing sulfur has been accomplished by a variety of inorganic reagents, this survey has been restricted to desulfurizations brought about by Raney nickel in which adsorbed hydrogen usually, but not always, has been retained. The symbol "Ni(H)" will be used to indicate such a reagent. Desulfurizations effected by nickel-aluminum alloy and aqueous alkali (Schwenk-Papa reduction) also are included. The analogous Raney nickel deselenization<sup>2, 3</sup> reaction has not been reviewed. Several facets of the Raney nickel desulfurization reaction have recently been reviewed by Challenger.<sup>4</sup>



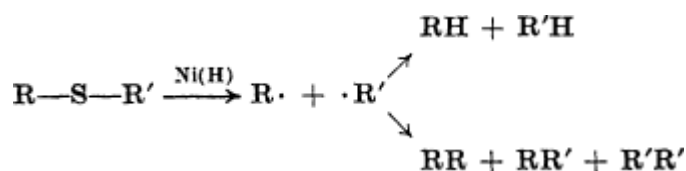
## 2. Mechanism

Associated with the problem of a hydrogenolytic desulfurization mechanism is the question of hydrogen source. Bougault<sup>5, 6</sup> in his initial investigations showed that Raney nickel, as ordinarily prepared, contains large quantities of hydrogen that is effective in reducing various organic and inorganic substances. Others<sup>7</sup> have expressed the belief that it is this "bound" hydrogen that participates in desulfurization reactions. On the other hand, the observation that acetaldehyde was formed in certain thioketal desulfurizations which were carried out in ethanol led to the proposal that it is the hydrogen produced in the dehydrogenation of ethanol to acetaldehyde that is utilized in the desulfurization.<sup>8</sup> Bonner later demonstrated that the source of hydrogen is actually the nickel and that the production of acetaldehyde from ethanol is simply a concurrent reaction.<sup>9</sup>

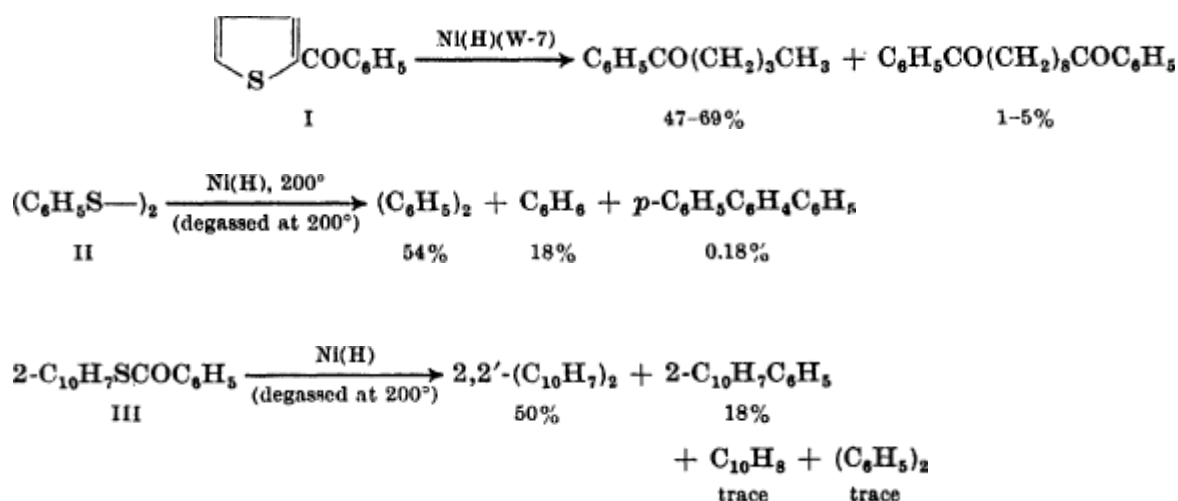
In an early paper Bougault suggested as the first step the formation of a nickel mercaptide, which then decomposes to nickel sulfide and a hydrocarbon.<sup>1</sup> Since then, several groups<sup>10-14</sup> have expressed the belief that free radicals are intermediates, and, indeed, such products as one might expect on this basis have been isolated.



At present it is believed<sup>11, 14</sup> that the first step in any desulfurization with Raney nickel involves chemisorption of the sulfur atom on the surface of the catalyst. This reaction is followed by fission of the carbon-sulfur bond giving rise to free radicals. The reaction may then proceed by hydrogenation or recombination of the radicals as shown in the accompanying equation. Both reactions have been observed, and the proportion of each is dependent upon the quantity of hydrogen available.



Deactivated catalysts afford greater yields of the dimeric products, while massive amounts of active Raney nickel favor hydrogenation. Desulfurization of 2-benzoylthiophene (I),<sup>14</sup> diphenyl disulfide (II),<sup>11</sup> and 2-naphthyl thiobenzoate (III)<sup>11</sup> may be cited as examples.



The disulfide II, on treatment at 140° with Raney nickel degassed at 200°, is converted to diphenyl sulfide in 87% yield.<sup>11</sup> Apparently at 140° the carbon-sulfur bonds remain intact for the most part, whereas in the vicinity of 200° they are cleaved to form phenyl radicals. The isolation of benzene indicates that even the small quantity of hydrogen remaining on the nickel after degassing at 200° is still available for hydrogenation. Utilization of Raney nickel degassed at 500° and containing 0.5 ml. of hydrogen per gram demonstrated<sup>11</sup> that the yield of biaryl was never less, and in some cases was more, than that observed when the catalyst degassed at 200° was used.

Because different products are obtained when nickel catalysts containing varying amounts of adsorbed hydrogen are employed, it has been suggested that this hydrogen actually causes the fission of the carbon-sulfur bond.<sup>11</sup>

The loss of carbon monoxide during the desulfurization of thioesters with degassed Raney nickel as illustrated with the ester III above has been confirmed.<sup>15</sup>

The stereochemical course of desulfurization has been studied by Bonner.<sup>16, 17</sup> The amides of both dextro- and levo-rotatory 2-phenyl-2-(phenylmercapto)propionic acid afforded completely racemized 2-phenylpropionamide, as did both optically pure forms of the corresponding sulfoxides. These results point to a radical mechanism. However, the sulfones corresponding to the same phenylmercaptoamides were converted with nearly complete retention of optical activity to the desulfurized products. Although the configurational relationships of the starting and desulfurized materials were not known, the rotational data suggest that desulfurization occurred with inversion. Bonner suggested initial adsorption of the sulfone on the nickel surface through the oxygen of the sulfone function, followed by interaction with an adjacent hydrogen atom in such a way as to break a carbon-sulfur bond and, simultaneously, to form an optically active reduction product.<sup>17a</sup>

The way in which the Schwenk-Papa method differs mechanistically (if at all) from desulfurization with prepared nickel catalysts is not known.

### 3. Scope and Limitations

A number of the side reactions that occur during desulfurizations with Raney nickel were foreshadowed by the early investigation of Mozingo, Spencer, and Folkers<sup>18</sup> who subjected various reducible substances to representative conditions of the desulfurization reaction. Olefins were found to become saturated, and aliphatic ketones were converted to the corresponding alcohols. Both azoxybenzene and hydrazobenzene suffered reductive cleavage of the nitrogen-nitrogen bond and, in ethanol as the solvent, yielded N-ethylaniline. The latter type of reaction subsequently was shown to be a general procedure for effecting N-alkylation.<sup>19-21</sup> Base-catalyzed C-alkylations with alcohols also have been observed to occur in the presence of Raney nickel.<sup>22-23a</sup> All these reactions have since been observed to occur during desulfurization.<sup>12, 14, 20, 24-35</sup> The work of Mozingo and collaborators, in addition, implied hydrogenolytic removal of oxygen from the benzylic position;<sup>36, 37</sup> aliphatic carboxyl and ester groups, however, appeared to be stable under desulfurization conditions. An exception to the latter generalization involves hydrogenolysis of ketol acetates.<sup>37a</sup>

Additional examples<sup>38-43</sup> indicate that complete hydrogenolysis, rather than selective desulfurization, of a carbon bound to both sulfur and nitrogen can take place. Furthermore, compounds having carbon singly bound to both sulfur and oxygen (hemithioacetal or hemithioacetal) can regenerate the parent carbonyl compound.<sup>44-46</sup>

Aromatic compounds containing nitrogen in various oxidized states have been reduced to primary amines concurrently with desulfurization; examples include nitro,<sup>47</sup> hydroxylamino,<sup>48, 49</sup> and nitroso<sup>50</sup> functions.

Several examples involving saturation of an aromatic ring have been reported,<sup>51-54</sup> although aromatic rings originally were reported to remain unchanged during nickel desulfurization.<sup>36</sup>

An early prediction by Schröter<sup>55</sup> concerning the possibility of using Raney nickel desulfurization for the quantitative determination of sulfur in carbon compounds has been realized. The nickel sulfide resulting from desulfurization is treated with acid, and the liberated hydrogen sulfide is determined by titration with mercuric acetate<sup>56</sup> or by a polarographic method.<sup>57</sup> The quantitative studies point out that approximately 95% of the original sulfur is converted to nickel sulfide during desulfurization. The fate of any remaining sulfur has not been established.<sup>56</sup>

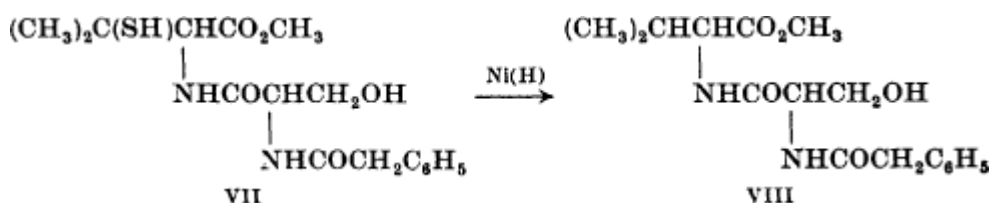
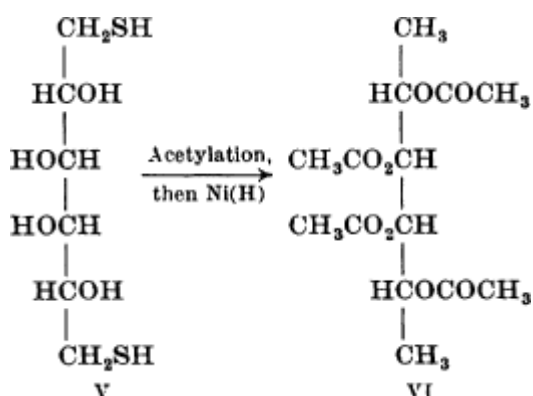
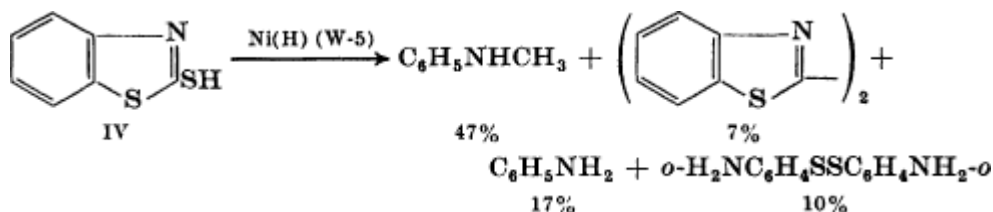
Many of the side reactions involving reduction described above can be used to advantage or circumvented by the use of deactivated, rather than active, Raney nickel. Several apparent discrepancies arise in the consideration of occurrence or absence of reduction accompanying desulfurization; these can be explained by assuming differences in reaction conditions or by differences in nickel reagents, which may vary in activity with age or method of preparation. In general, the Raney nickel reagent used for desulfurization may lead to side reactions involving reduction, oxidation, rearrangement, or condensation.<sup>58</sup>

#### 3.1. Thiols

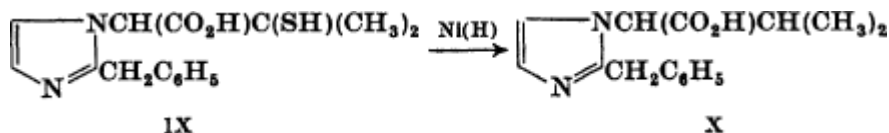
Aliphatic and aromatic mercaptans ordinarily can be desulfurized by treatment with Raney nickel, the product usually being the one resulting from cleavage of the carbon-sulfur bond and the formation of a new carbon-hydrogen bond. Such desulfurizations range from relatively simple examples like the formation of ethane from 1,2-ethanedithiol<sup>1</sup> or naphthalene from naphthalene- $\beta$ -thiol<sup>9</sup> to the more complex case involving the transformation of 2-mercaptobenzothiazole (IV) to the mixture of products shown. The reaction is carried out in boiling methanolic sodium hydroxide solution.<sup>41</sup>

The desulfurization of mercaptans (as well as other organic sulfur compounds) is characterized by a high order of selectivity; only occasionally do side reactions interfere, and rarely does an alternate reaction

supervene. A striking example is the desulfurization of 3-mercaptotetrahydrothiophene,<sup>59</sup> in which the mercapto group was removed without attack on the thioether linkage. On the other hand, N-( $\beta$ -mercaptoethyl)-2-benzoylisobutyramide suffered reduction of the keto carbonyl group on desulfurization.<sup>25</sup> Thiol derivatives of carbohydrates can be hydrogenolyzed without complication: for example, 1,6-dithiodulcitol (V) was converted, after acetylation, to the tetraacetyl derivative of 1,6-dideoxydulcitol (VI).<sup>60</sup>



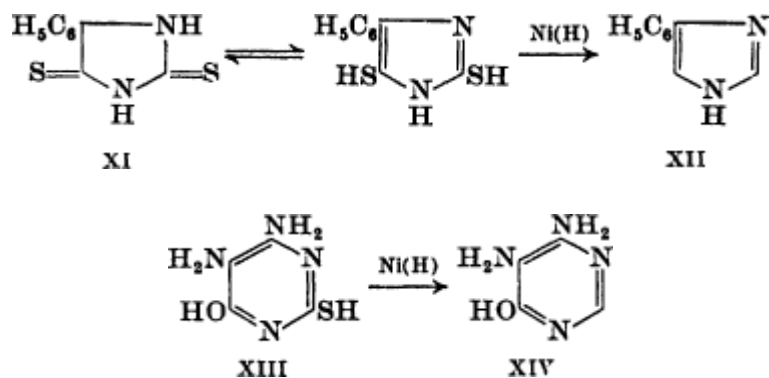
Desulfurization of thiols has been employed extensively for determination of structure, particularly in the penicillin series. For example, N-(N-phenylacetyl-l-seryl)-d-penicillamine methyl ester (VII) gave the corresponding D-valine methyl ester VIII,<sup>61</sup> and benzylpenillamine (IX) led to dethiobenzylpenillamine (X).<sup>62</sup>  $\beta$ ,  $\beta'$ -Dimercaptoisobutyric acid, the reduction product of a disulfide isolated from asparagus, was identified in part by desulfurization, which afforded isobutyric acid.<sup>63</sup>



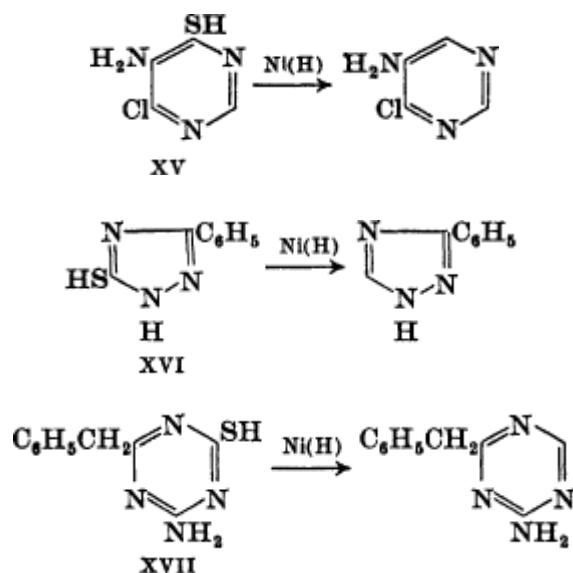
The literature is rich in examples of desulfurization of heterocyclic bases with one or more thiol groups attached directly to the aromatic ring. Such reactions have been used for the synthesis of otherwise difficultly obtainable substances. Thus imidazoles can be prepared by removal of sulfur from thiohydantoin, e.g., XI  $\rightarrow$  XII, which may be considered to react in the tautomeric 2,4-mercaptoimidazole form; imidazole itself was obtained in 25% yield by this method.<sup>64</sup> In a similar fashion, mercaptopyrimidines serve as useful precursors for pyrimidines; the parent heterocycle was formed in 17% yield when the reaction was carried out in water at 50°<sup>65</sup> Hydroxyl and amino substituents do not interfere; for example, 2-mercapto-5,6-diamino-4-hydroxypyrimidine (XIII) was transformed into the expected product XIV in 89% yield.<sup>66</sup> Selective removal of sulfur in the presence of a halogen



substituent may be exemplified by the desulfurization of 4-mercapto-5-amino-6-chloropyrimidine (XV) in 25% aqueous ammonia.<sup>67</sup>



Triazoles and triazines are obtainable by parallel reactions; desulfurizations of 3-phenyl-5-mercapto-1,2,4-triazole (XVI)<sup>68</sup> and 2-amino-4-mercapto-6-benzyl-1,3,5-triazine (XVII)<sup>69</sup> serve as illustrations.



Although a small amount of thiazole is formed on desulfurization of a 2-mercaptothiazole, the preponderant product usually is a completely desulfurized material. For example, acetophenone was obtained from 4-phenyl-2-mercaptothiazole (XVIII)<sup>43</sup> and aniline from 2-mercaptobenzothiazole (IV).<sup>43</sup> With a partially degassed W-7 Raney nickel catalyst<sup>70</sup> in methanol, desulfurization of the thiol IV follows a somewhat different course.<sup>41</sup>

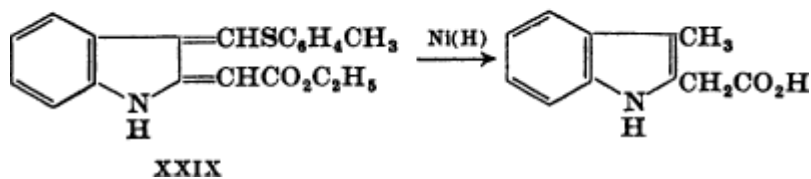
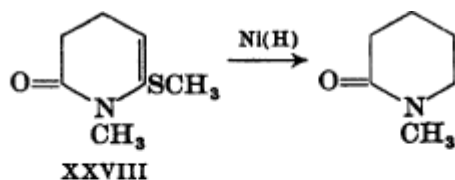
## 3.2. Thioethers

Desulfurization of thioethers can be carried out selectively in the presence of other reducible groups. Dibenzyl sulfide, 4-methylmercaptobutyric acid, and diphenyl sulfide are a few of the many sulfides which have been hydrogenolyzed in good yield to the expected products: toluene, butyric acid, and benzene, respectively.<sup>7</sup>

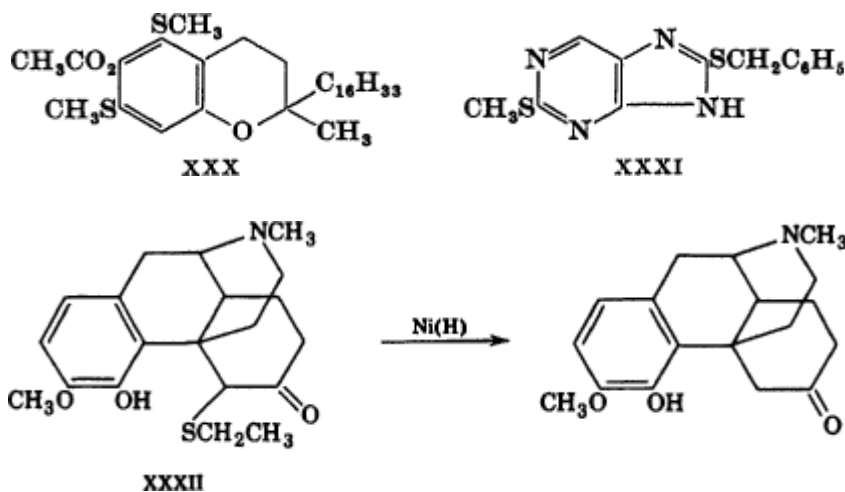
Ketones possessing a thioether function have been desulfurized successfully without reduction of the carbonyl group. For example,  $\alpha$ -thioethyldeoxybenzoin yielded deoxybenzoin<sup>75</sup> on treatment with Raney nickel partially deactivated by contact with acetone.

Intramolecular cyclization has been reported to occur during the desulfurization of certain cyclic thioethers.<sup>76</sup> Noteworthy is the production of bicyclo[2.2.1]heptane (XXIV) from the sulfide XXIII. The product of internal cyclization is usually obtained in poor yield. However, it is conceivable that the



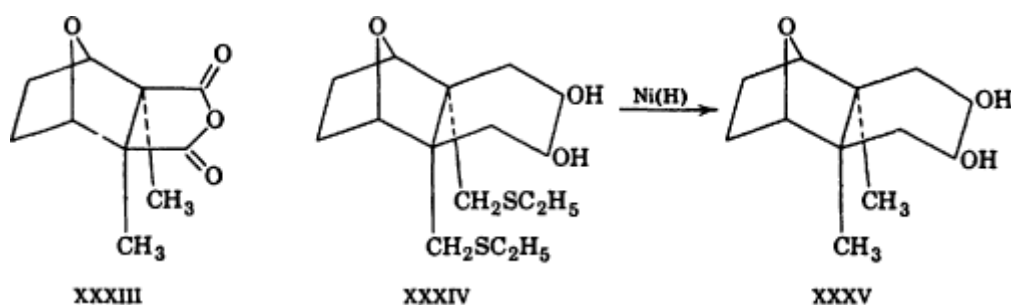


Two of the few unsuccessful attempts at desulfurization of thioethers involve the heterocyclic compounds XXX and XXXI; sulfur could not be abstracted from either molecule.<sup>82</sup> Failure to effect desulfurization of the purine XXXI was attributed to bond formation between the acidic single bond NH group and nickel.<sup>83</sup> However, ethylmercaptodihydrothebainone (XXXII), a thioether of some complexity, was smoothly converted to dihydrothebainone.<sup>84</sup>



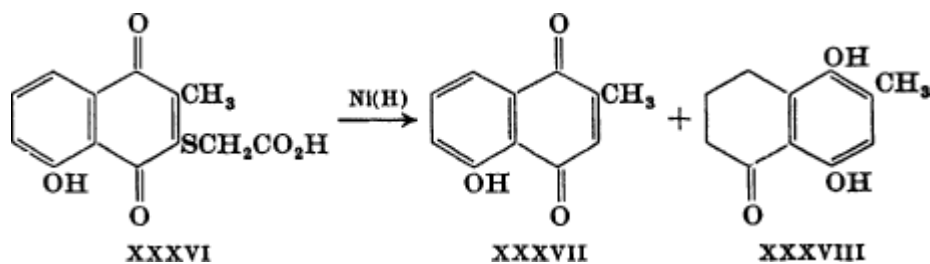
Various amino acids have been correlated stereochemically by the replacement of sulfur by hydrogen. (+)-Methionine, for example, afforded (-)- $\alpha$ -aminobutyric acid by a route that cannot involve inversion at the asymmetric center.<sup>85</sup>

As a purely synthetic tool, the desulfurization reaction was used to advantage in the total synthesis of cantharidin (XXXIII).<sup>24</sup> The tricyclic diol XXXIV was transformed into an intermediate (XXXV) possessing the desired angular methyl groups, after which stepwise oxidative degradation gave cantharidin.

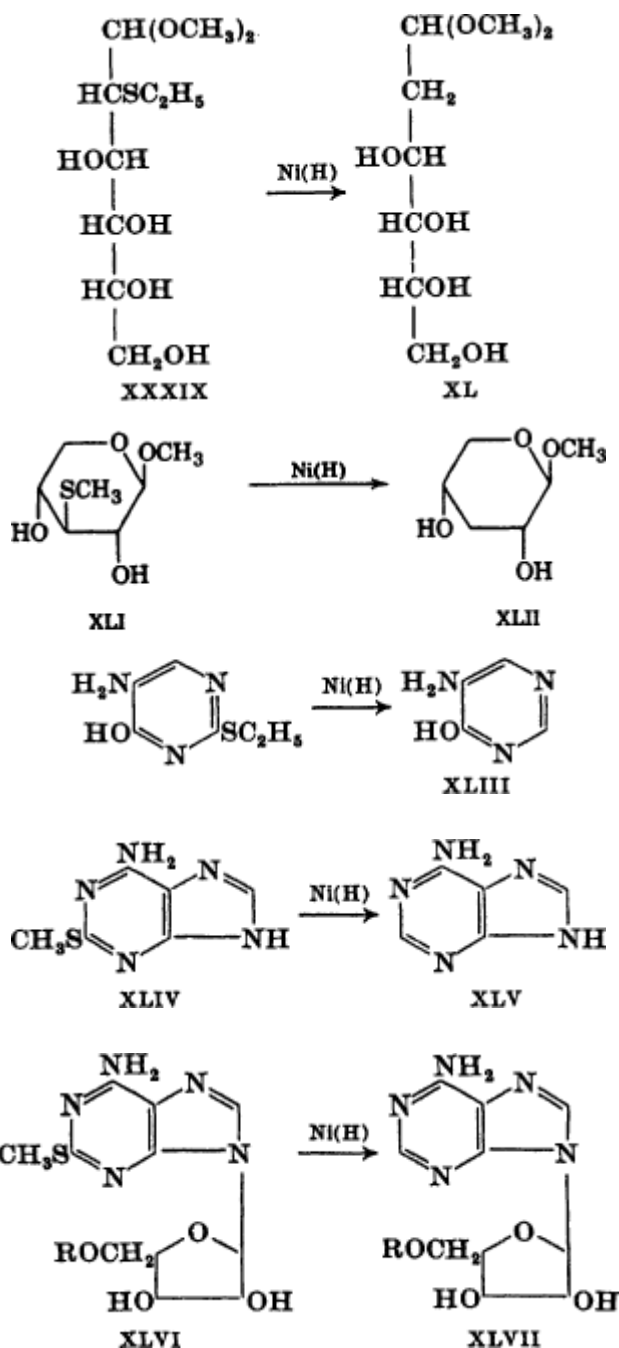


Removal of the thioglycolic acid side chain from the naphthoquinone XXXVI constituted a synthesis of plumbagin (XXXVII). Accompanying the latter in small amount was the product XXXVIII resulting from isomerization and further reduction.<sup>86, 87</sup> Several deoxy pentose and hexose derivatives have been obtained by desulfurization of the appropriate thioether. The dimethylacetal of 2-ethylthioglucose

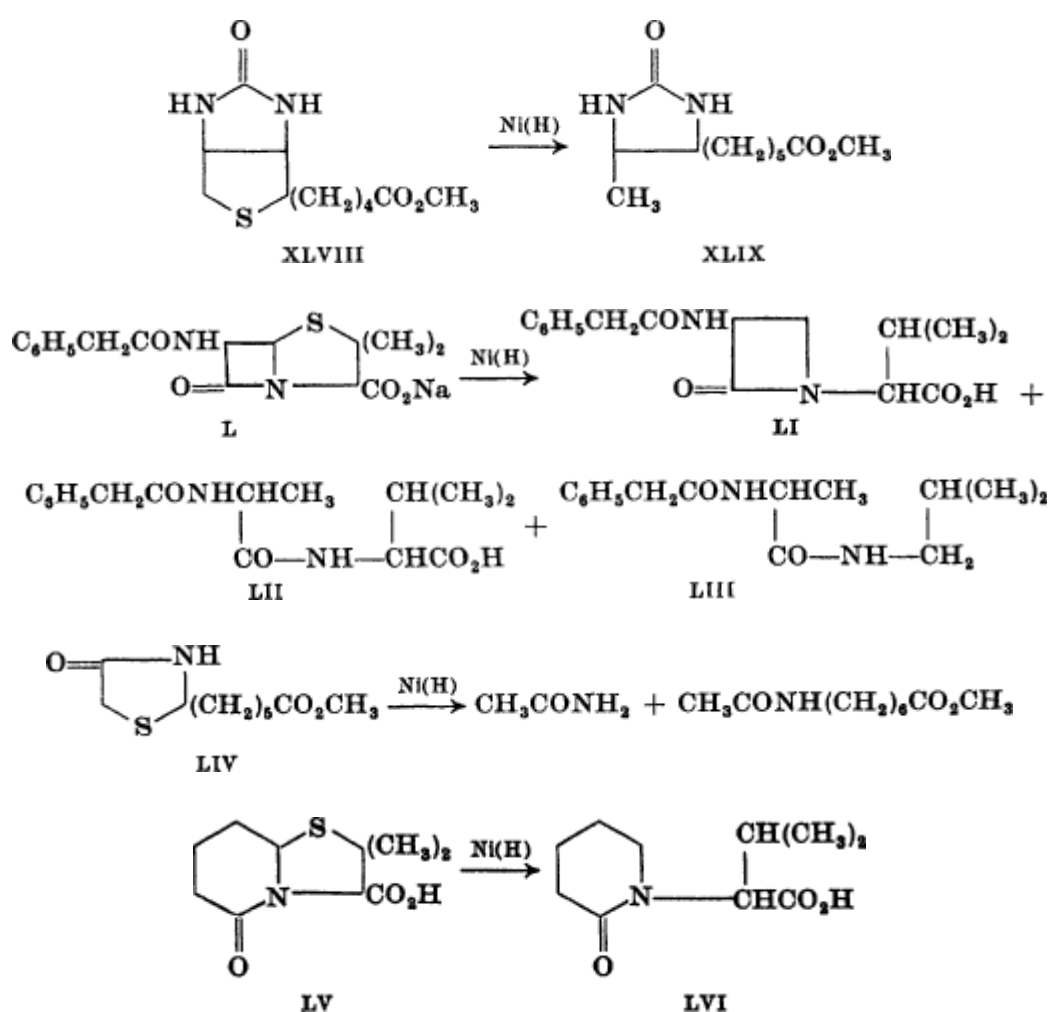
(XXXIX) yielded XL,<sup>88</sup> and 3-methylthio- $\beta$ -methyl-1-xylopyranoside (XLI) formed 3-deoxy- $\beta$ -methyl-1-xylopyranoside (XLII).<sup>89</sup>



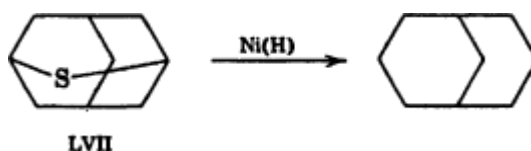
One finds in the thioether series, as in the thiol series, a number of transformations involving pyrimidines, among which may be cited the preparation of 4-hydroxy-5-aminopyrimidine (XLIII).<sup>90</sup> In the purine group, adenine (XLV) was prepared from the 2-methylmercapto derivative XLIV;<sup>91</sup> a new synthesis of adenosine (XLVII) was realized by the desulfurization of a 2-methylmercapto precursor<sup>92</sup> or its acetyl derivative, XLVI (R = H or CH<sub>3</sub>CO).<sup>93</sup>



Desulfurization has been employed in a number of important structural studies. One of the most revealing techniques of degradation applied in the study of biotin was desulfurization, which converted biotin methyl ester (XLVIII) to dethiobiotin methyl ester (XLIX).<sup>94</sup> Because one of the asymmetric centers is destroyed in the process of sulfur removal, the reaction also proved of value in the stereochemical correlation of various synthetic biotin isomers with the natural product.<sup>95</sup> Most carefully scrutinized in the penicillin series was benzylpenicillin (L),<sup>39, 96</sup> which, as the sodium salt, yielded three products: mainly dethiobenzylpenicillin (LI), along with phenylacetyl-L-alanyl-D-valine (LII) and the isobutylamide of phenylacetyl-L-alanine (LIII). The valine derivative arises by complete hydrogenolysis of the carbon atom bearing both nitrogen and sulfur, a phenomenon which is not unique; the formation of LIII, on the other hand, is a curious result which may involve a decarboxylation- $\beta$ -elimination followed by reduction. Hydrogenolysis of the type leading to LII was later encountered in investigation of the antibiotic actathiazone: acetamide, along with the anticipated methyl 7-acetamidoheptanoate, was obtained on desulfurization of the methyl ester LIV of the natural product.<sup>40</sup> Interestingly enough, a compound of similar constitution, LV, has been reported to form the amide LVI as a result of carbon-sulfur cleavage only.<sup>97</sup>

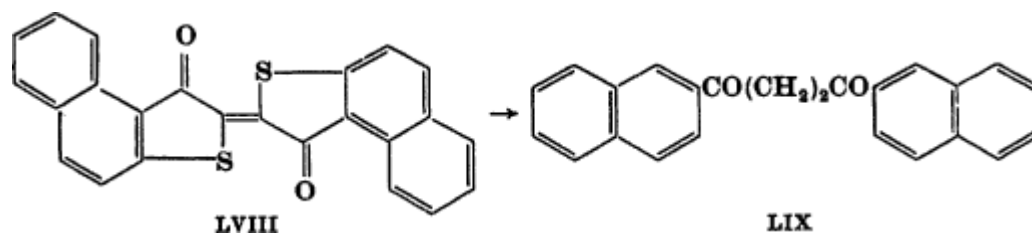


Thiadamantane, an unusual constituent of Middle East crude oil, was assigned the structure LVII, mainly on the basis of its desulfurization to bicyclo[3.3.1]nonane.<sup>98</sup>

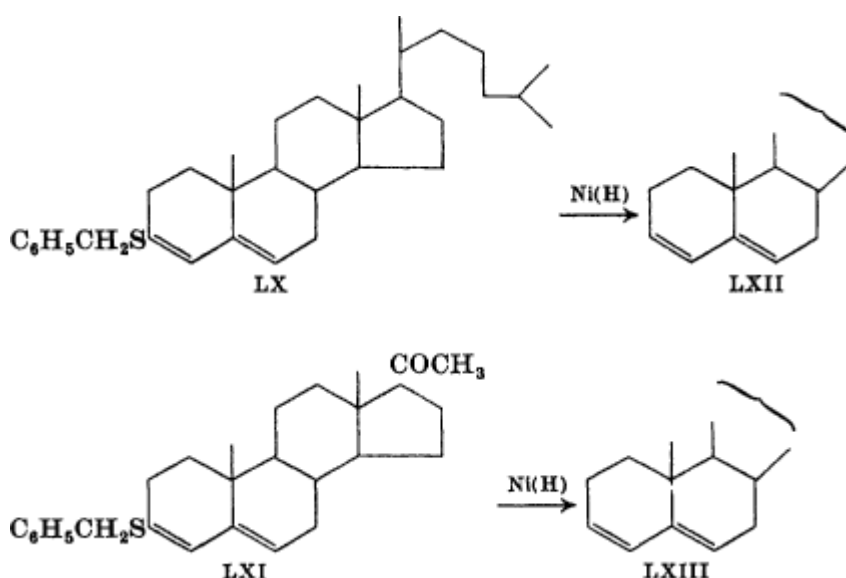


Desulfurization studies also have contributed to the knowledge of thioindigo dye chemistry.<sup>99</sup>

Hydrogenolysis of Durindone Brown GS (LVIII) with Raney nickel alloy in aqueous sodium hydroxide gave 1,2-di-( $\alpha$ -naphthyl)ethane (LIX) and a yellow liquid of unknown structure. Under essentially the same condition, Ciba Brown 2 R afforded similar products. In conjunction with other evidence, it was concluded that Ciba Brown 2 R is probably identical with Durindone Brown GS.<sup>19</sup>



Striking examples of selective hydrogenolytic removal of sulfur appear in the steroid field. Among these are the conversions of the benzyl thio enol ethers of cholestenone (LX) and progesterone (LXI) to 3,5-cholestadiene (LXII)<sup>100</sup> and 3,5-pregnadien-20-one (LXIII),<sup>101</sup> respectively.



Attack at the double bonds was prevented by the use of acetone deactivated nickel.

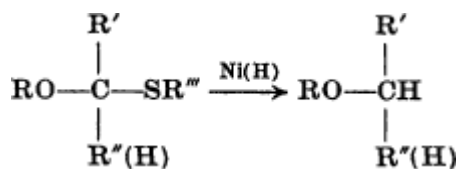
It is noteworthy that desulfurization of the steroidal sapogenin LXIV in acetone led to a mixture of 22 $\beta$ -spirosta-3,5,7-triene and the partially reduced 22 $\beta$ -spirosta-5,7-diene (LXV).<sup>102</sup> Both the double bond and the carbonyl group of 3-ethylthio-5-cholesten-7-one are reduced during desulfurization with ordinary nickel.<sup>103</sup>

### 3.3. Disulfides

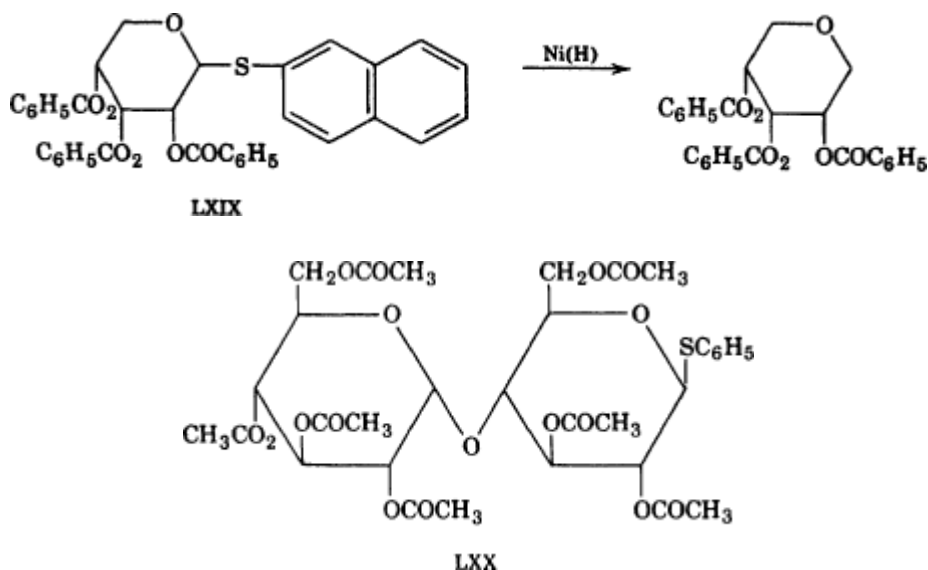
Desulfurization of disulfides proceeds as expected, the removal of both sulfur atoms being accompanied by the introduction of hydrogen. For example, L-cystine (LXVI) and its di-N-benzoyl derivative<sup>7</sup> yielded L-alanine.<sup>104</sup>

### 3.4. Hemithioacetals and Hemithioketals

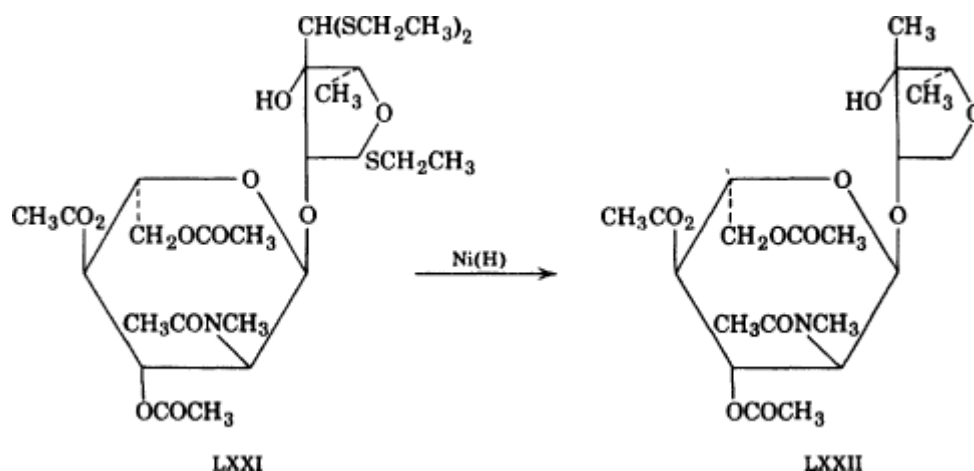
All the examples of hemithioacetal desulfurization are drawn from carbohydrate chemistry, a circumstance which reflects the ready preparation of this type of derivative from the saccharides. In every case, sulfur was removed from the hemithioacetal without disturbing the carbon-oxygen bond.



Ribose, as the tribenzoate of the 2-naphthylthiopyranoside (LXIX), is one of several pentoses and hexoses that have been converted to anhydrosugar alcohols.<sup>105</sup> Other examples demonstrate that the alcoholic hydroxyl groups need not be protected during the desulfurization process.<sup>106, 107</sup> The method is equally successful with disaccharides. For example, the maltose derivative LXX gave rise to the expected product in 78% yield.<sup>108</sup>



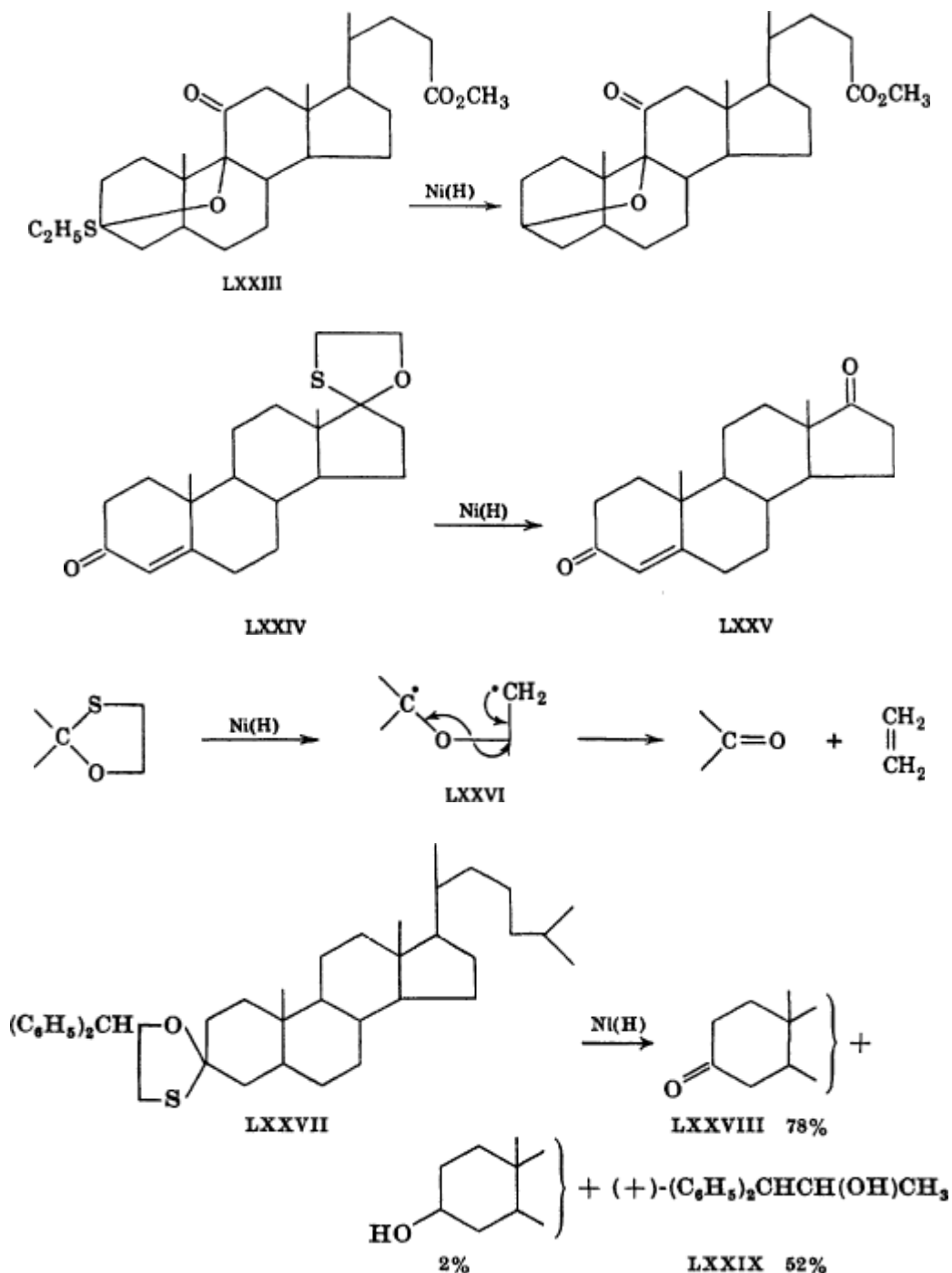
The structure of streptobiosamine, a major portion of the streptomycin molecule, was elucidated by desulfurization of the sulfur derivative LXXI to the bisdeoxy compound LXXII whose hydrolysis products were subsequently identified. When the thiostreptobiosamide LXXI was heated with aged (rather than freshly prepared) nickel, the terminal formyl group was regenerated.<sup>109</sup>



The first instance of hemithioacetal desulfurization involved the cholanic acid derivative LXXIII,<sup>110</sup> while the first example of carbonyl regeneration from a hemithioacetal was provided by LXXIV.<sup>111</sup> Desulfurization of androst-4-ene-3,17-dione 17-ethylenehemithioacetal (LXXIV) gave the original diketone LXXV. It appeared likely that the diketone LXXV might arise through collapse of a free-radical intermediate LXXVI.<sup>111</sup> However, subsequent work by Djerassi and collaborators<sup>45, 46</sup> clearly shows



that oxygen may have been introduced from another source. Three of the four possible diastereoisomeric forms of spiro-(5-benzhydryl-1,3-oxathiolane-2,3 $\phi$ -cholestane) were isolated and the isomer designated A (LXXVII), upon desulfurization in methyl ethyl ketone solution, gave cholestan-3-one (LXXVIII), (+)-1,1-diphenylpropan-2-ol (LXXIX), and cholestan-3 $\beta$ -ol. Isomer C (LXXVII), in a similar experiment, afforded the ketone LXXVIII in 80% yield accompanied by (-)-1,1-diphenyl-propan-2-ol (57%).<sup>45</sup> Analogous results have been obtained with other cyclic hemithioketals and Raney nickel in polar solvents (alcohols and ketones).<sup>44-46</sup>

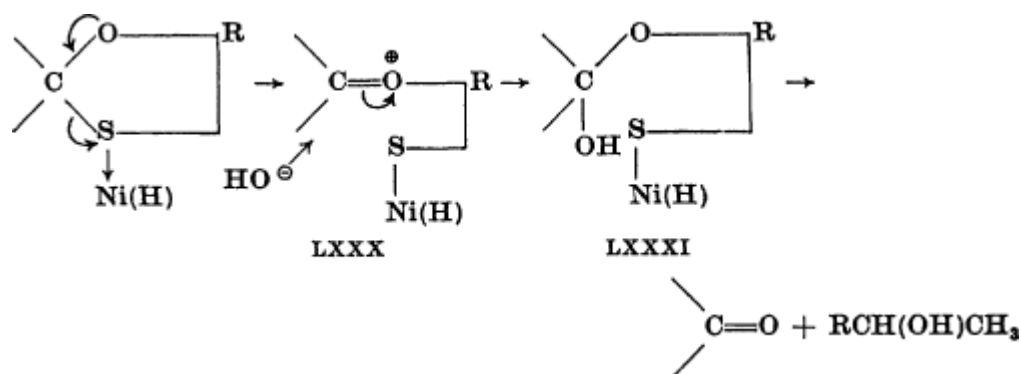


The total yield of oxygenated products demonstrates the introduction of oxygen during desulfurization, whereas preservation of asymmetric centers (e.g., LXXIX) indicates both loss of the ketone oxygen during hemithioketal formation and cleavage of the oxygen-carbon steroid bond during hydrogenolysis.<sup>45</sup>

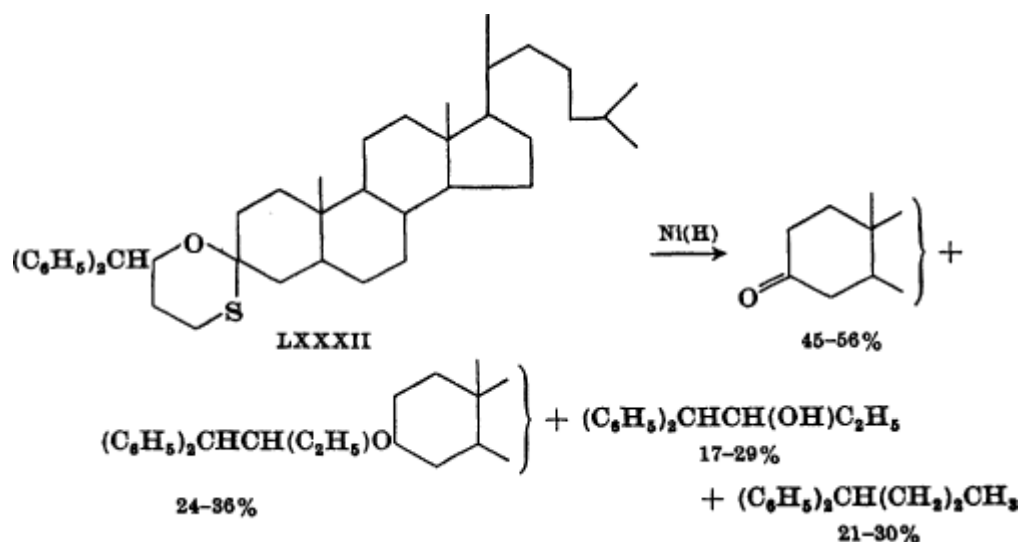
A possible mechanism for the “oxygen introduction” step has been suggested. After formation of a coordinate bond between sulfur and nickel, an intermediate such as LXXX might be available for attack by hydroxide ion (from the catalyst) to yield a hemiketal (LXXXI). The ketone and alcohol fragments



could then arise after desulfurization (via the usual free-radical pathway) and cleavage of the hemiketal (LXXXI). The latter step might take place during isolation.<sup>46</sup>



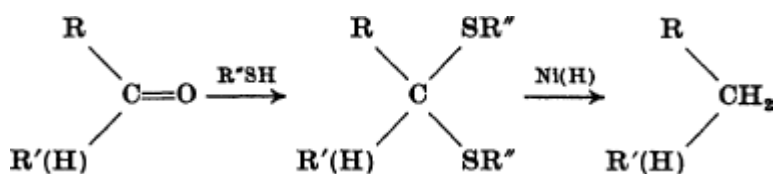
When desulfurization of a hemithioketal is allowed to occur in a nonpolar solvent, such as benzene, the reaction follows a more complex course. For example, spiro-(6-benzhydryl-1,3-oxathiane-2,3 $\beta$ -cholestane) (LXXXII) led to the compounds shown in the accompanying formulation. The formation of these products probably proceeds from a free-radical intermediate such as LXXVI above.<sup>46</sup>



The experiments described above have practical significance because isolated ketonic carbonyl groups can be converted preferentially to hemithioketals in the presence of  $\alpha$ ,  $\beta$ -unsaturated ketone functions and the reaction can be reversed simply with Raney nickel.

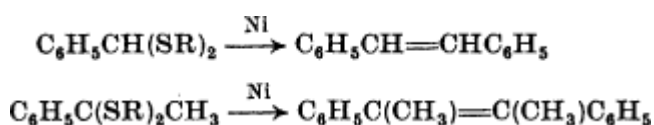
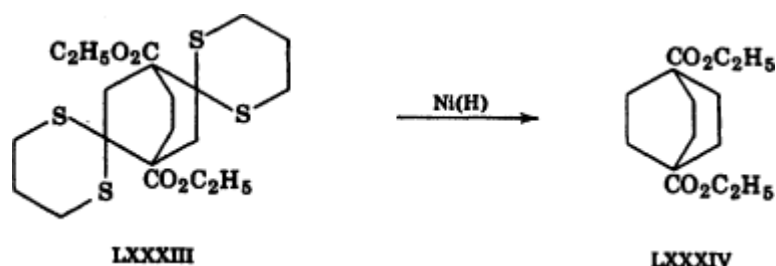
### 3.5. Dithioacetals and Dithioketals

Since dithioacetals (mercaptals) and dithioketals (mercaptols) can be hydrogenolyzed smoothly with Raney nickel, a route other than Clemmensen or Wolff-Kishner reduction is available whereby an aldehyde or ketone carbonyl group can be transformed into a methyl or methylene group. The desulfurization route is preferable on occasion because the reaction can be carried out in almost neutral media.

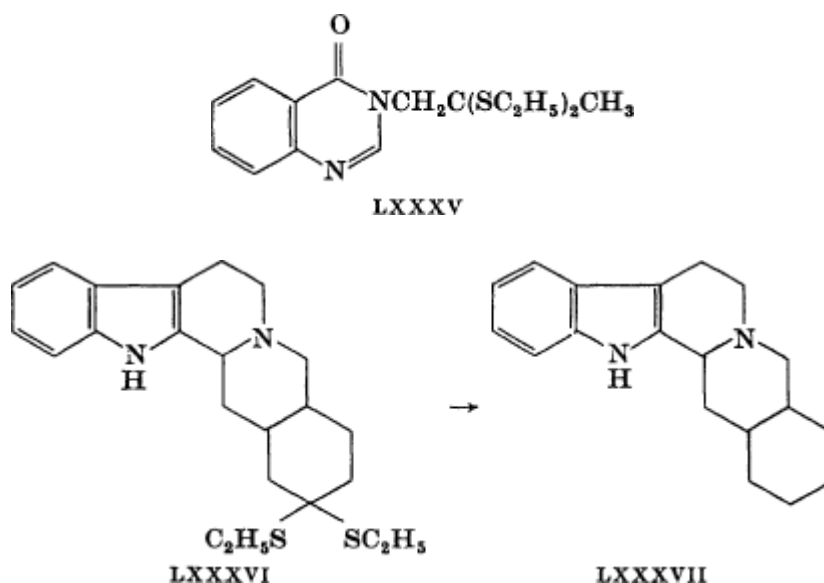


The first account of thioacetal and thioketal desulfurization was published in 1944 by Wolfrom, who obtained, for example, toluene and n-heptane in good yields from the ethyl mercaptan derivatives of benzaldehyde and heptanal or 2-heptanone, respectively.<sup>8</sup> The sequence has since been applied also to  $\alpha$ - and  $\beta$ -keto esters,<sup>112</sup> and 1,3-cyclobutanediones;<sup>31, 113</sup> a specific example is the synthesis of the dicarbethoxybicyclooctane LXXXIV from LXXXIII.<sup>114</sup>

Hauptman<sup>10</sup> has noted the behavior of mercaptols when heated in xylene with degassed Raney nickel. Those derived from benzaldehyde and from acetophenone yielded stilbenes.

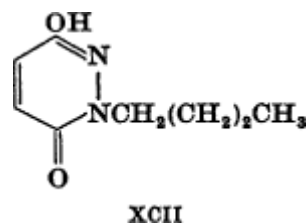
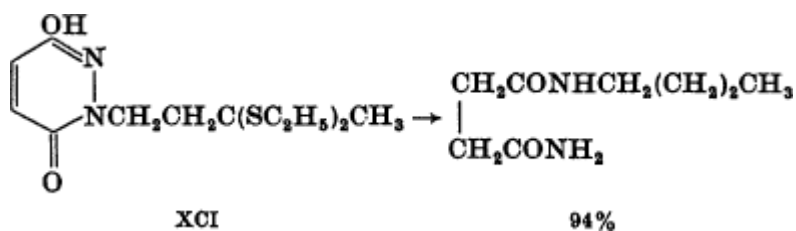
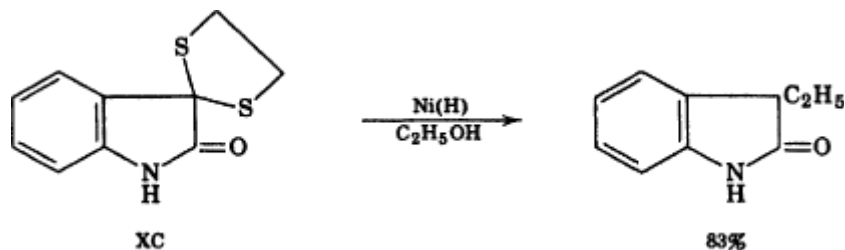
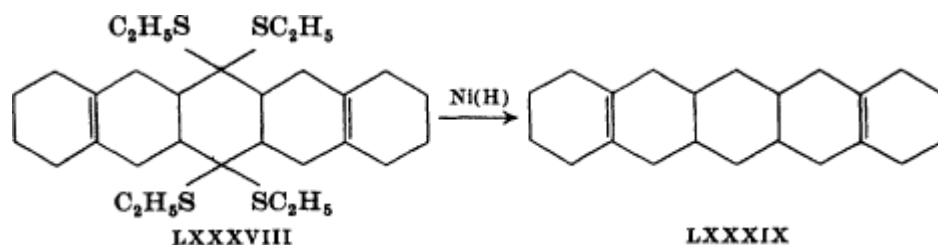


One very interesting failure to undergo hydrogenolysis has been reported. The quinazolone LXXXV was found to regenerate the parent ketone.<sup>115</sup> The dithioketal LXXXVI of the yohimbine degradation product yohimbone was unchanged by Raney nickel in boiling alcohol.<sup>116</sup>

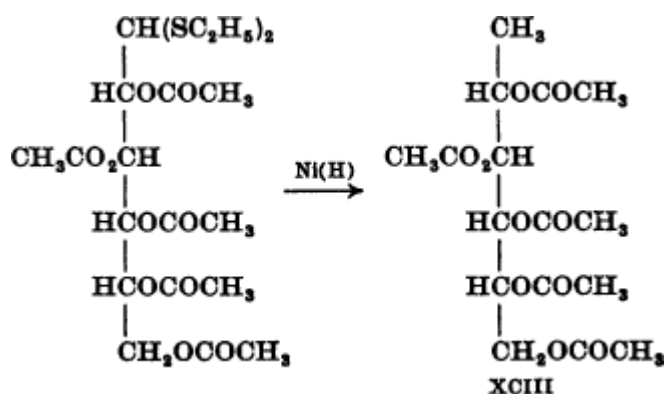


However, it was subsequently shown that desulfurization to yohimbane (LXXXVII) is possible when freshly prepared W-7 Raney nickel and dioxane are employed.<sup>117</sup>

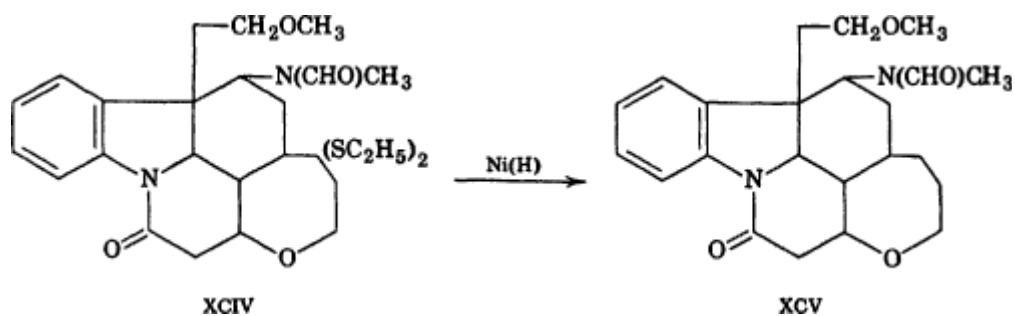
The conversion of the ethyl dithioketal LXXXVIII to the octadecahydropentacene LXXXIX in 55% yield illustrates the selectivity of the reaction.<sup>118</sup> An unexpected C-ethylation occurred during desulfurization of isatin ethylenethioketal (XC) in ethanol solution. With methyl or isopropyl alcohol as solvent, the yields of similar alkylated products were 16% and 32%, respectively.<sup>22</sup> Desulfurizations of certain N-substituted pyridazinones also have been found to follow an unpredicted course. Raney nickel desulfurization of the diethylmercaptol XCI in 70% ethanol led to n-butylsuccinamide. Under the same conditions, 2-n-butyl-6-hydroxy-3(2H)-pyridazinone (XCII) formed n-butylsuccinamide in 82% yield.



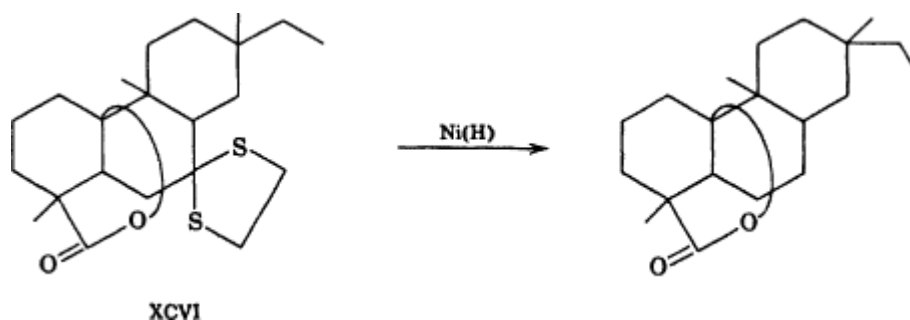
A number of deoxy sugars have been synthesized by application of the thioketal desulfurization sequence to various monosaccharides or their fully acetylated derivatives. The conversion of glucose pentaacetate to the deoxyglucitol (XCIII) in 60% yield was one of the first examples reported.<sup>8</sup> A lower yield (20%) was obtained in the only well-defined application to a ketose (fructose).<sup>8</sup>



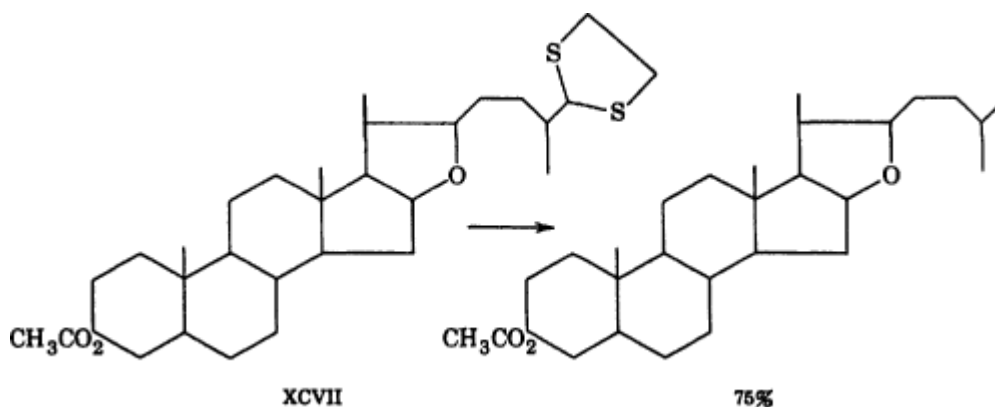
A decisive role has been played by mercaptol desulfurization in the structural investigation of a number of complex natural products. Of particular significance is the conversion of the strychnine transformation product methoxymethylchanodihydrostrychnone diethylmercaptol XCV to the deoxy product XCV.<sup>119</sup> Earlier attempts to effect the change by means of a Clemmensen reduction were attended by rearrangements, a result which obscured the nature of the strychnine neo-bases and thereby stood as an obstacle in the way of final acceptance of the correct strychnine formula.



One of the degradation procedures instrumental in elucidating the structure of the tricyclic diterpenoid rosenonolactone involved desulfurization of the ethylenethioketal XCVI.<sup>120</sup>

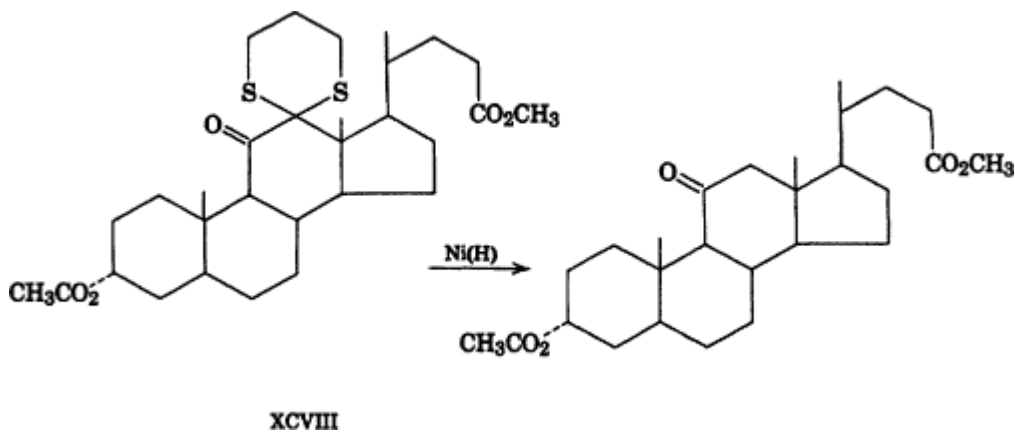


An attempt to utilize the boron trifluoride procedure<sup>121</sup> for the preparation of ethylenethioketals in the steroidal sapogenin series produced an interesting structural problem. Ethanedithiol in the presence of boron trifluoride etherate was found to react with the spiroketal system. Exact knowledge of the skeletal change which had taken place remained unknown until Raney nickel desulfurization of the compound subsequently shown to be  $5\alpha$ -furostan- $3\beta$ -ol acetate 26-ethylenethioketal (XCVII) provided  $5\alpha$ -furostan- $3\beta$ -ol acetate, an intermediate of known structure.<sup>122</sup>

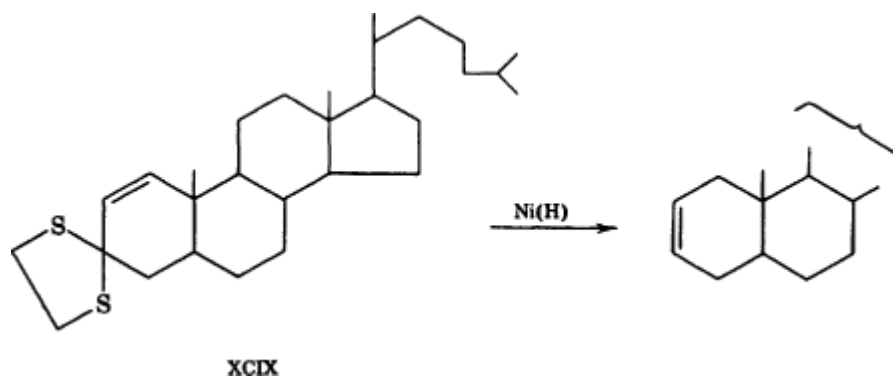


The steroid literature is replete with examples of the reaction under discussion. Carbonyl groups at positions 2, 3, 6, 7, 12, 15, 16, 17, and 19 on the steroid nucleus have been converted to methylene groups; no desulfurization failures have been reported.

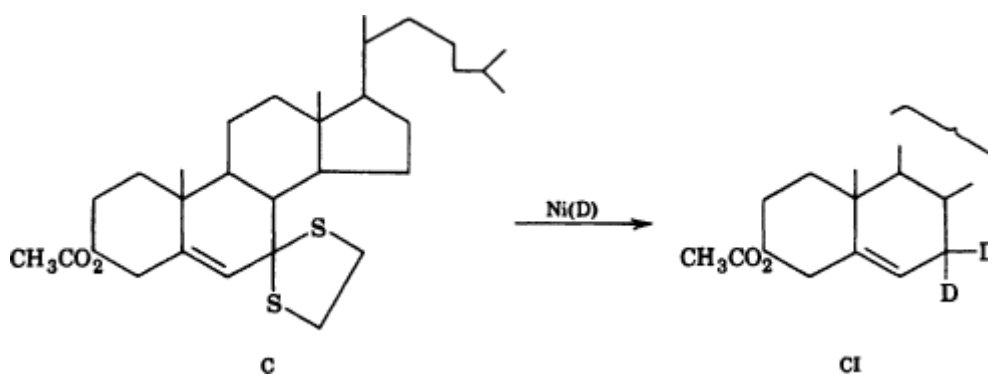
The following experiment is one of many that demonstrate the selective nature of the Raney nickel desulfurization reaction. Desulfurization of the 12-trimethylenethioketal XCVIII was accomplished in 86% yield by allowing the reaction to proceed for 15 minutes at room temperature. Extending the contact time to 6 hours raised the yield to 95%.<sup>123</sup>



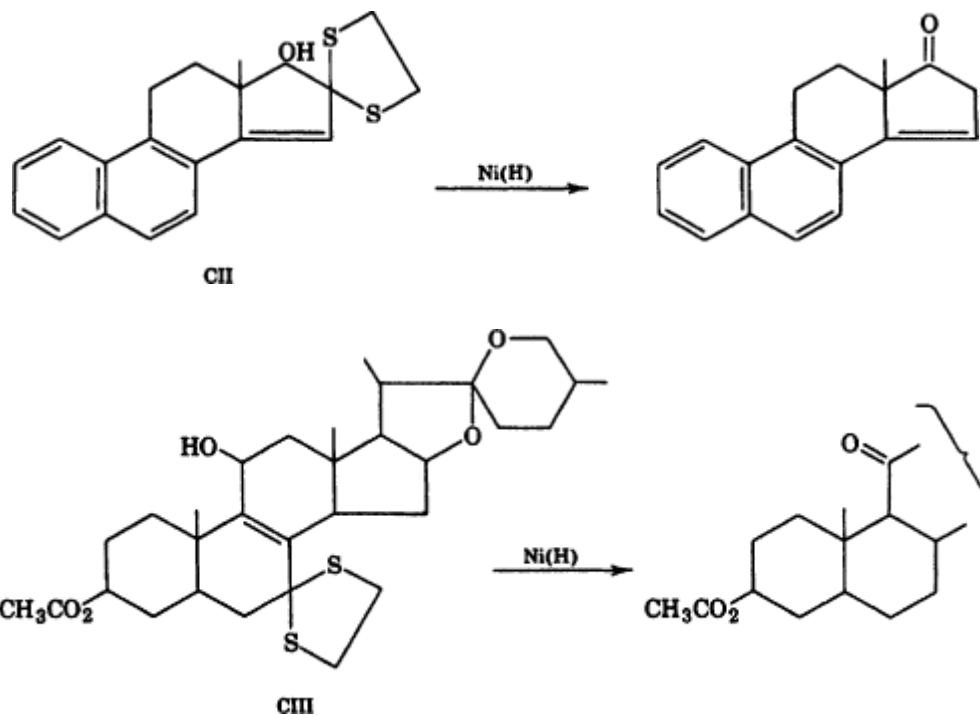
Olefin bonds need not interfere (cf. the isolation of 4-cholestene in 92% yield by the desulfurization of 4-cholesten-3-one dibenzylmercaptol).<sup>77</sup> However, the choice of experimental conditions is usually quite important, as for example in the desulfurization of cholest-1-ene 3-ethylenethioketal (XCIX). Hydrogenolysis in refluxing benzene-methyl ethyl ketone solution over a 9-hour period gave a fair yield of cholest-2-ene.<sup>124</sup> When the thioketal XCIX was subjected to a 40-hour reaction period, in boiling dioxane, only cholestane was isolated.<sup>125</sup>



Treatment of the 7-ketocholesterol derivative C with deuterized Raney nickel resulted in the formation of 7,7-d<sub>2</sub>-cholesterol (CI).<sup>126</sup> This is one of several examples of the introduction of deuterium by means of Raney nickel.



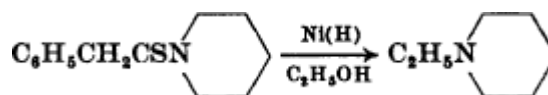
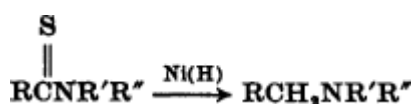
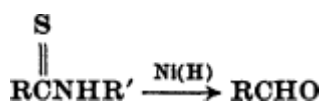
The action of aged nickel in refluxing dioxane on the ketol derivative CII gave hydrogenolysis accompanied by oxidation at C-17;<sup>32</sup> protection of the hydroxyl group by acetylation prevents this interesting side reaction.<sup>32, 127, 128</sup> In a somewhat similar vein, the spirostene derivative CIII led to the C-11 ketone,<sup>129</sup> an intermediate in a synthetic approach to cortisone.



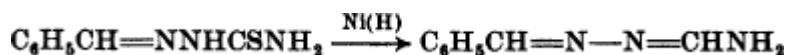
Similar conversions have been conducted with several triterpenoids and lanosterol derivatives. Interestingly enough, the mono dithioether of acetoxy lanostendione (CIV) afforded the  $\beta$ ,  $\gamma$ -unsaturated ketone CV, rather than the  $\alpha$ ,  $\beta$ -unsaturated ketone on desulfurization.<sup>130</sup> Oleanolic acid, after reduction to the aldehyde followed by conversion to the ethylenethioether and desulfurization, gave 12,13-oleanene (CVI).<sup>131</sup> The ethylenethioether CVII, a derivative of the cactus triterpene dumortierigenin, was also readily reduced without affecting the remaining portion of the molecule.<sup>132</sup>

### 3.6. Thioamides

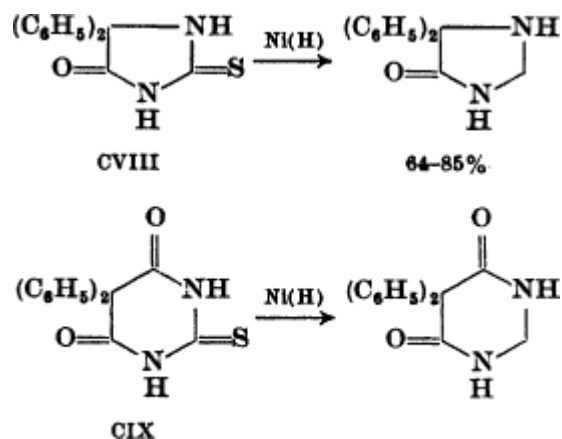
Desulfurization of thioamides can take divergent courses, depending upon the nature of the Raney nickel. Partial deactivation carried out in boiling acetone affords a reagent that will convert a thioamide to an aldehyde in good yield.<sup>133</sup> Raney nickel as ordinarily prepared, however, brings about replacement of thiocarbonyl by methylene groups.<sup>27</sup> A relatively large number of transformations of the latter type have been carried out by Kornfeld,<sup>27</sup> who varied considerably the nature of R, R', and R''. Extended heating of certain amides in ethanol with Raney nickel led to replacement of the N-alkyl group by an ethyl group, e.g., the benzyl thioamide shown in the accompanying formula gave a 44% yield of N-ethylpiperidine.<sup>27, 38</sup>



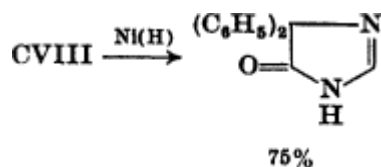
In all the thiourea desulfurizations reported, formamidines have been the observed products.<sup>62, 134</sup> Even thiosemicarbazones conform to this reaction pattern.<sup>135</sup>

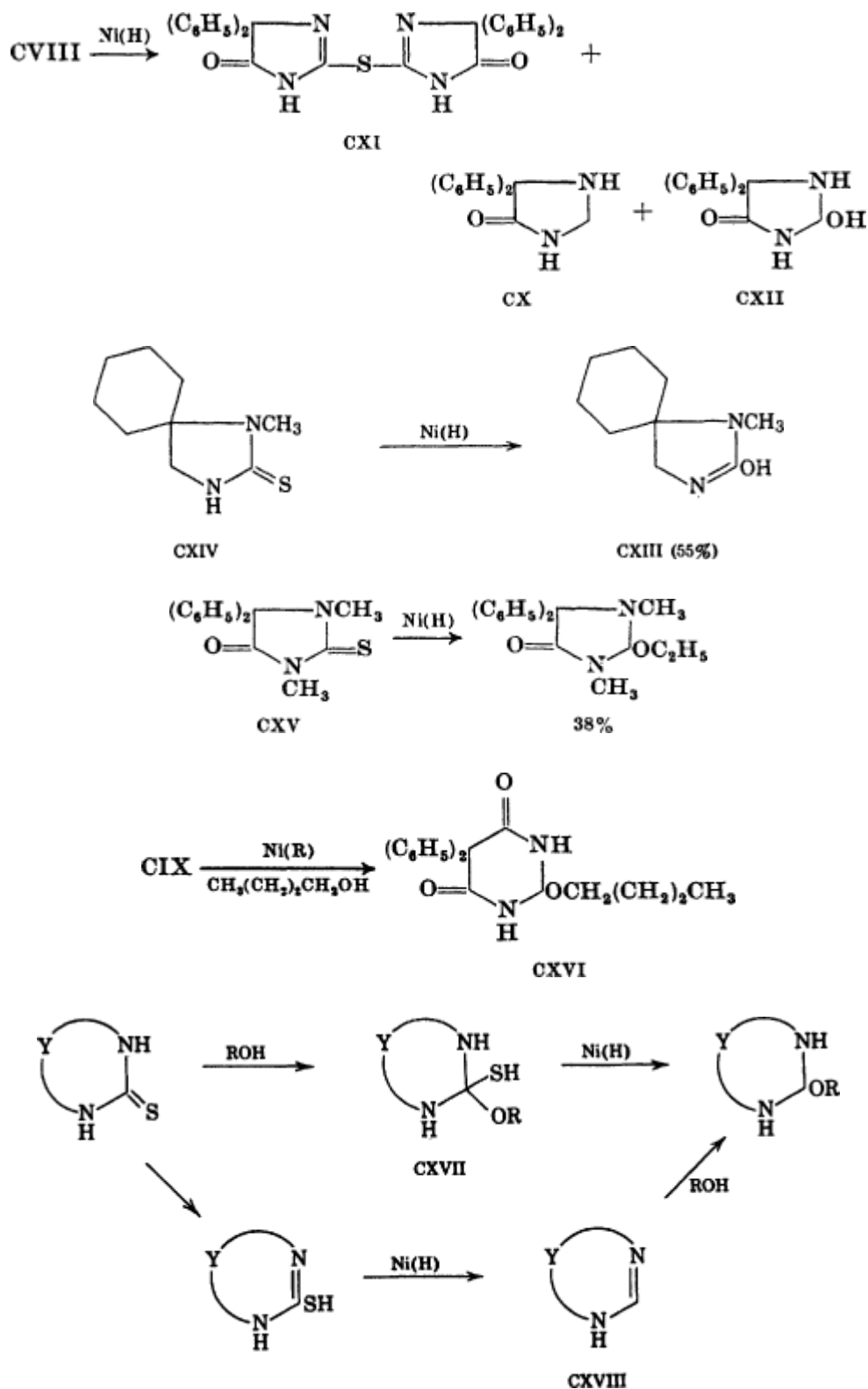


Among heterocyclic thioamides, study of thiohydantions and thiobarbituric acids has received major emphasis. Generally, desulfurization in ethanol solution (2–5 hours at reflux) results in replacement of sulfur by hydrogen. The desulfurization of 5,5-diphenyl-2-thiohydantoin (CVIII)<sup>136, 137</sup> and 5-ethyl-5-phenyl-2-thiobarbituric acid (CIX)<sup>138</sup> may be considered illustrative.

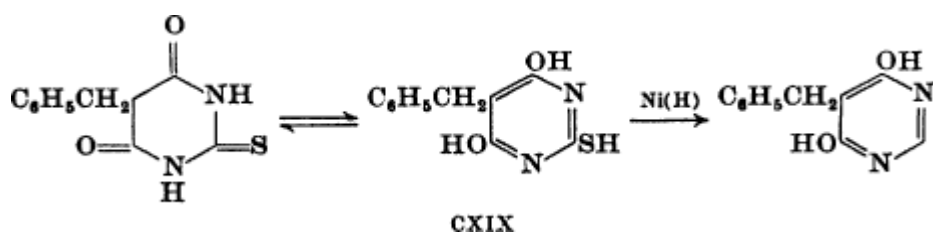


Several experimental variations have been reported, the results of which provide a more comprehensive picture of the normal desulfurization process. Addition of sodium ethoxide to an ethanol solution of the thiohydantoin CVIII apparently allows the tautomeric thiol form to undergo desulfurization without further reduction.<sup>139</sup> The same result may be achieved by using a limited quantity of catalyst.<sup>140</sup> With a 30-minute reflux period and a 1:5 ratio by weight of thioamide CVIII to Raney nickel, approximately equal amounts of 5,5-diphenyl-4-imidazolidone (CX) and di-2-(4,4-diphenyl-5-oxo-2-imidazolyl) sulfide (CXI) were formed. A small quantity of 5,5-diphenyl-2-hydroxy-4-imidazolidone (CXII) was also isolated.<sup>141</sup> Upon further treatment (2 hours in boiling ethanol) with Raney nickel, the hydroxyl compound CXII is reduced to the imidazolidone CX in quantitative yield.<sup>141</sup> The tendency to form 2-hydroxy derivatives analogous to CXIII becomes quite evident with the cyclohexyl derivative CXIV.<sup>136</sup> The tetrasubstituted thiohydantoin CXV, in ethanol solution, has been found to yield a 2-ethoxy derivative. Substitution of methanol, 1-propanol, or cyclohexane for ethanol produced the 2-hydroxy derivative.<sup>136</sup> However, it was possible to prepare a series of 2-alkoxy derivatives (e.g., CXVI) of the thiobarbituric acid CIX by limiting the reaction period to 30 minutes. Quantitative reduction to the normal desulfurization product resulted from further treatment with Raney nickel.<sup>141</sup> Formation of hydroxy and alkoxy intermediates such as CXII and CXVI has been attributed to one of two possible mechanistic routes (cf. CXVII and CXVIII where Y equals the remaining portion of the ring).<sup>141</sup>





Desulfurization of 5-monosubstituted-2-thioimides leads to the conclusion that these compounds are perhaps better represented as reacting through a tautomeric 2-pyrimidinethiol structure (cf. CXIX) since the product is invariably a 4,6-dihydropyrimidine.<sup>141</sup>

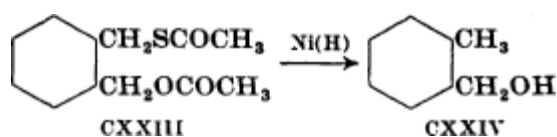
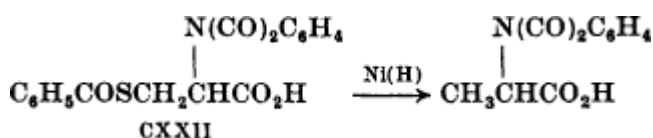
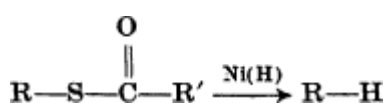




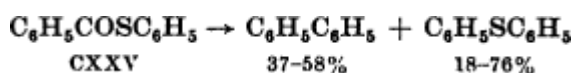
A series of 5-alkylidene- and 5-benzylidene-2-thiohydantoin, such as CXX, has been found to yield  $\alpha$ -formylamino acid amides when desulfurization is carried out in aqueous tetrahydrofuran. The reaction should find practical application as a route to  $\alpha$ -amino acids.<sup>137</sup> Desulfurization of 3,4,5-triphenyloxazole-2-thione (CXXI)<sup>142</sup> in ethanol apparently proceeds by a similar mechanistic pathway.

### 3.7. Thiol Esters

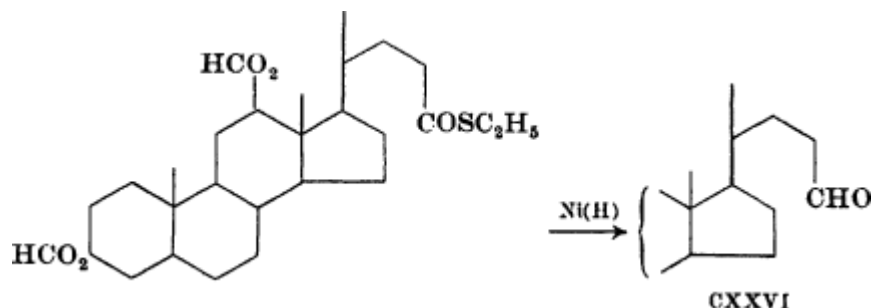
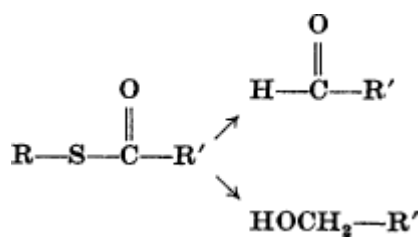
When the reductive desulfurization of a thiol ester is considered only in terms of bond cleavage between the sulfur atom and the alkyl or aryl, rather than the carbonyl, carbon atom, no particular problem arises: simple hydrogen-carbon bond formation occurs as in the numerous cases already cited. Cysteine and alanine have been interrelated stereochemically by carrying out a desulfurization on the S-benzoyl-N-phthaloyl derivative CXXII of the former.<sup>143</sup> The conversion of the acetatethioacetate CXXIII to the expected monohydric alcohol CXXIV is representative of a number of closely related transformations in the cyclohexane series.<sup>144</sup>



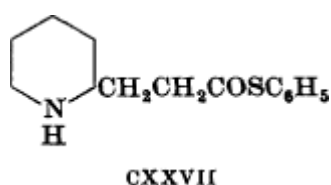
The consequences of limiting the supply of available hydrogen during desulfurization of thiol esters have been explored.<sup>11</sup> The reaction between phenyl thiobenzoate (CXXV) and degassed (200°) Raney nickel, at either 180° or 220° in xylene solution, provides an example.



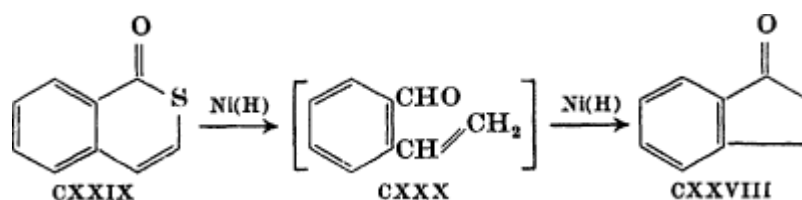
Cleavage of the sulfur-carbonyl carbon bond produces either an aldehyde,<sup>145</sup> which can be considered the primary hydrogenolysis product, or an alcohol resulting from further reduction. Instances of the controlled cleavage were reported first by Wolfrom, who transformed ethyl thiobenzoate and ethyl thiopropionate into benzaldehyde and propionaldehyde, respectively, in good yield, but did not define exactly the nature of the nickel used.<sup>146</sup> Somewhat later, Spero, McIntosh, and Levin<sup>147</sup> noted that the character of the reagent was of importance and demonstrated that good yields of aldehydes, such as the diformoxycholanal CXXVI, could be obtained provided the nickel was first partially deactivated by heating briefly in boiling acetone; failure to observe this expedient usually resulted in reduction to the alcohol. Aldehyde formation by this process has been successful with a number of other steroids. In addition, succinaldehyde<sup>148</sup> and 2,2-dimethyl-3-carbomethoxycyclo-propanecarboxaldehyde<sup>149</sup> have been obtained by using this technique.<sup>149a</sup>



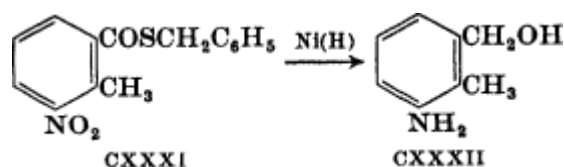
However, the piperidyl thiopropionate CXXVII has been reported only to cyclize to the lactam under desulfurization conditions,<sup>148</sup> and 3,4,5-trimethoxybenzaldehyde apparently cannot be obtained from thiol esters of O-trimethylgallic acid.<sup>150, 150a</sup>



A novel observation is the production of 1-indanone (CXXVIII) from 1,2-dihydro-1-keto-2-thianaphthalene (CXXIX).<sup>151</sup> It has been suggested<sup>151</sup> that the initial product is o-vinylbenzaldehyde (CXXX), which is known to cyclize to 1-indanone.



Just as the method described above constitutes a means of transforming an acid into the corresponding aldehyde, desulfurization of a thiol ester by ordinary (not acetone-deactivated) nickel allows the selective, over-all reduction of an acid to an alcohol. Various simple thiol esters, such as benzyl thiobenzoate or methyl thiopalmitate, yielded the expected alcohols;<sup>152</sup> beyond that, one carboxyl of a dibasic acid, e.g., adipic acid,<sup>152</sup> can be reduced to carbinol by carrying out the desulfurization on a monothiol ester. Alanine has been reduced via the methyl thioester to optically active 2-aminopropanol.<sup>153</sup> An illustration of reduction as a side reaction is one involving the nitro group in benzyl 3-nitro-2-methylthiobenzoate (CXXXI).<sup>47</sup>



A number of thiol esters of steroids have been converted to primary alcohols.<sup>154</sup> Double bonds and

carboxylic ester functions usually remain undisturbed. However, interaction of a carbomethoxyl group is illustrated in the desulfurization of the etiobilenic thiol ester CXXXIII, which led to the  $\delta$ -lactone CXXXIV.<sup>155, 156</sup> The transformation of benzyl 12,13-oleanen-30-thiolate (CXXXV) into the oleanenol CXXXVI<sup>157</sup> is one of a number of cases reported in the terpene field.

### 3.8. Isothiouronium Salts

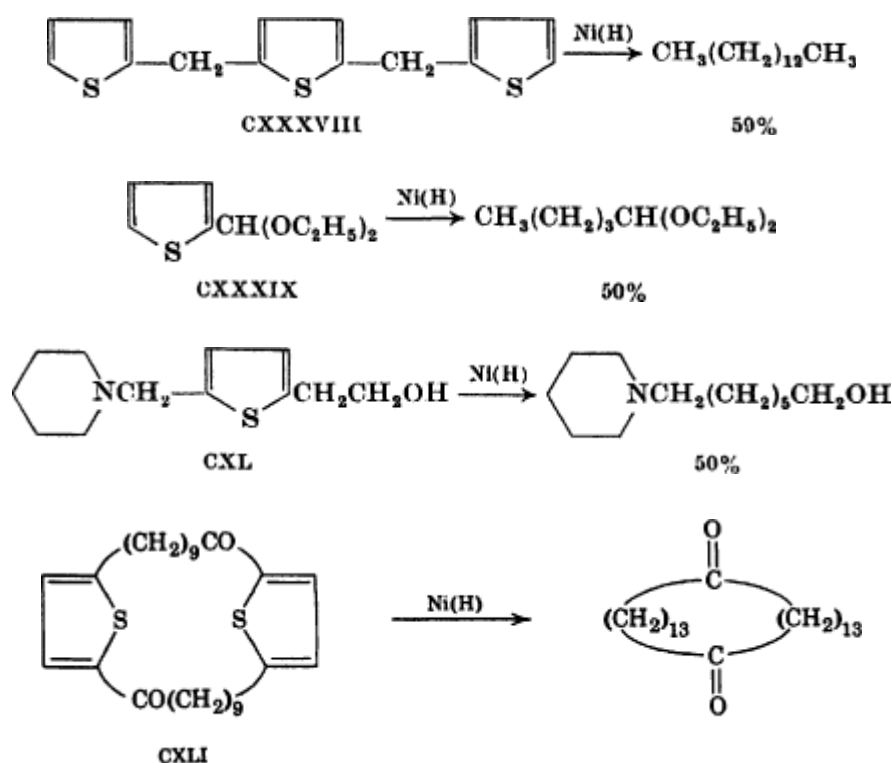
Although the fate of the thiourea portion of an isothiuronium salt during desulfurization has not been reported, the alkyl group attached to sulfur is hydrogenolyzed. The salt obtained by treatment of 1,8-di(bromomethyl)anthracene with thiourea was transformed in good yield into 1,8-dimethylantracene.<sup>158</sup> Isobornyl isothiuronium p-toluenesulfonate (CXXXVII) gave camphane without skeletal rearrangement.<sup>159</sup>

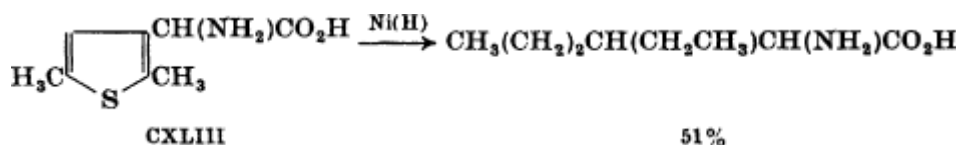
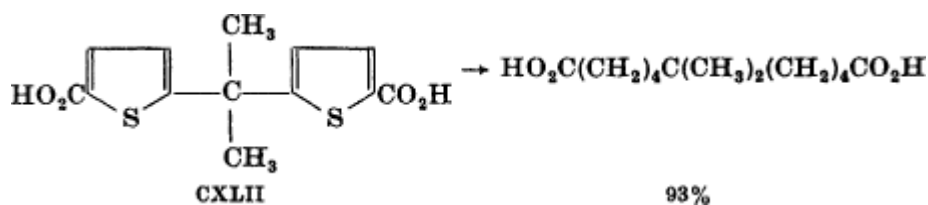
### 3.9. Thiophenes and Thiazoles

Inclusion of sulfur in an aromatic nucleus does not preclude hydrogenolysis. Preliminary evidence of this was recognized as early as 1940 when Bougault<sup>160</sup> reported the preparation of thiophene-free benzene and toluene by desulfurization with Raney nickel. The desulfurization of thiophene derivatives has since received wide application as a synthetic route to a variety of compounds.

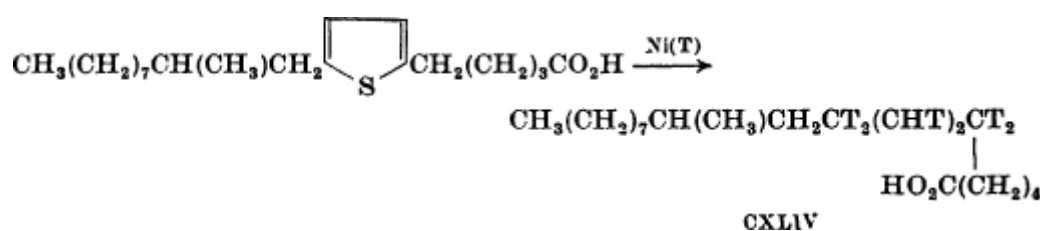
The possibility of using substituted thiophenes as precursors of more difficultly accessible long-chain aliphatic compounds has led to more work on the desulfurization of thiophenes than of any other group of compounds. Notable is the recent work of Badger,<sup>14, 70, 161-164</sup> Buu-Hoi,<sup>33, 108, 165-172</sup> Gol'dfarb,<sup>34, 49, (173-184f)</sup> and Wynberg.<sup>185, 186</sup> By early 1960, Raney nickel desulfurization of approximately 190 thiophenes had been described.

Raney nickel hydrogenolysis of thiophene hydrocarbons (CXXXVIII),<sup>173</sup> acetals (CXXXIX),<sup>182</sup> alcohols (CXL),<sup>178</sup> ketones (CXLI),<sup>184</sup> acids (CXLII),<sup>164, 187, 187a</sup> and amino acids (CXLIII)<sup>175</sup> usually does not present any special difficulty. The examples given represent the normal path of thiophene desulfurization and emphasize several practical applications.

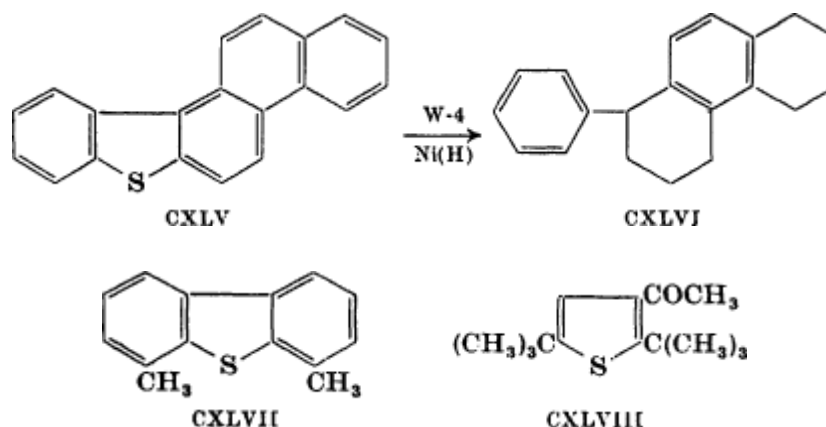




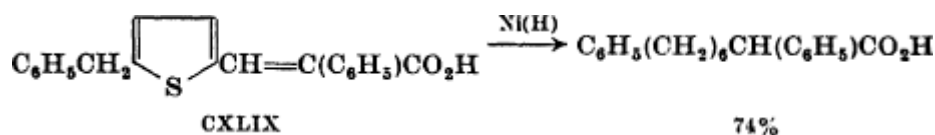
Buu-Hoï has recently prepared deuterium-labeled<sup>188</sup> and tritium-labeled<sup>165</sup> carboxylic acids by subjecting the appropriate thiophene derivative to Raney nickel desulfurization in deuterated or tritiated water. The catalyst was prepared in situ from Raney nickel alloy. Tuberculostearic acid (CXLIV, T = tritium), labeled at four positions with tritium, provides an example.

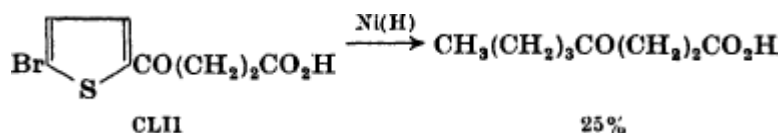
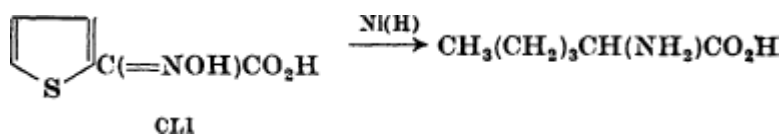
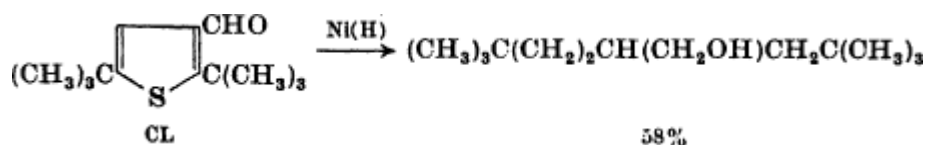


As illustrated above, removal of sulfur is usually accompanied by saturation of the annular double bonds. Unsaturation in an adjacent benzenoid system is almost always retained. One exception to the latter generalization involved the thiafluorene CXLV which was reduced to an octahydro-1-phenylphenanthrene, presumably CXLVI.<sup>53</sup> Limited amounts of Raney nickel have been used to remove bromine<sup>189</sup> or reduce nitro groups<sup>190, 191</sup> without affecting the thiophene nucleus. Only a few isolated failures of desulfurization were reported, and two of these involved a 1-substituted dibenzothiophene (e.g., CXLVII).<sup>192, 193</sup> The trisubstituted 2,5-di-*t*-butyl-3-acetylthiophene (CXLVIII) also resisted desulfurization.<sup>34</sup>

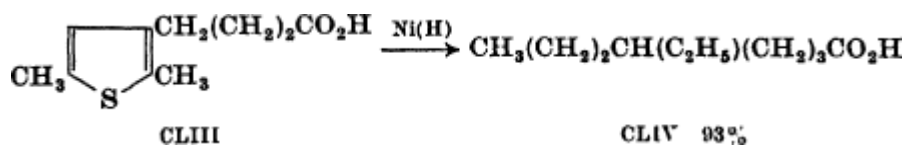


Reductions of olefin (CXLIX),<sup>33</sup> aldehyde (CL),<sup>34</sup> and oxime (CLI)<sup>175</sup> groups are predictable side reactions. Carbon-halogen bond hydrogenolysis (cf., CLII)<sup>164</sup> is usually observed,<sup>194</sup> and, in a few instances, ketone to alcohol reductions have occurred.<sup>14, 185, 187a, 195</sup>

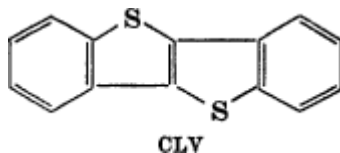




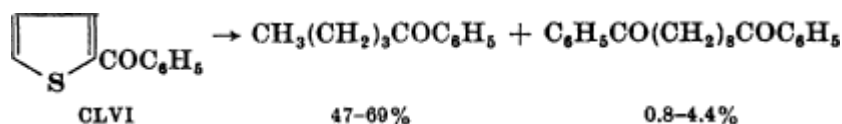
The yield and type of reaction product encountered may be markedly influenced by the choice of experimental conditions. Desulfurization of thiophene carboxylic acid derivatives such as  $\gamma$ -(2,5-dimethyl-3-thienyl) butyric acid (CLIII),<sup>163</sup> proceeds in highest yield, in basic aqueous solution. Only a 41% conversion to the saturated acid CLIV was realized when an organic solvent was used.



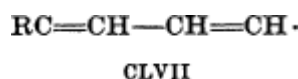
Although the thiophene CLV afforded bibenzyl when desulfurized in methanol, 1,2,3,4-tetraphenylcyclobutane resulted when the reaction was carried out in ethanol.<sup>13</sup> The latter product apparently arises by coupling two bibenzyl diradicals.



A deactivated catalyst leads to increased production of dimeric product. Desulfurization of 2-benzoylthiophene (CLVI) with a deactivated W-7 Raney nickel in methanol illustrates this side reaction.<sup>14</sup>



In every case studied, recombination of radicals has involved union at the unsubstituted terminal carbon of the thiophene ring, while 2,5-disubstituted thiophenes fail to yield dimeric products. In view of these observations, Badger has suggested that the desulfurization mechanism involves a 2,5-diradical (i.e., CLVII). Since steric hindrance by the R group would be relatively unimportant in solution, the diradical probably undergoes dimerization while still adsorbed on the catalyst surface.<sup>14, 161</sup>



The greater resistance to desulfurization encountered with thiazoles has been attributed to competition between sulfur and nitrogen for the catalyst surface.<sup>41</sup>

The nature of the products derived from thiazoles appears to depend on the experimental conditions. For example, 2-amino-4-phenylthiazole (CLVIII) gave acetophenone as the main product,<sup>43</sup> whereas 2-amino-4-hydroxythiazole (CLIX) yielded either acetamide<sup>43</sup> or its N-formyl derivative.<sup>42</sup> If a hydroxyl group is interposed between the thiazole nitrogen and sulfur, and an amino group is attached in the 5 position, a rearrangement to a 2-hydroxyimidazole (e.g., CLX) takes place.<sup>196</sup> It is claimed that the dibromothiazole CLXI on attempted desulfurization underwent only hydrogenolysis of halogen at the 2 position.<sup>197</sup> A careful study of the desulfurization reaction with 2-amino-4-phenylthiazole (CLXII) and several related compounds, employing W-6 (neutral) or W-7 (alkaline) Raney nickel, has indicated that two competitive mechanisms are operative.<sup>41, 161</sup> For example, CLXII yielded both acetophenone and  $\alpha$ -phenylethylamine.

### 3.10. Sulfoxides

Sulfoxides can be desulfurized successfully by Raney nickel. Instances in the literature are few, although only one unsuccessful attempt has been reported.<sup>194</sup> Diphenyl sulfoxide is hydrogenolyzed to benzene in good yield;<sup>7, 198</sup> n-propyl 2-hydroxy-2-phenylethyl sulfoxide is converted to the expected 1-phenylethanol along with some acetophenone.<sup>199</sup> The latter possibly arises from a nickel-catalyzed hydrogenation-dehydrogenation equilibrium.

The sulfoxide group can be removed selectively from the androstene and pregnene derivatives CLXIII and CLXIV,<sup>101</sup> leaving the double bonds and the carbonyl group intact. Of especial interest is the role that desulfurization played in the development of the structure CLXV for sulphoraphen, a natural product whose optical activity is due to the asymmetry of sulfur. The urea CLXVa derived from this substance furnished N,N $\phi$ -di-n-butylurea on treatment with Raney nickel.<sup>200</sup>

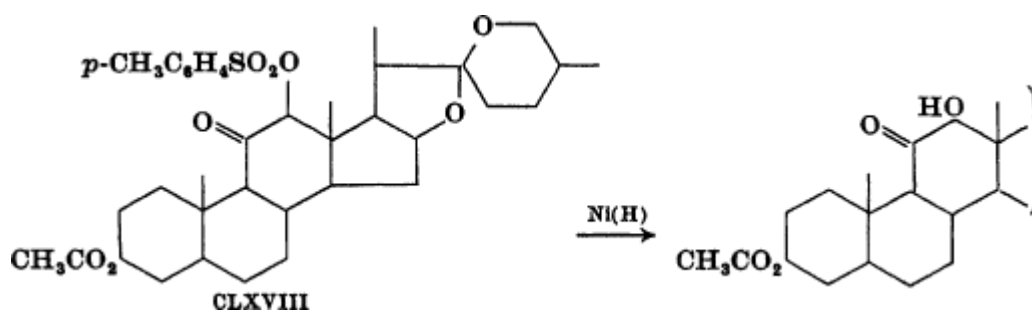
### 3.11. Sulfones

Among the sporadic examples of sulfone desulfurization appearing in the literature are the transformations of diphenyl sulfone to benzene,<sup>7, 201</sup> ethyl 1,1-diphenyl-3-(N,N-dimethylamino)-n-butyl sulfone to 1,1-diphenyl-3-dimethylaminobutane,<sup>202</sup> and thianaphthene sulfone dimer to ethylbenzene.<sup>203</sup> Thianaphthene 1,1-dioxide (CLXVI) gave an oil which has not been identified.<sup>203a</sup> The monosaccharide derivative CLXVII is reported to undergo only olefinic saturation on attempted desulfurization.<sup>204</sup> Tetrahydrothiapyran sulfone<sup>76</sup> also has been found to resist desulfurization.

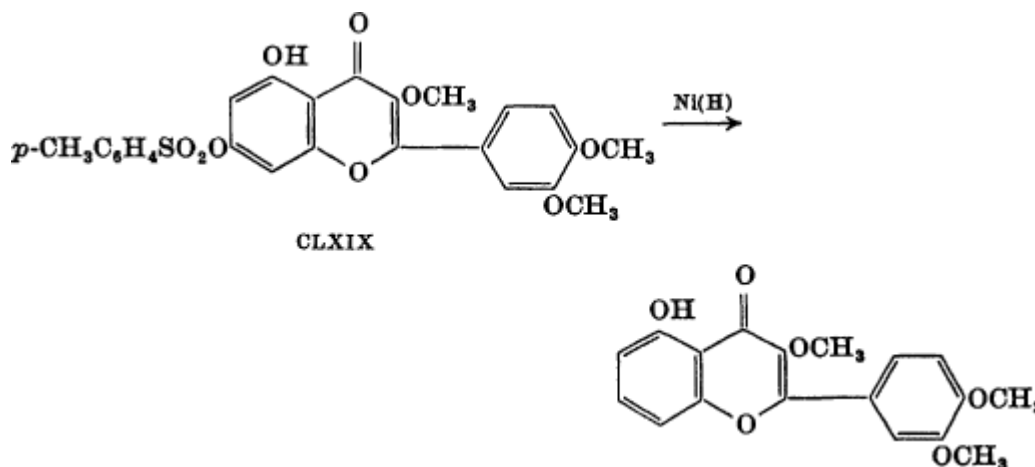
### 3.12. Sulfonic Acids, Esters, and Amides

Although sulfonic acids are inert toward prepared nickel catalysts, they can be desulfurized successfully by the Schwenk-Papa method.<sup>205</sup> Thus benzenesulfonic acid and naphthalene- $\beta$ -sulfonic acid afford the parent hydrocarbons; sulfobenzoic acids and naphtholsulfonic acids also give the expected products.

Treating an alkyl ester of p-toluenesulfonic acid under conditions of the Raney nickel reaction yields an alcohol.<sup>206</sup> One example of this conversion involved a steroidal sapogenin 12 $\beta$ -tosylate CLXVIII.<sup>207</sup>



Aryl esters, however, give aromatic hydrocarbons upon treatment with Raney nickel.<sup>206</sup> Venkataraman has found the hydrogenolysis of aromatic p-toluene sulfonates advantageous in the synthesis of several flavones.<sup>208</sup> Selective removal of the 7-hydroxyl group from 5,7-dihydroxy-3, 3', 4'-trimethoxyflavone was accomplished via the 7-tosyl derivative CLXIX.<sup>209</sup>



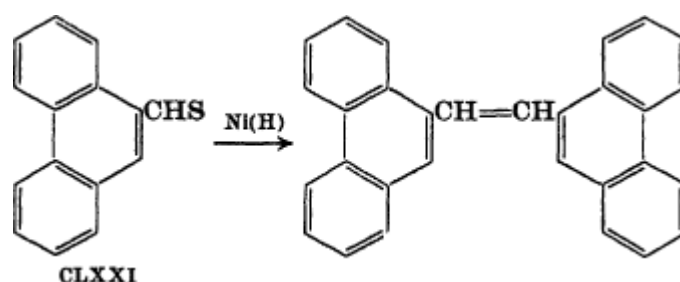
It has been claimed that hydrogenolysis of aryl sulfonic esters does not proceed by desulfurization but rather by formation of a nickel sulfonate.<sup>206</sup> Consequently the two preceding examples (CLXVIII and CLXIX) may simply involve hydrolysis and hydrogenolysis, respectively, without cleavage of the C single bond S bond.

Initial experiments have indicated that benzylsulfonamides respond particularly well to desulfurization, while p-toluenesulfonamides will probably require more vigorous conditions than those hitherto employed.<sup>206</sup>

Preliminary studies<sup>51, 210</sup> involving the Raney nickel desulfurization of N-alkylsaccharin derivatives (e.g., CLXX) shows that hydrogenolysis to benzamides is easily accomplished in boiling ethanol. Since sodium saccharin is readily alkylated by normally reactive halogen compounds,<sup>211, 212</sup> desulfurization of the product, in principle, presents a mild procedure for conversion of alkyl halides to benzamides, amines, or, for example, amino acids.

### 3.13. Miscellaneous

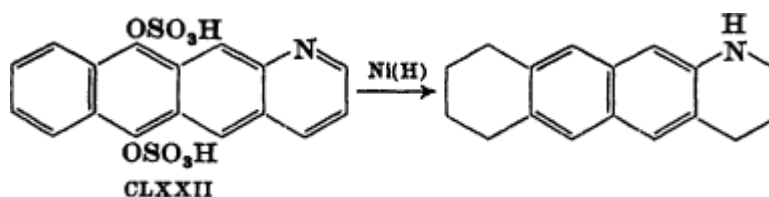
Among the various examples of desulfurizations not belonging to one of the previously discussed types, but proceeding by simple desulfurization, are those falling in the thiocyanate,<sup>213</sup> 1,3,4-trithiacyclopentane,<sup>214</sup> dithiocarboxylic acid,<sup>38</sup>  $\alpha$ -thioadipic acid,<sup>215</sup> xanthate,<sup>216</sup> and trithiocarbonate<sup>217</sup> classes. In addition, mention should be made of the conversion of diacetyl sulfide to acetaldehyde<sup>217a</sup> and of o-tolyl isothiocyanate to o-toluidine.<sup>43</sup> Thioacetophenone trimer<sup>218</sup> and thiophenanthraldehyde (CLXXI) as the trimer<sup>219</sup> form stilbenes.



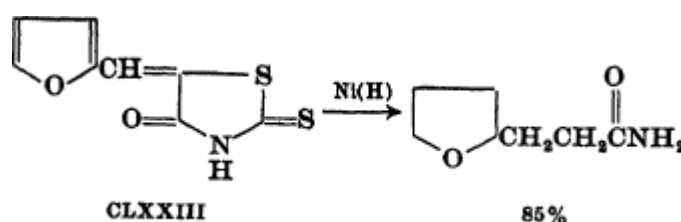
Hydrogenolysis of hydroquinone disulfuric esters in dilute sodium hydroxide solution constitutes part of a method for the complete reduction of a quinone to the corresponding hydrocarbon.<sup>220</sup> However, partial



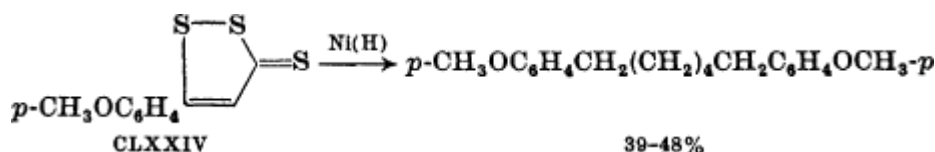
saturation of the aromatic system is commonly encountered. Reduction of leuco 1-azanaphthacene-6,11-dione disulfuric ester (CLXXII) to an octahydro-1-azanaphthacene adequately illustrates this observation.



Extension of the desulfurization reaction to 5-substituted rhodanines (cf. CLXXIII) has resulted in discovery of a useful route to  $\beta$ -substituted propionic acid amides.<sup>221</sup> Loss of the carbon atom adjoining both hetero atoms is reminiscent of the behavior of thiazoles.<sup>41</sup>



Reduction of 3-(*p*-methoxyphenyl)trithione (CLXXIV) with partially degassed Raney nickel in xylene emphasizes the tendency for radical recombination in the absence of available hydrogen.<sup>35</sup>



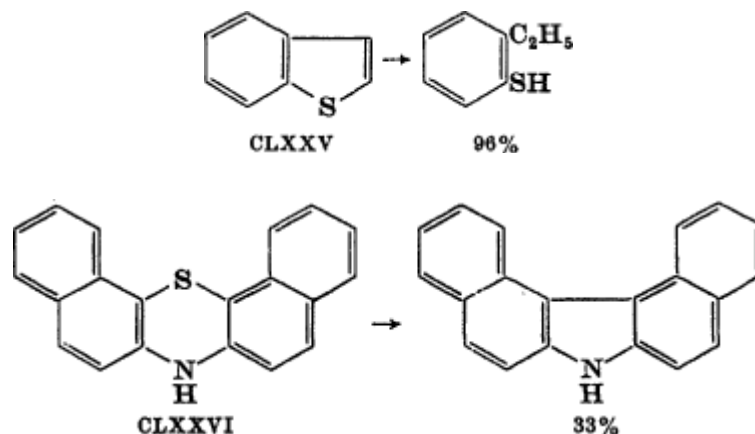
## 4. Comparison with Other Methods

Certain desulfurizations may be accomplished by reagents other than Raney nickel, principally other metals or oxidizing agents. None of these reagents exhibits the versatility of Raney nickel.

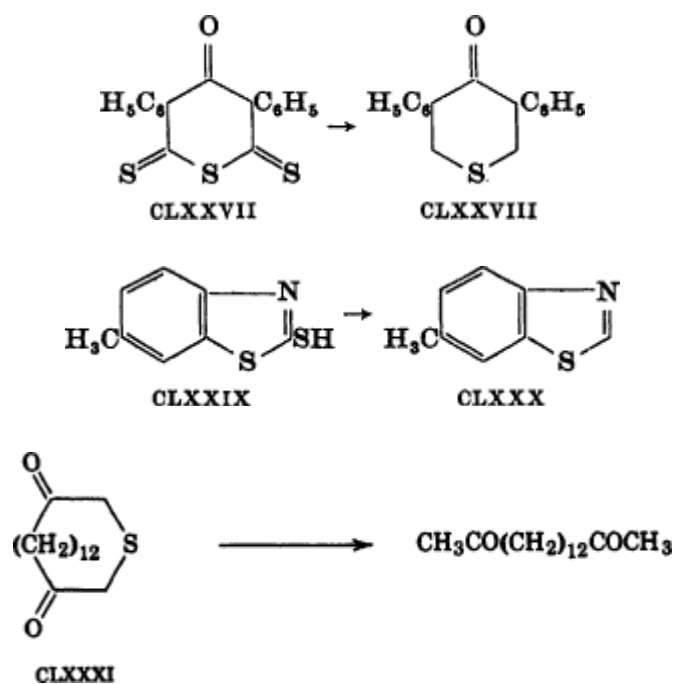
Raney cobalt appears to be somewhat less effective than Raney nickel, but it may prove to be useful where reduction, other than hydrogenolysis of carbon-sulfur bonds, must be avoided. Pyridine can be used as a solvent with Raney cobalt, whereas a prepared nickel catalyst causes the formation of 2,2'-dipyridyl.<sup>162</sup> The use of Raney iron and copper has remained essentially unexplored.<sup>55, 221a</sup>

Sodium, when used in conjunction with liquid ammonia, has been useful for the debenylation of benzyl sulfides<sup>222</sup> and sulfones;<sup>223</sup> since the reduction leaves non-benzylic carbon-sulfur bonds intact, the process is often used for the protection of sulfhydryl groups. Calcium in liquid ammonia affords similar results.<sup>224</sup> With this reagent, it was possible to cleave benzothiophene (CLXXV) selectively.<sup>224</sup> Lithium has also been used frequently for cleaving a carbon-sulfur bond.<sup>225</sup> Desulfurization of the dibenzophenothiazine (CLXXVI) with lithium in tetrahydrofuran represents an interesting application.<sup>226, 226a</sup>

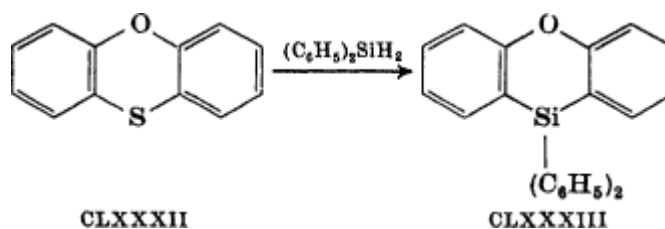




An early degradative technique applied to the antibiotic gliotoxin<sup>227</sup> was disruption of the disulfide linkage by the use of aluminum. Selective desulfurizations have been accomplished by zinc dust and hydrochloric acid as well as with iron powder in an alkaline medium: the trithioacid anhydride CLXXVII was transformed into the thiapyranone CLXXVIII by zinc and acid,<sup>228</sup> and the 2-thiothiazole CLXXIX was converted to the parent CLXXX by iron and alkali.<sup>229</sup> Warming a mixture of the thioether CLXXXI and zinc amalgam in a mixture of acetic and hydrochloric acid afforded a 91% yield of sulfur-free product. Reductive cleavage of a carbon-sulfur bond at position 2 or 3 in 1,4-naphthoquinones has been shown to occur in a boiling solution of stannous chloride in hydrochloric and acetic acids.<sup>230</sup>

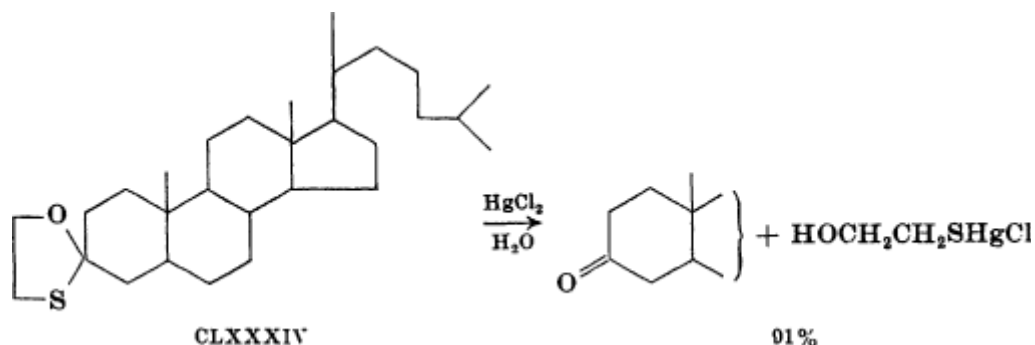


Selenium dioxide<sup>231</sup> has been used to replace a thiol group by hydroxyl. Diphenylsilane has been shown to displace sulfur from certain aromatic systems (e.g., CLXXXII  $\rightarrow$  CLXXXIII).<sup>225</sup>

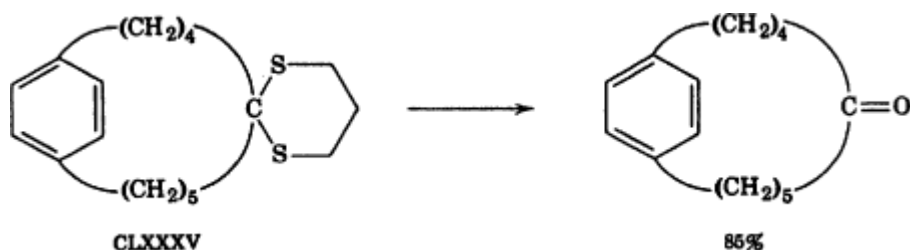


Oxidizing agents such as nitric acid<sup>232</sup> and hydrogen peroxide<sup>233</sup> have been used for the desulfurization of various heterocycles, including pyrimidine-2-thiols and thiazole-2-thiols, to the parent aromatic compounds.

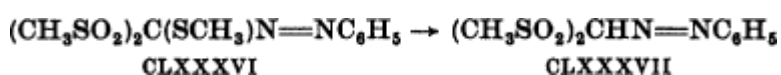
Mercuric oxide has been used frequently for desulfurization of sugar mercaptals.[234](#), [235](#) Mercuric sulfate,[236](#) lithium aluminum hydride,[225](#), [237](#) copper, aluminum bromide, and organolithium compounds have also been used to remove sulfur from various organic compounds.[225](#) Mercuric chloride has been found to regenerate ketones from hemithioketals (e.g., CLXXXIV),[46](#) and a mixture of mercuric chloride and cadmium carbonate has been utilized in reversing thioketal (cf. CLXXXV) formation.[238](#), [239](#)



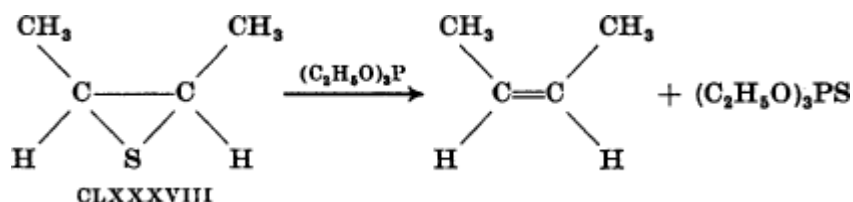
Thiophenes may be desulfurized by high-pressure hydrogenation in the presence of a tungsten-nickel sulfide catalyst.[240](#)



In two exceptional cases, desulfurization occurred in boiling piperidine (CLXXXVI  $\rightarrow$  CLXXXVII)[241](#) and during the chromatography of certain azothiobenzenes on alumina.[242](#)



Triethyl phosphite has recently been introduced as a desulfurization reagent.[243-245](#) The stereoselective removal of sulfur from thiranes (e.g., CLXXXVIII) is indicative of the potential value of this reagent.[246](#)

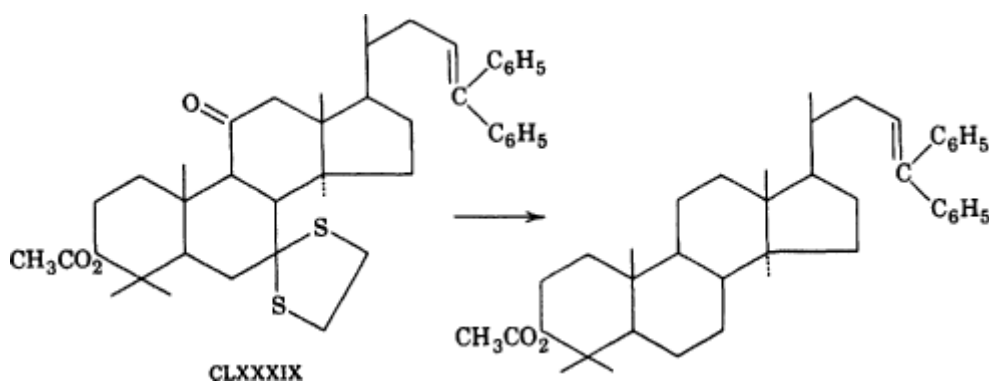


Another new desulfurization procedure involves the use of hydrazine and potassium hydroxide. The experimental procedure is reminiscent of the Wolff-Kishner reduction.[247](#) Wolff-Kishner reduction of the lanostane derivative CLXXXIX using vigorous conditions also resulted in desulfurization.[248](#) (Equation on p. 407.)

## 5. Experimental Conditions

### 5.1.1. Raney Nickel

The Raney nickel catalysts have been designated W-1, W-2, W-3, W-4, W-5, W-6, and W-7 according to the procedure employed for their preparation.<sup>249</sup> Although the W-2 catalyst has been extensively used in desulfurization studies, the W-4 and W-7 catalysts appear to be superior. Many examples of desulfurization have been reported in which the catalyst is generated in situ from nickel aluminum alloy.<sup>33, 99</sup> Decomposition of Raney nickel alloy by strong base appears to constitute the most powerful desulfurizing conditions known, since only by means of this method can sulfonic acids be cleaved. Unfortunately, many authors have not designated the particular type of nickel used, and, therefore, generalizations are difficult to formulate.



The different modifications of Raney nickel vary in the amount of hydrogen absorbed. For example, if a temperature of 80° is attained in the preparation, the nickel contains 40–42 ml. of hydrogen per gram; if the temperature is maintained at 50°, 1 g. of the product contains about 120 ml. of hydrogen.<sup>7</sup> The quantity of hydrogen adsorbed becomes of considerable importance if the nickel is heated to 100–200° before the desulfurization. As Hauptman has shown, partial desulfurization or desulfurization without hydrogenolysis is the usual course of reaction with “hydrogen-poor” or “hydrogen-free” nickel.<sup>11, 78</sup> Badger<sup>41</sup> has described the preparation of a partially degassed W-7 Raney nickel catalyst. Depending on conditions, the degassing process may be attended by an explosion hazard.<sup>250</sup>

In the usual case, the Raney nickel reagent is used in large excess by weight (at least ten times the weight of the sulfur compound) and is added as a suspension to a solution of the substance to be desulfurized. The quantity of nickel is best measured by weighing the nickel-aluminum alloy before preparing the nickel by treatment with base, or by measuring the nickel suspension by volume. For reproducible results, the nickel should be prepared on the order of hours or days before use; aging of the reagent for some weeks or months is attended by a noticeable deactivation.

Controlled hydrogenolysis of thiol esters and thioamides to produce aldehydes is ordinarily accomplished by subjecting a suspension of the desired amount of nickel to the action of boiling acetone for a short time (usually about an hour or two) before adding the substance to be desulfurized.<sup>149a</sup> Apparently this treatment with acetone, a hydrogen acceptor, destroys most of the active centers on the nickel surface, producing a reagent more selective in its action. This treatment also seems to aid in preserving olefinic bonds<sup>100</sup> or carbonyl groups<sup>75</sup> which otherwise are reduced.

Occasionally workers have observed that strong adsorption of the desulfurized material on the nickel results in a poor recovery under the usual conditions of isolation. The difficulty has been surmounted by removing the product from the nickel with a suitable solvent in a Soxhlet extractor,<sup>251</sup> or by dissolving the nickel in a mineral acid.<sup>163, 252</sup>

### 5.1.2. Solvent

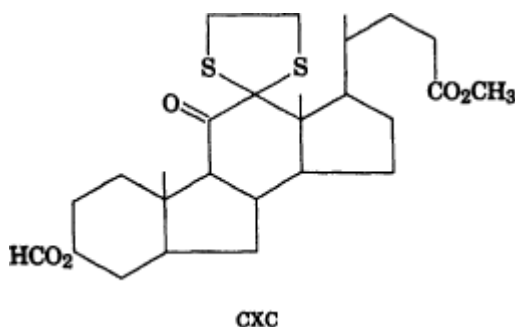
In general, solvent effects have seldom been noted. Neutral solvents such as water, methanol, ethanol, and dioxane are commonly used. Solvents which have been used less frequently include acetone,[28](#) benzene,[46](#), [253](#) butanol,[46](#), [98](#) decalin,[254](#) dimethylformamide,[98](#) ethylene glycol,[255](#) ethyl acetate,[28](#) methyl ethyl ketone,[46](#) mesitylene,[98](#) methyl Cellosolve,[83](#) Phillips 66, Soltrol 170,[254](#) tetrahydrofuran,[137](#) toluene,[183](#) and xylene.[35](#), [41](#) Occasionally, acetone[45](#) and low-boiling alcohols[65](#), [98](#) prove ineffective as solvents. Desulfurization of thiols can be carried out in aqueous ammonia,[71](#), [256](#) while certain acids can be reduced conveniently in aqueous potassium carbonate,[257](#) sodium carbonate,[163](#), [180](#) sodium bicarbonate,[258](#) or sodium hydroxide.[170](#), [259](#), [260](#)

Because of explosion hazard, dioxane must not be used with Raney nickel above 210°. [261](#) Pyridine has been found to yield 2, 2'-dipyridyl when employed as a solvent with Raney nickel,[250](#), [261a-262](#) while alcohols, ethanol in particular, may lead to N-alkylated products during desulfurization of amines.[18](#), [20](#), [21](#) An example of base-catalyzed C-alkylation by alcohols has recently been reported during desulfurization.[22](#)

The reaction mixture may be stirred, but this is usually not necessary if it is boiled under reflux. However, reactions employing large amounts of nickel (>25–50 g.) should be stirred.

### 5.1.3. Time and Temperature

It is very likely that the conditions used in many reported desulfurizations, viz., heating for several hours in a suitable solvent, are more vigorous than necessary. The mild conditions often sufficient for complete removal of sulfur are shown by the hydrogenolysis of a thiol ester to a primary alcohol, which can be accomplished quantitatively with W-4 nickel at room temperature in a few minutes;[154](#) and by the desulfurization of the thioketal CXC which proceeds in 90% yield by heating in boiling methanol for 1 hour, and in 86% yield by shaking at room temperature for 15 minutes in the same solvent.[263](#)



## 6. Experimental Procedures

### 6.1.1. Degassed Raney Nickel Catalyst[11](#)

Raney nickel (53 g.) was transferred with benzene to a Carius tube and the solvent was evaporated under reduced pressure, while the nickel was held in place by means of a magnet. The dry nickel was degassed by heating for 2 hours at 200° and 2 mm.

### 6.1.2. 4-Hydroxy-6-methyl-7-phenylpyrido(2,3-d)pyrimidine[71a](#)

Six grams of 2-mercapto-4-hydroxy-6-methyl-7-phenyl-pyrido(2,3-d)pyrimidine, m.p. 240–242°, was added to 1.8 l. of 95% ethanol and 150 ml. of concentrated aqueous ammonia. After the addition of approximately 18–20 g. of Raney nickel catalyst, the reaction mixture was heated under reflux for 6 hours on a steam bath. The catalyst was then removed by filtration and extracted with 300 ml. of boiling 95% ethanol. The combined filtrates were evaporated under reduced pressure on a steam bath until the volume was about 100 ml. The hot solution was adjusted to pH 5 with dilute acetic acid and allowed to cool. The crude yield of white needles was 4.4 g., m.p. 245–248°. Recrystallization from ethanol-water raised the melting point to 248–250°.

### 6.1.3. 3,5-Androstadien-17 $\beta$ -ol from the 3-Benzylthio Enol Ether of Testosterone<sup>100</sup>

A suspension of 30 g. of Raney nickel in 150 ml. of acetone was heated under reflux for 1 hour, 3.0 g. of the 3-benzylthio enol ether of testosterone in 150 ml. of acetone was added, and refluxing was continued for 4 hours. The nickel was separated by filtration and washed with acetone. The filtrates were evaporated to dryness, and the residue was recrystallized from ethanol. The yield was 1.8 g. (87%) of needles of 3,5-androstadien-17 $\beta$ -ol, m.p. 156°,  $[\alpha]_D^{20} - 139^\circ$  (CHCl<sub>3</sub>).

### 6.1.4. Benzoyl-L(+)-alanine from Benzoyl-L(-)-cystine<sup>7</sup>

To a suspension of 25–35 g. of Raney nickel catalyst in 125 ml. of ethanol and 10 ml. of water was added 2.0 g. of benzoyl-L(-)-cystine, m.p. 178–180°. The mixture was refluxed for  $\frac{11}{4}$  hours and cooled. The material was transferred to a centrifuge bottle and the nickel separated and washed six times by suspending it in dilute sodium hydroxide solution and centrifuging. The combined extracts were evaporated to dryness at 40–50° under reduced pressure and taken up in water. The water solution was acidified to Congo red and continuously extracted with chloroform. The chloroform solution was evaporated and the product crystallized from water to constant melting point. The yield was 1.40 g. (81%) of benzoyl-L(+)-alanine, m.p. 144–145°;  $[\alpha]_D^{25} + 9.7^\circ$ .

### 6.1.5. Desulfurization of 3 $\beta$ -Acetoxy-5 $\alpha$ -furostane 12,26-Bisethylenethioketal<sup>122</sup>

The thioketal (1.0 g., 0.0016 mole) was dissolved in 100 ml. of ethanol and heated under reflux for 4 hours with about 14 g. of Raney nickel (W-4). The mixture was filtered through Celite and the collected nickel by-products were washed with several portions of hot benzene. Concentration of the solvents to about 5 ml. left a clear ethanol solution which on cooling furnished 0.53 g. (74%) of colorless crystals, m.p. 82.0–84.5°. An analytical sample, recrystallized from ethanol, melted at 83.5–84.5°,  $[\alpha]_D^{25} - 14^\circ$ .

### 6.1.6. 1,5-Anhydro-4-( $\beta$ -D-glucopyranosyl)-D-glucitol Heptaacetate from Phenyl 1-Thio- $\beta$ -cellobioside Heptaacetate<sup>264</sup>

Ten grams of phenyl 1-thio- $\beta$ -cellobioside heptaacetate melting at 225–226°,  $[\alpha]_D^{20} - 28.7^\circ$  ( $c = 1.36$ , CHCl<sub>3</sub>), was suspended in 100 ml. of absolute ethanol, treated with approximately 100 g. of freshly prepared Raney nickel in absolute ethanol, and then boiled gently for 1 hour. After cooling, the supernatant solution was decanted and the nickel washed by decantation with three successive 100-ml. portions of absolute ethanol. The combined decantates, after filtration through a fine sintered-glass plate, were concentrated at 80° (bath) under a slight vacuum to a volume of 125 ml.; crystallization of the product as a mass of very fine needles was spontaneous. Concentration of the mother liquor afforded a very small quantity of

additional material; the yield was 5.9 g. (69%). Two recrystallizations from warm 95% ethanol furnished (with little loss) material melting at 194–195°,  $[\alpha]_D^{20} + 4.0^\circ$  ( $c = 1.39\%$ , chloroform).

### 6.1.7. Desulfurization of Spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3 $\epsilon$ -cholestane)[45](#)

Twenty grams of W-2 Raney nickel catalyst, 3 days old, was refluxed with stirring for 1 hour with 250 ml. of methyl ethyl ketone; 2.0 g. of the hemithioketal isomer A (m.p. 193–194°) was added and refluxing was continued with stirring for 24 hours. (When the reaction was carried out in acetone solution, up to 80% of the hemithioketal was recovered.)

The catalyst was separated on a filter, the solvent was removed, and the residue was chromatographed in 36 fractions over 30 g. of Merck acid-washed alumina. The first 23 fractions, eluted with petroleum ether, furnished 975 mg. (78%) of cholestan-3-one, m.p. 126–127°, while from the petroleum ether-benzene (1:1) eluates 20 mg. (2%) of cholestan-3 $\beta$ -ol, m.p. 138–139°, was obtained. The last 6 fractions, eluted with benzene, were combined and treated in pyridine solution with 3,5-dinitrobenzoyl chloride in the usual fashion. Crystallization from hexane gave 676 mg. (52%) of the 3,5-dinitrobenzoate of (+)1,1-diphenylpropan-2-ol as needles, m.p. 154.5–155°,  $[\alpha]_D^{25} - 46.1^\circ$  (CHCl<sub>3</sub>).

Desulfurization of 1.0 g. of the hemithioketal isomer C (m.p. 152–153°), under precisely the same conditions, yielded 80% of cholestan-3-one and 57% of the 3,5-dinitrobenzoate of (–)1,1-diphenylpropan-2-ol, m.p. 154.5–155°,  $[\alpha]_D^{25} + 44^\circ$  ( $c = 1.7\%$ , chloroform). Admixture with the above antipode lowered the melting point to 129–130°, which corresponds to the melting point of the racemic derivative which had been prepared independently.

### 6.1.8. Desulfurization of $\gamma$ -2-Thienylbutyric Acid[14](#)

The W-7 Raney nickel catalyst from 125 g. of alloy was added in one portion to 300 ml. of an aqueous solution of 20 g. of  $\gamma$ -2-thienylbutyric acid in dilute sodium carbonate solution. After 2 hours' stirring at 90–95° in an open beaker, the volume was 190 ml. The mixture was added slowly to excess hydrochloric acid (condenser), and the resulting solution was continuously extracted with ether. Distillation of the product gave: (a) 11.5 g. of n-octanoic acid, b.p. 165–170°/22 mm. (p-bromophenacyl ester, m.p. 67°); (b) 3 g. of  $\gamma$ -2-thienylbutyric acid, b.p. 127–130°/0.6 mm. (p-bromophenacyl ester, m.p. 56.5–57.5°); and (c) 1 g. of residue. The residue was taken up in aqueous sodium carbonate, treated with charcoal, reprecipitated, recrystallized from ether, sublimed at 200°/23 mm., and recrystallized from concentrated nitric acid. This furnished 0.05 g. of hexadecane-1,16-dioic acid as plates, m.p. 123–124°.

### 6.1.9. Hydrogenolysis of 5-t-Butyl-2-thenoic Acid[170](#)

To a well-stirred solution of 12 g. of the thenoic acid in 100 ml. of 10% aqueous sodium hydroxide heated at 90°, 100 g. of Raney nickel was added in small portions (with a few drops of isoamyl alcohol to prevent excessive frothing). The mixture was then heated for 2 hours, filtered while hot, and the cooled filtrate was acidified with hydrochloric acid. The product was extracted with ether and purified by vacuum distillation. The 6,6-dimethylheptanoic acid, thus obtained in 70% yield, was a pale yellow oil with an unpleasant rancid smell, b.p. 143°/17 mm.,  $n_D^{22} 1.4375$ .

### 6.1.10. Desulfurization of N-Benzylsaccharin[210](#)

A mixture of 1 g. of N-benzylsaccharin, 100 ml. of ethanol, and 15 ml. of W-4 Raney nickel (10 weeks old) was heated at reflux, with stirring, over a 13-hour period. The reaction mixture was filtered through a layer of Celite and the collected catalyst was washed with hot ethanol. After removal of the solvent under reduced pressure the crystalline residue was recrystallized from ethanol. The yield of colorless crystals, m.p. 96–99°, was 0.6 g. (78%). Three recrystallizations from ethanol gave pure benzylbenzamide, m.p. 104.0–104.5°.

## 7. Tabular Survey

Unless otherwise noted, desulfurization of each of the indicated structures involves only replacement of sulfur by hydrogen. Compounds which contain more than one type of sulfur group will generally be found in the first table that would ordinarily describe one of the sulfur units. For example, a mercaptothiazole would be found among the thiols (Table I) instead of among the thiazoles. Location within each table is usually determined by whether the compound is aliphatic, aromatic, heterocyclic, carbohydrate, steroid, or a substance related to the steroids. In general, the entries are arranged by increasing carbon content, number of and size of rings, and in the order of increasing numbers of hetero atoms.

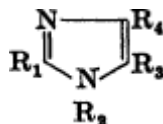
Table I. Raney Nickel Desulfurization of Thiols

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In most cases, compounds of the same basic structure are listed under a general formula, e.g., In the individual entries, the substituents only are listed so that any R group not named is hydrogen.



Yields given in these tables represent products obtained in reasonably high purity as evident from melting point or boiling point data; in most cases, yields of crude products or products of questionable purity have been omitted.

The literature available through February 1960 has been reviewed, and a number of more recent articles have been included.

Table II. Raney Nickel Desulfurization of Thioethers

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Table III. Raney Nickel Desulfurization of Disulfides

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Table IV. Raney Nickel Desulfurization of Hemithioacetals and Hemithioketals



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Table V. Raney Nickel Desulfurization of Dithioacetals and Dithioketals

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Table VI. Raney Nickel Desulfurization of Thioamides

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Table VII. Raney Nickel Desulfurization of Thiol Esters

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Table VIII. Raney Nickel Desulfurization of Isothiouonium Salts

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Table IX. Raney Nickel Desulfurization of Thiophenes and Thiazoles

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Table X. Raney Nickel Desulfurization of Sulfoxides

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Table XI. Raney Nickel Desulfurization of Sulfones

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Table XII. Raney Nickel Desulfurization of Sulfonic Acids, Esters, and Amides

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Table XIII. Raney Nickel Desulfurization of Miscellaneous Organic Sulfur Compounds



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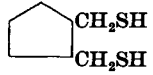
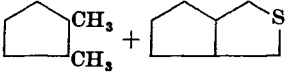
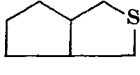


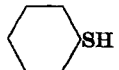
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TABLE I  
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
HSCH <sub>2</sub> CO <sub>2</sub> H		—	1
HSCH <sub>2</sub> CH <sub>2</sub> SH		—	1
HSCH <sub>2</sub> CH(OH)CH <sub>2</sub> SH		—	59, 265
HSCH <sub>2</sub> CH(SH)CH <sub>2</sub> OH		—	59, 265
HSCH <sub>2</sub> (CHOH) <sub>4</sub> CH <sub>2</sub> SH (1,6-dithiodulcitol)		—	60
CH <sub>3</sub> CH[CH(SH)CO <sub>2</sub> H] <sub>2</sub>		—	266
(CH <sub>3</sub> ) <sub>2</sub> C(OH)CH(SH)COCH <sub>3</sub>		—	275
(CH <sub>2</sub> SH) <sub>2</sub> CHCO <sub>2</sub> H		—	63
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>2</sub> SH		—	56
	 + 	—	267
		—	59
		—	56
C <sub>6</sub> H <sub>5</sub> SH	Biphenyl	— 23†	56 11

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

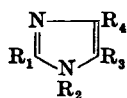
† Degassed Raney nickel was used.

DESULFURIZATION WITH RANEY NICKEL

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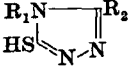
TABLE I—Continued  
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
2,6-(HO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SH		—	268
<i>o</i> -HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> SH		—	269
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SH		—	269
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SH		80	269
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> SH		—	270
C <sub>6</sub> H <sub>5</sub> NHCOCH <sub>2</sub> SH		—	1
C <sub>6</sub> H <sub>5</sub> CH=C(SH)CO <sub>2</sub> H		—	1
C <sub>6</sub> H <sub>5</sub> CH(SH)CH(NH <sub>2</sub> )CO <sub>2</sub> H·HCl		40	271
C <sub>6</sub> H <sub>5</sub> COC(CH <sub>3</sub> ) <sub>2</sub> CONHCH <sub>2</sub> CH <sub>2</sub> SH	C <sub>6</sub> H <sub>5</sub> CHOHC(CH <sub>3</sub> ) <sub>2</sub> CONHCH <sub>2</sub> CH <sub>3</sub>	—	25
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C(SH)CO <sub>2</sub> H		—	272
C <sub>6</sub> H <sub>5</sub> CH(SH)CH(OH)C <sub>6</sub> H <sub>5</sub>	(a) † C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CHOHC <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> , and C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> COC <sub>6</sub> H <sub>5</sub>	—	45
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(OH)CH <sub>2</sub> SH	(b) § C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCOCH <sub>3</sub>	— 55, — 24, —	45, 273 45, 273
2-C <sub>10</sub> H <sub>7</sub> SH		Quant.	9, 56
2-(Mercaptomethyl)anthraquinone	2-Methylanthraquinone, bis(2-anthraquinonylmethyl) sulfide, 2-hydroxyanthraquinone, and 2-anthraquinone-carboxylic acid	—	274
(CH <sub>3</sub> ) <sub>2</sub> C(SH)CHCO <sub>2</sub> CH <sub>3</sub>   NHCOCH(CH <sub>2</sub> OH)NHCOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		81	61



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ORGANIC REACTIONS

$R_1 = R_3 = \text{SH}$	—	64
$R_1 = \text{SH}, R_4 = \text{CH}_2\text{CH}_2\text{OH}$	—	276
$R_1 = R_4 = \text{SH}, R_3 = \text{CH}=\text{C}(\text{CO}_2\text{CH}_3)\text{NHCOC}_6\text{H}_5, R_2 = \text{CH}_2\text{CH}(\text{CO}_2\text{CH}_3)\text{NHCOC}_6\text{H}_5$	42	277
$R_1 = R_4 = \text{SH}, R_3 = \text{C}_6\text{H}_5$	31	278
$R_1 = R_4 = \text{SH}, R_3 = \text{CO}_2\text{C}_2\text{H}_5$	—	279
$R_1 = \text{OH}, R_3 = \text{CO}_2\text{C}_2\text{H}_5, R_4 = \text{SH}$	59	196
$R_1 = \text{SH}, R_3 = \text{NHCOC}_6\text{H}_5$	65	280
$R_1 = \text{SH}, R_3 = \text{NHCO}_2\text{C}_2\text{H}_5$	—	281
$R_1 = \text{SH}, R_3 = \text{NHCO}_2\text{C}_2\text{H}_5, R_4 = \text{CH}_3$	65	281
$R_1 = \text{SH}, R_3 = \text{NHCO}_2\text{C}_2\text{H}_5, R_4 = \text{C}_6\text{H}_5$	—	281
$R_1 = \text{SH}, R_3 = (\text{CHOH})_2\text{CH}_2\text{OH}$	—	282
$R_1 = \text{C}_6\text{H}_5\text{CH}_2, R_2 = \text{CH}(\text{CO}_2\text{H})\text{C}(\text{SH})(\text{CH}_3)_2$	—	62
$R_1 = \text{SH}, R_2 = \text{CH}_3, R_3 = \text{NH}_2$	—	283
$R_1 = \text{SH}, R_2 = \text{CH}_3, R_3 = \text{NH}_2, R_4 = \text{CO}_2\text{C}_2\text{H}_5$	—	283
$R_1 = \text{SH}, R_2 = \text{CH}_3, R_3 = \text{NH}_2, R_4 = \text{CONH}_2$	—	283
		
$R_2 = \text{C}_6\text{H}_5$	73	68
$R_2 = p\text{-CH}_3\text{OC}_6\text{H}_4$	59	68
$R_2 = p\text{-ClC}_6\text{H}_4$	55	68
$R_2 = \text{NHN}=\text{CHC}_6\text{H}_5$	47	284
$R_1 = \text{NH}_2, R_2 = \text{C}_6\text{H}_5$	41	284 <sub>a</sub>
$R_1 = R_2 = \text{NH}_2$	33	284
$R_1 = \text{C}_6\text{H}_5\text{CH}=\text{N}, R_2 = \text{NHN}=\text{CHC}_6\text{H}_5$	26	284

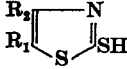
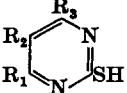

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Acetone was used as the solvent.

§ Ethanol was used as the solvent.

TABLE I—Continued  
RANEY NICKEL DESULFURIZATION OF THIOLS

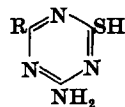
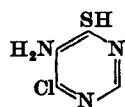
Thiol	Product*	Yield, %	References
			
$R_2 = \text{OH}$	$\text{CH}_3\text{CHO}$	72	43
$R_2 = \text{C}_6\text{H}_5$	$R_2 = \text{C}_6\text{H}_6 + \text{C}_6\text{H}_5\text{COCH}_3$	15, 48	43
$R_1 = \text{NH}_2, R_2 = \text{C}_6\text{H}_5$	—	—	278
$R_1 = \text{NHCOCH}_3, R_2 = \text{C}_6\text{H}_5$	—	—	278
$R_1 = \text{CH}_2\text{CH}_2\text{OH}, R_2 = \text{CH}_3$	—	—	285
			
$R_1 \dots R_3 = \text{H}$	—	—	65
$R_1 = R_3 = \text{CH}_3$	54	65	
$R_1 = \text{CH}_3(\text{CH}_2)_4\text{NH}$	66	286	
$R_1 =$ 	65	286	
$R_3 = \text{NH}_2$	20, 61	286 <sub>a</sub> , 287	
$R_1 = \text{NH}_2, R_3 = \text{OH}$	16	142	
$R_1 = R_3 = \text{NH}_2$	24, 85	286 <sub>a</sub> , 287	
$R_2 = R_3 = \text{NH}_2$	—, 66	288, 72	
$R_1 = \text{OH}$	82	287	



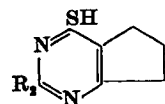
$R_1 = R_2 = \text{NH}_2, R_3 = \text{OH}$   
 $R_1 = R_2 = \text{NH}_2, R_3 = \text{NO}$   
 $R_1 = R_2 = R_3 = \text{NH}_2$   
 $R_1 = \text{SH}$

$R_1 = R_2 = R_3 = \text{NH}_2$

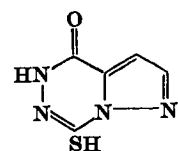
76, 89  
 47  
 78  
 17  
 72, 66, 73  
 50  
 50  
 65



$R = \text{C}_2\text{H}_5\text{CH}_2$   
 $R = p\text{-ClC}_6\text{H}_4\text{CH}_2$



$R_2 = \text{H}$   
 $R_3 = \text{NH}_2$



— 67

— 69  
— 69

58 288a  
55 288a

— 289

DESULFURIZATION WITH RANEY NICKEL

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Note: References 265 to 490 are on pp. 525-529.


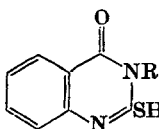
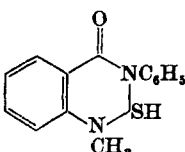
\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE I—Continued  
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
		41-48	71, 290
$R_1 = \text{SH}$ $R_1 = R_2 = \text{SH}$ $R_1 = \text{SH}, R_2 = \text{CH}_3$		35 —	71 291
		—	256
$R = \text{H}$ $R = \text{CH}_3$		—	292
		53	293

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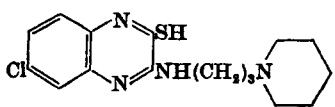
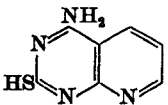
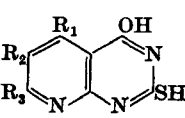
ORGANIC REACTIONS

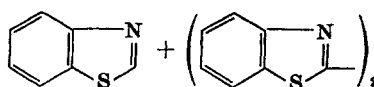
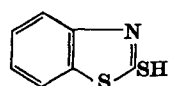
$R_1 = \text{CH}_3, R_2 = \text{OH}$	—	294
$R_1 = \text{C}_2\text{H}_5, R_2 = \text{OH}$	—	294
$R_1 = i\text{-C}_6\text{H}_5, R_2 = \text{OH}$	—	294
$R_1 = p\text{-ClC}_6\text{H}_4, R_2 = \text{OH}$	—	294
$R_1 = \text{CH}_3, R_2 = \text{NH}_2$	—	294
$R_1 = \text{C}_2\text{H}_5, R_2 = \text{NH}_2$	—	294
$R_1 = \text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2, R_2 = \text{NH}_2$	—	294
	30	295
		
$R = \text{H}$	90	296
$R = \text{C}_6\text{H}_5$	57	296
$R = \text{C}_6\text{H}_5\text{CH}_2$	57	296
	—	297

Note: References 265 to 490 are on pp. 525-529.

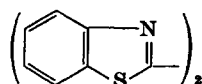
\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE I—Continued  
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
		—	298
		—	298a
			
$R_1 = R_3 = \text{CH}_3$		83	71a
$R_2 = R_3 = \text{CH}_3$		69	71a
$R_2 = \text{CH}_3, R_3 = \text{C}_2\text{H}_5$		80	71a
$R_2 = \text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2$		66	71a
$R_2 = \text{C}_2\text{H}_5, R_3 = n\text{-C}_3\text{H}_7$		80	71a
$R_2 = \text{CH}_3, R_3 = n\text{-C}_4\text{H}_9$		76	71a
$R_2 = \text{C}_6\text{H}_5$		44	71a
$R_2 = p\text{-CH}_3\text{C}_6\text{H}_4$		74	71a
$R_3 = p\text{-ClC}_6\text{H}_4$		64	71a
$R_3 = \text{CH}_3, R_2 = \text{C}_6\text{H}_5$		84	71a
$R_3 = \text{C}_2\text{H}_5, R_2 = \text{C}_6\text{H}_5$		58	71a
$R_2 = \text{C}_6\text{H}_5, R_3 = \text{C}_6\text{H}_5\text{CH}_2$		68	71a



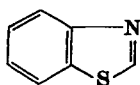
55 41, 299, 43



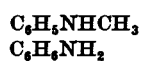
7, || 6† 41



10, || —† 41, 43



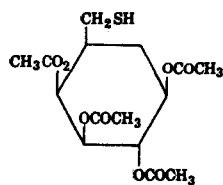
—, || 35† 41



47, || 22† 41  
17, || 7† 41, 43

— 300

2-Methyl-5-mercaptopyrimidopyridine



70 301

2β-Mercaptocholestan-3β-ol

(a) Cholestan-3β-ol and cholestan-3-one†  
(b) Cholestan-3-one¶

— 45  
80 45

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.

‡ Acetone was used as the solvent.

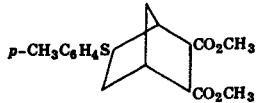
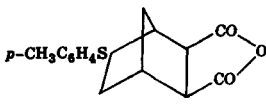
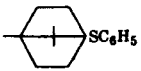
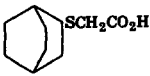
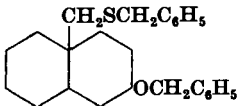
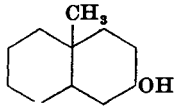
|| Sodium hydroxide solution and W-5 Raney nickel were used.

¶ Benzene was used as the solvent.

DESULFURIZATION WITH RANEY NICKEL

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TABLE II  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

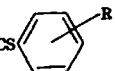
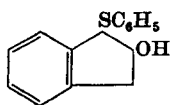
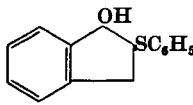
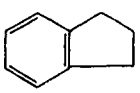
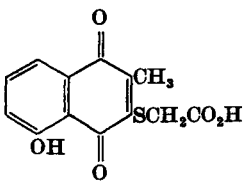
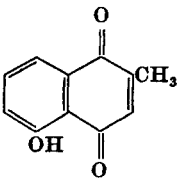
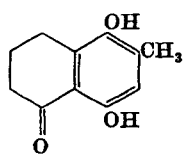
Thioether	Product*	Yield, %	References
$n\text{-C}_4\text{H}_9\text{SCH}_3$		—	56
$(n\text{-C}_7\text{H}_{15})_2\text{S}$		—	56
$[\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2]_2\text{S}$		—	56
$\text{CH}_3\text{S}(\text{CH}_2)_3\text{CO}_2\text{H}$		95	7
D(+)-Methionine	D(-)- $\alpha$ -Aminobutyric acid	17	104
L(-)-Methionine	L(+)- $\alpha$ -Aminobutyric acid	—	85
$\text{CH}_3\text{SCH}=\text{C}(\text{SCH}_3)\text{CO}_2\text{H}$	$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	86	260
$\text{S}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H})_2$		94	7
$[\text{HO}_2\text{CCH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{SCH}_2]_2$		—	304
$\text{HOCH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{SCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$		—	306
$\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{SC}_6\text{H}_5$		—	302
$\text{HO}_2\text{CCH}(\text{NH}_2)\text{CH}_2\text{SCH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{CO}_2\text{H} (?)$		—	303
$[(\text{CH}_3)_2\text{CHCOC}(\text{CH}_3)_2\text{SCH}_2]_2\text{N}$		—	305
		76	253
		38	253
<i>cis</i> -3-Methyl-3-benzylthiocyclohexyl $\beta$ -naphthoate		89	307
<i>trans</i> -3-Methyl-3-benzylthiocyclohexyl $\beta$ -naphthoate		88	307
		53	307
		—	308
		63	37
Petroleum thioethers		—	309
$p\text{-CH}_3\text{C}_6\text{H}_4\text{SCH}_3$		87	7
$p\text{-CH}_3\text{C}_6\text{H}_4\text{SCH}_2\text{CH}_3$	$p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$	21	11
	$(p\text{-CH}_3\text{C}_6\text{H}_4)_2$	10	
$o\text{-HO}_2\text{CC}_6\text{H}_4\text{SCH}_2\text{CO}_2\text{H}$		91	
$\text{H}_2\text{NCH}_2\text{CH}(\text{SC}_6\text{H}_5)\text{CO}_2\text{H}$		—	310
$(\text{C}_6\text{H}_5)_2\text{S}$	(a)	68, —	7, 56
	(b)† $(\text{C}_6\text{H}_5)_2$	75	11
	<i>p</i> -Terphenyl	6	

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.

TABLE II—Continued  
 RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
$(C_6H_5)_2S + 2,2'-(C_{10}H_7)_2S$	Biphenyl	63	11
	2,2'-Binaphthyl	63	
	2-Phenylnaphthalene	25	
	Benzene†	7	
$C_6H_5CH_2SC_6H_5$	$C_6H_5CH_2CH_2C_6H_5$ †	—	78
$(C_6H_5CH_2)_2S$		85	7
$(p-CH_3C_6H_4)_2S$		87	7
$(p-CH_3OC_6H_4)_2S$	$(p-CH_3OC_6H_4)_2$ †	50	78
$C_6H_5CH(SC_6H_5)CONH_2$		68	311
$1,1'-(C_{10}H_7)_2S$		89	312
$C_6H_5C(CH_3)(CO_2H)SC_6H_5$		41	16
$C_6H_5C(CH_3)(CONH_2)SC_6H_5$		85	16
$C_6H_5SC(CO_2H)=CHC_6H_4OH-p$	$HO_2CCH_2CH_2C_6H_4OH-p$	—	269
$C_6H_5COCH(C_6H_5)SCH_2CH_3$		—	98
$p-CH_3OC_6H_4COCH(C_6H_5)SCH_2CO_2H$		—	75
$C_6H_5COCH(C_6H_4OCH_3-p)SCH_2CO_2H$		—	75
$C_6H_5COCH(C_6H_5)SC(CH_3)_2CO_2H$		—	75
$p-(CH_3)_2NC_6H_4COCH(C_6H_5)SCH_2CO_2H$		—	75
$CH_3C(C_6H_5)_2CH_2CH_2SCH_2(CH_2)_2CH_3$		Quant.	313
$S(CH_2CH(NHCOC_6H_5)CO_2H)_2$	$CH_3CH(NHCOC_6H_5)CO_2H$	60	314
$o-CH_3OC_6H_4CH(C_6H_5)SCH_2C_6H_5$	$C_6H_5CH_3$ and $[o-CH_3OC_6H_4CH(C_6H_5)]_2$	—	315
$o-C_6H_5CH_2SC_6H_4CONHCH_2C_6H_5$	$C_6H_5CONHCH_2C_6H_5$ and $(C_4H_8CH_2)_2$ (traces)	—	13
$(C_6H_5)_2CS$ 			
R = H		60	316
R = <i>o</i> -CH <sub>3</sub>		58	316
R = <i>m</i> -CH <sub>3</sub>		54	316
R = <i>p</i> -CH <sub>3</sub>		62	316
$C_6H_5COCH(C_6H_5)SCH_2CONHC_6H_5$		—	75
$C_6H_5CH(SC_6H_4CH_3-p)N(COCH_3)C_6H_5$	$C_6H_5CH_2N(COCH_3)C_6H_5$ $C_6H_5CH_3$	90	317
		50	79
		—	79
	 and 	—	86, 87

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.

TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

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ORGANIC REACTIONS

Thioether	Product*	Yield, %	References
		75	318
		75	319
		30	320
		—	81
		—	81
		—	321
		70	7
		56	318
R <sub>1</sub> = R <sub>2</sub> = C <sub>6</sub> H <sub>5</sub>		45	136
R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> , R <sub>2</sub> = CH <sub>3</sub>		60	136
R <sub>1</sub> = R <sub>2</sub> = C <sub>6</sub> H <sub>5</sub> , R <sub>3</sub> = CH <sub>3</sub>		55	136
R <sub>1</sub> , R <sub>2</sub> = cyclopentyl		61	136

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

DESULFURIZATION WITH RANEY NICKEL

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TABLE II—Continued  
 RANEY NICKEL DESULFURIZATION OF THIOETHERS

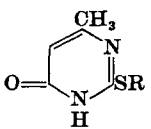
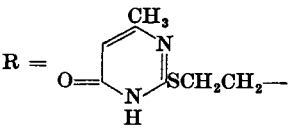
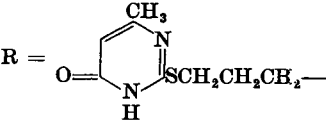
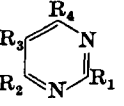

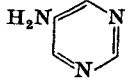
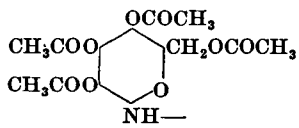
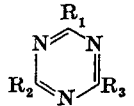
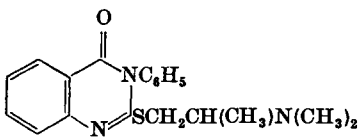
Thioether	Product*	Yield, %	References
	 I                      II		
$R_1 = R_2 = H$	(a) II	79	139
	(b)† I	75	139
$R_2 = CH_3$	Mixture of I and II	—	139
$R_1 = R_2 = CH_3$	(a) 3:1 mixture of I and II	—	139
	(b)† I	84	139
$R_2 = CH_2C_6H_5$	(a) Mixture of I and II containing 25% of I	—	139
	(b)† I	85	139
$R_2 =$		Quant.	141
		75	322
		62	318
		—	80
		—	48
$R_2 = CH_3$		28	296
$R_1 = C_6H_5, R_2 = CH_3$		51	296
$R_1 = C_6H_5, R_2 = C_6H_5CH_2$		59	296
		58	84

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Sodium ethoxide was added to the reaction mixture.

TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
			
R = CH <sub>3</sub>		—	323
R = C <sub>2</sub> H <sub>5</sub>		—	323
		—	323
		—	323
		—	65
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>3</sub> = Br			
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>3</sub> = NO <sub>2</sub>		75	325
R <sub>1</sub> = SC <sub>2</sub> H <sub>5</sub> , R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = OH		—	90
R <sub>1</sub> = SCH <sub>2</sub> CO <sub>2</sub> H, R <sub>2</sub> = <i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> NH		—	286
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = OH, R <sub>3</sub> = C <sub>6</sub> H <sub>5</sub> CONH		—	90
R <sub>1</sub> = SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> , R <sub>2</sub> = C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCH <sub>2</sub> , R <sub>4</sub> = OH		48	324
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = NHCHO, R <sub>4</sub> = N(CH <sub>3</sub> ) <sub>2</sub>		69	83
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = N=NC <sub>6</sub> H <sub>5</sub> Cl <sub>2</sub> , R <sub>4</sub> =		Low	12
			
R <sub>1</sub> . . . R <sub>3</sub> = SCH <sub>3</sub>		10	254
R <sub>1</sub> = CH <sub>3</sub> , R <sub>2</sub> = R <sub>3</sub> = SCH <sub>3</sub>		32	254
R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> , R <sub>2</sub> = R <sub>3</sub> = SCH <sub>3</sub>		32	327
R <sub>1</sub> = R <sub>3</sub> = C <sub>6</sub> H <sub>5</sub> , R <sub>2</sub> = SCH <sub>3</sub>		81	327
		—	326

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

ORGANIC REACTIONS

DESULFURIZATION WITH RANEY NICKEL

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TABLE II—Continued  
 RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
		25	293
R <sub>1</sub> = CH <sub>3</sub> S, R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = CH <sub>3</sub>		—	328
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub> , R <sub>3</sub> = CH <sub>3</sub> , R <sub>4</sub> = SCH <sub>3</sub>		72	331
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub> , R <sub>3</sub> = C <sub>2</sub> H <sub>5</sub> , R <sub>4</sub> = SCH <sub>3</sub>		74	331
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub> , R <sub>4</sub> = SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		0	83
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub>		43	83
R <sub>1</sub> = R <sub>4</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub>		16	83
R <sub>1</sub> = R <sub>4</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub> , R <sub>5</sub> = CH <sub>3</sub>		50	331
R <sub>1</sub> = R <sub>4</sub> = SCH <sub>3</sub> , R <sub>2</sub> = N(CH <sub>3</sub> ) <sub>2</sub> , R <sub>5</sub> = C <sub>2</sub> H <sub>5</sub>		42	331
R <sub>1</sub> = CH <sub>3</sub> S, R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = triacetyl-D-xylopyranosido-		—	328
R <sub>1</sub> = CH <sub>3</sub> S, R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = tetraacetyl-D-glucopyranosido-		—	329
R <sub>1</sub> = CH <sub>3</sub> S, R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = tetraacetyl-D-mannopyranosido-		—	330
R <sub>1</sub> = CH <sub>3</sub> S, R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = β-D-ribofuranosyl-		50, —	92, 93
R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = NH <sub>2</sub> , R <sub>3</sub> = triacetyl-5-benzyl-D-ribofuranosyl		—	93
6-Acetamido-9-[3',5'-di-O-acetyl-2'-deoxy-2'-(ethylthio)-β-D-arabinofuranosyl]purine		—	332

ORGANIC REACTIONS

		Fair	333
		72	334
	C <sub>6</sub> H <sub>5</sub> CONH <sub>2</sub>	45	284a
		62	90
	C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> CONH 	27-29	96, 39
	C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> CONHCHCH <sub>3</sub> 		
	C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> CONHCHCH <sub>3</sub> 		

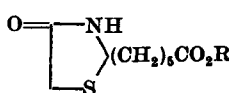
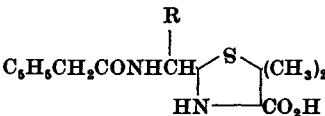
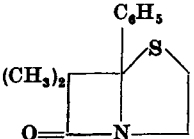
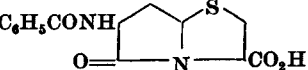
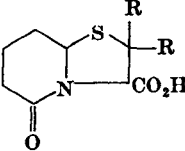
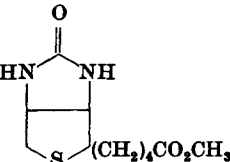
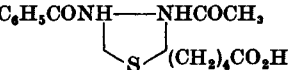
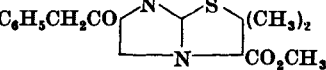
DESULFURIZATION WITH RANEY NICKEL

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

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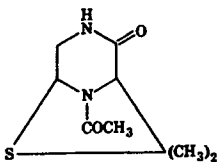


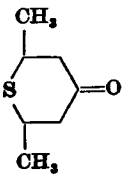
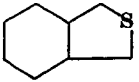
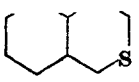
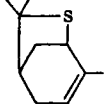
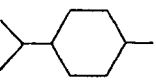
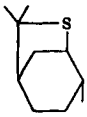
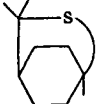
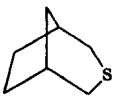
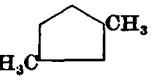
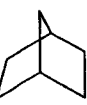
TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
			
R = H		—	40
R = CH <sub>3</sub>		—	40
			
R = CO <sub>2</sub> CH <sub>3</sub>		—	39
R = H		—	335
		—	39, 336
		—	337
			
R = H		30	97
R = CH <sub>3</sub>		35	97
Bacitracin A		—	338
		—	94
(Biotin methyl ester)			
Biotin		56-66	95
		—	95
			339

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

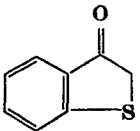
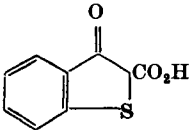
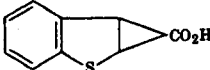
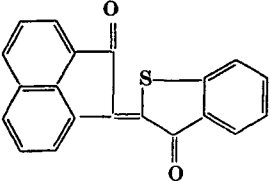
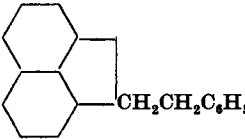
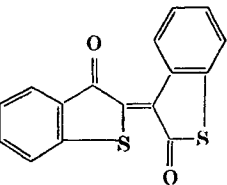
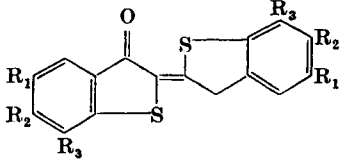
TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
		56	340
		—	56
		1	76
	+ $n\text{-C}_5\text{H}_{12}$ and olefins	—	
			340a
		—	341
		—	341
		—	342
	<i>cis and trans</i>		
	<i>cis and trans</i>	—	342
	<i>cis and trans</i>	—	342
		Good	76
	<i>cis + trans</i>		
	+		
		1	76

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
		72	99
	(a)§ C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H, C <sub>6</sub> H <sub>5</sub> CHOHCH <sub>2</sub> CO <sub>2</sub> H	—	99
	(b)   C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub> , C <sub>6</sub> H <sub>5</sub> CHOHCH <sub>2</sub> CO <sub>2</sub> H	—	99
	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	—	70
 (Ciba Scarlet G)	(a)§  (?)	—	99
	(b)   1-Phenacyltetrahydroacenaphthene (?)	—	99
	(a) C <sub>6</sub> H <sub>5</sub> CHOH(CH <sub>2</sub> ) <sub>2</sub> CHOHC <sub>6</sub> H <sub>5</sub> (?)	—	99
	(b)   CH <sub>3</sub> CH(C <sub>6</sub> H <sub>5</sub> )CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (?)	—	99
			
R <sub>1</sub> . . . R <sub>3</sub> = H	(a) C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>4</sub> C <sub>6</sub> H <sub>5</sub>	76	99
	(b) C <sub>6</sub> H <sub>5</sub> COCH <sub>2</sub> CH <sub>2</sub> COC <sub>6</sub> H <sub>5</sub>	1	343
	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>4</sub> C <sub>6</sub> H <sub>5</sub>	14	
	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	5	
R <sub>2</sub> = C <sub>2</sub> H <sub>5</sub> O	<i>p</i> -C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub> C <sub>6</sub> H <sub>4</sub> OC <sub>2</sub> H <sub>5</sub> - <i>p</i>	59	99
R <sub>1</sub> = Cl, R <sub>3</sub> = CH <sub>3</sub>	(a) <i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHOH(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> - <i>m</i>	—	99
(Durindone Red 3BS)	(b)§ 3-Cl,5-CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO(CH <sub>2</sub> ) <sub>2</sub> COC <sub>6</sub> H <sub>3</sub> Cl-3,CH <sub>3</sub> -5, —	—	99
	3-Cl,5-CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO(CH <sub>2</sub> ) <sub>2</sub> COC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> -3, and 3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHOH(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> -3	—	99
	(c)§ Unidentified chlorine-free oil	—	99

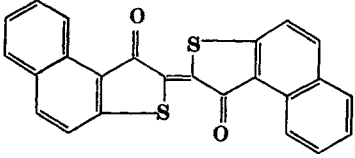
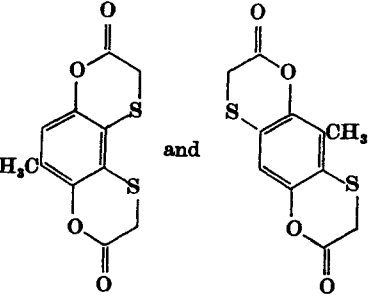
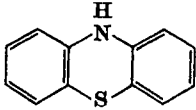
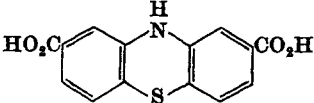
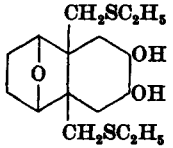
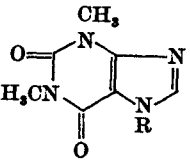
Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

§ Aqueous sodium hydroxide was used in this experiment.

|| Ethanol was used as the solvent.

TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
 (Durindone Brown GS)	(a)§ 1-C <sub>10</sub> H <sub>7</sub> CO(CH <sub>2</sub> ) <sub>2</sub> COC <sub>10</sub> H <sub>7</sub> -1 and yellow liquid (b)   Colorless liquid	—	99
Ciba Brown 2R¶	1-C <sub>10</sub> H <sub>7</sub> CHOH(CH <sub>2</sub> )CHOHC <sub>10</sub> H <sub>7</sub> -1 1-C <sub>10</sub> H <sub>7</sub> CO(CH <sub>2</sub> ) <sub>2</sub> COC <sub>10</sub> H <sub>7</sub> -1	Trace —	99
 (Mixture of isomers)		26, 39	344
		Fair	345
		94	346
		75	24
3-Thiomethyl-4,6-benzylidene-β-methyl-d-idoside		92	36
2-Thiomethyl-4,6-benzylidene-α-methyl-d-idoside	2-Deoxy-4,6-benzylidene-α-methyl-d-guloside	57	347
4,6-Benzylidene-α-methyl-2-methylthio-2-deoxyaltroside		—	348
4,6-Benzylidene-α-methyl-2-ethylthio-2-deoxyaltroside		—	349
		—	350
R = 5'-trityl-3'-deoxy-3'-thioethyl-7-β-D-xylofuranosyl		—	350
R = 3'-thioethyl-O,O-diacetyl-7-α-D-arabofuranosyl		28	350

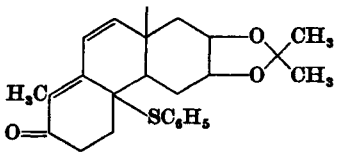
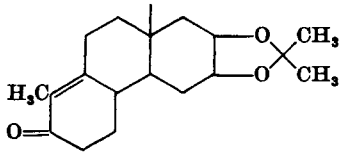
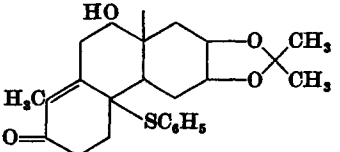
Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

§ Aqueous sodium hydroxide was used in this experiment.

|| Ethanol was used as the solvent.

TABLE II—Continued  
RANEY NICKEL DESULFURIZATION OF THIOETHERS

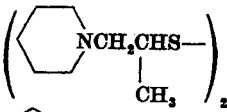
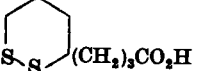
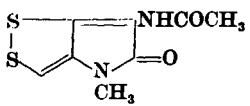
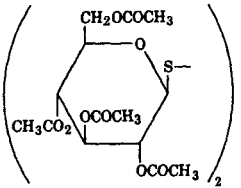
Thioether	Product*	Yield, %	References
2-Thioethyl-D-glucose dimethyl acetal (or tetrabenzoyl derivative)		82	88
3-Thiomethyl- $\beta$ -methylxylopyranoside		70–75	89
2-Acetamido-2-deoxy- $\alpha$ -D-glucopyranosylthioethane		—	351
2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosylthioethane		—	351
		—	28
		—	28
3-Benzyl thio enol ether of 4-androstene-3,17-dione	Androstan-17 $\beta$ -ol** and 3,5-androstadien-17-one	—	100
3-Benzyl thio enol ether of testosterone	(a) 3,5-Androstadien-17- $\beta$ -ol** (b) Androstan-17- $\beta$ -ol	87 —	100
3- $\beta$ -Hydroxyethyl thio enol ether of testosterone	3,5-Androstadien-17- $\beta$ -ol and androstan-17- $\beta$ -ol	—	100
3- $\beta$ -Hydroxyethyl thio enol ether of testosterone		83	100
3-Benzyl thio enol ether of 16-dehydropregesterone		70	101
3-Benzyl thio enol ether of progesterone		69	101
21-Thiomethylpregnane-3 $\alpha$ ,20 $\alpha$ -diol-11-one		—	352
21-Thiomethylpregnane-3 $\alpha$ ,20 $\beta$ -diacetoxo-17 $\alpha$ -hydroxy-11-one		—	352
3 $\beta$ -Acetoxy-20-ethyl thio enol ether of 5-pregnen-20-one		82	353
3 $\beta$ -Acetoxy-16-thiobenzyl-5-pregnen-20-one		90	101
3-Benzyl thio enol ether of deoxycorticosterone 21-acetate		78	101
3-Thioethyl-5-cholesten-7-one	7-Cholestanol	55	103
Benzyl thio enol ether of cholestenone	(a) 3,5-Cholestadiene** (b) Cholestane	88 —	100
3,3'-Thiodi-(5 $\alpha$ -cholestane)		—	354
22 $\beta$ -3-( $\beta$ -Hydroxyethylmercapto)spirosta-3,5,7-triene	22 $\beta$ -Spirosta-3,5,7-triene + 5,7-diene	— —	102 102
Benzyl thio enol ether of 4-isospirosten-3-one		78	101

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

\*\* Raney nickel deactivated with acetone was used.

TABLE III  
RANEY NICKEL DESULFURIZATION OF DISULFIDES

Disulfide	Product*	Yield, %	References
$(C_2H_5S)_2$		—	56
$(n-C_4H_9S)_2$		—	56
$(SCH_2CO_2H)_2$		—	1
$[SCH_2CH(NH_2)CO_2H]_2$		—	104
		25	355
		—	356, 357
$(C_6H_5S)_2$	(a) Benzene	—	299
	(b)† Biphenyl	78	11
	<i>p</i> -Terphenyl	Trace	
	(c)‡ $(C_6H_5)_2S$	87	11
	(d)§ Biphenyl	54, —	11, 113
	Benzene	18	
	<i>p</i> -Terphenyl	0.2	
$(m-CH_3C_6H_4S)_2$	(a)† $(m-CH_3C_6H_4)_2S$	75	11
$(p-CH_3OC_6H_4S)_2$	(b)   $(m-CH_3C_6H_4)_2$	58	
$(C_6H_5CH_2S)_2$	$(p-CH_3OC_6H_4)_2$ (degassed nickel)	—	78
$[SCH_2CH(NHCOC_6H_5)CO_2H]_2$		81	7
$(2-C_{10}H_7S)_2$ †	(2- $C_{10}H_7$ ) <sub>2</sub>	68–81	11
	Naphthalene	8–19	
$(C_6H_5S)_2 + (2-C_{10}H_7S)_2$ †	(2- $C_{10}H_7$ ) <sub>2</sub>	32	11
	2- $C_{10}H_7C_6H_5$	23	
	Biphenyl	9	
	Naphthalene	—	
	Benzene	—	
Bis-(2-anthraquinonylmethyl) disulfide	2-Methylantraquinone, 2-hydroxyanthraquinone, and anthraquinone-2-carboxylic acid	—	274
		70	358
Dibenzothiazole disulfide	(a) Benzothiazole	—	299
	(b)¶ $C_6H_5NHCH_3$ and $C_6H_5NH_2$		
		14	359

Note: References 265 to 490 are on pp. 525–529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed (200°) Raney nickel was used without solvent at 220°.

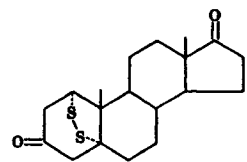
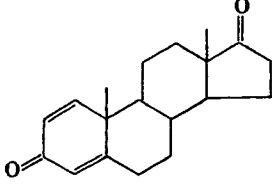
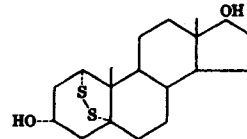
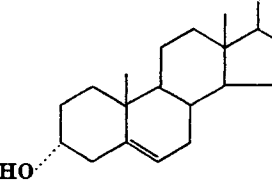
‡ Degassed (200°) Raney nickel was used with benzene at 140°.

§ Degassed (200°) Raney nickel was used with benzene at 180°.

|| Degassed (200°) Raney nickel was used with benzene at 220°.

¶ This experiment was run in basic solution.

TABLE III—*Continued*  
 RANEY NICKEL DESULFURIZATION OF DISULFIDES

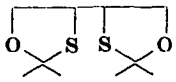
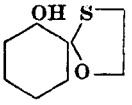
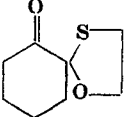
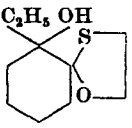
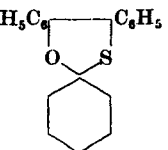
Disulfide	Product*	Yield, %	References
		—	360
		20	360

*Note:* References 265 to 490 are on pp. 525–259.

\* Products resulting from replacement of sulfur by hydrogen are not shown.



TABLE IV.  
RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioacetal	Product*	Yield, %	Reference
	HO(CH <sub>2</sub> ) <sub>4</sub> OH	—	361
	Cyclohexane-1,2-diol and 2-hydroxycyclohexanone†	—	44
	2-Ethoxycyclohexanone, 2-ethoxycyclohexanol, 2-hydroxycyclohexanone, and cyclohexane-1,2-dione†	—	44
	2-Ethyl-2-hydroxycyclohexanone†	—	44
	Cyclohexanone C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CHOHC <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> COC <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>5</sub> CH=CHC <sub>6</sub> H <sub>5</sub> †	70 42 — —	45

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

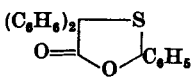
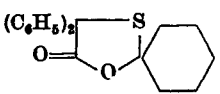
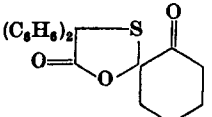
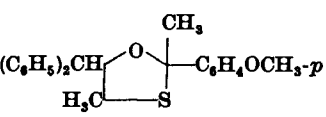
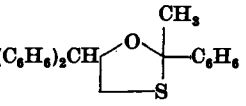
† Acetone was used as the solvent.

DESULFURIZATION WITH RANEY NICKEL

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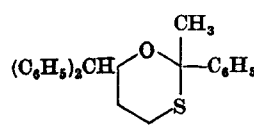
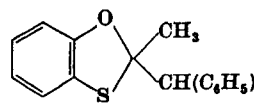
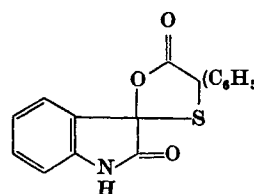
TABLE IV—Continued

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioacetal	Product*	Yield, %	Reference
	(a)† (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> H and (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (b)† (O <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> H and C <sub>6</sub> H <sub>5</sub> CHO	— —	272
	(a)† (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> and (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> OH (b)† (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> H and cyclohexanone (c)§ (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> OH and cyclohexanone	— — —	272
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> H and cyclohexanediol†	—	272
	(a)§ (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>3</sub> p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub> (b)† (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(CH <sub>3</sub> )OCH(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -p p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(OH)CH <sub>3</sub>	81 72 42 36 27	46
	(a)   C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(CH <sub>3</sub> )OCH(CH <sub>3</sub> )C <sub>6</sub> H <sub>5</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=CHCH <sub>3</sub> (b)§ (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=CHCH <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(OH)CH <sub>3</sub>	47-71 37-62 19-32 0-32 0-4 90-96 2-5	46

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ORGANIC REACTIONS

	<p>(a)    C<sub>6</sub>H<sub>5</sub>COCH<sub>3</sub> 72-81  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCHOHCH<sub>2</sub>CH<sub>3</sub> 56-59  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCH(C<sub>2</sub>H<sub>5</sub>)OCH(CH<sub>3</sub>)C<sub>6</sub>H<sub>5</sub> 13-20  (b) § C<sub>6</sub>H<sub>5</sub>COCH<sub>3</sub> 45-57  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> 19-57  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCH(C<sub>2</sub>H<sub>5</sub>)OCH(CH<sub>3</sub>)C<sub>6</sub>H<sub>5</sub> 27-36  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCHOHCH<sub>2</sub>CH<sub>3</sub> 4-23</p>	46
	<p>(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCH<sub>2</sub>CH<sub>3</sub> 90  (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCH=CH<sub>2</sub> 10  C<sub>6</sub>H<sub>5</sub>OH¶ Trace</p>	46
	<p>(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHCO<sub>2</sub>H and oxindol†</p>	— 272

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Acetone was used as the solvent.

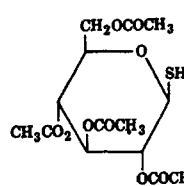
‡ Ethanol was used as the solvent.

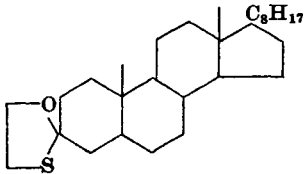
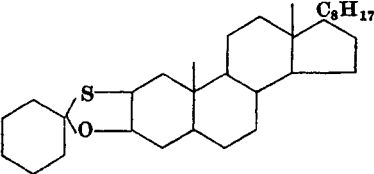
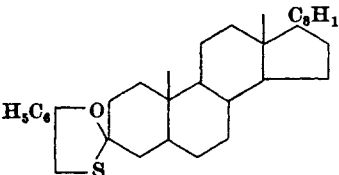
§ Benzene was used as the solvent.

|| Acetone or methyl ethyl ketone was used as the solvent.

¶ Benzene or acetone was used as the solvent.

TABLE IV—Continued  
RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioacetal	Product*	Yield, %	References
		—	359
	Phenyl-1-thio-β-D-xylopyranoside triacetate	71	362
	2'-Naphthyl-1-thio-β-D-ribofuranoside tribenzoate	73	105
	2'-Naphthyl-1-thio-α-D-arabinopyranoside triacetate	—	363
	Phenyl-1-thio-α-D-arabinopyranoside triacetate	—	363
	Ethyl thio-α-D-glucofuranoside	27	107
	2'-Naphthyl-1-thio-β-D-galactopyranoside tetraacetate	73	264
	Ethyl-1-thio-β-D-mannopyranoside tetraacetate	80	364
	2'-Naphthyl-1-thio-β-lactopyranoside	63	106
	Phenyl-1-thio-β-maltopyranoside heptaacetate	78	106
	Phenyl-1-thio-β-gentiobioside heptaacetate	72	264
	Phenyl-1-thio-β-cellobioside heptaacetate	69	264
	Ethyl thio-β-D-galactopyranoside tetraacetate	78	109
	Ethyl dihydrothiostreptobiosaminide pentaacetate	—	365
	3-Thioethyl-3α,9α-oxido-11-ketocholanic acid methyl ester	23	110

	(a)** Cholestan-3-one	64-87	46
	3 $\beta$ -Cholestanol	6-19	
	3 $\alpha$ -Ethoxycholestane	3-13	
	3 $\alpha$ -Cholestanol	2-12	
	(b)§ Cholestan-3-one	34-58	45
	3 $\alpha$ -Ethoxycholestane	10-31	
	3 $\alpha$ -Cholestanol	0-18	
	3 $\beta$ -Cholestanol	0-14	
	Cyclohexanone	64	45
	Cholestan-3-one	21	
	Cholestan-3 $\beta$ -ol	60	
	Cholestan-3-one	56	
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> OH	43		
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CHO†	—		

Note: References 265 to 490 are on pp. 525-529.

\*Products resulting from replacement of sulfur by hydrogen are not shown.

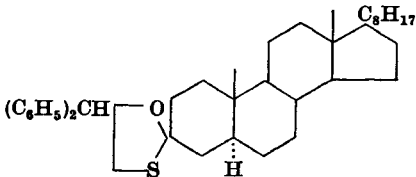
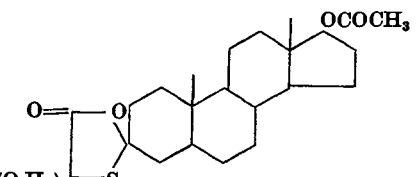
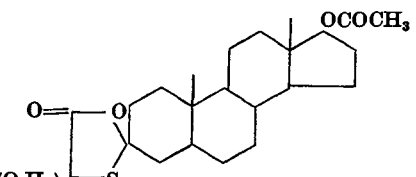
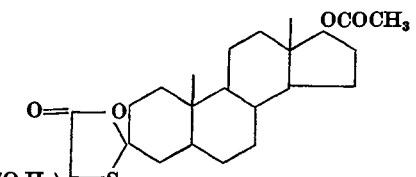
† Acetone was used as the solvent.

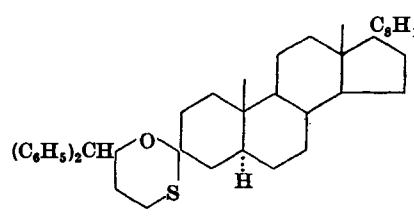
§ Benzene was used as the solvent.

\*\* This experiment was done in acetone solution at various pH values.

TABLE IV—Continued

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioacetal	Product*	Yield, %	References
	(a)†† Cholestan-3-one	78	45
	Cholestan-3 $\beta$ -ol	2	
	(+)-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>3</sub>	52	45
	(b)‡‡ Cholestan-3-one	80	
	(-)-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>3</sub>	57	46
	(c)§§ Cholestan-3-one	55-90	
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>3</sub>	64-89	46	
(d)¶¶ Cholestan-3-one	86		
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>3</sub>	80		
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=CHCH <sub>3</sub>	10	46
	(e)§ Cholestan-3-one	53-98	
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>3</sub>	69-98	
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=CHCH <sub>3</sub>	0-20	
	(f)¶¶¶ Cholestan-3-one	42	46
	C <sub>6</sub> H <sub>5</sub> CHCHOHCH <sub>3</sub>	56-75	
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> ,	—	272
	17 $\beta$ -acetoxy-5 $\alpha$ -androstane and 3 $\beta$ -hydroxy-17 $\beta$ -acetoxy-5 $\alpha$ -androstane		

	(a)§§ Cholestan-3-one	72	46
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>2</sub> CH <sub>3</sub>	67	
	(b)§ Cholestan-3-one	45-56	46
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH(C <sub>2</sub> H <sub>5</sub> )O	24-36	
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	21-30	
	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCHOHCH <sub>2</sub> CH <sub>3</sub>	17-29	

*Note:* References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

§ Benzene was used as the solvent.

†† This reaction was run with "isomer A" in methyl ethyl ketone.

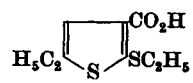
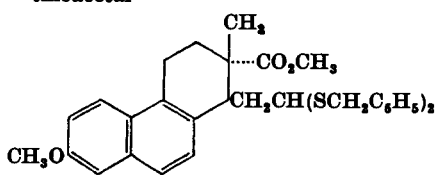
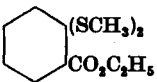
‡‡ This reaction was run with "isomer C" in methyl ethyl ketone.

§§ Methyl ethyl ketone solution was used.

||| Benzene-methyl ethyl ketone solution was used.

¶¶ Benzene-*n*-butanol solution was used.

TABLE V  
RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>A. Dithioacetals</i>			
$\text{CH}_2(\text{SC}_2\text{H}_5)_2$	$(\text{C}_2\text{H}_5)_2^b$	9	10
$n\text{-C}_3\text{H}_7\text{CH}(\text{SC}_2\text{H}_5)_2$		40	8
$\text{C}_6\text{H}_5\text{CH}(\text{SC}_2\text{H}_5)_2$		65	8
$\text{C}_6\text{H}_5\text{CH}(\text{SCH}_2\text{C}_6\text{H}_5)_2$	$\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5 + (\text{C}_6\text{H}_5\text{CH}_2)_2^b$	—	10
$\text{CH}_2[\text{CH}(\text{NHCO}_2\text{C}_6\text{H}_5)\text{CH}(\text{SC}_2\text{H}_5)_2]_2$		—	366
	$\text{CH}_3(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$	—	373
D-Xylose diethylthioacetal		—	367
D-Glucose diethylthioacetal pentaacetate		60	8
2-Methyl-D-glucose diethylthioacetal tetraacetate		92	368
D-Galactose diethylthioacetal pentaacetate		66	8
D-Altrose diethylthioacetal		97	369
6-Deoxy-L-glucose diethylthioacetal		—	370
L-Fucose diethylthioacetal		68	369
L-Rhamnose diethylthioacetal		85	369
D-Glucosamine diethylthioacetal pentaacetate		—	370
Methyl 3-carbamyl-4-methylnovobioside diethylthioacetal		—	372
		—	374
Strophanthidin-3-acetate ethylenedithioacetal		—	375
Methyl 12,13-oleanen-23-carboxylate 2-ethylenethioacetal		—	131
Methyl 2-acetoxy-28-formyl-12,13-oleanene-23-carboxylate ethylenedithioacetal		—	131
<i>B. Dithioketals</i>			
$n\text{-C}_5\text{H}_{11}\text{C}(\text{SC}_2\text{H}_5)_2\text{CH}_3$		50	8
$\text{CH}_3\text{C}(\text{SCH}_2)_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$		70	112
$[\text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_n\text{C}(\text{SC}_2\text{H}_5)_2\text{CH}_2]_2$ $n = 4$	(a) <sup>c</sup> $\text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_{13}\text{CO}_2\text{C}_2\text{H}_5$ (b) <sup>d</sup> $\text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_{12}\text{CO}_2\text{C}_2\text{H}_5$ $\text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_6\text{CO}_2\text{C}_2\text{H}_5$ (c)	Good 58 41 84	29 29 376
$n = 5$		53	376
$n = 8$		73	376
$[\text{CH}_2\text{O}_2\text{C}(\text{CH}_2)_n\text{C}(\text{SC}_2\text{H}_5)_2\text{CH}_2]_2$ $n = 9$ $n = 21$	(a) (b) <sup>e</sup> $\text{CH}_2\text{O}_2\text{C}(\text{CH}_2)_{46}\text{CO}_2\text{CH}_3$	— —	30 30
		75	112

Note: References 265 to 490 are on pp. 525-529.

- <sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.
- <sup>b</sup> Degassed Raney nickel was employed.
- <sup>c</sup> Ethanol was used as the solvent.
- <sup>d</sup> Raney nickel deactivated by treatment with acetone was used.
- <sup>e</sup> Hydrogenation over Adams catalyst was employed before isolation.

TABLE V—Continued  
 RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product*	Yield, %	References
<i>B. Dithioketals—Continued</i>			
		70	112
		64	377
	and	—	378
		81	379
		61	380
		—	380
		50-70	114
		—	380a
		83	31
		—	113

ORGANIC REACTIONS

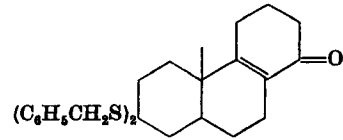
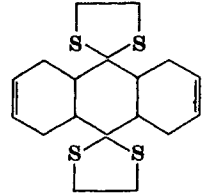
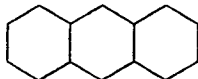
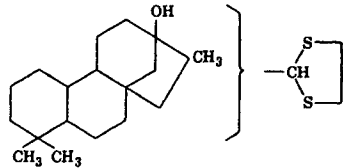
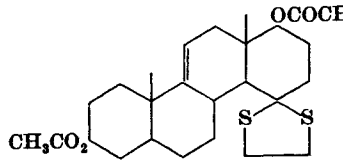
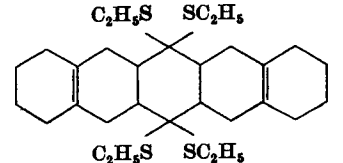
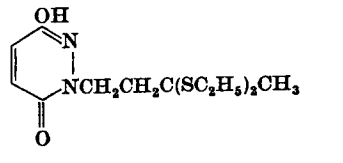
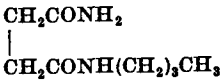
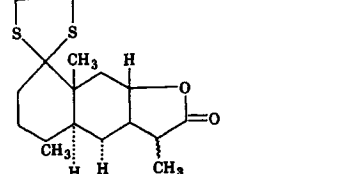
DESULFURIZATION WITH RANEY NICKEL

457

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

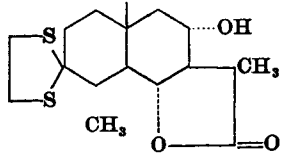
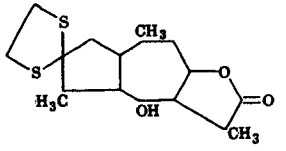
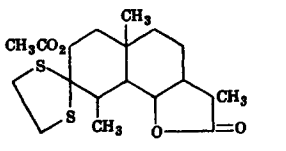
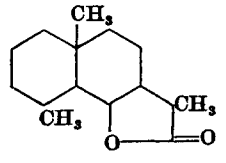
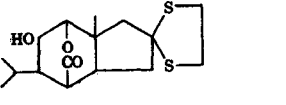
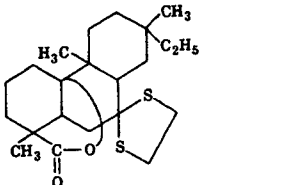
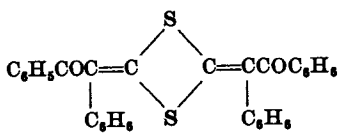
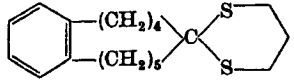
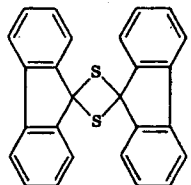
TABLE V—Continued  
RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
		—	381
		—	382
		—	383
		—	384
		55	118
		94	385
		—	386

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE V—Continued  
RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

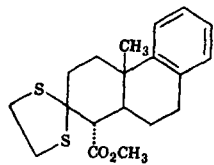
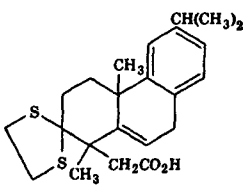
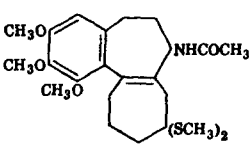
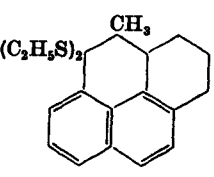
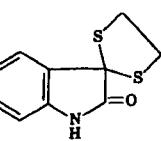
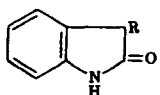
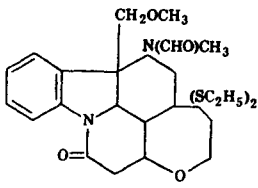
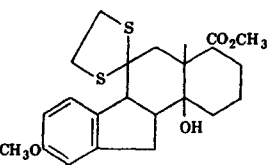
Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
		Good	387
		—	388
<b>Tetrahydroaldulin</b>		—	389
		—	390, 391
		—	392
		—	120
$C_6H_5C(SC_2H_5)_2CH_3$		66	8
$C_6H_5C(SCH_3)_2CH_2CO_2C_2H_5$		77	112
$C_6H_5C(SCH_3)_2CO_2C_2H_5$		79	112
$C_6H_5C(SC_2H_5)_2C_6H_5$		77	8
$C_6H_5C(CH_3)(S_2C_2H_4)$	$C_6H_5CCH_3=CCH_3C_6H_5$	30	10
	$C_6H_5COCH(C_6H_5)CH_3$ and $C_6H_5CHOHCH(C_6H_5)CH_3$	—	393
		—	394
		82	214

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.



TABLE V—Continued  
 RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
		—	395
		—	398
		—	396
		58–63	397
			
	R = CH <sub>3</sub> R = C <sub>2</sub> H <sub>5</sub> R = (CH <sub>3</sub> ) <sub>2</sub> CH	16' 83 <sup>c</sup> 32 <sup>f</sup>	22 22 22
		50	119
D-Fructose diethylthioacetal pentaacetate		20	8
		—	399

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

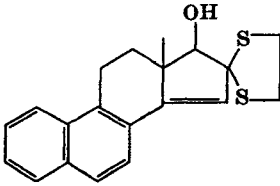
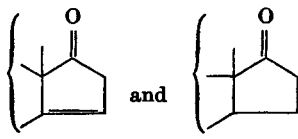
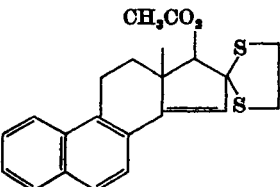
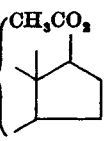
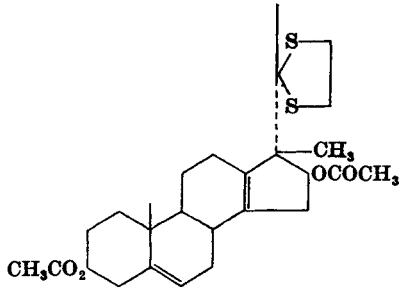
<sup>c</sup> Ethanol was used as the solvent.

<sup>f</sup> Methanol was used as the solvent.

<sup>g</sup> 2-Propanol was used as the solvent.

TABLE V—Continued

## RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
		—	32
		—	32
17α-Acetoxy-3-methoxyestradiol 16-ethylene-thioacetal		—	127
17β-Acetoxy-3-methoxyestradiol 16-trimethylene-thioacetal		—	400
Dihydrotestosterone acetate 3- <i>o</i> -hydroxyphenyl-thioacetal		67	401
3β-Acetoxy-17β-benzoyloxy-5-androstene 7-ethylenethioacetal	3β-Acetoxy-17β-benzoyloxy-7,7-d <sub>2</sub> -5-androstene <sup>b</sup>	50-60	126
3β,17β-Diacetoxy-5α-androstan-11-one 7-ethylene-thioacetal		—	402
3β,17β-Diacetoxy-5-androstene 16-ethylenethioacetal		21	128
3β-Acetoxy-5-androstene 17-dibenzylthioacetal		—	403
		—	407
3β-20β-Diacetoxy-5-pregnene 7-ethylenethioacetal		85	404
Ethyl 3β-benzoyloxy-pregnan-21-oate 16-ethylene-thioacetal		—	405
Pregnane-11-one 3,20-bisethylenethioacetal		45	406
20β-Acetoxy-5α-pregnane 7-ethylenethioacetal		72	404
3β,11α,20-Trihydroxy-5α-pregnane 7-ethylenethioacetal		—	129
3β,20β-Diacetoxy-5α-pregnan-11-one 7-ethylene-thioacetal		—	129
3β-Acetoxy-5α-pregnane 20-diethylthioacetal		52	406
5α-Pregnane 3,20-bisethylenethioacetal		40	406
Methyl cholanate 3-diethylthioacetal		70	252

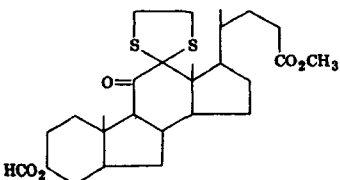
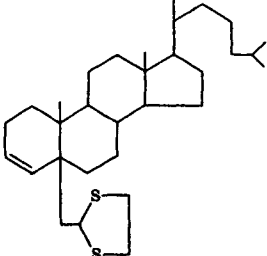
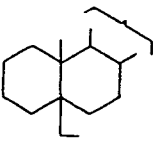
Note: References 265 to 490 are on pp. 525-529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

<sup>b</sup> Deuterized Raney nickel was employed.

TABLE V—Continued

## RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
Dehydrocholic acid 3-diphenylthioketal		72	77
Ethyl dehydrocholate 3-diethylthioketal		91	77
3 $\alpha$ ,6 $\alpha$ -Diacetoxycholanic acid 7-ethylenethioketal		—	408
Methyl 3 $\alpha$ ,7 $\alpha$ -diacetoxycholanate 12-ethylene-thioketal		90	414
Methyl 3 $\alpha$ -acetoxy-11-ketocholanate 7-ethylene-thioketal		—	409, 410, 411
Ethyl dehydrocholate trisethylenethioketal		—	77
Methyl 3 $\alpha$ -acetoxy-11-ketocholanate 12-tri-methylenethioketal		95	123
Methyl 3 $\alpha$ -hydroxy-11-ketocholanate 12-tri-methylenethioketal		Good	123
Methyl 3 $\alpha$ -carbethoxy-11-ketocholanate 12-tri-methylenethioketal		Good	123
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl methyl ketone ethylenethioketal		69	412
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl ethyl ketone ethylenethioketal		80	412
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl <i>n</i> -propyl ketone ethylenethioketal		98	413
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl isopropyl ketone ethylenethioketal		80	412
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl <i>n</i> -butyl ketone ethylenethioketal		91	413
3 $\beta$ -Acetoxy- $\Delta^5$ -ternorcholanyl <i>n</i> -butyl ketone ethylenethioketal		—	412
		95	263
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl isobutyl ketone ethylenethioketal		—	415
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl isoamyl ketone ethylenethioketal		—	415
3 $\beta$ -Acetoxy- $\Delta^5$ -norcholanyl benzyl ketone ethylenethioketal		88	413
Cholest-1-ene 3-ethylenethioketal	(a) <sup>i</sup> Cholest-1-ene	—	125
	(b) <sup>j</sup> Cholest-2-ene	Fair	124
3 $\beta$ -Acetoxycholestane 2-diethylthioketal	Cholestane	70	417
3 $\beta$ -Acetoxycholestane 2-ethylenethioketal	Cholestane	80	417
		—	418

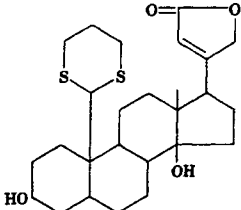
Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

<sup>i</sup> Dioxane was used as the solvent.

<sup>j</sup> Benzene-methyl ethyl ketone was used as solvent.

TABLE V—Continued  
RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
4 $\alpha$ ,5-Dihydroxycholestane 3-ethylenethioketal		—	419
4 $\beta$ ,5-Dihydroxycoprostane 3-ethylenethioketal		—	419
4-Cholestene 3-dibenzylthioketal		92	77
3 $\beta$ -Acetoxy-5-cholestene 7-ethylenethioketal	3 $\beta$ -Acetoxy-5 $\alpha$ -7,7-d <sub>2</sub> -5-cholestene <sup>b</sup>	50–60	126, 103
4-Cholestene 3,6-bisethylenethioketal		— <sup>k</sup>	121
Diethyl 3 $\beta$ -cholesterylmalonate 7-ethylene-thioketal		—	416
$\Delta^4$ -Cholesten-6-one 3-ethylenethioketal	(a) <sup>i</sup> Cholestan-6-one (b) <sup>d</sup> 4-Cholesten-6-one	—	121
Cholestan-3-one diethylthioketal		91	252
1-Benzylmercaptocholestane 3-dibenzylthioketal		—	125
3 $\beta$ -26-Diacetoxycholestan-22-one 16-ethylene-thioketal		—	419 <sup>a</sup>
Cholestan-6-one 3-ethylenethioketal		—	121
3 $\beta$ -Acetoxycholestan-11-one 7-ethylenethioketal		—	419 <sup>b</sup>
3 $\beta$ -Acetoxy-5 $\alpha$ -cholestan-11-one 7-ethylenethioketal		—	402
Cholestan-3,6-bisethylenethioketal		Fair	121
4,4-Dimethyl-5-cholesten-3-one 2-ethylenethioketal		Good <sup>d</sup>	420
3 $\beta$ -Acetoxy-22-ergosten-11-one 7-ethylenethioketal	3 $\beta$ -Acetoxyergostan-11-one	—	410
5 $\alpha$ -Furostane 26-ethylenethioketal		87	122
5 $\alpha$ -Furostane 3,26-bisethylenethioketal		69–76	122
3 $\beta$ -Acetoxy-5 $\alpha$ -furostane 26-ethylenethioketal		75	122
3 $\beta$ -Acetoxy-5 $\beta$ -furostane 26-ethylenethioketal		75	122
3 $\beta$ -Acetoxy-5-furostane 26-ethylenethioketal		60	122
3 $\beta$ -Acetoxy-5 $\alpha$ -furostane 12,26-bisethyl- enethioketal	(a) <sup>i</sup> 5-Furostan-3 $\beta$ -ol acetate (b) <sup>m</sup> 5 $\alpha$ -Furostan-3 $\beta$ -ol acetate 12-ethylene- thioketal	74 60	122
3 $\beta$ -Acetoxy-5 $\alpha$ -furostane 26-trimethylenethioketal		67	122
3 $\beta$ -Acetoxy-5 $\alpha$ -furostane 12,26-bistrimethylene- thioketal		67	122
$\Delta^4$ -Diosgenone ethylenethioketal		—	422
Tigogenone ethylenethioketal		—	423
3 $\beta$ -Acetoxy-9 $\alpha$ ,11 $\alpha$ -oxido-5 $\alpha$ ,22 $\beta$ -spirostane 7-ethyl- enethioketal		60	424
3 $\beta$ -Acetoxy-5 $\alpha$ ,22 $\beta$ -spirostan-11-one 7-ethylene- thioketal		—	129
5 $\alpha$ -Spirostan-3 $\beta$ -ol-11-one 12-ethylenethioketal		38	207
9(11)-Dehydrohecogenin acetate 12-ethylene- thioketal		88	337
5 $\alpha$ -Spirostan-2 $\alpha$ ,3 $\beta$ -dicathylate 15-ethylene- thioketal		—	425
5 $\alpha$ -Spirostan-3 $\beta$ -ol-11-one 12-ethylenethioketal		—	426
		—	421

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

<sup>b</sup> Raney nickel deactivated by treatment with acetone was used.

<sup>k</sup> Deuterized Raney nickel was employed.

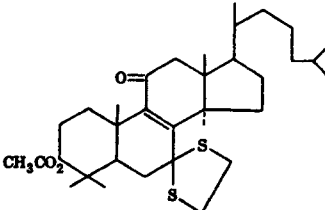
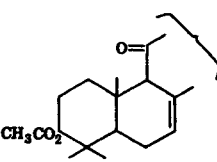
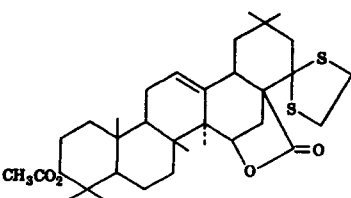
<sup>i</sup> Dioxane was used as the solvent.

<sup>k</sup> The product was a mixture of 4- and 5-cholestene.

<sup>l</sup> W-4 Raney nickel was used in this experiment.

<sup>m</sup> W-2 Raney nickel was used in this experiment.


TABLE V—Continued  
 RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product <sup>a</sup>	Yield, %	References
<i>B. Dithioketals—Continued</i>			
3- <i>o</i> -Acetylstrophanthidin trimethylenethioketal		—	427
Methyl 3 $\beta$ -acetoxy-11-keto-4,4,14 $\alpha$ -trimethyl cholanate 7-ethylenethioketal		—	429
		—	130
3 $\beta$ -Acetoxylanostan-11-one 7-ethylenethioketal		—	428
3 $\beta$ ,11-Diacetoxylanostane 7-ethylenethioketal		—	130
Methyl 12(13)-oleanene-23-carboxylate 2-ethylene-thioketal		—	131
		Good	132

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE VI  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
$\text{NH}_2\text{CSNH}_2$	(a) $\text{CH}_3\text{NH}_2$	—	1
	(b) $\text{NH}_2\text{CH}=\text{NH}$	—	134
$\text{CH}_3(\text{CH}_2)_{12}\text{CSNH}_2$	$(n\text{-C}_{14}\text{H}_{29})_2\text{NH}$	40	27
		04	26
$\text{C}_6\text{H}_5\text{CSNH}_2$	$\text{C}_6\text{H}_5\text{CHO}$	32, 77	430, 133
$p\text{-CH}_3\text{C}_6\text{H}_4\text{CSNH}_2$	$p\text{-CH}_3\text{C}_6\text{H}_4\text{CHO}$	42	430
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNH}_2$	$(\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2)_2\text{NH}$	45	27
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CSNHC}_6\text{H}_5$	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHO}$	96	133
$\text{C}_6\text{H}_5\text{CH}_2\text{NHCSNH}_2$	$\text{CH}_3\text{NH}_2 + \text{C}_6\text{H}_5\text{CH}_3$	—	1
$o\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$	$o\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	82	43
$\text{C}_6\text{H}_5\text{CH}=\text{NNHCSNH}_2$	$\text{C}_6\text{H}_5\text{CH}=\text{NN}=\text{CHNH}_2$	—	135
$\text{C}_6\text{H}_5\text{CSN}(\text{CH}_3)_2$		25	27
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{NNHCSNH}_2$	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{NN}=\text{CHNH}_2$	68	135
$n\text{-C}_3\text{H}_7\text{CSNHC}_6\text{H}_5$	$n\text{-C}_3\text{H}_7\text{CHO}$	32	133
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNHCH}_2\text{CH}_2\text{OH}$		15	27
$(\text{CH}_3)_2\text{CHCH}_2\text{CSNHC}_6\text{H}_5$	$(\text{CH}_3)_2\text{CHCH}_2\text{CHO}$	32	133
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNHC}_6\text{H}_5\text{-}n$		49	27
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$		55	27









Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

DESULFURIZATION WITH RANEY NICKEL



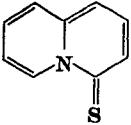
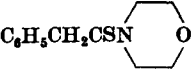




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TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
$p\text{-HOC}_6\text{H}_4\text{CSNHC}_6\text{H}_5$	$p\text{-HOC}_6\text{H}_4\text{CHO}$	78	133
$\text{C}_6\text{H}_5\text{CSNHC}_6\text{H}_5$		59, 86	27
$(\text{C}_6\text{H}_5\text{NH})_2\text{CS}$	$\text{C}_6\text{H}_5\text{N}=\text{CHNHC}_6\text{H}_5$	—	61
$(\text{C}_6\text{H}_5)_2\text{CHCSNH}_2$		10	27
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNH}$ 	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$ or $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}$ 	—	38
$\text{C}_6\text{H}_5\text{CH}_2\text{CSNH}(\text{CH}_2)_2\text{C}_6\text{H}_5$		34	27
$\text{C}_6\text{H}_5\text{CH}_2\text{CSN}$ 	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{N}$  or	63	27
	$\text{H}_5\text{C}_2\text{N}$ 	44	
$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{CH}_2\text{CSN}$ 		73	27
$2\text{-C}_{10}\text{H}_7\text{CH}_2\text{CSN}$ 		56	27
		41	431

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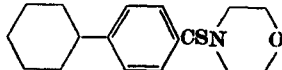

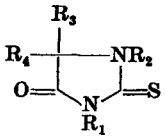
ORGANIC REACTIONS

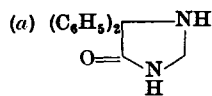
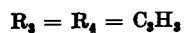
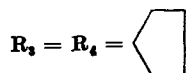
	38	27	
	40	27	
	—	432	
	$C_6H_5CH_2CH_3$ or $C_6H_5CH_2CH_2N$ 	—	38
$m\text{-}CH_3OC_6H_4CH_2CSN$ 	69	27	
$p\text{-}CH_3OC_6H_4(CH_2)_2CSN$ 	65	27	
$2\text{-}C_{10}H_7CH_2CSN$ 	68	27	

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

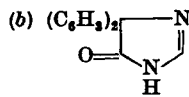
Thioamide	Product*	Yield, %	References
		57	27
$p\text{-}C_6H_5C_6H_4CH_2CSN$ 		63	27
$(\text{O} \text{---} \text{NCSCH}_2\text{C}_6\text{H}_4\text{---})_2$		72	27
2,4-Dimethyl-5-carbethoxy-3-morpholinoethylpyrrole		72	433
			
$R_3 = CH_3$	(a) $CH_3CH(NHCHO)_2$ (b) Oil	—	137 141
$R_2 = COCH_3$		—	435
$R_3 = C_6H_5$	Oil	—	141
$R_2 = COC_6H_5$		—	435
$R_3 = R_4 = CH_3$	$(CH_3)_2CH(NHCHO)CONH_2$ (?)	—	141
$R_2 = COCH_3, R_3 = CH_3$		—	435
$R_3 = CH_3, R_4 = C_6H_5$		21	136
$R_3 = C_2H_5, R_2 = C_6H_5$		46	136
$R_2 = COCH_3, R_3 = CH_2C_6H_5$		—	435



64, 85

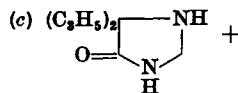
136

136, 137



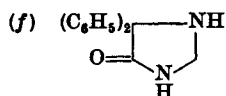
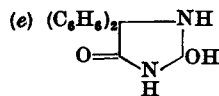
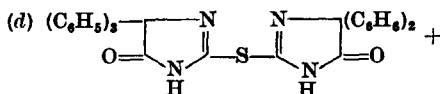
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434



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141



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DESULFURIZATION WITH RANEY NICKEL

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Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

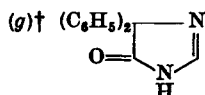
Thioamide  
 $R_3 = R_4 = C_6H_5$  (continued)

Product\*

Yield, %

References

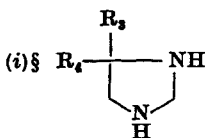
476



75

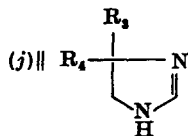
(h)‡ Mixture of (f) and (g)

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140



$R_3 = R_4 = p\text{-CH}_3\text{OC}_6\text{H}_4$   
 $R_3 = R_4 = \text{CH}_3, R_4 = C_6H_5$

22

136

10

136

$R_2 = \text{CH}_3, R_3 = R_4 = \text{Cyclopentyl}$

—

136

$R_3 = \text{CH}_3, R_3 = R_4 = C_6H_5$   
 $R_1 = R_2 = R_3 = \text{CH}_3, R_4 = C_6H_5$

$\text{CH}_3\text{CH}(C_6H_5)\text{CONHCH}_3$

—, 41

136

—

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ORGANIC REACTIONS



$R_3 = R_4 = \text{CH}_3$	39	136
$R_3 = R_4 = \square$	26	136
$R_3 = R_4 = \text{pentagon}$	40	136
$R_3 = R_4 = \text{cyclopentane with } \text{CH}_3 \text{ at } 1\text{-position}$	43	136
$R_1 = \text{CH}_3, R_3 = R_4 = \text{pentagon}$	17	136
$R_3 = \text{CH}_3, R_3 = R_4 = \text{pentagon}$	55	136
$R_1 = R_3 = \text{CH}_3, R_3 = R_4 = \text{pentagon}$	7	136
$R_1 = R_2 = \text{CH}_3, R_3 = R_4 = \text{C}_3\text{H}_5$	38	136
$R_5 = \text{C}_2\text{H}_5$ ¶		

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Ethanol containing sodium ethoxide was used as the solvent.

‡ Ammoniacal ethanol was used as the solvent.

§ The ratio by weight of compound to Raney nickel was 1:5.

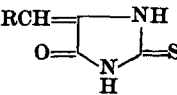
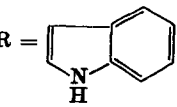
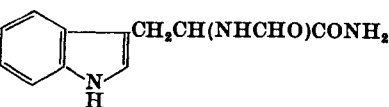
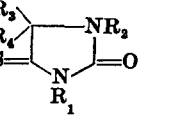
¶ The ratio by weight of compound to Raney nickel was 1:2.

¶ With methanol, propanol, or cyclohexane in place of ethanol as solvent the normal desulfurization product ( $R_5 = \text{H}$ ) was obtained in 48% yield.

DESULFURIZATION WITH RANEY NICKEL


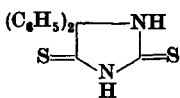
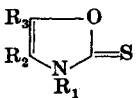
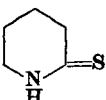
477

TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
$\text{RCH}=\text{N}(\text{H})\text{C}(=\text{S})\text{N}(\text{H})\text{C}(=\text{O})\text{R}$ 	$\text{RCH}_2\text{CH}(\text{NHCHO})\text{CONH}_2$		
$\text{R} = \text{CH}(\text{CH}_3)_2$		—	137
$\text{R} = \text{CH}_2\text{CO}_2\text{CH}(\text{CH}_3)_2$		—	137
$\text{R} = \text{C}_6\text{H}_5$		—	137
$\text{R} = p\text{-HOC}_6\text{H}_4$		—	137
$\text{R} = p\text{-CH}_3\text{OC}_6\text{H}_4$		—	137
$\text{R} = 3,4\text{-CH}_2\text{O}_2\text{C}_6\text{H}_3$		—	137
$\text{R} = p\text{-ClC}_6\text{H}_4$		—	137
$\text{R} = \text{indol-3-yl}$ 	$\text{indol-3-yl-CH}_2\text{CH}(\text{NHCHO})\text{CONH}_2$ 	—	137
$\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4$ 			
$\text{R}_1 = \text{R}_3 = \text{CH}_3, \text{R}_4 = \text{C}_6\text{H}_5$		44	136

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ORGANIC REACTIONS

$R_1 = \text{CH}_3, R_3 = R_4 = $ 	46	136
$R_1 = \text{CH}_3, R_3 = R_4 = \text{C}_6\text{H}_5$	56	136
$R_1 = R_2 = \text{CH}_3, R_3 = R_4 = \text{C}_6\text{H}_5$	43	136
	—**	439
	$\longrightarrow$	$\begin{matrix} \text{R}_2\text{CHCOR}_3 \\   \\ \text{R}_1\text{NCHO} \end{matrix}$
$R_1 = \text{CH}_3, R_2 = R_3 = \text{C}_6\text{H}_5$	74	437
$R_1 \dots R_3 = \text{C}_6\text{H}_5$	86	437
$R_1 = 2\text{-C}_{10}\text{H}_7, R_2 = R_3 = \text{C}_6\text{H}_5$	58	437
$R_2 = R_3 = n\text{-C}_3\text{H}_7$	49	437
	13	438

Note: References 265 to 490 are on pp. 525-529.

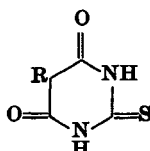
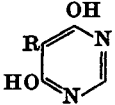
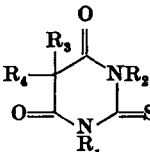
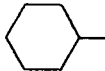
\* Products resulting from replacement of sulfur by hydrogen are not shown.

\*\* Desulfurization was not observed.

DESULFURIZATION WITH RANEY NICKEL

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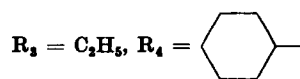
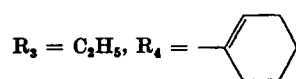
TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
			
$R = \text{C}_3\text{H}_6$		37	141
$R = \text{C}_6\text{H}_{11}\text{-}i$		58	141
$R = \text{C}_6\text{H}_5$		—	138, 141††
$R = \text{CH}_2\text{C}_6\text{H}_5$		69	141
			
$R_1 \dots R_4 = \text{H}$		—	436
$R_1 = R_2 = \text{C}_6\text{H}_5$		—	436
$R_3 = R_4 = \text{C}_2\text{H}_5$		70	141
$R_3 = \text{C}_2\text{H}_5, R_4 = \text{C}_5\text{H}_{11}\text{-}i$		71	141
$R_2 = \text{C}_6\text{H}_5, R_3 = \text{C}_2\text{H}_5, R_4 = \text{C}_6\text{H}_5$		—	138
$R_3 = \text{C}_2\text{H}_5, R_4 = $ 		—	138

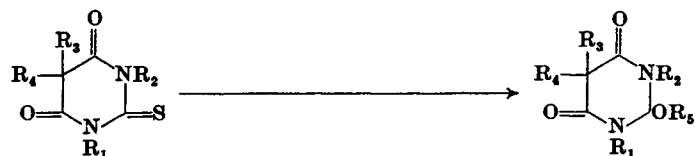
480

ORGANIC REACTIONS

$R_1 = R_3 = C_2H_5, R_4 = C_6H_5$	—	138
$R_1 = R_2 = CH_3, R_3 = C_2H_5, R_4 = C_6H_5$	—	138
$R_2 = CH_3, R_3 = C_2H_5, R_4 = C_6H_5$	—	138
$R_1 = R_2 = CH_3, R_3 = C_6H_5$	—	138



$R_3 = C_2H_5, R_4 = C_2H_5$	—	138
$R_3 = C_2H_5, R_4 = o\text{-ClC}_6\text{H}_4$	—	138
$R_3 = C_2H_5, R_4 = m\text{-ClC}_6\text{H}_4$	—	138
$R_3 = C_2H_5, R_4 = p\text{-ClC}_6\text{H}_4$	—	138
$R_3 = C_2H_5, R_4 = C_6H_5$	—	138
$R_3 = C_2H_5, R_4 = C_6H_5$	—	138
$R_3 = C_2H_5, R_4 = C_6H_5$	—	138



$R_3 = R_4 = C_6H_5$	(a) $R_5 = CH_3$	4††	141
	(b) $R_5 = C_2H_5$	48††	141
$R_3 = R_4 = C_2H_5$	(a) $R_5 = n\text{-C}_3\text{H}_7$	41§§	141
	(b) $R_5 = n\text{-C}_4\text{H}_9$	30††	141
$R_3 = C_2H_5, R_4 = C_2H_5$	(a) $R_5 = CH_3$	—§§	138
	(b) $R_5 = C_2H_5$	—§§	138
$R_3 = CH_3, R_4 = C_2H_5, R_5 = C_6H_5$	$R_5 = CH_3$	—§§	138
$R_1 = R_2 = CH_3, R_3 = C_2H_5, R_4 = C_6H_5$	$R_5 = CH_3$	—§§	138

Note: References 265 to 490 are on pp. 525-529.

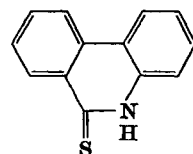
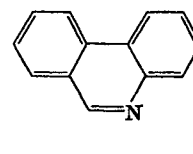
\* Products resulting from replacement of sulfur by hydrogen are not shown.

†† No definite product was isolated.

‡‡ This experiment was run with the alcohol  $R_5OH$  as solvent and a 30-minute reflux period. An extended reaction time afforded the expected product of desulfurization. 481

§§ This experiment was run with the alcohol  $R_5OH$  as solvent and a 4-hour reflux period.

TABLE VI—Continued  
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

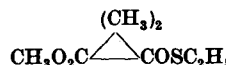
Thioamide	Product*	Yield, %	References
		72,     95	162, 440

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

||| Raney cobalt and ethanol-dimethylformamide were used.

TABLE VII  
RANEY NICKEL DESULFURIZATION OF THIOL ESTERS  
A. Formation of Aldehydes, Hydrocarbons, and Sulfides\*

Thiol Ester	Product			References
	Aldehyde (%)	Hydrocarbon (%)	Sulfide (%)	
CH <sub>3</sub> COSC <sub>2</sub> H <sub>5</sub>	73			441
CH <sub>3</sub> COSC <sub>6</sub> H <sub>5</sub>		(a) Biphenyl (29)† (b) Biphenyl (47) and toluene (10)‡		15 11
CH <sub>3</sub> CH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub>	80			441
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> COR§	—			442
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COR§	—			442
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> COR§	—			442
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COSC <sub>2</sub> H <sub>5</sub>	—, 92			442, 441
(CH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	48			441
CH <sub>2</sub> (CH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	70			441
(CH <sub>2</sub> CH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	77			441
(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	66			441
(CH <sub>2</sub> COSC <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	34			148
	—			149

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Raney nickel degassed at 200° was used.

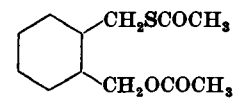
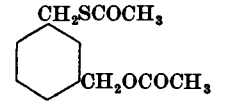
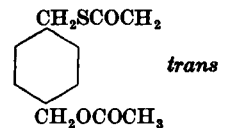
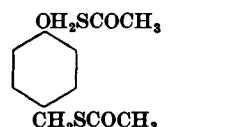
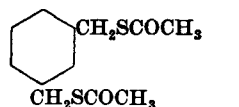
‡ This reaction was run in benzene solution at 220° with Raney nickel degassed at 500°.

§ R = SC<sub>2</sub>H<sub>5</sub> or SCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>.

DESULFURIZATION WITH RANEY NICKEL

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TABLE VII—Continued  
RANEY NICKEL DESULFURIZATION OF THIOL ESTERS  
A. Formation of Aldehydes, Hydrocarbons, and Sulfides\*—Continued

Thiol Ester	Product			References
	Aldehyde (%)	Hydrocarbon (%)	Sulfide (%)	
		<i>cis</i> (50) <i>trans</i> (40)		144
		<i>cis</i> (76) <i>trans</i> (48)		144
		60		144
		<i>cis</i> (17) <i>trans</i> (20)		144
		<i>cis</i> (23) <i>trans</i> (11)		144

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ORGANIC REACTIONS

$C_6H_5COSC_2H_5$	(a) 51, 60, 62		441, 150a, 146
$C_6H_5COSC_6H_5$		(b) Biphenyl (28)† (a) Biphenyl (46)	15
$C_6H_5COSCH_2C_6H_5$		(c) Biphenyl (37-56) $(C_6H_5CH_2)_2$ (8)	(b) $(C_6H_5)_2S$ (71, 36)† 15, 11 $(C_6H_5)_2S$ (74)¶ 11 $C_6H_5SCH_2C_6H_5$ (45) 15 and $(C_6H_5)_2S$ (—)†
$C_6H_5CH_2COSC_2H_5$	79		441
$C_6H_5CH=CHCOSC_2H_5$	$C_6H_5CH_2CH_2CHO$ (45)		441
$C_6H_5CH_2CH_2COSC_2H_5$	84		441
$CH_3C(C_6H_5)_2CH_2CH_2SCOCH_3$	92		313
<i>dl</i> - $(C_6H_5)_2CHCH(OCOC_6H_5)CH_2SCOC_6H_5$	—		273
<i>(-)</i> - $(C_6H_5)_2CHCH(OCOC_6H_5)CH_2SCOC_6H_5$	—		273
1- $C_{10}H_7CH_2COSC_2H_5$	66		441
1- $C_{10}H_7SCOC_6H_5$			15
		$(C_6H_5)_2S$ (23), 1- $C_{10}H_7SC_6H_5$ (53), and 1- $C_{10}H_7)_2S$ (20)†	
2- $C_{10}H_7SCOC_6H_5$		(a) $(C_6H_5)_2S$ (20), 2- $C_{10}H_7SC_6H_5$ (42), and 2- $C_{10}H_7)_2S$ (39)†	15
		(b) 2- $C_{10}H_7)_2$ (50), 2- $C_{10}H_7C_6H_5$ (18), $C_{10}H_8$ and $(C_6H_5)_2$ (—)**	11

DESULFURIZATION WITH RANEY NICKEL

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

† Raney nickel degassed at 200° was used.

‡ Raney nickel degassed at 100° was used.

¶ This reaction was run in xylene at 180° or 200° with Raney nickel degassed at 500°.

\*\* Raney nickel degassed at 200° was used without solvent at 200°.

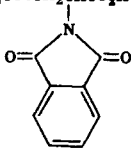
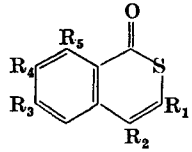

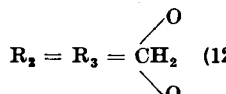
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TABLE VII—Continued

RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

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A. Formation of Aldehydes, Hydrocarbons, and Sulfides\*—Continued

Thiol Ester	Product			References
	Aldehyde (%)	Hydrocarbon (%)	Sulfide (%)	
$C_6H_5COSCH_2CHCO_2H$ 		40		143
				
$R_1 \dots R_5 = H$ $R_1 = CO_2H$ $R_1 = CO_2H, R_2 = CH_3$ $R_1 = CO_2H, R_4 = R_5 = CH_3O$ $R_1 = CO_2H, R_3 = R_4 = CH_3O$		$R_1 \dots R_4 = H$ $R_1 = R_4 = H$ $R_1 = CH_3$ $R_3 = R_4 = CH_3O$ $R_2 = R_3 = CH_3O$		151 151 151 443
$R_1 = CO_2H, R_3 = R_4 =$ 		$R_2 = R_3 =$  (12)		443

ORGANIC REACTIONS

$\begin{array}{c} \text{COSC}_2\text{H}_5 \\   \\ \text{HCOCOCH}_3 \\   \\ \text{HCOCOCH}_3 \\   \\ \text{HCOCOCH}_3 \\   \\ \text{CH}_2\text{OCOCH}_3 \end{array}$	22	146
Ethyl 3 $\beta$ -acetoxybisor-5-thiocholenate	50-55 $\dagger\dagger$	444
Ethyl 3 $\alpha$ -acetoxythiocholanate	39	154
Ethyl 3 $\alpha$ -formoxythiocholanate	78	154
Ethyl 3 $\beta$ -acetoxy-5-thiocholenate	50-55 $\dagger\dagger$	444
Ethyl 3 $\alpha$ -acetoxy-11-thiocholenate	53	154
Ethyl 12 $\alpha$ -acetoxythiocholanate	64	154
Ethyl 3 $\alpha$ ,12 $\alpha$ -diacetoxynorthiocholanate	69	154
Ethyl (or benzyl) 3 $\alpha$ ,12 $\alpha$ -diformoxythiocholanate	60-80 $\dagger\dagger$	147

DESULFURIZATION WITH RANEY METAL

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 B. Preparation of Alcohols $\dagger\dagger$ 

Thiol Ester	Product*	Yield, %	References
$n\text{-C}_8\text{H}_{17}\text{COSC}_2\text{H}_5$		—	152
$n\text{-C}_{15}\text{H}_{31}\text{COSC}_2\text{H}_5$		80-98	153
$\text{CH}_3\text{O}_2\text{C}(\text{CH}_2)_4\text{COSC}_2\text{H}_5$		—	153
$\text{CH}_3\text{O}_2\text{C}(\text{CH}_2)_9\text{COSC}_2\text{H}_5$		—	445

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

$\dagger\dagger$  Nickel that had not been deactivated gave the alcohol rather than the aldehyde.

$\ddagger\dagger$  The yield is based on the formation of alcohol unless otherwise noted.

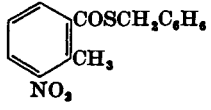
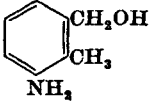
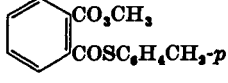
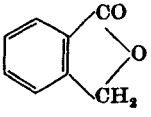
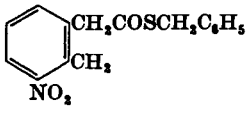
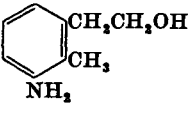
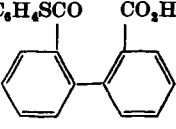
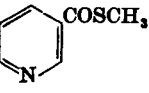
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TABLE VII—Continued  
RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

 B. Preparation of Alcohols $\dagger\dagger$ —Continued

Thiol Ester	Product	Yield, %	References
$\text{C}_6\text{H}_5\text{COSC}_2\text{H}_5$ (or free acid)		63-66	153
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{COSC}_2\text{H}_5$		—	153
$\text{CH}_2\text{CH}(\text{NHCO}_2\text{CH}_2\text{C}_6\text{H}_5)\text{COSC}_2\text{H}_5$		—	153
$p\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CHO} + \text{C}_6\text{H}_5\text{CH}_2\text{OH}$	10, 23	150a
$\text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_4\text{COSC}_2\text{H}_5$		—	152
$\text{C}_6\text{H}_5\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{H}$	$\gamma$ -Butyrolactone	10	449
	$\text{CH}_2\text{CHO}$	9	
	$\text{CH}_2\text{CO}_2\text{H}$		
$\text{C}_6\text{H}_5\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$		52	449
$o\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{H}$		—	449
$o\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$		73	449
$p\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{H}$		27	449
$p\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$		74	449
$o\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{OH}$		—	449
$o\text{-C}_6\text{H}_4\text{CH}_2\text{SCOC}_6\text{H}_4\text{OCH}_3$		51	449
$\text{C}_6\text{H}_5\text{CH}_2\text{CHCO}_2\text{R}$ (R = $\text{CH}_3$ or $\text{C}_2\text{H}_5$ )		—	450
$\text{CH}_2\text{COSC}_2\text{H}_5$			
$\text{C}_6\text{H}_5\text{CH}_2\text{CHCO}_2\text{CH}_3$		—	450
$\text{CH}_2\text{COSC}_2\text{H}_5$			

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		—	47
		—	150a
		—	47
3,4,5-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> COSC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -p	1,2,3-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	20-30	52
(CH <sub>3</sub> ) <sub>4</sub> (COSC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	3,4,5-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CH <sub>2</sub> OH	40	52
C <sub>6</sub> H <sub>5</sub> COSC <sub>6</sub> H <sub>4</sub>		—	152
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SCO		—	152
		—	150a
2-C <sub>10</sub> H <sub>7</sub> (CH <sub>2</sub> ) <sub>3</sub> COSC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>		—	446
		52, 82	153, 447

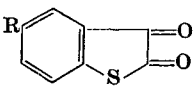
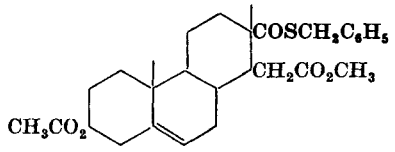
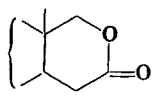
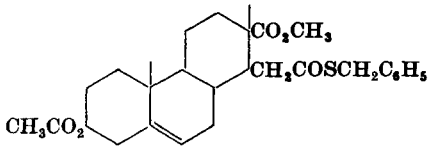
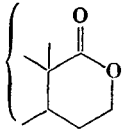
Note: References 265 to 490 are on pp. 525-529.

‡‡ The yield is based on the formation of alcohol unless otherwise noted.

DESULFURIZATION WITH RANEY NICKEL

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TABLE VII—Continued  
RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

Thiol Ester	Product	Yield, %	References
B. Preparation of Alcohols‡‡			
			
R = H	C <sub>6</sub> H <sub>5</sub> CHOHCO <sub>2</sub> H	54	269
R = CH <sub>3</sub>	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH(OH)CO <sub>2</sub> H	70	269
Methyl 7-methylbisdehydrothioisynolate		—	448
		76-87	155, 156
		39	155, 156
Methyl 3β-acetoxy-5α-thioetiocholanate		93	153
Methyl 3β-acetoxy-5β-thioetiocholanate		—	153
Benzyl 12,13-oleanen-30-thiolate		90	157
Methyl 2-acetoxy-12,13-oleanen-28-thiolate		87	451
Methyl 2-acetoxy-10,11-ursen-12-one-28-thiolate		—	452
Methyl 2,29-diacetoxythioechinocystate		—	453

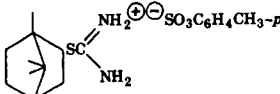
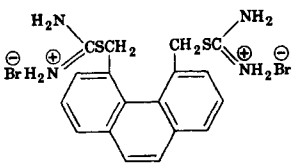
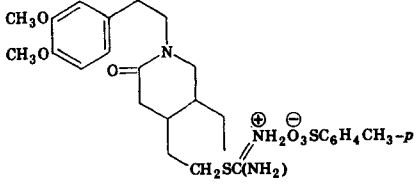
Note: References 265 to 490 are on pp. 525-529.

‡‡ The yield is based on the formation of alcohol unless otherwise noted.

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TABLE VIII  
RANEY NICKEL DESULFURIZATION OF ISOTHIURONIUM SALTS

Isothiuronium Salt	Product*	Yield, %	Reference
$\text{CH}_3\text{CH}[\text{N}(\text{CH}_3)_2]\text{CH}_2\text{SC}(\text{NH}_2)_2^{\oplus} \text{Cl}^{\ominus}$		—	326
		84	159
		76	158
		—	453a

Note: References 265 to 490 are on pp. 525-529.

\* In each example reported, desulfurization involved only replacement of sulfur by hydrogen.

DESULFURIZATION WITH RANEY NICKEL

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TABLE VIII—Continued  
RANEY NICKEL DESULFURIZATION OF ISOTHIURONIUM SALTS

Isothiuronium Salt	Product*	Yield, %	Reference
S-(Tetraacetyl- $\beta$ -D-glucopyranosyl) isothiuronium bromide		—	454
D-Glucose 6-isothiuronium iodide 1,2,3,4-tetraacetate		55	455
3 $\beta$ ,5 $\alpha$ -Dihydroxycholestane 6-isothiuronium <i>p</i> -toluenesulfonate		88-95	456

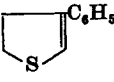
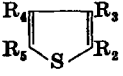
Note: References 265 to 490 are on pp. 525-529.

\* In each example reported, desulfurization involved only replacement of sulfur by hydrogen.

ORGANIC REACTIONS



TABLE IX  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
	CH <sub>3</sub> CH(C <sub>6</sub> H <sub>5</sub> )CH <sub>2</sub> CH <sub>3</sub>	65	186
			
R <sub>2</sub> . . . R <sub>5</sub> = H	(a) <sup>b</sup> CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H and HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	Poor	160, 56
R <sub>2</sub> = CO <sub>2</sub> H	(b) CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	70, —	457, 269
	(c) CHD <sub>2</sub> (CHD) <sub>2</sub> CD <sub>2</sub> CO <sub>2</sub> H	— <sup>f</sup>	188
	(d) CHT <sub>2</sub> (CHT) <sub>2</sub> CT <sub>2</sub> CO <sub>2</sub> H	— <sup>g</sup>	165
R <sub>2</sub> = COCH <sub>3</sub>	(a) CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COCH <sub>3</sub>	77	43, 14
	CH <sub>3</sub> CH <sub>2</sub> OH and CH <sub>3</sub> CHO	—	
	(b) <sup>c</sup> CH <sub>3</sub> CHO and CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>3</sub> COCH <sub>3</sub>	—	164
	(c) <sup>d</sup> CH <sub>3</sub> CHO, CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> , and CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>3</sub> COCH <sub>3</sub>	—	164

Note: References 265 to 490 are on pp. 525-529.

<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

<sup>c</sup> W-7 Raney nickel was used.

<sup>d</sup> W-6 Raney nickel was used.

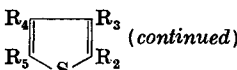

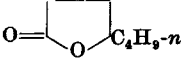
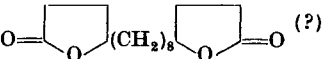
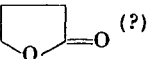
<sup>f</sup> Deuterium oxide and Raney nickel were employed.

<sup>g</sup> Tritiated water was used in the reaction.

DESULFURIZATION WITH RANEY NICKEL

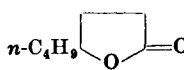
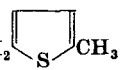
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TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
 (continued)			
R <sub>2</sub> = CH <sub>2</sub> CO <sub>2</sub> H	CHT <sub>2</sub> (CHT) <sub>2</sub> CT <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	— <sup>g</sup>	165
R <sub>2</sub> = CHOHCOC <sub>2</sub> H (d and l)		—	458
R <sub>2</sub> = C(=NOH)CO <sub>2</sub> H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> H	50 <sup>b</sup>	175
R <sub>2</sub> = CH(NH <sub>2</sub> )CO <sub>2</sub> H		59 <sup>b</sup>	175
R <sub>2</sub> = 		42	184b
R <sub>2</sub> = COC <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> COC <sub>4</sub> H <sub>9-n</sub> and C <sub>2</sub> H <sub>5</sub> CO(CH <sub>2</sub> ) <sub>8</sub> COC <sub>2</sub> H <sub>5</sub> (?)	—	14
R <sub>2</sub> = CH=CHCO <sub>2</sub> H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	36	269
	CHT <sub>2</sub> (CHT) <sub>2</sub> CT <sub>2</sub> (CHT) <sub>2</sub> CO <sub>2</sub> H	—	165
R <sub>2</sub> = CH(NH <sub>2</sub> )CH <sub>2</sub> CO <sub>2</sub> H		79	176
R <sub>2</sub> = CH(CO <sub>2</sub> H)CH <sub>2</sub> CO <sub>2</sub> H and the (+) isomer		—	257
R <sub>2</sub> = CO(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	(a) 	—	14
	 (CH <sub>2</sub> ) <sub>8</sub>  (?)	—	
	n-C <sub>4</sub> H <sub>9</sub> CO(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	—	
	HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> CO(CH <sub>2</sub> ) <sub>8</sub> CO(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H (?)	—	

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ORGANIC REACTIONS

$R_2 = \text{CO}(\text{CH}_2)_2\text{CO}_2\text{H}$	(b) $n\text{-C}_4\text{H}_9\text{CO}(\text{CH}_2)_2\text{CO}_2\text{H}$ and	—	269
			
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$	(c) $n\text{-C}_4\text{H}_9\text{CO}(\text{CH}_2)_2\text{CO}_2\text{H}$	57 <sup>b</sup>	164
	(a) $n\text{-C}_7\text{H}_{15}\text{CO}_2\text{H}$	73 <sup>b</sup>	163
	(b) $n\text{-C}_7\text{H}_{15}\text{CO}_2\text{H}$	Fair	14
	$\text{HO}_2\text{C}(\text{CH}_2)_{14}\text{CO}_2\text{H}$	Trace	
$R_2 = \text{CH}(\text{OC}_2\text{H}_5)_2$		40	269
$R_2 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$		50	182
$R_2 = \text{COC}(\text{CH}_3)_3$		54	177
$R_2 = \text{C}(\text{OH})(\text{CH}_3)(\text{CH}_2)_2\text{CH}_3$		41	184b
	(a) 4-Methyl-4-octanol	—	185
	(b) $\text{C}_{15}\text{H}_{33}$ (?)	82	
	(c) $\text{CH}_3(\text{CH}_2)_2\text{CH}(\text{CH}_3)(\text{CH}_2)_3$	— <sup>c</sup>	
$R_2 = \text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$		61	182
$R_2 = \text{CH}_2\text{C}_6\text{H}_5$		25	240
$R_2 = \text{COC}_6\text{H}_5$	(a) $\text{C}_6\text{H}_5\text{COC}_4\text{H}_9\text{-}n$	47-69	14
	$\text{C}_6\text{H}_5\text{CO}(\text{CH}_2)_8\text{COC}_6\text{H}_5$	1-4	
	(b) $\text{C}_6\text{H}_5\text{COC}_4\text{H}_9\text{-}n$	75, —	457, 459
$R_2 = \text{CH}_2\text{OCH}_2\text{CH}_2$ 		50	182

Note: References 265 to 490 are on pp. 525-529.

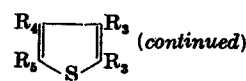
<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.


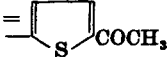

<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

<sup>c</sup> The starting material was subjected to dehydration conditions before desulfurization.

<sup>d</sup> Tritiated water was used in the reaction.

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
 (continued)			
$R_2 = \text{CH}=\text{C}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	$n\text{-C}_4\text{H}_9\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	75 <sup>b</sup>	108
$R_2 = \text{CO}(\text{CH}_2)_8\text{CO}_2\text{H}$	$n\text{-C}_4\text{H}_9\text{CHOH}(\text{CH}_2)_8\text{CO}_2\text{H}$	—	269
$R_2 = \text{CH}_2(\text{CH}_2)_{14}\text{CH}_3$		Fair	185
$R_2 = \text{CO}(\text{CH}_2)_{14}\text{CH}_3$	5-Eicosanol	90	185
$R_2 = \text{C}(\text{C}_6\text{H}_5)_2$		—	183
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{NO}_2$	$\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	—	184f
$R_2 = \text{CO}_2\text{H}$ , $R_5 = \text{CH}_3$		68	269
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{OH}$		60	269
$R_2 = \text{CO}_2\text{H}$ , $R_5 = \text{OCH}_3$		82 <sup>A</sup>	258
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{OCH}_3$		Fair	460
$R_2 = \text{CO}_2\text{H}$ , $R_5 = \text{C}_2\text{H}_5$		—	259
$R_2 = \text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ , $R_5 = \text{CH}_3$		53 <sup>b</sup>	174, 175
$R_2 = \text{CO}_2\text{H}$ , $R_5 = \text{NHCOCH}_3$	(a) $\text{H}_2\text{N}(\text{CH}_2)_4\text{CO}_2\text{H}$	— <sup>b</sup>	108
	(b) $\text{CH}_3\text{CONH}(\text{CH}_2)_4\text{CO}_2\text{H}$	—	184a
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{NHCOCH}_3$	$\text{CH}_3\text{CH}(\text{NH}_2)(\text{CH}_2)_2\text{CO}_2\text{H}$	— <sup>b</sup>	108
$R_2 = \text{COCH}_3$ , $R_5 = \text{SCH}_3$	$n\text{-C}_4\text{H}_9\text{COCH}_3$ and $\text{CH}_3\text{CO}(\text{CH}_2)_8\text{COCH}_3$	—	373
$R_2 = \text{CH}(\text{NH}_2)\text{CH}_2\text{CO}_2\text{H}$ , $R_5 = \text{CH}_3$		Poor	176
$R_2 = \text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ , $R_5 = \text{C}_2\text{H}_5$		41 <sup>b</sup>	174, 175
$R_2 = \text{COCH}_3$ , $R_5 = \text{C}_2\text{H}_5$		—	14
$R_2 = \text{CO}(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{Br}$	$n\text{-C}_3\text{H}_7\text{CO}(\text{CH}_2)_2\text{CO}_2\text{H}$	25 <sup>c</sup>	164
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{CH}(\text{CH}_3)_2$		—	461
$R_2 = \text{CO}_2\text{H}$ , $R_4 = \text{CH}(\text{CH}_3)_2$		—	461

$R_2 = \text{CO}_2\text{H}, R_5 = \text{C}(\text{CH}_3)_3$		70 <sup>d</sup>	170
$R_2 = \text{CHO}, R_5 = n\text{-C}_4\text{H}_9$	$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\text{OH}$	65	34
$R_2 = \text{CHO}, R_5 = \text{C}(\text{CH}_3)_3$	$(\text{CH}_3)_3\text{C}(\text{CH}_2)_4\text{CH}_2\text{OH}$	50	34
$R_2 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2, R_5 = \text{CH}_3$		46	177
$R_2 = \text{CH}(\text{NH}_2)\text{CO}_2\text{H}, R_5 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$		83	49
$R_2 = \text{CH}_3(\text{CH}_2)_2\text{CO}_2\text{H}, R_5 = \text{C}_2\text{H}_5$		51 <sup>b</sup>	163
$R_2 = \text{CH}_3, R_5 = $ 	5-Decanol	—	34
$R_2 = \text{CH}_2\text{CH}_2\text{OH}, R_5 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$		44	178
$R_2 = \text{CH}(\text{OCH}_2)_2, R_5 = n\text{-C}_4\text{H}_9$		58	184b
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}, R_5 = \text{CH}_2\text{NHCOCH}_3$		83	462
$R_2 = \text{CH}_2(\text{CH}_2)_3\text{CO}_2\text{H}, R_5 = \text{CH}_2\text{NHCOCH}_3$		72	462
$R_2 = \text{CH}(\text{NHCOCH}_3)\text{CH}_2\text{CO}_2\text{H}, R_5 = \text{C}_2\text{H}_5$		77	176
$R_2 = \text{CH}(\text{NH}_2)\text{CO}_2\text{H}, R_5 = \text{CH}_2(\text{CH}_2)_3\text{CO}_2\text{H}$		—	49
$R_2 = \text{COCH}_3, R_5 = $ 		91	185
$R_2 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2, R_5 = \text{C}_2\text{H}_5$		54	177
$R_2 = \text{CH}_2\text{CH}_2\text{OH}, R_5 = \text{CH}_2\text{N}$ 		50	178

Note: References 265 to 490 are on pp. 525-529.

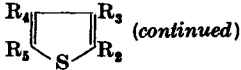
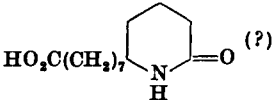
<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.




<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

<sup>c</sup> Aqueous sodium bicarbonate was used as the solvent.

<sup>d</sup> Aqueous sodium hydroxide was used as the solvent.

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
$R_4$  (continued)			
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}, R_5 = \text{C}(\text{CH}_3)_3$		— <sup>d</sup>	171
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}, R_5 = \text{CH}(\text{NHCOCH}_3)\text{CH}_3$	$\text{CH}_3\text{CH}(\text{NHCOCH}_3)(\text{CH}_2)_2\text{CO}_2\text{H}$	50	184c
$R_2 = \text{CH}(\text{OC}_2\text{H}_5)_2, R_5 = n\text{-C}_4\text{H}_9$	$n\text{-C}_8\text{H}_{17}\text{CH}(\text{OC}_2\text{H}_5)_2$ and $n\text{-C}_8\text{H}_{16}\text{OC}_2\text{H}_5$	—	182
$R_2 = \text{CH}_2(\text{CH}_2)_4\text{CO}_2\text{H}, R_5 = \text{CH}_2\text{NHCOCH}_3$		65	462
$R_2 = \text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{H}, R_5 = \text{CH}_2\text{NHCOCH}_3$		62	462
$R_2 = \text{C}_2\text{H}_5, R_5 = \text{COC}_2\text{H}_5$		90	164
$R_2 = \text{CH}_2(\text{CH}_2)_3\text{CO}_2\text{H}, R_5 = \text{CH}(\text{NHCOCH}_3)\text{CH}_3$	$\text{CH}_3\text{CH}(\text{NHCOCH}_3)(\text{CH}_2)_3\text{CO}_2\text{H}$	49	184c
$R_2 = \text{C}(\text{NOH})(\text{CH}_2)_3\text{CO}_2\text{H}, R_5 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$	$\text{HO}_2\text{C}(\text{CH}_2)_7\text{CH}(\text{NH}_2)(\text{CH}_2)_3\text{CO}_2\text{H}$ and	—	49
			
$R_2 = \text{CH}_2\text{C}_6\text{H}_4\text{CO}_2\text{H-}p, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	167
$R_2 = \text{CH}(\text{NHCOCH}_3)\text{CH}_2\text{CO}_2\text{H}, R_5 = \text{C}(\text{CH}_3)_3$		55	176
$R_2 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	463
$R_2 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{CO}_2\text{H-}p, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	167
$R_2 = \text{CH}_2(\text{CH}_2)_4\text{CO}_2\text{H}, R_5 = \text{CH}(\text{NHCOCH}_3)\text{CH}_3$	$\text{CH}_3\text{CH}(\text{NHCOCH}_3)(\text{CH}_2)_{10}\text{CO}_2\text{H}$	24	184c
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{C}_6\text{H}_5, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	463
$R_2 = \text{CH}_2(\text{CH}_2)_3\text{C}_6\text{H}_5, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	463
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{C}_6\text{H}_4\text{CO}_2\text{H-}p, R_5 = \text{CO}_2\text{H}$		— <sup>d</sup>	463
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}, R_5 = \text{CH}_2\text{C}_6\text{H}_5$		— <sup>d</sup>	171

$R_2 = \text{CH}=\text{C}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$ , $R_5 = \text{C}_2\text{H}_5$	$n\text{-C}_7\text{H}_{15}\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	— <sup>b</sup>	108
$R_2 = \text{CH}_3$ , $R_5 = \text{C}_{10}\text{H}_{21}\text{-}n$		63	185
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{C}_7\text{H}_{15}\text{-}n$		82	164
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_3 = \text{CH}_2(\text{CH}_2)_2$ 		—	166
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$		— <sup>i</sup>	171
$R_2 = \text{CH}_2(\text{CH}_2)_3\text{C}_3\text{H}_4\text{CO}_2\text{H-}p$ , $R = \text{CO}_2\text{H}$		— <sup>i</sup>	463
$R_2 = \text{CH}_2(\text{CH}_2)_7\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$		—	168
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2(\text{CH}_2)_2$ 		—	166
$R_2 = \text{CH}_2(\text{CH}_2)_6\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2(\text{CH}_2)_4\text{CH}_3$	$\text{CH}_3(\text{CH}_2)_5\text{CT}_2(\text{CHT})_2\text{CT}_2(\text{CH}_2)_7\text{CO}_2\text{H}$	— <sup>g</sup>	165
$R_2 = \text{CH}_2(\text{CH}_2)_4\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2(\text{CH}_2)_2$ 		—	166
$R_2 = \text{C}_4\text{H}_9\text{-}n$ , $R_5 = \text{CO}(\text{CH}_2)_6\text{CO}_2\text{H}$		—	459
$R_2 = \text{CH}_2(\text{CH}_2)_4\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2(\text{CH}_2)_7\text{CO}_2\text{H}$		—	168
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2)_7\text{CH}_3$		—	172
$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{C}_{11}\text{H}_{23}\text{-}n$		99 <sup>b</sup>	164

Note: References 265 to 490 are on pp. 525-529.

<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

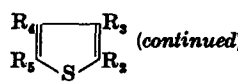
<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

<sup>g</sup> Tritiated water was used in the reaction.

<sup>i</sup> Aqueous sodium hydroxide was used as the solvent.

TABLE IX—Continued

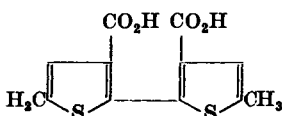
## RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
 (continued)			
$R_3 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$ , $R_5 = \text{CH}_3(\text{CH}_2)_2\text{CH}(\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CH}_3$		73 <sup>b</sup>	164
$R_3 = \text{CH}=\text{C}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2\text{C}_2\text{H}_5$	$\text{C}_6\text{H}_5(\text{CH}_2)_6\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	74	33
$R_3 = \text{CH}=\text{C}(\text{C}_2\text{H}_5)\text{CO}_2\text{H}$ , $R_5 = \text{CH}_2\text{CH}_2\text{C}_2\text{H}_5$	$\text{C}_6\text{H}_5(\text{CH}_2)_7\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	—	33
$R_3 = R_5 = \text{C}(\text{CH}_3)_2\text{C}_2\text{H}_5$		—	183
$R_3 = \text{CH}=\text{C}(\text{C}_2\text{H}_5)\text{CO}_2\text{H}$ , $R_5 = \text{CH}_3(\text{CH}_2)_2\text{C}_2\text{H}_5$	$\text{C}_6\text{H}_5(\text{CH}_2)_8\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{H}$	—	33
$R_3 = \text{CH}_2(\text{CH}_2)_7\text{CO}_2\text{H}$ , $R_5 = \text{CH}_3(\text{CH}_2)_7\text{CO}_2\text{H}$		—	168
$R_3 = \text{CO}_2\text{H}$ , $R_5 = \text{C}_{18}\text{H}_{37}\text{-}n$		—	185
$R_3 = \text{C}_{16}\text{H}_{33}\text{-}n$ , $R_5 = \text{CHOH}(\text{CH}_2)_5\text{CO}_2\text{H}$		68	464
$R_3 = \text{COCH}_3$ , $R_5 = \text{C}_{18}\text{H}_{37}\text{-}n$	$\text{CH}_3\text{CH}(\text{OH})(\text{CH}_2)_{21}\text{CH}_3$	83	185
$R_3 = \text{C}_{16}\text{H}_{33}\text{-}n$ , $R_5 = \text{CHOH}(\text{CH}_2)_4\text{CO}_2\text{H}$		64	464
$R_3 = \text{C}_{14}\text{H}_{29}\text{-}n$ , $R_5 = \text{CHOH}(\text{CH}_2)_6\text{CO}_2\text{H}$		75	464
$R_3 = R_5 = \text{C}(\text{C}_6\text{H}_5)_2\text{CH}_3$		—	183
$R_3 = \text{C}_{12}\text{H}_{27}\text{-}n$ , $R_5 = \text{CHOH}(\text{CH}_2)_8\text{CO}_2\text{H}$		75	464
$R_3 = \text{CO}_2\text{H}$ , $R_4 = \text{NO}_2$ , $R_5 = \text{CH}_3$	$\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	76	184 <sup>f</sup>
$R_3 = R_5 = \text{OH}$ , $R_4 = \text{CO}_2\text{H}$		— <sup>i</sup>	171
$R_3 = \text{CO}_2\text{H}$ , $R_4 = \text{NO}_2$ , $R_5 = \text{C}_2\text{H}_5$	$\text{CH}_3(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	72	184 <sup>f</sup>
$R_3 = R_5 = \text{CH}_3$ , $R_4 = \text{CH}(\text{NH}_2)\text{CO}_2\text{H}$		51 <sup>b</sup>	175
$R_3 = \text{CO}_2\text{H}$ , $R_4 = \text{NO}_2$ , $R_5 = \text{C}_4\text{H}_9\text{-}i$	$(\text{CH}_3)_2\text{CH}(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	84	184 <sup>f</sup>

$R_2 = CH_3, R_3 \text{ or } R_4 = CHO, R_5 = C(CH_3)_3 (?)$	—	34
$R_2 = R_5 = C_3H_7-n, R_3 = CO_2H$	93, <sup>b</sup> — <sup>i</sup>	163, 171
$R_2 = R_5 = C_2H_5, R_3 = CH_2(CH_2)_2CO_2H$	— <sup>j</sup>	172
$R_2 = R_5 = C(CH_3)_3, R_3 = CHO$	(CH <sub>3</sub> ) <sub>3</sub> CCH <sub>2</sub> CH(CH <sub>2</sub> OH)CH <sub>2</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	58
$R_2 = R_5 = C(CH_3)_3, R_3 = COCH_3$	— <sup>j</sup>	34
$R_2 = R_5 = C_3H_7-n, R_3 = CH_2(CH_2)_2CO_2H$	— <sup>j</sup>	172
$R_2 = R_3 = R_4 = R_5 = CO_2H$	— <sup>i</sup>	169
$R_2 = R_5 = CH_3, R_3 = CO(CH_2)_2CO_2H, R_4 = C_2H_5$	— <sup>b</sup>	163
$R_2 = R_5 = C(CH_3)_3, R_3 = R_4 = CH_2OCH_3$	56	182
$R_2 = R_5 = CO_2H, R_3 = R_4 = C_6H_5$	78 <sup>i</sup>	169
$R_2 = R_3 = R_4 = R_5 = C_6H_5$	(a) <sup>k</sup> 1,2,3,4-tetraphenylbutane	Poor
	(b) <sup>l</sup> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> and 1,2,3,4-tetra-phenylbutane	—
		98



67 195



— 465

Note: References 265 to 490 are on pp. 525-529.

<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

<sup>i</sup> Aqueous sodium hydroxide was used as the solvent.

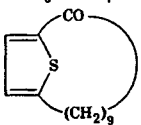
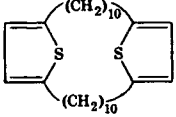
<sup>j</sup> Desulfurization did not occur.

<sup>k</sup> *n*-Butanol was employed as the solvent.

<sup>l</sup> Xylene was employed as the solvent.

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIOAZOLES

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
$R_2 = HC \begin{array}{l} \diagup O \\ \diagdown O \end{array}$		33	184b
$R_2 = CHO$	1-Decanol	35	173
$R_2 = CO_2H$		—	179
$R_2 = CH_2CH_2OH$		76	179
$R_2 = CH_2(CH_2)_2CO_2H$		66 <sup>b</sup>	181
$R_2 = CH_2(CH_2)_3CO_2H$		73 <sup>b</sup>	181
$R_2 = H_2C \begin{array}{l} \diagup S \\ \diagdown S \end{array}$		59	173
$R_2 = CHO, R_5 = CH_3$	1-Undecanol	64	34
$R_2 = CO_2H, R_5 = CH_3$		69	184d
$R_2 = R_5 = CO_2H$		— <sup>b</sup>	167
$R_2 = CO_2H, R_5 = CH_2CH_2OH$		94 <sup>b</sup>	180
$R_2 = R_5 = CH_2CH_2OH$		80	179
$R_2 = CO_2H, R_5 = CH_2(CH_2)_4CO_2H$		—	168
$R_2 = CH_2CH_2OH, R_6 = CH_2N(C_2H_5)_2$		45	178

$R_2 = R_5 = \text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{H}$	Poor <sup>b</sup>	180
$R_2 = R_5 = \text{CH}_2(\text{CH}_2)_3\text{CO}_2\text{H}$	69 <sup>b</sup>	181
$R_2 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2, R_6 = \text{CH}_3, R_7 = \text{C}_2\text{H}_5$	66	177
$R_2 = \text{HC} \begin{array}{l} \diagup \text{O} \\ \diagdown \text{O} \end{array}, R_6 = \text{CH}_3, R_7 = \text{C}_2\text{H}_5$	43	184b
$R_2 = \text{CH}_2\text{CH}_2\text{OH}, R_5 = \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2, R_6 = \text{CH}_3,$ $R_7 = \text{C}_2\text{H}_5$	—	178
$R_2 = R_5 = \text{CO}_2\text{H}, R_6 = R_7 = \text{CH}_3$	93 <sup>b</sup>	164
$R_2 = \text{CO}_2\text{H}, R_5 = \text{C}(\text{CH}_3)_2 \begin{array}{c} \diagup \\ \diagdown \end{array} \text{S} \begin{array}{c} \diagdown \\ \diagup \end{array} \text{CO}_2\text{H},$ $R_6 = R_7 = \text{CH}_3$	— <sup>i</sup>	169
	71	184e
	—	184e

Note: References 265 to 490 are on pp. 525–529.

<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

<sup>b</sup> Aqueous sodium carbonate was used as the solvent.

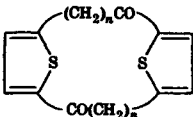
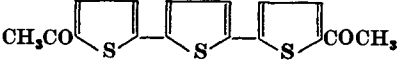
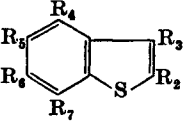
<sup>i</sup> Aqueous sodium hydroxide was used as the solvent.

DESULFURIZATION WITH RANEY NICKEL

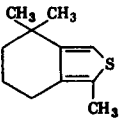
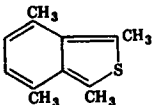
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TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

504

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
			
$n = 5$		90	184, 184e
$n = 8$		—, 64	184, 184e
$n = 9$		—, 68	184, 184e
		69	195
			
$R_2 \dots R_7 = \text{H}$		75	457
$R_3 = \text{OH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$	86	457
$R_4 = \text{OH}$		42	269
$R_2 = \text{CO}_2\text{H}$		93	466
$R_3 = \text{CO}_2\text{H}$		93	457
$R_3 = \text{COCH}_3$	$\text{CH}_3\text{COCH}(\text{C}_6\text{H}_5)\text{CH}_3$ and unidentified oil	—	14

ORGANIC REACTIONS

$R_2 = R_7 = \text{OCH}_3$	Sweet-smelling oil <sup>m</sup>	—	469
$R_2 = \text{CH}_2\text{CO}_2\text{H}$		85	466
$R_2 = \text{CH}_2\text{CO}_2\text{H}$		98	466
$R_2 = \text{C}(\text{CH}_3)_2$		85	470
$R_2 = \text{CH}_2\text{COCH}_3, R_3 = \text{CH}_3$		—	487
$R_2 = \text{C}_2\text{H}_5$	Riphenyl	94	468
		—	255
		—	255
$R_2 = p\text{-CH}_3\text{OC}_6\text{H}_4$		—	255
$R_2 = \text{C}_2\text{H}_5, R_3 = \text{CH}_3$		—	255
$R_2 = \text{C}_2\text{H}_5, R_3 = \text{CH}_3$		—	255
$R_2 = \text{C}_6\text{H}_5, R_3 = \text{CH}_3$		—	255
$R_2 = \text{C}_2\text{H}_5, R_6 = \text{OCH}_3$		—	255
$R_2 = \text{C}(\text{C}_2\text{H}_5)_2\text{CO}_2\text{H}$		82	457
		—	471
		—	472

DESULFURIZATION WITH RANEY NICKEL

Note: References 265 to 490 are on pp. 525–529.

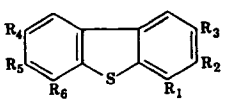
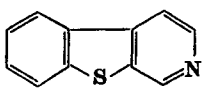
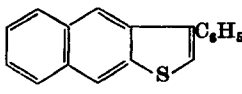
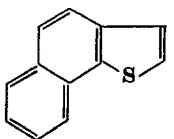
<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

<sup>m</sup> Ethylene glycol was used as the solvent. Oxidation of the product gave veratric acid.

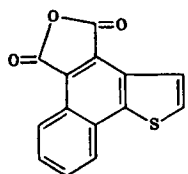
505

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

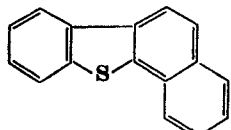
506

Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
			
$R_1 \dots R_6 = \text{H}$		98, 66, —	14, 3, 457,
$R_2 = \text{Rr}$	Riphenyl	—	194
$R_1 = R_4 = \text{CH}_3$		31	194
$R_1 = R_2 = R_4 = R_5 = \text{CH}_3$		—	193
		—	473
		—	474
		—	475
		59, —	476, 477

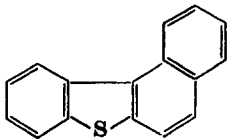
ORGANIC REACTIONS



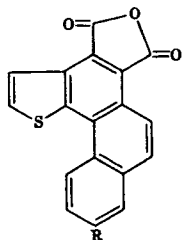
50 251



— 43



— 43



R = H  
R = OCH<sub>3</sub>

88 251

67 251

Note: References 265 to 490 are on pp. 525-529.

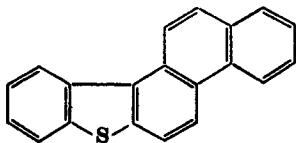
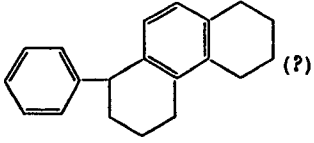
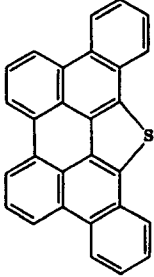
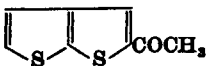
<sup>a</sup> Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

DESULFURIZATION WITH RANEY NICKEL

507

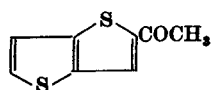
508

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

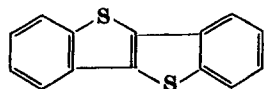
Substance Desulfurized	Product	Yield, %	References
<i>A. Thiophenes<sup>a</sup>—Continued</i>			
		—	53
		— <sup>a</sup>	162
	CH <sub>3</sub> CHOH(CH <sub>2</sub> ) <sub>2</sub> C(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	—	478

ORGANIC REACTIONS

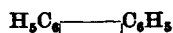




— 479, 478

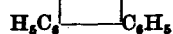


66



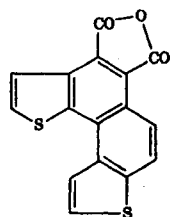
55

13



39

251





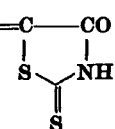
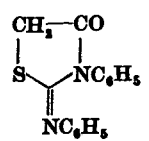
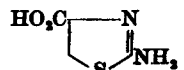
Note: References 265 to 490 are on pp. 525-529.

\* Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

" A special W-7 Raney nickel was employed.

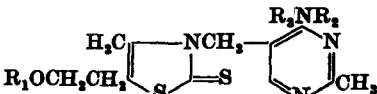
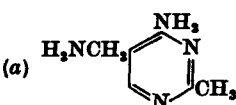
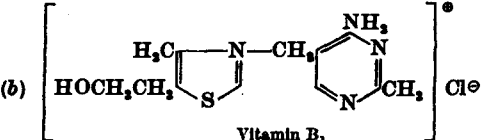

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

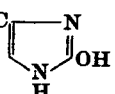
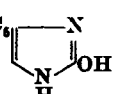
Substance Desulfurized	Product	Yield, %	References
<i>B. Thiazoles</i>			
	$R_1CH_2CH_2CONHR_2$		
$R_1 = C_2H_5$	$R_1 = C_6H_5$	70	221
$R_1 = p-ClC_6H_4$	$R_1 = p-ClC_6H_4$	62	221
$R_1 = p-CH_2OC_6H_4$	$R_1 = p-CH_2OC_6H_4$	86	221
$R_1 = p-(CH_2)_2NC_6H_4$	$R_1 = p-(CH_2)_2NC_6H_4$	78	221
$R_1 = 3,4-CH_2O_2C_6H_3$	$R_1 = 3,4-CH_2O_2C_6H_3$	73	221
$R_1 = $	$R_1 = $	85	221
$R_1 = p-NO_2C_6H_4$	$R_1 = p-NH_2C_6H_4$	Fair	221
$R_1 = p-CH_2OC_6H_4, R_2 = C_2H_5$	$R_1 = p-CH_2OC_6H_4, R_2 = C_2H_5$	89	221
$R_1 = p-(CH_2)_2NC_6H_4, R_2 = C_2H_5$	$R_1 = p-(CH_2)_2NC_6H_4, R_2 = C_2H_5$	77	221

$R_1 = $  , $R_2 = C_2H_5$	$R_1 = $  , $R_2 = C_2H_5$	54	221
$B_1 = p\text{-NO}_2C_6H_4$ , $R_2 = C_2H_5$	$R_1 = p\text{-NH}_2C_6H_4$ , $R_2 = C_2H_5$	78	221
$HO_2C(CH_2)_2C(CH_2)_2C(=S)NH$ 	$HO_2C(CH_2)_2CH(CH_2)_2CH_2CO_2H$	—	215
	$CH_3CONHC_2H_5$	—	42
	$CH_3CH(NH_2)CO_2H$	60	480

Note: References 265 to 490 are on pp. 525-529.

TABLE IX—Continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
<i>B. Thiazoles—Continued</i>			
			
$R_1 \dots R_2 = H$	(a) 	—	285
$R_1 = COCH_3$ , $R_2 = R_3 = H$ $R_1 \dots R_3 = COCH_3$	(b) 	—	285
	Vitamin B <sub>1</sub> acetate	—	285
$R_2 = C_2H_5$	Vitamin B <sub>1</sub>	—	285
	(a) <sup>o</sup> $C_6H_5CH(CH_2)NH_2$	25	41
	(b) <sup>p</sup> $C_6H_5CH(NH_2)CH_3$	20	41
	$C_6H_5COCH_3$	10	
	$CH_3NH_2$	—	

$R_1 = \text{NH}_2, R_2 = \text{OH}$	(a) $\text{CH}_3\text{CONHCHO}$	—	42
	(b) $\text{CH}_3\text{CONH}_2$	91	43
$R_1 = \text{NH}_2, R_2 = \text{C}_2\text{H}_5$	(a) $\text{C}_2\text{H}_5\text{COCH}_2$	45	43
	$\text{CH}_2\text{NH}_2$	13	
	$\text{C}_2\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_3$	9	
	(b) <sup>c</sup> $\text{C}_2\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_3, \text{CH}_2\text{NH}_2,$ and $\text{NH}_2$	Fair	41
	(c) <sup>d</sup> $\text{C}_2\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_3$ and $\text{C}_2\text{H}_5\text{COCH}_2$	—	41
$R_1 = R_2 = \text{C}_6\text{H}_5$	$\text{C}_2\text{H}_5\text{CHO}$	28	41
	$\text{C}_2\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_3^e$	19	44
$R_1 = 1\text{-C}_{10}\text{H}_7, R_2 = \text{C}_6\text{H}_5$	$1\text{-C}_{10}\text{H}_7\text{CHO}, \text{C}_6\text{H}_5\text{COCH}_2, 1\text{-C}_{10}\text{H}_7\text{CH}_2,$ and $\text{C}_6\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_2$	—	41
$R_1 = \text{NH}_2, R_2 = \text{CH}_2\text{CH}_2\text{NHCOCH}_3, R_3 = \text{OH}$	$\text{CH}_2\text{CH}_2\text{NHCOCH}_2\text{CH}_2\text{CONH}_2$	30	481
$R_1 = \text{OH}, R_2 = \text{NH}_2, R_3 = \text{CO}_2\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{O}_2\text{C}$ 	20	196
$R_1 = \text{NH}_2, R_2 = \text{C}_6\text{H}_5, R_3 = \text{CH}_3$	(a) <sup>e</sup> $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2, \text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_3,$ and $\text{NH}_2$	—	41
	(b) <sup>f</sup> $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2$ and $\text{NH}_2$	—	
$R_1 = \text{OH}, R_2 = \text{NH}_2, R_3 = \text{C}_2\text{H}_5$	$\text{H}_2\text{C}$ 	36	196

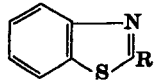
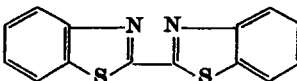
Note: References 265 to 490 are on pp. 525-529.

<sup>c</sup> W-7 Raney nickel in methanol was used.

<sup>d</sup> W-6 Raney nickel in methanol was used.

<sup>e</sup> Employing either W-6 or W-7 Raney nickel and methanol solution.

TABLE IX—continued  
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

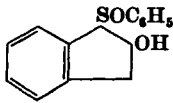
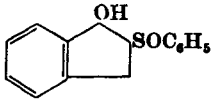
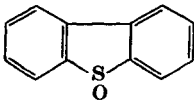
Substance Desulfurized	Product	Yield, %	References
<i>B. Thiazoles—Continued</i>			
			
$R = \text{H}$	(a) $\text{C}_6\text{H}_5\text{NHCH}_2$	84-86, —	41, 56
	(b) <sup>r</sup> $\text{C}_6\text{H}_5\text{NHCH}_2$	7	41
	$\text{C}_2\text{H}_5\text{NH}_2$	29	
	(c) <sup>s</sup> 	0.2	41
$R = \text{CH}_3$	$\text{C}_6\text{H}_5\text{NHCH}_2\text{CH}_3$	—	41

Note: References 265 to 490 are on pp. 525-529.

<sup>r</sup> Sodium hydroxide in methanol was used.

<sup>s</sup> A special W-7 Raney nickel in xylene was employed.

TABLE X  
RANEY NICKEL DESULFURIZATION OF SULFOXIDES

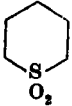
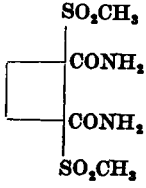
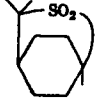

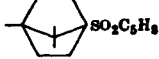
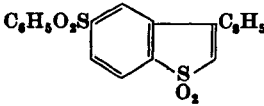
Sulfoxide	Product*	Yield, %	References
$[\text{CH}_2\text{SO}(\text{CH}_2)_4\text{NH}]_2\text{CO}$		—	200
$(\text{C}_6\text{H}_5)_2\text{SO}$		75	7, 198
$\text{C}_6\text{H}_5\text{CHOHCH}_2\text{SO}(\text{CH}_2)_4\text{CH}_3$	$\text{C}_6\text{H}_5\text{COCH}_3 + \text{C}_6\text{H}_5\text{CHOHCH}_3$	—	199
$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)(\text{CONH}_2)\text{SOC}_6\text{H}_5$		60	17
		20	79
	Indane	—	79
	Unidentified oil	—	194
Sulfoxide of 3β-acetoxy-16-thiobenzylpregnen-20-one		75	101
Sulfoxide of 3-benzyl thio enol ether of 4-androsten-3,17-dione		58	101

Note: References 265 to 490 are on pp. 525-529.

\* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE XI  
RANEY NICKEL DESULFURIZATION OF SULFONES

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Sulfone	Product*	Yield, %	References
$(n-C_7H_{15})_2SO_2$		—†	56
$(n-C_8H_{17})_2SO_2$		—†	56
		—‡	76
	<i>cis</i>	—	484
	<i>cis-p</i> -Menthane	—	342
	<i>cis</i> - and <i>trans-p</i> -Menthane	—	342
$(C_6H_5)_2SO_2$		65, —	7, 56, 20f
$C_6H_5CH_2C(SO_2C_2H_5)_2CH_2CH_2CO_2H$		—	482
$C_6H_5CH(SO_2C_2H_5)CONH_2$		72	311
$C_6H_5C(CH_3)(CONH_2)SO_2C_2H_5$		67	16
$(i-C_3H_7)_2C(SO_2C_2H_5)_2$	$(i-C_3H_7)_2CHSO_2C_2H_5$	—	482
		78	482
$C_6H_5C(CH_3)(CO_2C_6H_5)SO_2C_6H_5$		63	16
$(C_6H_5)_2C(SO_2C_2H_5)CH_2CH(CH_3)N(CH_3)_2$		42	202
$C_6H_5CH_2CH(C_6H_5)SO_2CH_2C_6H_5$		Poor	483
$(C_6H_5CH_2SO_2CHC_6H_5)_2$		Poor	483
<i>cis</i> -3-Methyl-3-benzosulfonylcyclohexyl $\beta$ -naphthoate		43	307
<i>trans</i> -3-Methyl-3-benzosulfonylcyclohexyl $\beta$ -naphthoate		46	307
		61	307
	$(C_6H_5)_2CHCH_3$	—	475

ORGANIC REACTIONS

DESULFURIZATION WITH RANEY NICKEL

Note: References 265 to 490 are on pp. 525–529.

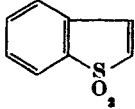
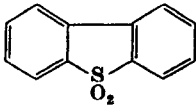
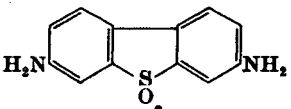
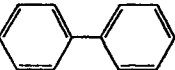
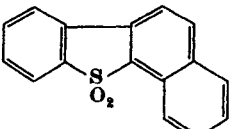
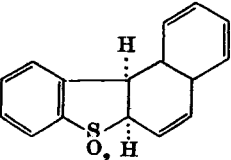
\* Products representing only replacement of sulfur by hydrogen are not shown.

† Desulfurization was not observed.

‡ Desulfurization was not observed when Raney nickel in ethanol was used.

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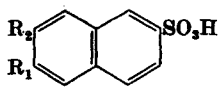
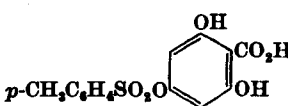
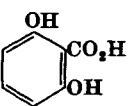
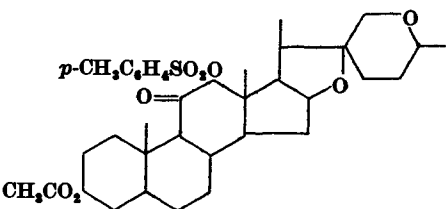
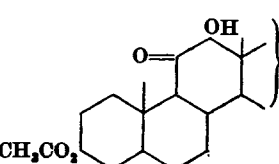
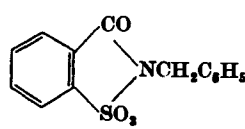
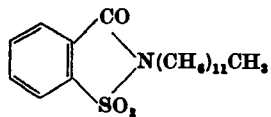
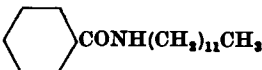
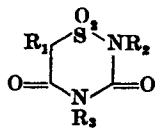
TABLE XI—Continued  
 RANEY NICKEL DESULFURIZATION OF SULFONES

Sulfone	Product*	Yield, %	References
	Unidentified oil	—	203a
	Unidentified oil	—	194
	$C_6H_5NH$  $NHC_6H_5$	70	345
Thionaphthen sulfone dimer	$C_6H_5CH_2CH_3$	—	203
	—	—	485
	—	—	485a

Note: References 265 to 490 are on pp. 525-529.

\* Products representing only replacement of sulfur by hydrogen are not shown.

TABLE XII  
RANEY NICKEL DESULFURIZATION OF SULFONIC ACIDS, ESTERS, AND AMIDES

Substance Desulfurized	Product*	Yield, %	References
<b>A. Sulfonic Acids</b>			
$C_6H_5SO_3H$		10, —	205, 56
<i>o</i> -HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H		40	205
<i>m</i> -HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H		50	205
			
$R_1 = R_2 = H$		40	205
$R_1 = OH$		30	205
$R_1 = OH, R_2 = SO_3H$		30	205
<b>B. Sulfonates</b>			
1,2-3,4β-Tetraacetylglucose benzylsulfonate	Unidentified oil	—	206
1,2-3,4-Diisopropylidene-galactose benzylsulfonate	Diisopropylidene-galactose	95	206
1,2-5,6-Diisopropylidene-glucose benzylsulfonate	Diisopropylidene-glucose	100	206
2,3,4-Triacetyl-β-phenylglucoside <i>p</i> -toluenesulfonate	Unidentified oil	—	206
1,2-Isopropylidene-glucose 5,6-di- <i>p</i> -toluenesulfonate	1,2-Isopropylidene-glucose	25	206
1,2-Isopropylidene-glucose 6- <i>p</i> -toluenesulfonate	1,2-Isopropylidene-glucose	39	206
1,2-5,6-Diisopropylidene-glucose <i>p</i> -toluenesulfonate	1,2-5,6-Diisopropylidene-glucose	96	206
		—	486
5-Hydroxy-7-tosyloxyflavone	5-Hydroxyflavone	—	208
3-Methoxy-5-hydroxy-7-tosyloxyflavone	5-Hydroxy-3-methoxyflavone	—	208
5-Hydroxy-3,3',4'-trimethoxy-7-tosyloxyflavone	5-Hydroxy-3,3',4'-trimethoxyflavone	—	209
		—	207
<b>C. Sulfonamides</b>			
$C_6H_5CH_2SO_2NHC_6H_5$	$C_6H_5NH_2$	53	206
		70	210
		81	51
			
$R_1 = R_2 = H$		79	42
$R_1 = CH_3$		—	42
$R_2 = R_3 = C_6H_5$	$(C_6H_5NH)_2CO$	—	42

Note: References 265 to 490 are on pp. 525-529.

\* Products representing only replacement of sulfur by hydrogen are not shown.

DESULFURIZATION WITH RANEY NICKEL

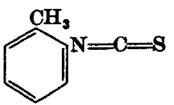
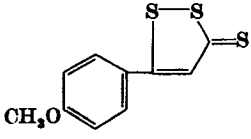
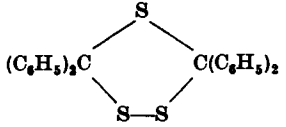
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ORGANIC REACTIONS

TABLE XIII

## RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS

Substance Desulfurized	Product*	Yield, %	Reference
$(\text{CH}_3\text{CO})_2\text{S}$		33	51
$(\text{C}_2\text{H}_5\text{O})_2\text{SO}$		—	56
$n\text{-C}_4\text{H}_9\text{NCS}$		—	56
$\text{C}_6\text{H}_5\text{CSCH}_3$ (trimer)	$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)\text{C}_6\text{H}_5$	18	218
	$o\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	64	43
$\text{C}_6\text{H}_5\text{CH}_2\text{CS}_2\text{CH}_3$		60	38
$\text{HO}_2\text{C}(\text{CH}_2)_2\text{CH}(\text{C}_6\text{H}_5)\text{CSCO}_2\text{H}$		40	215
	$[p\text{-CH}_3\text{OC}_6\text{H}_4(\text{CH}_2)_3]_2$	39-48	35
		85	214

Note: References 265 to 490 are on pp. 525-529.

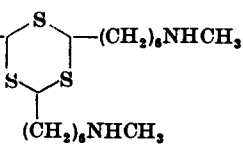
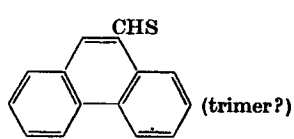
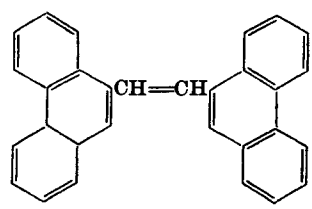
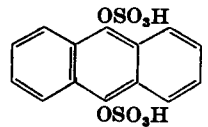
\* Products representing only replacement of sulfur by hydrogen are not shown.

DESULFURIZATION WITH RANEY NICKEL

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TABLE XIII—Continued

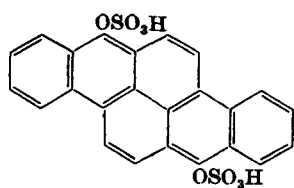
## RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS

Substance Desulfurized	Product*	Yield, %	Reference
$\text{CH}_3\text{NH}(\text{CH}_2)_6$  $(\text{CH}_2)_6\text{NHCH}_3$	$\text{C}_2\text{H}_5\text{N}(\text{CH}_3)(\text{CH}_2)_6\text{CH}_3^\dagger$	—	487
Unknown intermediate	2,4,3'-Trimethylbiphenyl	—	488
 (trimer?)		20	219
$\text{C}_6\text{H}_5\text{SO}_3\text{H}$		—	56
	Unidentified product <sup>‡</sup>		220
Leuco benz[a]anthracene-7,12-dione sulfuric ester	Benz[a]anthracene <sup>§</sup>	—	489
Leuco 4-chloro-3-methylbenz[a]anthracene-7,12-dione sulfuric ester	3-Methylbenz[a]anthracene <sup>§</sup>	—	489

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ORGANIC REACTIONS

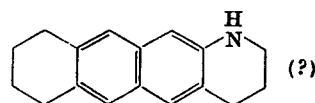
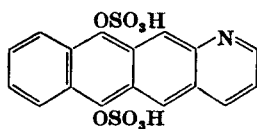




Dibenzopyrene

—

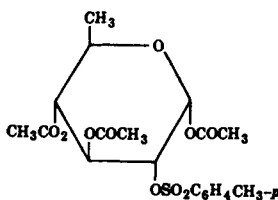
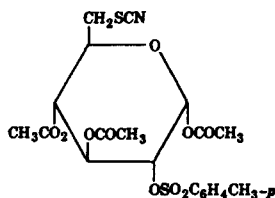
220



(?)

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54



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301

- 1-Thiocyano-1-deoxy-2,4:3,5-dimethylene-DL-xylitol  
 1,2-Isopropylidene-5,6-dideoxy-glucofuranose 5,6-trithiocarbonate  
 1,3:2,4-Diethylidene-5,6-dideoxysorbitol 5,6-trithiocarbonate  
 1,2:3,4-Diisopropylidene-5,6-dideoxymannitol-5,6-trithiocarbonate

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—

217

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Note: References 265 to 490 are on pp. 525-529.

\* Products representing only replacement of sulfur by hydrogen are not shown.

† Ethanol was used as the solvent.

‡ The product gave anthracene after selenium dehydrogenation.

§ The product was dehydrogenated before isolation.

DESULFURIZATION WITH RANEY NICKEL

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TABLE XIII—Continued

RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS

Substance Desulfurized	Product*	Yield, %	Reference
		—	490
		—	354

(C<sub>27</sub>H<sub>44</sub>=3-cholesteryl-4-ene)

Note: References 265 to 490 are on pp. 525-529.

\* Products representing only replacement of sulfur by hydrogen are not shown.

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