order rate coefficient was calculated according to the following stoichiometry.

$$2PhCHO + NH_2CH_2CO_2^- \longrightarrow PhCH(OH)-CH(N{=}CHPh)CO_2^- + H_2O$$

A blank reaction under the reaction conditions without glycine shows a decrease in benzaldehyde below 4% in 2.5 hr which is negligibly small compared with the phenylserine formation (over 70% conversion in 2.5 hr). Phenylserine was isolated from the reaction solution in a yield of 44%: mp 187–189° (lit. mp 192–194°); ν_{max} (KBr) 3500–2500 (NH_3^+, OH), 1630 (CO_2^-), 760 and 710 cm^{-1} (monosubstituted phenyl).

Formation of the Schiff Base.—Condensation of ethyl glycinate with benzaldehyde in benzene containing anhydrous $MgSO_4$ as a dehydrating agent at room temperature gives *N*-benzylideneglycine ethyl ester almost quantitatively. This product was confirmed by ir and nmr: ν_{max} (KBr) 1740 (C=O), 1640 (C=N), 1180 [CC(=O)O)], 750 and 686 cm^{-1} (monosubstituted phenyl); τ (CCl_4) 1.81 (s, CH=N, 1 H), 2.27–2.63 (m, aromatic H, 5 H), 5.73 [s, (C=N)CH_2–, 2 H], 5.85 [q, –$CH_2(CH_3)$] 2 H], 8.75 (t, CH_3, 3 H).

Condensation of glycine with benzaldehyde in benzene or ethanol containing anhydrous $MgSO_4$ gives *N*-benzylidenemethylamine and *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, but *N*-benzylideneglycine could not be isolated. The infrared spectrum of the former was consistent with that of the authentic sample and the latter was identified by ir and nmr: mp 106–108°; ν_{max} (KBr) 3350–3000 (NH, OH), 1650 (C=N), 750 and 690 cm^{-1} (monosubstituted phenyl); τ (DMSO) 1.74 (s, CH=N, 1 H), 2.24–2.57 (m, aromatic H, 10 H), 4.59 (b, OH, 1 H), 5.06 (q, CH, 1 H), 6.20 (d, CH_2, 2 H).

The infrared spectrum of the ethanolic mixture of benzaldehyde, glycine, and potassium hydroxide at an early stage of reaction had C=N absorption at 1640 cm^{-1}.

Reaction of Ethyl *N*-Benzylideneglycinate.—To a solution of KOH (5.61 g, 0.1 mol) and ethyl *N*-benzylideneglycinate (9.56 g, 0.05 mol) in absolute ethanol (75 ml), there was added a solution of benzaldehyde (5.31 g, 0.05 mol) in absolute ethanol (25 ml). The mixture was allowed to stand at room temperature. A crystalline product was separated. Ethanol was decanted and the residual crystals were dissolved in a mixture of 2 *N* hydrochloric acid (20 ml) and benzene (20 ml). The solution was concentrated under vacuum until all ethanol was removed. After neutralization with concentrated ammonia, crystalline phenylserine (2.52 g, 27%) was obtained, which was identified by ir and melting point with the authentic specimen. Phenylserine ethyl ester was separated from ethanol solution by means of tlc: ν_{max} (KBr) 3450–3300 (NH_2, OH), 1730 (C=O), 1210–1190 [CC(=O)O], 750 and 700 cm^{-1} (monosubstituted phenyl); τ ($CDCl_3$) 2.70 (m, aromatic H), 4.97 (s, OH, 1 H), 5.35 (d, CH, 1 H), 5.73 (d, CH, 1 H), 6.06 (q, CH_2, 2 H), 7.24 (s, NH_2, 2 H), 9.24 (t, CH_3, 3 H).

Registry No.—Glycine, 56-40-6; benzaldehyde, 100-52-7; phenylserine, 1078-17-7; ethyl glycinate, 459-73-4; *N*-benzylideneglycine ethyl ester, 40682-54-0; *N*-benzylidenemethylamine, 622-29-7; *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, 25558-12-7; phenylserine ethyl ester, 40682-56-2.

Amino Group Protection in Peptide Synthesis. The 4,5-Diphenyl-4-oxazolin-2-one Group[1]

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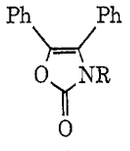
Received March 16, 1973

The preparation and properties of 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives (1) of amino acids are described and these derivatives evaluated as protected intermediates in peptide synthesis. The Ox group—one of the few protecting groups which mask both hydrogens of a primary amino function—is unreactive under the usual conditions used to remove protecting groups, but may be cleaved under mild reductive or oxidative conditions. The use of Ox protection for the ε-amino group of lysine is described.

The previously described properties of the 4,5-diphenyl-4-oxazolin-2-ones[2] (1) have indicated the



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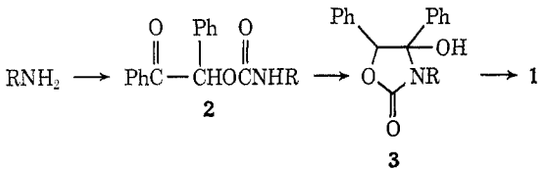
potential of this heterocyclic system[3] as a protecting group for primary amines, one of the few protecting groups which mask both hydrogens of a primary amine function.

Compounds of this type are extremely stable and unreactive under a variety of rigorous conditions. Methods existed for the preparation of this cyclic system through the easily prepared benzoin urethanes. The oxazolinones are highly crystalline, yet reasonably soluble in organic solvents; because of the *cis*-stilbene moiety present in the system, they are also highly fluorescent. Finally, possibilities existed for the removal of the protecting group under mild oxidative or reductive conditions.

The proposed preparation of the 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives involved a two-step reaction sequence: the preparation of benzoin urethanes, followed by cyclization and simultaneous dehydration of the urethanes to oxazolinones in an acid medium.



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In contrast to the usual methods of preparing urethanes, a novel method is available for the preparation of the benzoin urethanes. Treatment of benzoin with phosgene in the presence of *N*,*N*-dimethylaniline, followed by thermal cyclization of the intermediate, unstable chloroformate affords a cyclic unsaturated carbonate (4) in good yield.[4] Treatment of this

(1) Dedicated to Professor Dr. Theodor Wieland on the occasion of his 60th birthday, June 5, 1973.

(2) J. C. Sheehan and F. Guziec, Jr., *J. Amer. Chem. Soc.*, **94**, 6561 (1972).

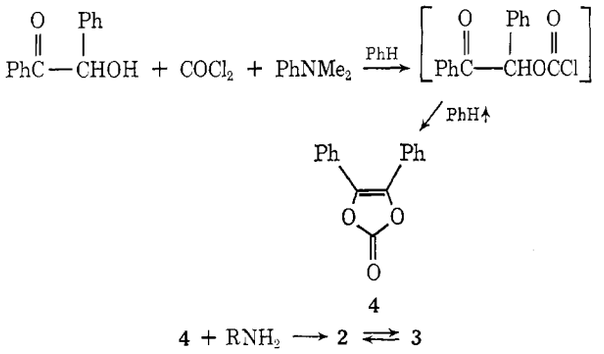
(3) Reviewed by R. Filler, "Advances in Heterocyclic Chemistry," Vol. IV, Academic Press, New York, N. Y., 1965, p 103.

(4) A minor by-product is desyl chloride, formed in a reaction analogous to the thionyl chloride–pyridine chlorination of alcohols. This compound becomes the major product of the reaction unless *N*,*N*-dimethylaniline hydrochloride is removed prior to the chloroformate cyclization.

TABLE I
OX AMINO ACID DERIVATIVES[a]

Registry no.	Amino acid	Registry no.[g]	Yield,[b] %	Mp,[c] °C	Optical rotation, deg (c, MeOH)
56-40-6	Gly	40691-13-2	79	178–179[d]	
56-41-7	L-Ala	37628-69-2	77	202–204[d] (subl)	$[\alpha]^{25}D$ −31.5 (1.02)
63-91-2	L-Phe	37628-66-3	84	196–197[d] (subl)	$[\alpha]^{25}D$ −176 (1.02)
72-18-4	L-Val	37628-67-4	75	234–236[d] (subl)	$[\alpha]^{24}D$ −69.3 (0.99)
61-90-5	L-Leu	40719-38-8	85	203–204[d]	$[\alpha]^{26}D$ −24.6 (1.02)
73-32-5	L-Ile	40719-39-9	74	225–226[d] (subl)	$[\alpha]^{26}D$ −44.8 (1.08)
60-18-4	L-Tyr	40719-40-2	70	198–202[d] dec	$[\alpha]^{25}D$ −150 (1.00)
63-68-3	L-Met	40719-41-3	82	168–169[d]	$[\alpha]^{25}D$ −51.6 (1.01)
40719-34-4	L-Ser (DCHA salt)	40719-42-4	73	196–198[e] dec	$[\alpha]^{24}D$ −4.3 (0.97)
56-85-9	L-Gln	50719-43-5	67	163.5–165[f]	$[\alpha]^{25}D$ −32.4 (1.04)
40719-35-5	α-Z-L-Lys (DCHA salt)	40719-44-6	82	147–149[e]	$[\alpha]^{26}D$ +4.5 (1.03)

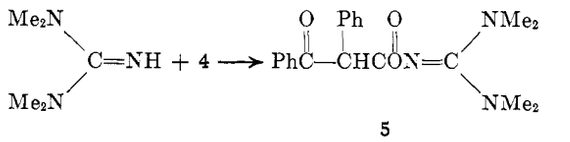
[a] All compounds gave satisfactory elemental analyses. [b] Based on a single recrystallization. [c] All melting points are uncorrected. [d] Recrystallized from ethyl acetate–pentane. [e] Recrystallized from absolute ethanol–ether. [f] Recrystallized from acetone–water. [g] Of Ox derivative.



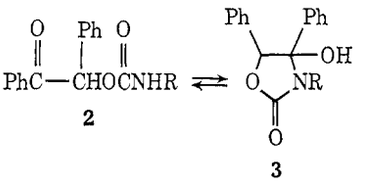
carbonate with a primary amine affords the benzoin urethane in high yield.

Although urethanes of simple primary amines could be prepared without difficulty using the cyclic carbonate in organic solvents, the normal conditions of amino acid acylation in aqueous solvents led to significant hydrolysis of the cyclic carbonate. The catalytic nature of this hydrolysis resulted in poor yields in the acylation reaction. The use of tetramethylammonium or 1,1,3,3-tetramethylguanidine salts of amino acids in anhydrous dimethylformamide, however, offered a reasonable alternative to aqueous systems.

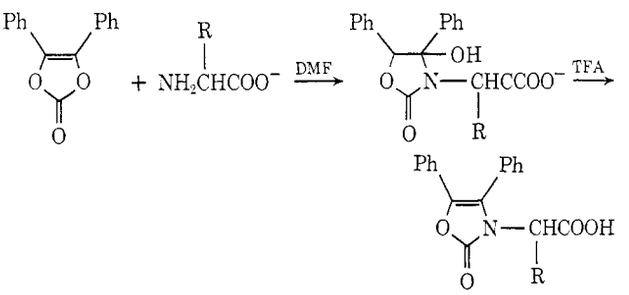
The tetramethylammonium salts of amino acids react with the cyclic carbonate to afford the benzoin urethanes in consistently high yields (70–85%). The use of tetramethylguanidine as a base in the acylation, however, led to high yields of the urethanes only when the amino acid salts were very soluble in dimethylformamide. In those cases where the amino acid salts were only moderately soluble, low yields of the urethanes were obtained due to the acylation of tetramethylguanidine by the cyclic carbonate.



The benzoin urethanes prepared in the acylation reaction were obtained in two major isomeric forms. While the urethanes of glycine, L-alanine, and L-phenylalanine were always obtained as hydroxyoxazolidinone mixtures (**3**) [ir 1770–1750 cm^{-1}; nmr δ 7.7–7.0 (m, 10 H)], the urethanes of L-valine, L-leucine, L-isoleucine, and L-serine were obtained in either the hydroxyoxazolidinone form, or as the desyl urethanes (**2**) [ir 1735–1725 cm^{-1}; nmr δ 8.1–7.8 (m, 2H), δ 7.7–6.7



(m, 8 H)], depending on the conditions of the acylation and work-up. Acylation or work-up conditions involving aqueous base led to the predominant formation of the desyl urethanes, while immediate acidification of an anhydrous acylation mixture led to the isolation of the urethane in the hydroxyoxazolidinone form. Because the dehydration of the hydroxyoxazolidinones to oxazolinones occurs under conditions (trifluoroacetic acid, 1–2 hr, quantitative yield) much milder than those required for the cyclization and dehydration of desyl urethanes,[5] the conditions favoring hydroxyoxazolidinone formation were used in a general procedure for the preparation of oxazolinone derivatives of amino acids. The most convenient procedure for the synthesis of 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives of amino acids therefore involved the treatment of an amino acid tetramethylammonium salt in dimethylformamide at room temperature with 1 equiv of the cyclic carbonate, acidification and isolation of the resulting hydroxyoxazolidinone mixture, and dehydration of this mixture to the desired oxazolinone in trifluoroacetic acid. Pure Ox derivatives of a variety of amino acids could be obtained in consistently high yields using this procedure (Table I). A single recrystallization in each case afforded analytically pure derivatives.

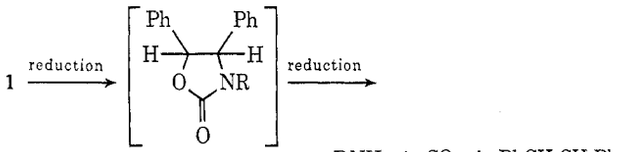


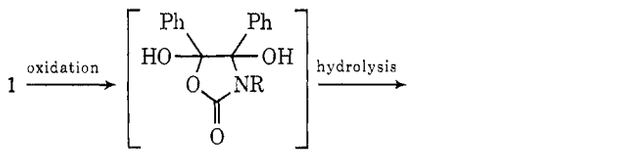
(5) M. Sarttone, *J. Org. Chem.*, **31**, 1959 (1966); K. Auwers and H. Mauss, *Biochem. Z.*, **192**, 200 (1928).

The Ox amino acids are generally high melting crystalline solids. The infrared spectra of Ox derivatives typically exhibit an extremely intense band near 1750 cm^{-1} and a band of moderate intensity near 1370 cm^{-1}, characteristic of the oxazolinone carbonyl.[6a] The nmr spectrum exhibits a characteristic pattern in the aromatic region, a broad singlet or multiplet (5 H) near δ 7.4 and a singlet (5 H) near δ 7.2. The compounds show an intense absorption (ϵ 1.5 $\times$ 10^4) in the ultraviolet near 287 nm (EtOH) and are extremely fluorescent upon irradiation with ultraviolet light [excitation (max) 312 nm, emission (max) 395 nm], also characteristic of the 4,5-diphenyl-4-oxazolin-2-ones.[6b]

In an investigation of the stability of Ox derivatives under the normal conditions used in peptide synthesis, Ox-L-Ala was used as a model compound. This derivative was stable to aqueous sodium hydroxide (48 hr at room temperature), hydrazine (2 hr in refluxing ethanol), hydrogen bromide in acetic acid (24 hr at room temperature), trifluoroacetic acid (3 hr at reflux), and anhydrous hydrogen fluoride (3 hr at 20°). In each case recovered yields were greater than 95%, the compounds were homogeneous on thin layer chromatography, and melting point, spectra, and optical rotation remained unchanged.

Although the Ox amino acid derivatives were found to be extremely stable and unreactive under the normal conditions used to remove peptide protecting groups, two possible methods of removal of the Ox protecting group were evident from the oxazolinone structure. The 4,5-diphenyl-4-oxazolin-2-ones could be considered "protected" *N*-carbobenzoxy-*N*-benzylamine derivatives; saturation of the double bond followed by cleavage of the benzyl urethane and benzylamine bonds would free the protected amine. Alternatively, the vinyl oxygen, vinyl nitrogen moieties of the oxazolinone system could be considered as potential carbonyl functions. Oxidation of the oxazolinone to a species equivalent to a dihydroxyoxazolidinone followed by solvolytic cleavage would also remove the protecting group.





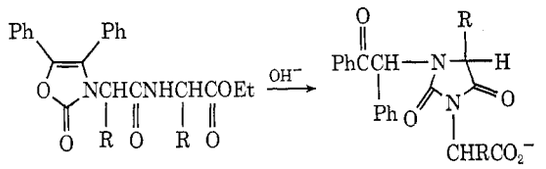
Low-pressure catalytic hydrogenation using 10% palladium-on-charcoal catalyst was found to be the most convenient method of removing the Ox group. Quantitative yields were obtained in the cleavage reaction when the hydrogenations were carried out in ethanol or dimethylformamide containing an equivalent of aqueous acid. In no case could any intermediate hydrogenation product be detected under these conditions, even when the hydrogenation was interrupted prior to completion, suggesting that the slow step in the hydrogenation reaction is the saturation of the oxazolinone double bond. Bibenzyl, the by-product from the reaction, did not interfere with the isolation or characterization of hydrogenation products. When anhydrous solvents were used for the hydrogenation reaction, the cleavage was relatively slow, and small amounts of by-products presumed to be 1,2-diphenylethyl derivatives could be detected by thin layer chromatography during the course of the hydrogenation.

In an alternative reductive procedure the Ox group could be removed from amino acids using sodium in liquid ammonia. Crude products were homogeneous on thin layer chromatography; ion exchange desalting afforded pure amino acids in greater than 70% isolated yield. The main by-product in the reduction was not bibenzyl, but an ether-insoluble material presumed to be a bibenzyl polymer.

Although oxidative removal of amine protecting groups has been limited due to the ready oxidation of a number of amino acids, an amine protecting group removed under very mild oxidative conditions would be very useful in peptide synthesis.[7] Oxidation of the Ox group with 2 equiv of *m*-chloroperbenzoic acid in trifluoroacetic acid cleaves the protecting group in 85% yield. When 1 equiv of the oxidizing agent was used, 52% cleavage of the protecting group was observed along with 40% recovered starting material. Although these oxidative conditions are too vigorous for general use with sensitive amino acids, it is possible that appropriately substituted oxazolinone groups will allow oxidative cleavage under conditions sufficiently mild to be generally useful in peptide synthesis.

Model Ox peptide derivatives could be prepared in good yield using the water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. In contrast to the Ox amino acids which are generally highly crystalline compounds, the Ox peptide derivatives often are difficult to crystallize even when pure. Cleavage of the protecting group followed by hydrolysis afforded pure peptides in good yield. No racemization in peptide couplings could be observed at the 1% level using the "two-spot" chromatographic method for determination of peptide diastereomers.[8]

Alkaline hydrolysis of α-Ox dipeptide esters was hampered by simultaneous hydantoin formation. Although hydantoin formation has been noted in the alkaline hydrolysis of other protected peptide esters,[9] the catalytic nature of the formation of the desyl hydantoin limits the usefulness of Ox protection



(6) (a) R. Gompper and H. Herlinger, *Chem. Ber.*, **89**, 2825 (1956); (b) R. Gompper and H. Herlinger, *ibid.*, **89**, 2816 (1956).

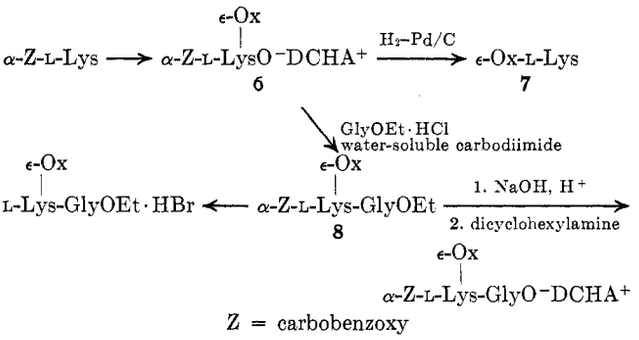
(7) M. Bodanszky and M. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966, p 32.

(8) E. Taschner, A. Chimiak, J. Biernat, T. Solokowska, Cz. Wasielewski, and B. Rzeszotarksa, "Proceedings of the Fifth European Peptide Symposium, Oxford, 1962," Pergamon Press, Oxford, 1963, p 109.

(9) J. MacLaren, *Aust. J. Chem.*, **11**, 360 (1968).

for α-amino groups in conjunction with protecting groups cleaved with aqueous alkali.

Because the Ox group is extremely stable under conditions used to remove most protecting groups, and because of its fluorescent properties, the protecting group was potentially useful for the protection of the ε-amino function of L-lysine. To investigate this possibility the α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one) derivative of L-lysine (**6**) was prepared from α-carbobenzoxy-L-lysine in good yield according to the general procedure. This compound could be selectively hydrogenated to ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysine (**7**), a potentially useful intermediate for the



preparation of ε-Ox peptide derivatives. The diprotected lysine derivatives could be coupled without difficulty and either the carbobenzoxy or ester groups removed in excellent yield in the presence of Ox protection. Cleavage of the protecting groups under the usual conditions afforded L-lysylglycine hydrochloride in excellent yield.

Experimental Section

General.—Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer. Optical rotations were measured at 546 and 578 nm on a Zeiss photoelectric precision polarimeter and $[\alpha]_D$ calculated in the usual manner. Elemental analyses were performed by Galbraith Laboratories.

Water-immiscible extracts were washed with saturated NaCl and dried over Na_2SO_4. Benzene was dried over sodium wire. *N,N*-Dimethylaniline was distilled at reduced pressure from a mixture with 2% acetic anhydride, and triethylamine distilled from a mixture with 2% phenyl isocyanate. Thin layer chromatography was performed on fluorescent Baker-Flex silica gel 1B-F plates using the following solvent system: (A) absolute ether; (B) 95% ethanol; (C) 1-butanol–acetic acid–water (3:1:1 v/v); (D) pyridine–1-butanol–water (1:2:2 v/v upper phase). Reduced pressure evaporations were performed on a rotary evaporator. Reactions were run at 25° unless otherwise stated. Typical spectra are reported; all compounds gave satisfactory spectral data.

1,2-Diphenyl-1,2-ethenediol Cyclic Carbonate (4).—Into a cooled (5°) 200-ml three-necked flask, equipped with Dry Ice–acetone condenser, gas-inlet tube, pressure-equalizing dropping funnel, and magnetic stirrer, and charged with a well-stirred suspension of 17.0 g (80 mmol) of benzoin in 100 ml of dry benzene, was distilled 6.4 ml (88 mmol) of liquefied phosgene. To the resulting mixture was added dropwise, over 30 min, 10.2 ml (80 mmol) of distilled *N,N*-dimethylaniline. The mixture slowly was allowed to come to room temperature, stoppered, and stirred in a room temperature water bath overnight. After cooling for a short time in an ice bath, the mixture was filtered from *N,N*-dimethylaniline hydrochloride and the hydrochloride washed with 20 ml of cold benzene. The combined benzene solutions were refluxed 3 hr, cooled to room temperature, consecutively washed with 60 ml 0.5 *N* HCl and 60 ml water, and dried. Removal of solvent under reduced pressure gave a pale yellow oil which crystallized from a minimum of warm 95% ethanol upon scratching. The crude carbonate was recrystallized from ethanol, affording 12.5 g (66%) of the cyclic carbonate: mp 75–76°; ir (CCl_4) 1870, 1840 (sh), 1820 cm^{-1}; nmr (CCl_4) δ 7.45 (m); mass spectrum molecular ion *m/e* 238. A 0.5-mol scale reaction required mechanical stirring; 400 ml of dry benzene was used and *N,N*-dimethylaniline added over 1 hr. The per cent yield was comparable to the small-scale reaction. The pure cyclic carbonate is stable indefinitely at room temperature.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.62; H, 4.09.

A small amount of desyl chloride generally contaminates the crude isolated carbonate: mp 66–67° [lit.[10] 66–67°]; ir (CCl_4) 1705, 1690 cm^{-1}; nmr (CCl_4) δ 8.07 (d, 1 H), 7.94 (d, 1 H), 7.61–7.24 (m, 8 H), 6.14 (s, 1 H). This by-product occasionally becomes the main product of the reaction unless *N,N*-dimethylaniline hydrochloride is removed from the mixture prior to refluxing.

4,5-Diphenyl-4-oxazolin-2-one Derivative of L-Phenylalanine,[11] Ox-L-Phe. General Procedure.—A mixture of 3.30 g (20 mmol) of L-phenylalanine and 6.52 g (20 mmol) of tetramethylammonium hydroxide solution (Aldrich, 27.9% in methanol, by titration) was evaporated on a rotary evaporator under reduced pressure. The residual oil was twice taken up in absolute ethanol (20 ml) and solvent removed under reduced pressure, yielding the amino acid tetramethylammonium salt as a colorless solid. The salt was taken up in 20 ml of dimethylformamide and the stirred suspension treated with 4.76 (20 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate, giving an intense yellow color which rapidly faded. At 30 min the mixture was acidified with 20 ml 2 *N* HCl, diluted with 100 ml of ethyl acetate, washed with water (3 × 75 ml), and dried. Removal of solvent under reduced pressure afforded the hydroxyoxazolidinone as a pale yellow foam.

The foam was taken up in 20 ml of trifluoroacetic acid and allowed to stand 2 hr at room temperature, at which time most of the trifluoroacetic acid was removed at room temperature under reduced pressure. The residue was taken up in 75 ml of methylene chloride, washed with water (3 × 30 ml), and dried. Removal of solvent under reduced pressure afforded a colorless fluorescent solid which was recrystallized from ethyl acetate–pentane, yielding 6.45 g (84%) of the oxazolinone derivative as colorless crystals: mp 196–197° (sublimes); ir (KBr) 1755, 1710, 1380 cm^{-1}; nmr ($CDCl_4$) δ 11.05 (s, 1 H), 7.46–6.59 (m, 15 H), 4.33–3.14 (m, 3 H); $[\alpha]^{25}D$ −176° (*c* 1.02, MeOH); uv (95% EtOH) λ_{max} 286 nm (ε 1.5 × 10); fluorescence spectrum (absolute EtOH) excitation (max) 312 nm, emission (max) 392 nm (at 312 nm).

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 75.07; H, 5.06; N, 3.40.

α-Phenylphenacyl [Bis(dimethylamino)methylene]carbamate (5).—To a stirred solution of 2.4 g (10 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate (**4**) in 30 ml of dimethyl sulfoxide was added 1.2 g (10 mmol) of distilled 1,1,3,3-tetramethylguanidine. After stirring for 1 hr, the reaction mixture was diluted with 70 ml of ethyl acetate, washed with water (3 × 35 ml), and dried. Removal of solvent under reduced pressure and recrystallization of the colorless solid residue from carbon tetrachloride afforded 2.2 g (61%) of **5** as colorless crystals: mp 117–119°; ir (KBr) 1690, 1685 (sh), 1650, 1640 (sh) cm^{-1}; nmr ($CDCl_3$) δ 8.13 (d, 1 H), 8.02 (d, 1 H), 7.72–7.23 (m, 8 H), 6.73 (s, 1 H), 2.84 (s, 12 H). An analytical sample melted at 118–119°. The yield of **5** was 50% using dimethylformamide as a solvent.

Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.05; H, 6.59; N, 12.00.

4,5-Diphenyl-4-oxazolin-2-one Derivative of 2-Phenethylamine.—To a stirred solution of 6.1 g (50 mmol) of 2-phenethylamine in 40 ml of dimethylformamide was added 11.9 g (50 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate (**4**). After 1 hr

(10) A. Ward, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1959, p 159.

(11) Alternatively, *N*-carboxy-*N*-(2-hydroxy-1,2-diphenylvinyl)-L-phenylalanine γ-lactone.

the solution was diluted with 75 ml of ethyl acetate, consecutively washed with 40 ml of 0.5 *N* HCl and 80 ml of distilled water, and dried. After removal of solvent under reduced pressure, the residual yellow oil was taken up in 50 ml of trifluoroacetic acid and allowed to stand 2 hr. After removal of most of the solvent under reduced pressure at room temperature, the residue was taken up in 125 ml of methylene chloride, consecutively washed with water (2 × 50 ml) and 0.5 *N* NaOH (30 ml), and dried. Removal of solvent under reduced pressure and trituration of the residual oil with petroleum ether afforded a slightly yellow solid which was recrystallized from 95% ethanol, affording 13.5 g (79%) of the oxazolinone as colorless plates: mp 121–122°; ir ($CHCl_3$) 1735, 1355 cm^{-1}; nmr ($CDCl_3$) δ 7.55–6.83 (m, 15 H), 3.64 (m, 2 H), 2.78 (m, 2 H); uv (95% EtOH) λ_{max} 288 nm (ϵ 1.5 × 10^4); fluorescence spectrum (absolute EtOH) excitation (max) 316 nm, emission (max) 399 nm (at 316 nm). An analytical sample melted at 123.5–124.5°.

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.16; H, 5.61; N, 3.92.

Investigation of the Stability of 4,5-Diphenyl-4-oxazolin-2-one Derivatives. A. In 1 *N* NaOH.—A solution of 618 mg of (2 mmol) Ox-L-Ala was dissolved in 10 ml of 1 *N* NaOH and allowed to stand at room temperature for 48 hr. The mixture was acidified with 8 ml of 2 *N* HCl and extracted with ethyl acetate (3 × 10 ml); the combined extracts were dried. Removal of solvent under reduced pressure afforded 610 mg (99%) of the starting oxazolinone, mp 201–202°, $[\alpha]^{26}D$ −31.6° (*c* 1.03, MeOH). The infrared spectrum was identical with the starting material's, spectrum and a single spot was observed on thin layer chromatography (B, C, D).

B. Upon Treatment with Hydrazine.—A solution of 618 mg (2 mmol) of Ox-L-Ala and 400 mg (8 mmol) of hydrazine hydrate in 20 ml of 95% ethanol was refluxed for 2 hr. The colorless mixture was cooled to room temperature, most of the ethanol removed under reduced pressure, the residue taken up in a mixture of 25 ml of ether and 20 ml of 1 *N* HCl, and the ether layer washed with 20 ml of 0.5 *N* HCl and dried. Removal of the solvent under reduced pressure afforded 589 mg (95%) of the starting oxazolinone as a colorless solid which turned slightly yellow on standing, mp 201–203°, $[\alpha]^{26}D$ −30.0° (*c* 0.88, MeOH). The material was homogeneous on tlc and had an infrared spectrum identical with that of the starting material.

C. Upon Treatment with Mineral Acids.—A solution of 618 mg (2 mmol) of Ox-L-Ala in 15 g of 45% HBr in acetic acid was stirred overnight at room temperature, protected by a calcium chloride drying tube. The mixture was diluted with 150 ml of absolute ether and cooled to 0° for 1 hr. When no cloudiness appeared, the mixture was washed with water (3 × 100 ml) and dried; the solvent was removed under reduced pressure, yielding 583 mg (94%) of the starting oxazolinone as a slightly yellow solid, mp 202–203°, $[\alpha]^{27}D$ −31.9° (*c* 0.97, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

D. In Refluxing Trifluoroacetic Acid.—A solution of 618 mg (2 mmol) of Ox-L-Ala in 5 ml of trifluoroacetic acid was refluxed 3 hr, protected by a drying tube. The colorless solution was cooled, the solvent removed under reduced pressure, and the residual oil triturated with ethyl acetate–petroleum ether affording 607 mg (98%) of the oxazolinone as colorless crystals, mp 202–203°, $[\alpha]^{26}D$ −31.6° (*c* 0.97, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

E. In Anhydrous Liquid Hydrogen Fluoride.—A solution of 309 mg (1 mmol) of Ox-L-Ala in 15 ml of liquid hydrogen fluoride was stirred for 2 hr at 20° in a polypropylene reaction vessel, at which time the colorless solution was allowed to evaporate at room temperature, affording colorless crystals of the oxazolinone. This residue was taken up in 20 ml of ether, washed with water (2 × 20 ml), and dried. Removal of the solvent under reduced pressure afforded 294 mg (95%) of the starting oxazolinone, mp 201–203°, $[\alpha]^{26}D$ −31.7° (*c* 0.91, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

Removal of the 4,5-Diphenyl-4-oxazolin-2-one Group. A. By Hydrogenation.—A mixture of 100 mg of 10% palladium on charcoal moistened with 1.00 ml of 2 *N* HCl and 618 mg (2 mmol) of Ox-L-Ala in 20 ml of absolute ethanol was hydrogenated overnight in a low-pressure hydrogenation apparatus (reaction vessel thoroughly cleaned with warm nitric acid) at 35 psi. When no fluorescent material was noted on thin layer chromatography (B,C,D), the mixture was filtered through Celite, the Celite washed with a small amount of 95% ethanol, and the filtrate evaporated under reduced pressure. The residue was taken up in a minimum of absolute ethanol and absolute ether added to precipitate L-alanine hydrochloride: 238 mg (95%); ir (KBr) 1730 (sh), 1720; nmr (D_2O) δ 4.17 (q, 2 H), 1.58 (d, 3 H). The hydrochloride was converted into the free amino acid either by ion-exchange desalting on a 50W-X8 column or by treating a warm solution of the hydrochloride in absolute ethanol with excess pyridine and cooling. The resulting amino acid was chromatographically pure (B,C,D) and was identical with authentic L-alanine (ir, nmr, optical rotation).

Evaporation of the ethanol–ether filtrate, trituration of the residual oil with a small amount of warm 95% ethanol, and cooling afforded 336 mg (92%) of bibenzyl as colorless crystals: mp 51.5–52° [lit.[12] 52°]; ir ($CHCl_3$) 1600 cm^{-1}; nmr (CCl_4) δ 7.09 (s, 10 H), 2.82 (s, 4 H). Hydrogenations also proceeded without difficulty using purified dimethylformamide with a slight excess of aqueous acid as a solvent.

B. By Sodium in Liquid Ammonia Reduction.—To a solution of 927 mg (3 mmol) of Ox-L-Ala in 100 ml of liquid ammonia (redistilled from sodium) was added, in small portions, metallic sodium (*ca.* 520 mg, 23 mmol) until a distinct blue color persisted for 1 min. The excess sodium was destroyed by addition of solid NH_4Cl, and the ammonia allowed to evaporate at room temperature. The solid residue was taken up in a mixture of 30 ml of ether and 30 ml of 0.5 *N* HCl; a slightly yellow residue remained. The aqueous extract was separated and exhibited a single ninhydrin active spot on tlc (B,C,D). Ion-exchange desalting afforded 201 mg (75%) of L-alanine as a colorless solid, identical with authentic L-alanine (ir, optical rotation, homogeneous on tlc). The yellow residue from the reduction exhibited an intense, very broad, infrared absorption near 1590 cm^{-1} (film deposited with $CHCl_3$).

C. By Oxidation.—To a solution of 1.36 g (4.0 mmol) of the Ox derivative of 2-phenethylamine in a mixture of 1.00 g (8.8 mmol) of trifluoroacetic acid and 10 ml of methylene chloride was added dropwise over 10 min 0.75 g (4.0 mmol) of *m*-chloroperbenzoic acid (92% by titration)[13] in 20 ml of methylene chloride, and the reaction was allowed to proceed overnight. The mixture, negative to KI–starch, was evaporated to dryness under reduced pressure, and the residue taken up in 8 ml of 1 *N* ethanolic HCl. Upon addition of absolute ether a colorless solid separated. Filtration afforded 0.25 g (52%) of phenethylamine hydrochloride, ir (KBr) 1600, 1480 (sh), 1415, 1455 cm^{-1} (identical with the authentic hydrochloride). The filtrate was evaporated to dryness under reduced pressure, the residue taken up in 25 ml of ether, washed with 0.5 *N* $NaHCO_3$, and dried, and the solvent removed under reduced pressure. Crystallization of the residue from ethanol–water with seeding afforded 0.54 g (40%) of the starting oxazolinone, mp 120–122°.

Oxidation of Ox-L-Ala (1.54 g, 5 mmol) with a twofold excess of the peracid in 10 ml of trifluoroacetic acid and similar work-up afforded 0.54 g (85%) of the amino acid, isolated as the hydrochloride.

Attempted oxidations without added trifluoroacetic acid led to mixtures of amine oxidation products.

The Coupling of 4,5-Diphenyl-4-oxazolin-2-one Derivatives of Amino Acids, Ox-L-Ala-Gly-OEt.—To a cooled (0°) stirred mixture of Ox-L-Ala (2.78 g, 10 mmol), glycine ethyl ester hydrochloride (1.40 g, 10 mmol), and purified triethylamine (1.40 g, 10 mmol) in 30 ml of methylene chloride was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride[14] (1.92 g, 10 mmol). The mixture was stirred at 0° for 1 hr and allowed to come to room temperature over 2 hr. The solvent was removed under reduced pressure, and the residue taken up in a mixture of 30 ml of ethyl acetate and 30 ml of water. The organic layer was consecutively washed with excess 1 *N* HCl, water, 0.5 *N* $NaHCO_3$, and water, and dried. Removal of solvent under reduced pressure yielded a colorless oil which was crystallized from ethyl acetate–pentane, affording the protected dipeptide as colorless plates: 3.17 g (81%), mp 129.5–130°; ir ($CHCl_3$) 1750, 1735 (sh), 1680, 1385 cm^{-1}; nmr ($CDCl_3$) δ 7.52 (s, 5 H), 7.47 (br s, 1 H), 7.23 (s, 5 H), 4.51–4.02 (m, 5 H), 1.58 (d, 3 H), 1.24 (t, 3 H); $[\alpha]^{26}D$ +3.4° (*c* 0.99, MeOH).

Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.16; H, 5.66; N, 6.92.

(12) R. Shriner and R. Fuson, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 358.

(13) D. Swern, "Organic Peroxides," Vol. 1, Wiley-Interscience, New York, N. Y., 1970, p 498.

(14) J. C. Sheehan and P. Cruickshank, *Org. Syn.*, **48**, 83 (1968).

The following were prepared analogously.

1. **Ox-Val-L-Val-OMe.**—Recrystallization from ether–pentane (seeded with material which spontaneously crystallized) afforded the protected compound as colorless crystals in 75% yield: mp 67–68°; ir (KBr) 1735, 1715 (sh), 1675, 1360 cm^{-1}; the nmr was consistent with the proposed structure.

Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.14; H, 6.77; N, 5.97.

2. **Ox-L-Phe-Gly-OEt.**—The compound was obtained as a colorless foam in 82% yield: ir (CCl_4) 1755, 1730 (sh), 1680, 1375, 1365 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B).

3. **Ox-L-Phe-L-Val-OMe.**—The compound was obtained as a colorless foam in 84% yield: ir (CCl_4) 1760, 1740, 1680, 1360 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B).

4. **Ox-L-Ser-L-Ser-OMe.**—The compound was obtained as a colorless oil in 80% yield: ir ($CHCl_3$) 1745, 1725 (sh), 1690, 1370 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B,C).

Alkaline Hydrolysis of Ox Dipeptide Derivatives.—To a solution of 1.97 g (5 mmol) of Ox-L-Ala-Gly-OEt in 25 ml of dioxane (distilled from $LiAlH_4$) was added 5.5 ml of 1.0 *N* NaOH. The solution immediately turned bright yellow. After 1 hr the mixture was diluted with 100 ml of water and extracted with ether (3 × 25 ml); the aqueous solution was acidified to pH 1 with 2 *N* HCl. Extraction with ether (3 × 30 ml), drying, and solvent removal afforded a yellow oil: ir ($CHCl_3$) 1770, 1745, 1720 cm^{-1}; nmr ($CDCl_3$) δ 8.2–7.8 (m, 2 H), 7.6–7.2 (m, 8 H), 6.9 (d, 1 H), 4.7–4.3 (m, 2 H), 1.8–0.7 (m, 3 H); consistent with a desyl hydantoin structure.

Removal of the Protecting Group from Peptide Esters. L-Valyl-L-valine.—A mixture of 1.8 g (4 mmol) of Ox-L-Val-L-Val-OMe in 45 ml of absolute methanol, and 400 mg of 10% palladium on charcoal moistened with 2.0 ml of 2.0 *N* HCl was hydrogenated at 30 psi overnight. The mixture was filtered through Celite, 10 ml of 1 *N* NaOH added, and the solution allowed to stand 30 min at room temperature. Removal of methanol under reduced pressure, extraction with ether (3 × 5 ml), and desalting of the aqueous solution on IRC-50 (NH_4^+) and 50 W-X8 (H^+) columns followed by removal of water under reduced pressure afforded the crude peptide as a colorless solid. Recrystallization from aqueous acetone afforded 0.71 g (82%) of the peptide as colorless crystals: mp 271–274° dec [lit.[15] 250–260°]; $[\alpha]^{25}D$ +14.9° (*c* 0.98, 1 *N* HCl) [lit.[15] $[\alpha]^{20}D$ +15.1° (*c* 1.0, 1 *N* HCl)]; homogeneous on tlc (C,D).

The following were prepared analogously.

1. **L-Alanylglycine.**—Recrystallization from water–ethanol afforded colorless crystals of the peptide in 86% yield mp 230–231° dec [lit.[16] 230–231.5° dec]; $[\alpha]^{24}D$ +50.7° (*c* 2.03, H_2O) [lit.[16] $[\alpha]^{21}D$ +50.9° (*c* 2.0, H_2O)]; homogeneous on tlc (C,D).

2. **L-Phenylalanylglycine.**—Recrystallization from water–acetone afforded slightly yellow crystals of the peptide in 76% yield: mp 259–261° [lit.[15] 258–262°]; $[\alpha]^{26}D$ +99.2° (*c* 2.0, H_2O) [lit.[15] $[\alpha]^{20}D$ +99.8° (*c* 2.0, H_2O)].

3. **L-Phenylalanyl-L-valine.**—Recrystallization from water–acetone afforded colorless crystals of the peptide in 83% yield: mp 260–262° dec [lit.[17] 256–258°]; $[\alpha]^{25}D$ +16.8° (*c* 1.0, 1 *N* HCl) [lit.[17] $[\alpha]^{25}D$ +16.8° (*c* 1.0, 1 *N* HCl)].

Test for Racemization. The "Two-Spot Method."[8]—Two samples of L-phenylalanyl-L-valine, prepared in the usual manner using the water-soluble carbodiimide and either Ox or carbobenzoxy amine protection, and a sample consisting of the LL and DL peptides prepared from DL-carbobenzoxyphenylalanine in the usual manner were chromatographed on Whatman No. 1 chromatography paper using two solvent systems: S_1, ethyl acetate–pyridine–acetic acid–water (5:5:1:3), and S_2, pyridine–water (4:1). The spots were visualized with ninhydrin. The LL-dipeptides gave single spots in each solvent system (S_1, R_f 0.87; S_2, R_f 0.68) even when 100-μg samples were chromatographed (slight tailing). A 2-μg sample of the diastereomeric mixture exhibited a double spot (S_1, R_f 0.87, 0.75; S_2, R_f 0.68, 0.57) suggesting that less than 1% racemization occurred upon coupling of the Ox group using water-soluble carbodiimide.

(15) D. Stevenson and G. Young, *J. Chem. Soc. C*, 2389 (1969).
(16) F. Stewart, *Aust. J. Chem.*, **19**, 1067 (1966).
(17) E. Schnabel, H. Klustermeyer, J. Dahlmans, and H. Zahn, *Justus Liebigs Ann. Chem.*, **707**, 227 (1967).

ε-(4,5-Diphenyl-4-oxazolin-2-one) Derivative of α-Carbobenzoxy-L-lysine Dicyclohexylammonium Salt, ε-Ox-α-Z-L-Lys·DCHA (6).—The compound was prepared according to the general procedure on a 30-mmol scale from α-carbobenzoxy-L-lysine,[18] yielding a colorless oil which could not be crystallized. The oil was taken up in 10 ml of warm absolute ethanol and treated with 5.43 g (30 mmol) of dicyclohexylamine in 20 ml of absolute ether. Absolute ether was added until the solution grew cloudy, and the mixture was scratched until the salt crystallized. Crystallization in two crops afforded 16.7 g (81.6%) as colorless fluorescent rosettes: mp 147–149°; ir (KBr) 1745, 1700, 1625, 1370 cm^{-1}; nmr ($CDCl_3$) δ 7.57 (m, 5 H), 7.40 (s, 5 H), 7.27 (s, 5 H), 5.75 (d, 1 H), 5.13 (s, 2 H), 4.09–3.68 (m, 1 H), 3.58–2.57 (m, 4 H), 2.15–0.76 (m, 28 H); $[\alpha]^{26}D$ +4.5° (*c* 1.08, MeOH). An analytical sample melted at 151–152°, $[\alpha]^{26}D$ +4.5° (*c* 1.03, MeOH).

Anal. Calcd for $C_{41}H_{51}N_3O_6$: C, 75.22; H, 7.54; N, 6.16. Found: C, 72.31; H, 7.60; N, 6.20.

ε-(4,5-Diphenyl-4-oxazolin-2-one) Derivative of L-Lysine Hydrate, ε-Ox-L-Lys·H_2O (7).—A solution of 1.366 g (2 mmol) of ε-Ox-α-Z-L-Lys·DCHA (6) was hydrogenated at atmospheric pressure in 50 ml of 95% ethanol containing 1 ml of acetic acid using 137 mg of 10% palladium-on-charcoal catalyst. At 1.5 hr tlc (B,C) indicated a single fluorescent spot, which was ninhydrin active. The mixture was filtered through Celite (Celite washed with small amount of 95% ethanol) and the solvent removed under reduced pressure yielding a colorless oil which crystallized under trituration with ethanol–water. The solid was dissolved in 20 ml of 2 *N* NH_4OH and extracted with ethyl acetate (3 × 10 ml), the aqueous solution evaporated under reduced pressure, and the colorless residue recrystallized from ethanol–water in two crops, affording 707 mg (92.5%) ε-Ox-L-Lys·H_2O (7): mp 172–174° dec; ir (KBr) 1745, 1730 (sh), 1630 cm^{-1}; nmr (TFA) δ 7.62 (m, 5 H), 7.49 (br s, 5 H), 7.33 (s, 5 H), 4.68–4.21 (m, 1 H), 4.02–3.44 (m, 2 H), 2.46–2.0 (m, 2 H), 2.0–1.36 (m, 4 H); $[\alpha]^{25}D$ +11.8° (*c* 0.96, 1 *N* HCl).

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.08; N, 7.14.

α-Carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine Ethyl Ester, α-Z-ε-Ox-L-Lys-Gly-OEt (8).—A mixture of finely powdered α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysine dicyclohexylammonium salt (6) (6.82 g, 10 mmol), 30 ml 4 *N* HCl, and 30 ml of ethyl acetate was vigorously shaken in a separatory funnel until homogeneous. The organic phase was dried and evaporated under reduced pressure and the coupling performed as usual using the water-soluble carbodiimide. Recrystallization of the oily residue from ethyl acetate–pentane in two crops afforded 4.7 g (80%) of the protected peptide ester as colorless crystals: mp 112–113°; ir (KBr) 1740, 1725 (sh), 1715 (sh), 1680, 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.44 (m, 5 H), 7.33 (s, 5 H), 7.23 (s, 5 H), 6.82 (t, 1 H), 5.62 (d, 1 H), 5.08 (s, 2 H), 4.35–3.87 (m, 5 H), 3.43 (m, 2 H), 2.00–1.08 (m, 9 H); $[\alpha]^{25}D$ −9.1° (*c* 0.99, MeOH).

Anal. Calcd for $C_{33}H_{35}N_3O_7$: C, 67.68; H, 6.02; N, 7.18. Found: C, 67.48; H, 6.03; N, 7.08.

α-Carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine Dicyclohexylammonium Salt.—Hydrolysis of crude 8 in dioxane with 1 *N* NaOH in the usual manner afforded a colorless oil which could not be crystallized. The oil was taken up in a minimum of warm absolute ethanol and treated with 1.6 g of dicyclohexylamine in 20 ml of absolute ether; ether was added until the mixture turned cloudy. The salt crystallized in two crops totaling 2.5 g (68% overall), as colorless crystals: mp 146–148°; ir (KBr) 1745, 1715, 1665 (sh), 1630 cm^{-1}; nmr consistent with proposed structure; $[\alpha]^{25}D$ −8.2° (*c* 1.02, MeOH).

Anal. Calcd for $C_{43}H_{54}N_4O_7$: C, 69.90; H, 7.37; N, 7.58. Found: C, 69.76; H, 7.29; N, 7.42.

ε-Ox-L-Lys-Gly-OEt·HBr.—Treatment of 1.17 g (2 mmol) of 8 with 5 ml of 45% hydrogen bromide in acetic acid over 2 hr followed by addition of absolute ether (60 ml) afforded the crude hydrobromide as a hygroscopic, slightly yellow gum: ir ($CHCl_3$) 1740, 1690, 1375 cm^{-1}; nmr consistent with the proposed structure

L-Lysylglycine Hydrochloride.—Hydrogenation of a crude α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine

(18) B. Bezas and L. Zervas, *J. Amer. Chem. Soc.*, **83**, 719 (1961).

(551 mg, 1 mmol) in 20 ml of dimethylformamide containing 1.1 ml of 2 *N* HCl over 100 mg of 10% palladium-on-charcoal catalyst, filtration through Celite, and removal of solvent under reduced pressure afforded a colorless solid which was treated with 3 ml of 1 *N* ethanolic HCl, and filtered. The filtrate was immediately treated with 5 ml of pyridine and cooled. The crude peptide hydrochloride separated as an amorphous solid which crystallized from water–methanol in two crops totaling 201 mg (88%): homogeneous on tlc (C,D); $[\alpha]^{25}D$ +69.1° (*c* 1.06, H_2O) [lit.[15] $[\alpha]^{20}D$ +69.5° (*c* 1.0, H_2O)].

Acknowledgments.—We are grateful to the National Institutes of Health for Predoctoral Fellowship 5 F01 GM 43911-03 granted to one of us (F. G.) by the General Medical Science Unit and to the Sloan Basic Research Fund (Grant No. 27609) for general support. We also wish to thank Mr. J. Farrington, Department of Chemistry, Boston College, for his assistance in the hydrogen fluoride reaction.

Registry No.—**4**, 21240-34-6; **5**, 40719-46-8; **7**, 40719-47-9; **8**, 40719-48-0; benzoin, 119-53-9; desyl chloride, 447-31-4; tetramethylammonium hydroxide, 75-59-2; 1,1,3,3-tetramethylguanidine, 80-70-6; 2-phenethylamine 4,5-diphenyl-4-oxazolin-2-one derivative, 37628-64-1; 2-phenethylamine, 64-04-0; Ox-L-Ala-Gly-OEt, 37628-68-5; glycine ethyl ester hydrochloride, 623-33-6; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 25952-53-8; Ox-L-Val-L-Val-OMe, 40719-51-5; Ox-L-Phe-Gly-OEt, 40719-52-6; Ox-L-Phe-L-Val-OMe, 40719-53-7; Ox-L-Ser-L-Ser-OMe, 40719-54-8; Ox-L-Ala-Gly-OEt hydrolysis derivative, 40719-55-9; L-valyl-L-valine, 3918-94-3; L-alanylglycine, 687-69-4; L-phenylalanylglycine, 721-90-4; L-phenylalanyl-L-valine, 3918-90-9; α-carbobenzoxy-L-lysine, 2212-75-1; dicyclohexylamine, 101-83-7; α-carbobenzoxy-ε-Ox-L-lysylglycine dicyclohexylammonium salt, 40719-56-0; ε-Ox-L-Lys-Gly-OEt·HBr, 40719-57-1; L-lysylglycine hydrochloride, 40719-58-2.

15-Oxa Steroids

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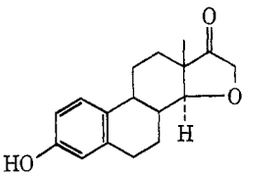
Received March 1, 1973

The preparation of the 15-oxa steroid **29** is described, using the half-ester 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) as starting material. Treatment of **5b** with lead tetraacetate affords the diacetate **9** which upon hydrolysis and reacetylation gave the acid **26**. Conversion to the diazo ketone **28** followed by treatment with boron trifluoride causes spontaneous ring closure to give 3β-hydroxy-15-oxa-5α-androstan-17-one (**29**). Its conversion to 15-oxaestrone (**1**) is described.

The steroid nucleus has over the past number of years undergone numerous structural modifications in an attempt to bring about an increase in biological activity as well as attempting to control or minimize undesirable side effects. One such modification is the insertion of an oxygen atom in place of a methylene group. This type of transformation has in several cases produced derivatives possessing interesting biological properties.[1] A review of the publications in this field reveals that the introduction of an oxygen atom into the steroid nucleus has produced synthetic modifications which can be generally classified into two main categories. The first of these is the formation of a lactone *via* an oxygen insertion α to a keto group.[2-4] This type of transformation would be expected to alter considerably the chemical nature of the original carbonyl function.

In the second category, the oxa steroid takes the form of a cyclic ether. In this class of compounds the heteroatom takes the place of a carbon atom in a position which is known to effect greatly the biological activity of the parent steroid, *e.g.*, C-11, C-17.[5,6]

The aim therefore of this present work was to prepare an oxa steroid in such a manner so as to (1) not compromise the functionality of the original carbonyl groups, and (2) replace a methylene for an oxygen atom while at the same time not affecting those positions which are known to be essential for biological activity. Such a compound is represented by structure **1**.



1

The starting material in our synthesis was 3β-hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic acid (**3**) which was obtained from the reaction of 3β-hydroxy-5α-androstan-17-one (**2**) with *o*-nitrobenzaldehyde.[7] Esterification and acetylation of **3** afforded **4b** which has been reported to give 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) when oxidized with chromium trioxide in acetic acid[3,8] (Scheme I).

We have found that the chromium trioxide oxidation of **4b** produced an acid whose melting point of 152–158° differed sharply from the reported figure of 204°[3] but was in fact consistent with a second reported value of 158–160°.[8] As a means of verifying structure **4**, and the acid ester obtained from its oxidation with chromium trioxide, a reductive ozonization was carried out which produced the aldehyde **6** in high yield. The nmr confirmed both the secondary nature of the aldehydic group and the axial conformation of the C-14 proton: δ 9.72 (d, 1, J = 3.5 Hz, CHO), 2.58 (d of d, 1, J = 3.5, 11 Hz, C-14 H). Furthermore, chromium trioxide oxidation of the alde-

(1) (a) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965); (b) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (c) H. D. Lennon and F. J. Saunders, *Steroids*, **4** (1964).

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(3) A. K. Banerjee and M. Gut, *J. Org. Chem.*, **34**, 1614 (1969).

(4) C. C. Bolt, *Recl. Trav. Chim. Pays-Bas*, **70**, 940 (1957).

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