Experimental Section[19]

General Procedure for Adduct Formation (See Table I).—Phenylhydrazine (5.40 g, 0.05 mol) was dissolved in ethanol (50 ml) and cooled to −40 ° in a Dry Ice–acetone bath. This solution was added dropwise to a second solution of dimethyl acetylenedicarboxylate (7.10 g, 0.05 mol) in ethanol (50 ml) also being maintained at −40°. After addition had been completed (*ca.* 20 min), the mixture, now containing a precipitated solid, was stirred at −40° for 30 min and filtered rapidly through a chilled filter funnel. A mixture of isomeric adducts (7.95 g, 64%) was obtained which nmr spectroscopy revealed to be 80% normal hydrazone and 20% enehydrazine by integration of the respective methylene and vinyl resonances. Two recrystallizations from methanol provided pure enehydrazine: mp 149–150°; nmr (DMSO-d_6) δ 3.50 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 4.84 (s, 1, =CH), 5.56 (broad s, 2, NHNH), and 7.3–7.5 (m, 5 ArH). If the initial adduct precipitate was recrystallized from benzene, pure normal hydrazone (imine) could be isolated: mp 118–119°; nmr (DMSO-d_6) δ 3.66 (s, 3, OCH_3), 3.73 (s, 2, CH_2), 3.76 (s, 3, OCH_3), 7.3–7.5 (m, 5, ArH), and 10.3 (broad s, 1, NH).

General Procedure for Adduct Cyclization (See Table II).—Dimethyl oxalacetate phenylhydrazone (1, 1.0 g, Ar = C_6H_5) was dissolved in methanol (10 ml) containing *p*-toluenesulfonic acid (0.1 g) and allowed to stand at room temperature for 0.5 hr. The solution was concentrated to half-volume and the precipitated material was removed by filtration. 1-Phenyl-3-carbomethoxypyrazolin-5-one (0.60 g, 69%) was obtained: mp 203–205° (lit.[20] mp 197°).

Preparation of Dimethyl Oxalacetate 2,4-Dinitrophenylhydrazone.—An equimolar (0.01 mol) mixture of dimethyl acetylenedicarboxylate and 2,4-dinitrophenylhydrazine in 1:1 DMSO–MeOH (50 ml) was allowed to stand at room temperature for 1.5 hr. The yellow needles which had precipitated were filtered off and recrystallized from MeOH to yield dimethyl oxalacetate 2,4-dinitrophenylhydrazone (1.80 g, 53%): mp 157–158.5°; ir (Nujol) 3250 (NH), 1730, and 1715 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 3.75 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.95 (s, 2, CH_2), 7.93–8.82 (m, 3, ArH), and 11.23 (s, 1, NH). Analytical data are reported in Table I.

Attempted Cyclization of Dimethyl Oxalacetate 2,4-Dinitrophenylhydrazone.—A solution of the hydrazone (300 mg) dissolved in benzene (10 ml) containing *p*-toluenesulfonic acid (50 mg) was refluxed for 2 hr. The solvent was evaporated *in vacuo* and the residue was recrystallized from methanol to yield 200 mg (66%) of crystalline solid: mp 174–175°; ir (Nujol) 3200 (NH), 1730, and 1695 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 3.71 and 3.73 (two s, 5, OCH_3 and CH_2), 3.90 (s, 3, OCH_3), and 8.1–8.9 (m, 3, ArH). Elemental analysis indicated that the material was isomeric with the starting hydrazone.

Anal. Calcd for $C_{12}H_{12}N_4O_8$: C, 42.60; H, 3.55. Found: C, 42.31; H, 3.61.

Registry No.—5, 22158-22-1; 6, 22158-23-2.

(19) Combustion analyses were provided by Dr. George I. Robertson, Microanalytical Laboratory, Florham Park, N. J. Melting points were obtained on a Fisher-Johns block and are uncorrected. Nmr spectra were run on a Varian A-60 nmr spectrometer and are reported in δ (parts per million) units standardized against TMS. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer and were calibrated against the polystyrene 1601-cm^{-1} band.

(20) W. Wislicenus and A. Grossman, *Ann.*, **277**, 375 (1893).

N-*t*-Butyl-β-acyloxycrotonamides

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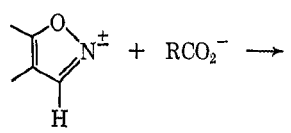
A study of the reaction of carbobenzoxyglycine and N-*t*-butyl-5-methylisoxazolium perchlorate (**7**) has brought to light a new side reaction in the reaction of carboxylic acids with 3-unsubstituted isoxazolium salts—formation of the N-*t*-butylamide of the carboxylic acid. Use of excess **7** in wet acetonitrile diminishes the extent of the side reaction and provides an efficient, generally useful method for the preparation of enol ester acylating agents. The product N-*t*-butyl esters are resistant to intramolecular rearrangement to diacylamides and are sufficiently stable to be isolated and stored.

The reaction of 3-unsubstituted isoxazolium salts (**1**) with carboxylate anions to give enol ester acylating agents (**2**) *via* intermediate acylketenimines (**3**)[1] has



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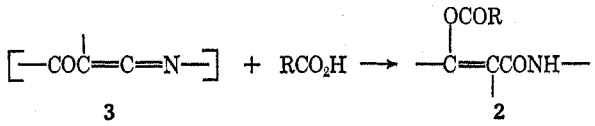
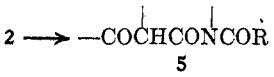


3 **2**

proven of value as a method for the conversion of N-protected amino acids into reactive intermediates for use in peptide synthesis.[2] One limitation associated with the original reagent, N-ethyl-5-phenylisoxazolium 3′-sulfonate (**4**), is instability of the derived enol esters, which is reflected in diminished yields of peptides when addition of the amine component to the ester solution is delayed.[2] A study of a model, unsulfonated N-methyl enol ester revealed spontaneous rearrangement to the diacylamide (**5**),[1] and yields in test peptide preparations with N-methylisoxazolium salts were found to be lower than with the N-ethyl compounds, suggesting that the N-ethyl esters are less susceptible to this mode of decomposition owing to the increased bulk of the ethyl group.[2] However, conversion of



5

the enol esters from **4** into the less useful diacylamides still would be expected to some extent even when addition of the amine component is not postponed, and diacylamide formation thus may be a yield-limiting factor under the optimum conditions for peptide synthesis with **4**. Therefore, attempts to design isoxazolium salts which would give enol esters that are completely stable relative to this side reaction are of interest, since such reagents might provide improved yields of peptides. Moreover, stable enol esters would allow the option of isolation, purification, and storage of

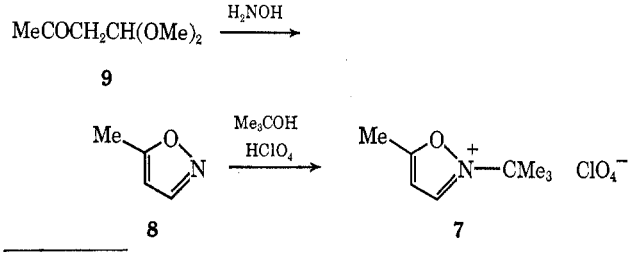
(1) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

(2) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron, Suppl.*, **8**, 321 (1966).

the intermediate acylating agents from isoxazolium salts for later synthetic use.

In view of the apparent superiority of the N-ethyl compared with the N-methylisoxazolium salts, further modification of the substituent on the nitrogen atom seemed promising as a way of preventing rearrangement of the enol esters to diacylamides.[3] In the first attempt along these lines, N-arylisoxazolium salts[7] were investigated in the hope that the reduction of the nucleophilicity of the nitrogen atom expected as a result of the combined steric and electronic influences of the attached aromatic group would retard the rate of O,N-acyl migration for the corresponding esters. Instead, it was found that the N-aryl enol esters were especially prone to rearrangement, *via* the anion, in the presence of even weak bases such as triethylamine salts of carboxylic acids.[8] The facile conversion in this case could be attributed to special stabilization of the N anion by the electron-withdrawing substituent, and it remained to be established whether or not ester decomposition could be prevented by a simple steric effect with a bulky alkyl group on nitrogen. It has now been found that stable N-*t*-butyl enol esters in fact are obtained from N-*t*-butyl-5-methylisoxazolium perchlorate (**7**),[9] and a study of the reaction of **7** with carbobenzoxyglycine has provided preliminary information as to the nature of side reactions involved in enol ester formation.

An obstacle in the investigation of the effect of a bulky alkyl substituent was the lack of a suitable synthetic method for the desired type of isoxazolium salts. Existing preparative routes were restricted to quaternization of isoxazoles with primary alkylating agents of the SN2 type.[10] This problem was overcome by the discovery of an isoxazole alkylation, utilizing perchloric acid and alcohols that are effective sources of carbonium ions, which has made available a wide variety of isoxazolium salts with branched quaternizing groups.[11] The present study has been concerned with the potential utility of the promising new reagent **7**.[12] One advantage of **7** is the ease of its preparation. The starting isoxazole **8** can be obtained directly in one step from hydroxylamine and 4,4-dimethoxybutanone (**9**)[13] and quaternization proceeds smoothly with *t*-butyl alcohol to give **7**. The perchlorate **7** is a completely stable reagent which, unlike many isoxazolium salts, is not hygroscopic, light sensitive, or explosive. Ring opening of **7** with triethylamine provides N-*t*-butylacetylketenimine (**10**), a relatively stable cumulene compound which can be isolated, purified, and stored indefinitely at low temperature.[12]



$$7 \xrightarrow{Et_3N} MeCOCH{=}C{=}NCMe_3$$
10

The combination of the purified ketenimine **10** with an exact equivalent of a carboxylic acid appeared a possible elegant method for the quantitative preparation of enol ester acylating agents free of any by-products. Although initial tests with acetic acid in carbon tetrachloride did provide the pure acetyl ester (**11**) in 95% yield, side reactions when acids were combined with **10** in polar solvents, of interest for use with N-protected amino acids, led to substantial contamination of the products with impurities.[9] Since quantitative

$$10 + MeCO_2H \longrightarrow \underset{\displaystyle MeC{=}CHCONHCMe_3}{\overset{\displaystyle OCOMe}{|}}$$
11

ester formation thus was not achieved with **10** under generally useful conditions, further efforts were directed toward development of a preparative method using the isoxazolium salt **7** itself as the reagent, which would offer the convenience of handling a stable, solid compound and eliminate the additional effort involved in the isolation and purification of **10**.

Carbobenzoxyglycine (Z-GlyOH) was chosen as a representative N-protected amino acid to determine the optimum conditions in test ester preparations in which the salt **7** was added to a mixture of the acid and triethylamine to generate the intermediate **10** *in situ*. Because the addition of carboxylic acids to the N-*t*-butylacylketenimine **10** is relatively slow, it was decided to concentrate the mixtures by evaporation to force the reaction to completion. Merely stirring the residue with water was selected as the simplest technique to remove the by-product triethylammonium perchlorate and isolate the product. This approach with an acetonitrile solution initially 0.1 *M* in each reactant gave the solid ester **12** in 78% yield. In tests

$$\underset{\displaystyle MeC{=}CHCONHCMe_3}{\overset{\displaystyle Z\text{-}GlyO}{|}}$$
12

with Z-GlyOH in acetonitrile using the ketenimine **10**, rather than **7** and triethylamine, the yield of **12** after purification was comparable with the above result,[9] indicating that the ring-opening step and the presence of triethylammonium perchlorate in the reaction mixture do not introduce any major additional difficulties. It should be noted, however, that isomerization of **10** to β-*t*-butoxycrotononitrile (**13**) in the pres-

$$10 \xrightarrow{7} \underset{\displaystyle MeC{=}CHCN}{\overset{\displaystyle OCMe_3}{|}}$$
13

(3) An alternate approach utilizing the N-ethylbenzisoxazolium cation (**6**) has provided stable enol esters,[4] and acylating agents also have been isolated from derivatives of **6**.[5,6]

(4) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

(5) S. Rajappa and A. S. Akerkar, *Chem. Commun.*, 826 (1966).

(6) D. S. Kemp and S. W. Chien, *J. Amer. Chem. Soc.*, **89**, 2743 (1967).

(7) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).

(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *ibid.*, **32**, 388 (1967).

(9) For an account of preliminary results in this study, see R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **90**, 1371 (1968).

(10) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3**, 2 (1964).

(11) D. J. Woodman, *J. Org. Chem.*, **33**, 2397 (1968).

(12) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

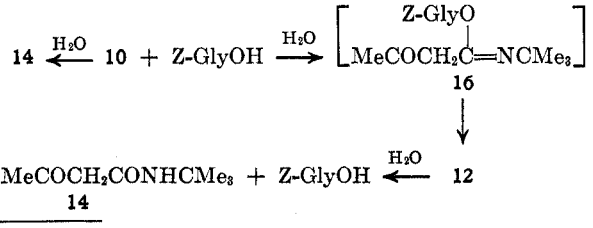
(13) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963). This direct preparation of **8** produces some of the isomeric 3-methylisoxazole. After alkylation, the 3-methylisoxazolium salt may be removed by repeated precipitation from acetone with ether. Alternatively, pure **8** can be prepared from the piperidino derivative of **9**.[14]

(14) B. D. Wilson and D. M. Burness, *J. Org. Chem.*, **31**, 1565 (1966).

ence of **7** has been found to be a side reaction when ring opening is conducted by addition of base to a solution of **7**. In the present study, no **13** has been observed in nmr spectral analyses of products when **7** was added last to the reaction mixtures.

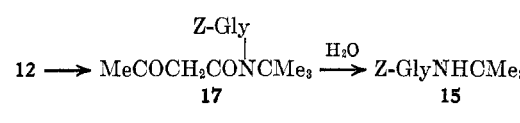
Further investigation confirmed that side reactions were responsible for the low yield of **12**.[15] The possibility that instead the isolation method simply might involve large mechanical losses was excluded by a control experiment in which **12** was recovered in 95% yield by evaporation followed by the work-up procedure from an acetonitrile solution containing triethylammonium perchlorate. Examination of the nmr spectrum of the residue from a reaction mixture showed also that complete consumption of the ketenimine **10** had been achieved during the evaporation. The spectrum, either of the product mixture after the triethylammonium salt was removed by extraction of a dichloromethane solution of an evaporation residue or of a reaction mixture of Z-GlyOH and pure **10** in deuteriochloroform, contained several similar prominent impurity signals. One impurity, detected as a methylene doublet, could be separated by extraction of a solution of the product mixture with aqueous bicarbonate and was isolated and identified as the starting acid Z-GlyOH. Two additional impurity signals were assigned to the acetyl methyl and methylene singlets of N-*t*-butylacetoacetamide (**14**), and **14** appeared to be a major component of the residue after removal of the ester **12** and Z-GlyOH from the crude product mixture. A remaining contaminant found in the product from the reaction both in acetonitrile and deuteriochloroform was detected as a second methylene doublet, indicating a derivative of glycine. After separation of **12** and Z-GlyOH from a product mixture, **14** was removed by sublimation at room temperature, leaving a residue shown by nmr and ir spectra to consist mainly of carbobenzoxyglycine N-*t*-butylamide (**15**). Identification of the third major impurity as **15** was confirmed by tlc comparison and mixture melting point determination with the isolated material and an authentic sample of the compound.

The presence of Z-GlyOH and **14** in the product was not unexpected, since both contaminants might originate from any of several possible anticipated reactions involving moisture present in the system. For example, hydration of **10** could give **14** and leave unconsumed Z-GlyOH. In addition, since ester formation is postulated to proceed *via* an initial adduct such as **16** as an intermediate,[1] hydrolysis of **16** in competition with its rearrangement to **12** could provide Z-GlyOH and **14**. Finally, hydrolysis of the product **12** itself could be the source of both compounds. To test the importance of moisture in the reaction mixture, a



duplicate experiment using **7** was performed with 100 equiv (>15% by volume) of water present at the outset. Surprisingly, the yield of **12** was not decreased. The insensitivity of the result to such a large initial water concentration indicates that the hydration of **10** by traces of moisture does not compete effectively with attack by Z-GlyOH under the original reaction conditions with **7**. Although the enol esters from **10** are susceptible to acid-catalyzed hydrolysis and **12** was found to hydrolyze slowly in wet acetonitrile containing Z-GlyOH, nmr spectral monitoring of the reaction of Z-GlyOH and **10** in deuteriochloroform demonstrated that **12** is not the source of Z-GlyOH and **14** under at least one set of conditions. While both impurities were observed in the deuteriochloroform test, the ester **12** was found to be resistant to hydrolysis in the same solvent containing Z-GlyOH for a longer period than was involved in the reaction. If hydration of **10** also is not an important source of Z-GlyOH and **14** in deuteriochloroform, it may be that these impurities result from a side reaction of an intermediate in this medium.

The remaining major by-product, **15**, is noteworthy in that the acyl group is attached to the nitrogen from the reagent. The N-acyl derivative is of special significance because of the interest in the possible O,N-acyl migration rearrangement of the N-*t*-butyl enol esters. Hydrolysis of the diacylamide (**17**) from rearrangement of **12** could account for the formation of **15**, but ester decomposition again may be excluded as the source of the impurity on the basis of control experiments. Neither ester rearrangement nor de-



composition to **15** was observed with **12**, either in the stability test in deuteriochloroform in the presence of Z-GlyOH or even on prolonged exposure to basic conditions. Alternative routes to **15** would involve acylation on nitrogen by a reactive intermediate such as **16** in competition with the desired rearrangement to **12**. A facile intramolecular N-acylation pathway would be iminoanhydride rearrangement[16] of **16** to give **17**, but intermolecular N-acylation reactions could also provide other potential precursors to **15**.

An important consequence of the observed side reactions is that conversion of the carboxylic acid into enol ester is incomplete, and, to the extent that the pathway(s) to Z-GlyOH are operative during the evaporation, it would be possible to use excess reagent to improve the yield of **12**. Thus, when the preparation was repeated with 25% excess **7** and triethylamine to generate additional **10**, the isolated yield of **12** was improved by 4% to 82%. Surprisingly, the yield increase associated with the use of excess reagent is substantially enhanced if water is added to the system. With 10 equiv of water present at the outset, the yield increases by 6% to 84%, while with 100 equiv the increase is 11% to 89%. The effect of water apparently is to increase the amount of Z-GlyOH available during the reaction at the expense of other by-products, which is supported by nmr analyses showing that, with 100 equiv of water

(15) In the preliminary examination of the reaction of **10** and acetic acid to give **11**, spectral monitoring established similarly that consumption of **10** proceeded to completion, and unidentified by-products were detected by their nmr signals.[9]

(16) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967).

present initially, the amount of the by-product **15** in the crude product mixture is reduced below the level of spectral detection (*ca.* 5%).

The observation of impurities in the preparation of N-*t*-butyl enol esters with the simple acids acetic acid[9] and Z-GlyOH provides additional evidence that the rearrangement of the presumed initial adducts from **10** and carboxylic acids to the enol esters is not a completely efficient process. Previously, in a study of azlactone formation in the reaction of N-acylamino acid anions with various isoxazolium salts, it was found that intramolecular O acylation of the N-acyl group leading to azlactone could compete with the O,O-acyl migration expected to convert the initial adduct into the enol ester.[17] In the present study, the detection of **15** indicates that the postulated reactive intermediate **16** to a slight extent acylates nitrogen in competition with the desired rearrangement or is subject to a competitive decomposition to some other high-energy acylating agent which ultimately gives **15**. The effect of water on the reaction is consistent with the latter possibility. Since the yield of ester does not decrease with a medium rich in water, the intermediate **16** itself must not be susceptible to attack by traces of moisture and would not likely be an effective acylating agent in other intermolecular reactions. On the other hand, **16** could be a source of Z-GlyOH and **14** *via* a decomposition pathway in which the rate-determining step precedes the actual attack of water. The increase in Z-GlyOH available during the evaporation for reaction with excess reagents, at the expense of the amount of **15** formed, could be rationalized on this basis, assuming the initial product of decomposition of **16** can lead either to **15** or, if intercepted by water, to Z-GlyOH and **14**.[18]

Regardless of the mechanistic interpretation of the above findings, the practical result is that improved yields of enol esters are obtained by the evaporation technique with excess **7** and triethylamine in acetonitrile containing water. The excess reagents present no difficulties for product isolation, since their use only results in the presence of greater amounts of triethylammonium salt and **14** in the product residue. Both the salt and **14** are efficiently removed when the residue is stirred with water. From Z-GlyOH, the solid ester **12** is obtained in approximately 90% yield with reaction times varying from 3–10 hr.[19] This method for ester formation has been found to have general applicability. For example, the hindered carboxylic acid pivalic acid and the simple N-protected amino acids N-phthaloylglycine, N-carbobenzoxyphenylalanine, and N-carbobenzoxyleucine all gave good yields of solid esters using the same technique. The main difficulty encountered has been the conversion of the product residues into solid material by stirring with water. Addition of seed crystals of the pure esters has been successful with the acids mentioned, but in some cases it has been necessary to resort to repeated, low-temperature precipitation to obtain the initial crystalline material.

The N-*t*-butyl enol esters have proven resistant to O,N-acyl migration. While the N-methyl enol ester of acetic acid isolated previously decomposes within a few days,[1] rearrangement of the esters from **7** was not observed even after months of storage. Rearrangement of less stable esters from other isoxazolium salts is subject to basic catalysis,[1,8] but **12** is unchanged even on prolonged exposure to the base triethylamine. Whether the apparent stability of the enol esters relative to this mode of decomposition is the result of a very low rate of rearrangement or an unfavorable equilibrium for diacylamide formation remains to be established. Clearly, the new enol esters are stable enough to allow their storage for later synthetic use. The only problem encountered in this regard has been partial hydrolysis when adequate precautions were not taken to protect the purified esters from atmospheric moisture. Acylation of benzylamine in nearly quantitative yield with **12**[9] further establishes that there is no unanticipated mode of decomposition of the enol esters under the reaction conditions for amide bond formation. A final advantage of the new esters is that the by-product **14** from the acylation of amines is freely soluble in either carbon tetrachloride or water and therefore readily removed from either hydrophobic or hydrophilic products.

Experimental Section[20]

Test Reactions of Carbobenzoxyglycine, Triethylamine, and N-*t*-Butyl-5-methylisoxazolium Perchlorate (7). **A.**—To a solution of 0.431 g (2.06 mmol) of Z-GlyOH in 20 ml of MeCN (Baker Reagent, dried over molecular seives) was added 0.208 g (2.06 mmol) of Et_3N (Eastman, White Label) with a calibrated syringe, followed by 0.494 g (2.06 mmol) of **7**. The resulting solution was concentrated at room temperature under water aspirator vacuum with a rotary evaporator for several hours. The residual gum was stirred with 30 ml of water and scratched to initiate crystallization. Filtration, washing with water, and drying in a vacuum desiccator (over P_2O_5) gave 0.560 g (78%) of solid ester **13**, mp 82–84°.

B.—The above procedure with MeCN containing 3.7 ml (206 mmol) of water gave 0.573 g (79%) of **13**, mp 85–86°.

C.—Procedure A with 0.425 g (2.03 mmol) of **12** and 25% excess of **7** (0.612 g, 2.55 mmol) and Et_3N (2.58 g, 2.55 mmol) gave 0.582 g (82%) of **12**, mp 80–84°.

D.—Procedure C, repeated with 0.36 ml (20 mmol) of water added first, gave 0.591 g (84%) of **12**, mp 84.5–85°.

E.—Procedure C, repeated with 3.6 ml (200 mmol) of water added first (reaction time 3 hr), gave 0.628 g (89%) of **12**, mp 84.5–86°.

F.—Procedure C, repeated with 7.2 ml (400 mmol) of water added first, gave 0.586 g (82%) of **12**, mp 85.5–86°.

G.—Procedure E, repeated with a 1.5-hr reaction time, gave 0.597 g (84%) of **12**, mp 83–85°.

H.—Procedure E, repeated with a 4-hr reaction time, gave 0.622 g (88%) of **12**, mp 81–83°.

I.—Procedure E, repeated with a 10-hr reaction time, gave 0.639 g (90%) of **12**, mp 83.5–85°.

Test of Recovery of 13.—A solution of 0.707 g (2.03 mmol) of **13**, 0.257 g (2.54 mmol) of Et_3N, 2.49 ml of 1.02 *M* $HClO_4$ (2.54 mmol of $HClO_4$, *ca.* 2.4 ml of water), and 1.2 ml of water (total

(17) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **34**, 2742 (1969).

(18) The possibility that instead the sources of **15** and of Z-GlyOH and **14** are different side reactions would also be consistent with the results if the added water were to repress the side reaction leading to **15** by a medium effect at the same time as increasing the extent of hydrolysis side reactions giving Z-GlyOH and **14**. That such side reactions may be operative in acetonitrile containing added water was confirmed in a test with 200 equiv of water and excess **7** and triethylamine. Instead of a further improvement in the results, the yield of **12** actually fell to 82%.

(19) The bulk of the solvent is removed during the first hour at room temperature under water aspirator vacuum with a rotary evaporator, but the yield of **12** is only 84% if the residue is worked up after 1.5 hr.

(20) Melting points were determined with a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra were run on a Varian A-60 spectrometer, and chemical shifts are reported in τ values relative to tetramethylsilane as an internal standard. The ir spectra were recorded on a Perkin-Elmer 137 spectrophotometer and the rotations were measured with a thermostated Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, West Germany.

water = 3.6 ml, 203 mmol) in 20 ml of MeCN was evaporated and treated with water as above, giving 0.669 g (95%) of **13**, mp 85–86°.

By-Product Isolation.—A reaction mixture identical with that in A above was worked up (after evaporation) by partition of the residual gum between CH_2Cl_2 and water to remove the triethylammonium perchlorate. The nmr spectrum ($CDCl_3$) of the organic products from the CH_2Cl_2 phase contained, in addition to the signals of **12**, singlets at τ 7.83 (CH_3CO) and 6.72 ($COCH_2CO$) characteristic of N-*t*-butylacetoacetamide, **14**, and two additional doublets (J = 6 Hz, $COCH_2NH$) at τ 6.13 and 6.33. No significant peaks were observed in the regions for the *t*-butyl or methyl signals of **10** or **13**. Extraction of a CH_2Cl_2 solution of the product mixture with 5% $NaHCO_3$ resulted in loss of the doublet at τ 6.13, and Z-GlyOH (mp 120–121°) was isolated upon acidification of the $NaHCO_3$ solution and extraction with CH_2Cl_2.

Similar work-up of a mixture identical with that in B gave a spectrum in which the doublet at τ 6.33 could not be detected.

When 0.349 g (1.67 mmol) of Z-GlyOH was added to 0.233 g (1.67 mmol) of **10** in 1 ml of $CDCl_3$ in small portions during 18 min, the nmr spectrum showed that the reaction was complete within 30 min after all the Z-GlyOH had been added. All of the impurity peaks mentioned above were again detected.

A product solution from the reaction of Z-GlyOH and **10** in $CDCl_3$ as above was evaporated and stirred with water to solidify the ester **12**. The organic by-products were extracted from the aqueous triturate with CH_2Cl_2, and the CH_2Cl_2 solution was washed with 5% $NaHCO_3$, dried, and evaporated. The nmr spectrum of the residue showed no peaks due to **12** or Z-GlyOH and contained prominent signals assigned to **15** at τ 2.66 (s, C_6H_5), 4.86 (s, $PhCH_2OCO$), 6.25 (d, J = 6 Hz, $COCH_2NH$), and 8.67 [s, $CONHC(CH_3)_3$] and to **14** at τ 6.68 (s, $COCH_2CO$), 7.75 (s, CH_3CO), and 8.65 [s, $CONHC(CH_3)_3$].

It was found that **14** could be removed from such a mixture by prolonged sublimation at room temperature under 0.05 mm, leaving a residue shown by nmr to be rich in **15**. At higher temperatures, additional material was observed to sublime from the residue. After an intermediate fraction was discarded, more sublimate was collected at 85–95°, which crystallized from petroleum ether (bp 40–60°), mp 72°. A mixture melting point determination with an authentic sample of **15** showed no depression. The sublimed material, authentic **15**, and a mixture of the two showed identical spots on development of a silica gel tlc plate with 9:1 EtOAc–heptane (phosphomolybdic acid visualization).

Carbobenzoxyglycine N-*t*-Butylamide (15).—To 0.183 g (2.5 mmol) of *t*-butylamine in 20 ml of MeCN was added 0.871 g (2.5 mmol) of the enol ester **13**. The solvent was evaporated on the following day, leaving a solid residue. Stirring with water on the steam bath, cooling, and filtering gave 0.602 g (91%) of white solid: mp 70.5–71° (no change on recrystallization); nmr ($CDCl_3$) τ 2.70 (s, 5), 3.73 (br, 1), 3.97 (br, 1), 4.90 (s, 2), 6.22 (d, 2, J = 6 Hz), and 8.69 (s, 9).

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.60; H, 7.64; N, 10.60; O, 18.16. Found: C, 63.47; H, 7.75; N, 10.68; O, 18.03.

Stability Tests with 12.—The nmr spectrum of an MeCN solution 0.8 M in **12** and containing 1.5 equiv of water showed no change on standing for 24 hr at room temperature. After addition of 0.2 equiv of Z-GlyOH and more water (6 equiv), signals assigned to the hydrolysis product **14** were observed to increase after the solution was allowed to stand longer.

The nmr spectrum of a $CDCl_3$ solution of **12** (0.8 M) saturated with Z-GlyOH (*ca.* 0.1 M) was unchanged after standing for several hours at room temperature.

The ir spectrum of a CH_2Cl_2 solution of **12** (0.1 M) and Et_3N (0.1 M) was unchanged after 24 hr at room temperature. After several days, some decomposition had taken place, as shown by the decrease in enol ester absorption at 5.65 μ. However, the nmr of the residue after evaporation of the solvent was free of the characteristic methylene doublet of **15** and only contained acetyl methyl peaks of the unchanged **12** and the hydrolysis product **14**.

General Procedure for Preparation of Enol Esters.—The method of test procedure H above (4-hr reaction time) was used for the preparation of the enol esters from the following acids. The best results summarized below were obtained by using seeds of the pure esters to initiate crystallization.

Carbobenzoxyglycine.—Repetition of test H with Z-GlyOH gave 89% **12**: mp 84–86° [on recrystallization from benzene–petroleum ether (bp 30–60°), mp 86–87°]; nmr τ 2.73 (s, 5), 4.26 (br, 2), 4.60 (unresolved m, 1), 4.91 (s, 2), 5.92 (d, 2, J = 6 Hz), 8.1 (unresolved m, 3), and 8.72 (s, 9).

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.26; H, 7.06; N, 8.07.

Pivalic Acid.—The procedure with Me_3CCO_2H gave 94% ester: mp 120–123° (on recrystallization from heptane–carbon tetrachloride, mp 121–123°); nmr τ 4.25 (br, 1), 4.58 (unresolved m, 1), 8.09 (unresolved m, 3), and 8.58–8.61 (m, 18).

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80; O, 19.89. Found: C, 64.59; H, 9.42; N, 5.89; O, 20.06.

Phthaloylglycine.—The procedure with Ph-GlyOH gave 81% ester: mp 78–101° (on recrystallization from ethyl acetate–petroleum ether, mp 102–103°); nmr τ 2.15 (m, 4), 4.2 (br, 1), 4.48 (unresolved m, 1), 5.35 (s, 2), 8.0 (unresolved m, 3), and 8.63 (s, 9).

Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.77; H, 5.87; N, 8.13; O, 23.23. Found: C, 62.79; H, 5.98; N, 8.28; O, 23.44.

Carbobenzoxyleucine.—The procedure with Z-LeuOH gave 85% ester: mp 64–74° (on recrystallization from benzene–petroleum ether, mp 76–78°); nmr τ 2.61 (s, 5), 4.28 (br, 2), 4.52 (unresolved m, 1), 4.82 (s, 2), 5.5 (m, 1), 8.08 (unresolved m, 3), 8.23 (broad m, 3), 8.69 (s, 9), and 9.02 (m, 6); $[\alpha]^{24}D$ −26.2° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.31; H, 7.99; N, 6.93. Found: C, 65.17; H, 7.78; N, 7.12.

Carbobenzoxyphenylalanine.—The procedure with Z-PheOH gave 92% ester: mp 105.5–109.5° (on recrystallization from benzene–petroleum ether, mp 112.5–114.5°); nmr τ 2.67–2.72 (m, 10), 4.31 (br, 2), 4.54 (unresolved m, 1), 4.89 (s, 2), 5.3 (m, 1), 6.75 (m, 2), 8.13 (unresolved m, 3), and 8.71 (s, 9); $[\alpha]^{24}D$ −15.5° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 68.46; H, 6.91; N, 6.39. Found: C, 68.48; H, 6.98; N, 6.18.

Registry No.—**12**, 19625-78-6; **13**, 10513-44-7; **15**, 21995-76-6; enol ester from pivalic acid, 21995-77-7; enol ester from phthaloylglycine, 21995-78-8; enol ester from carbobenzoxyleucine, 21996-52-1; enol ester from carbobenzoxyphenylalanine, 21996-53-2.