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Registry No. 1, 71742-31-9; 2, 71611-77-3; 3, 3588-80-5; 4, 72659-47-3; 6, 83-31-8; 8, 10075-66-8; 9, 72659-48-4; 10, 72659-49-5; 11, 61836-40-6; 12, 72659-50-8; 8-amino-1-naphthalenesulfonic acid, 82-75-7.

Azlactone Oxidation

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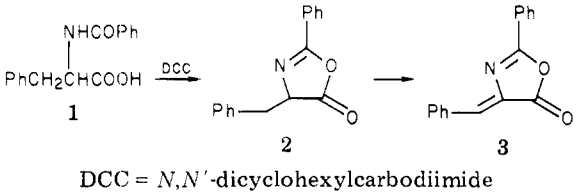
In our investigations into the synthesis of dehydropeptides, we saw at least two logical approaches: i.e., (1) the synthesis of dehydroamino acid derivatives followed by coupling of both the carboxyl and amino functions with other amino acids[1] and (2) the synthesis of dehydrodipeptides by direct oxidation[2] followed by coupling into the desired sequence. We have chosen to concentrate on the latter approach because it obviates the low-yield coupling of an activated amino acid derivative with an enamine nitrogen atom which is required in the first approach. Consequently, we have studied in some detail the oxidation of the carboxyl terminal amino acid of several dipeptides[2] and during these studies have used several *N*-benzoyl amino acids (e.g., 1) as models for the oxidation. We found



1 2 3

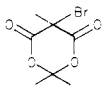
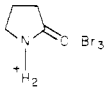
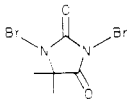
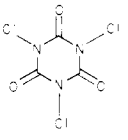
DCC = *N,N'*-dicyclohexylcarbodiimide

no reagent which would oxidize the acyl amino acid **1** itself, but azlactonization increased the susceptibility of the system to halogenation, to enolization and, consequently, to oxidation. This paper reports the results of a rather extensive investigation of the oxidation of several azlactones of the type **2**.

Azlactones have been previously halogenated[3] at the 4-position, albeit in low yields, for various purposes in the past. Initially we attempted to halogenate **2** by using bromine,[3a] *N*-bromosuccinimide (NBS), 2-pyrrolidinone hydrotribromide (PHT),[4] trichloroisocyanuric acid (TCIC),[5] isopropylidene 2-bromo-2-methylmalonate (Trost's reagent),[6] 1,3-dibromo-5,5-dimethylhydantoin (dibromantin),[7] and sulfuryl chloride.[3b] In most cases the reaction was carried out in carbon tetrachloride solution in the presence of solid potassium carbonate as proton acceptor. Table I shows the yields of **3** obtained by this halogenation–dehydrohalogenation method. In order to determine the possible effect of ring substituents on the yield of unsaturated azlactone, we prepared *N*-(*p*-methoxybenzoyl)- and *N*-(*p*-nitrobenzoyl)phenylalanine and oxidized them with a dibromantin/K_2CO_3 mixture. Yields of 47 and 54% of the 2-*p*-methoxyphenyl and 2-*p*-nitrophenyl azlactones, respectively, were obtained. The difference between these yields and that obtained from the unsubstituted compound appeared insignificant and indicated that electronic factors were unimportant in this reaction sequence.

Table I

$$2 \xrightarrow[CCl_4/K_2CO_3]{(O)} 3$$

reagent	yield, %[a]
Br_2	52[b]
SO_2Cl_2	43
 (NBS)	36[c]
 (Trost)	29
 (PHT)	47[d]
 (dibromantin)	54[e]
	44[f]

[a] Isolated yield. [b] 100-W bulb irradiation. [c] LiCl/$LiCO_3$/DMF used for the elimination. [d] THF used as solvent. [e] 100-W bulb and $(PhCO)_2O_2$. [f] Trace of $(PhCO)_2O_2$ added.

Table II

$2 \longrightarrow 3$

reagent	yield, %[a]	reagent	yield, %[a]
SeO_2/Ac_2O	55	$Pd(OAc)_2$[b]	23
$PhSeCl/H_2O_2$	28	DDQ/collidine[b]	31
t-BuOCl/K_2CO_3/Δ	66		

[a] Isolated yield. [b] Determined by quantitative high-pressure LC.

Table III

$4 \longrightarrow 3$

reagent	yield, %[a]	reagent	yield, %[a]
Br_2/K_2CO_3	62	DDQ	75
$Pd(OAc)_2$	24[b]		

[a] Isolated. [b] Determined by liquid chromatography.

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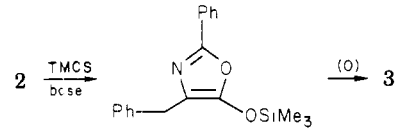
Other reagents tried in the 2→3 oxidation are enumerated in Table II. It has been reported[8] that an SeO_2/Ac_2O reagent is capable of oxidizing phenylsuccinic acid to phenylmaleic anhydride. In the case studied here, *N*-benzoylphenylalanine was azlactonized as expected by the acetic anhydride solvent prior to SeO_2 oxidation. Even though the 3 was produced in moderate yield and was sharp melting, the irritating odor of selenium easily detected in the solid makes this method unattractive. Treatment of 2 with a phenylselenyl chloride/Et_3N mixture in THF solution followed by 30% H_2O_2 gave only a 28% yield of 3 even though numerous reports[9] of the high efficacy of this method in the synthesis of α,β-unsaturated carbonyl compounds have appeared. Also, treatment of 2 with *tert*-butyl hypochlorite in carbon tetrachloride solution afforded a 4-chloro azlactone, as evidenced by a strong infrared band at 1836 cm^{-1}, which on heating with powdered potassium carbonate gave 3 in 66% yield.

Recent work on enol silyl ethers[10] has led us to prepare the trimethylsilyl enol ether 4 of 2 and to examine its



4

TMCS = $(CH_3)_3SiCl$

reactivity with various reagents (Table III). Bromination[11] of 4 followed by treatment of the 4-bromo azlactone with solid potassium carbonate in refluxing carbon tetrachloride gave 3 in 62% yield. The bromination occurred rapidly but the elimination step required 11 h. Palladium acetate[12] also oxidized 4, and as expected[13] the high-potential quinone dichlorodicyano-*p*-benzoquinone (DDQ) oxidized 4 in excellent yield.

It appears that the last method using DDQ and the enol silyl ether is the best oxidation procedure among those tried. The requirement that an aryl group be present on the β-carbon atom remains, however, even when the enol ether is used. Aliphatic amino acid azlactones are not oxidized by this method.

Experimental Section

Instrumentation. Melting points were determined on a Nalge micro hot stage or a Thomas-Hoover apparatus and are uncorrected. Infrared spectra (Nujol mull) were recorded on a Perkin-Elmer Model 257 or 631 recording spectrometer with polystyrene as the standard, and the proton NMR spectra were taken on a Varian HA-100 or T-60 spectrometer with tetramethylsilane as the internal or external standard. Elemental analyses were carried out by Atlantic Microlabs. Thin-layer chromatography was carried out on Kodak ultraviolet-sensitive silica gel sheets, which were visualized in a UV lamp box. Quantitative high-pressure LC analyses were recorded on a Waters Associates Model 6000 pump, equipped with a Waters Associates Model 440 UV detector (254 nm) and a 4.6 × 250 mm Partisil 10 column. Elution was carried out at a flow rate of 2.0 mL/min by using a 2:1 mixture of Burdick and Jackson glass-distilled hexane and ether. Yields were determined by a comparison of peak heights to those of standard solutions.

Materials. The α-amino acids were purchased from Sigma Chemical Co. and were used as received. *N*-Bromosuccinimide was recrystallized from water prior to use. Sulfuryl chloride was redistilled prior to use. Thionyl chloride was distilled from quinoline and then linseed oil. Pyridine and triethylamine were distilled from and stored over anhydrous barium oxide. Petroleum ether and diethyl ether were stored over sodium. Commercial selenium dioxide was sublimed before use. All other solvents and reagents were reagent grade and were used without further purification. Dioxane was dried over CaH_2 and stored over 4Å molecular sieves. Acetonitrile was dried and stored over 3Å molecular sieves. Silica gel 60 (40–63) μm) was supplied by F. Merck.

General Procedure for Unsaturated Azlactones (e.g., 3) from 1. To a solution of 10 mmol of 1 in 30 mL of THF was added 2.06 g (10 mmol) of DCC in 10 mL of THF. After the mixture was stirred at room temperature for 2 h, the *N,N'*-dicyclohexylurea (90%, mp 233 °C) was filtered. The filtrate was concentrated, and an infrared spectrum of the residue showed the following: 1830 (C=O), 1600 cm^{-1} (C_6H_5). The residue was dissolved in 35 mL of carbon tetrachloride. To this solution was added 10.2 mmol of a halogenating agent: SO_2Cl_2, NBS, Trost reagent, PHT, or bromine; 5.3 mmol of dibromantin or 3.5 mmol of trichloroisocyanuric acid. A catalytic amount of benzoyl peroxide was added, 3.0 g (21.8 mmol) of finely divided solid potassium carbonate was added immediately, and the resulting mixture was refluxed. At the end of this period the reaction mixture was diluted with chloroform and extracted with two 20-mL portions of H_2O. The organic layer was separated, dried (anhydrous $MgSO_4$), filtered, and concentrated in vacuo, and the residue was crystallized from 2-propanol: mp 164–166 °C (lit.[14] mp 164–166 °C); IR (Nujol) 1800, 1774 (C=O), 1655 (C=N), 1690 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.17 (s, 1 H, vinyl), 7.29–7.55 (m, 6 H, ArH), 8.08–8.18 (m, H, ArH).

Oxidation of 4 with K_2CO_3/Br_2. To a mixture of 4.0 mmol of 2 in 30 mL of dry CCl_4 containing 3.0 g (22 mmol) of finely divided anhydrous potassium carbonate was added 0.78 mL (6 mmol) of TMCS. After the mixture was stirred at room temperature for 6 h, 4 mmol of bromine was added, and this mixture was refluxed for 10 h. At the end of this time the reaction mixture was washed with two 30-mL portions of water and once with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo, leaving a crude solid residue which was crystallized from 2-propanol, mp 164–166 °C, identical with 3.

2-(*p*-Nitrophenyl)-4-benzylidene-2-oxazolin-5-one. To a solution of 1.38 g (4.4 mmol) of *N*-(*p*-nitrobenzoyl)-L-phenylalanine[15] in 25 mL of THF was added 0.9 g (4.4 mmol) of DCC in 10 mL of THF. After 1.5 h the *N,N'*-dicyclohexylurea was filtered (0.87 g); the filtrate was evaporated in vacuo, and the residue was triturated with CCl_4. A second crop of urea was filtered (0.24 g), and to the clear filtrate was added 0.66 g (2.3 mmol) of dibromantin, 1.52 g (11 mmol) of anhydrous K_2CO_3, and a trace of benzoyl peroxide. This mixture was refluxed 5 h, poured into a separatory funnel, diluted with $CHCl_3$, and washed three times with water. The organic layer was separated and dried with anhydrous Na_2SO_4, filtered, and evaporated in vacuo, leaving an orange oil. This was dissolved in $CHCl_3$, and hexane was added (5:1), yielding 0.38 g of 2-(*p*-nitrophenyl)-4-benzylidene-2-oxazolin-5-one, mp 232–235 °C. Concentration of the filtrate and dissolution in CH_3NO_2 gave another 0.32 g (total yield 54%) of product: mp 233 °C (lit.[16] mp 229 °C); IR (Nujol) 1810 (sh), 1790, 1770 (C=O), 1658 cm^{-1} (C=N).

2-(*p*-Methoxyphenyl)-4-benzylidene-2-oxazolin-5-one. The same procedure used for the synthesis of the *p*-nitro compound was followed here. The product, 2-(*p*-methoxyphenyl)-4-benzylidene-2-oxazolin-5-one, recrystallized from 5:1 chloro-

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form-hexane, mp 214-217 °C (lit.[17] mp 217 °C from ethanol), was obtained in 47% yield: IR (Nujol) 1785 (vs), 1765 (m), 1745 (w), (C=O), 1650 (C=N); NMR (TFA) δ 4.06 (s, 3 H, OCH_3), 7.23 (d, J = 10 Hz, 2 H), 7.39-7.90 (m, 6 H, vinyl H and C_6H_5), 8.33 (d, J = 10 Hz, 2 H).

Oxidation of 1 with SeO_2. A mixture of 1.0 g (3.72 mmol) of 1 in 25 mL of acetic anhydride containing 1 drop of pyridine and 0.67 g (6 mmol) of SeO_2 was refluxed for 18.5 h. After cooling, the mixture was diluted with ether to precipitate selenium, which was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in ether (300 mL) and washed three times with H_2O and then with saturated $NaHCO_3$ solution (until the washes were basic). The ether solution was dried (Na_2SO_4), filtered, and concentrated in vacuo, leaving a solid residue which was dissolved in hot isopropyl alcohol, yielding 0.51 g (55%) of 3, mp 163-166 °C.

Oxidation of 2 with Phenylselenyl Chloride/H_2O_2. To a solution of 0.77 g (3.55 mmol) of 2 in 40 mL of ethyl acetate was added 0.77 g (4 mmol) of PhSeCl. The solution was stirred 8 h at room temperature followed by 6 h at reflux. Triethylamine (0.49 mL, 3.55 mmol) was added, and 30 min later TEA·HCl (0.31 g, 60%) was filtered. To the filtrate was added 0.7 mL (8.0 mmol) of 30% H_2O_2, and this solution stirred at room temperature for 4 h. At the end of this time the solution was washed with two 25-mL portions of water and once with saturated Na_2CO_3 solution. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo, leaving a yellow solid residue. Crystallization from isopropyl alcohol gave 157 mg (21%) of crystalline 3, mp 165-167 °C.

Oxidation of 2 with *t*-BuOCl in the Presence of K_2CO_3. A mixture of 0.62 g (2.48 mmol) of 2, 0.4 mL (3.36 mmol) of *t*-BuOCl, and 2.0 g (14.5 mmol) of finely divided anhydrous K_2CO_3 in 60 mL of CCl_4 was stirred at room temperature for 16 h and then refluxed 6.5 h. The reaction mixture was filtered and concentrated to dryness in vacuo, leaving a yellow solid residue. A yield of 0.4 g (66%) of 3, mp 161-164 °C, was obtained by crystallization from isopropyl alcohol.

Oxidation of 2 with DDQ. To a dry three-necked flask was added 0.269 g (1.00 mmol) of 1, 0.206 g (1.00 mmol) of DCC, and 5 mL of dioxane under nitrogen. The mixture was stirred for 1 h at room temperature, the DCU was filtered by positive nitrogen pressure, and the filtrate was transferred to a flask containing 0.381 mL (3.00 mmol) of TMCS, 0.836 mL (6.00 mmol) of triethylamine, and 5 mL of dioxane under nitrogen. The mixture was stirred for 1 h and transferred to a flask containing 0.227 g (1.00 mmol) of DDQ and 0.124 mL (0.50 mmol) of disilylacetamide in 5 mL of dioxane under nitrogen. The reaction mixture was stirred 1 h and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed twice with saturated $NaHSO_3$, twice with saturated $NaHCO_3$, and once with saturated NaCl. The solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a yellow solid which was crystallized from 2-propanol to yield 187 mg (75%) of 3.

Oxidation of 2 with Palladium(II) Acetate. In a dry three-necked flask, 1.00 mmol of 1 was converted into 2 as before, and the filtrate was transferred into a flask containing 0.381 mL (3.00 mmol) of TMCS, 0.836 mL (6.00 mmol) of TEA, and 5 mL of dioxane under nitrogen. The mixture was stirred for 1 h, filtered by positive nitrogen pressure, and evaporated under reduced pressure to give a light yellow oil which was taken up in 3 mL of CH_3CN and transferred into a flask containing 0.225 g (1.00 mmol) of $Pd(OAc)_2$ in 3 mL of CH_3CN under nitrogen. The reaction mixture was stirred for 40 h at room temperature. Quantitative liquid chromatography detected 3 present in 24% yield. Filtration of the reaction mixture, followed by evaporation at reduced pressure, yielded a crude yellow solid which was purified on a 3 × 15 cm silica gel column by using 4% EtOAc in petroleum ether as the eluant. Fractions containing 3 were combined and evaporated under reduced pressure to give 39 mg (16% yield) of 3.

Oxidation of 4 with DDQ. To 0.269 g (1.00 mmol) of benzoylphenylalanine in 5 mL of dioxane was added 0.206 g (1.00 mmol) of DCC. The reaction was stirred for 1 h. The DCU was filtered and the filtrate transferred to a flask containing 0.227 g (1.00 mmol) of DDQ and 0.132 mL (1.00 mmol) of collidine in 1 mL of dioxane. The reaction was stirred for 24 h and yielded 30% of 3 by quantitative high-pressure LC.

Oxidation of 4 with Palladium Acetate. To 1.00 mmol of benzoylphenylalanine in 5 mL of dioxane was added 1.00 mmol of DCC. The reaction was stirred for 1 h and the DCU filtered. The dioxane was evaporated under reduced pressure to give an oil which was dissolved in 5 mL of acetonitrile and added to a flask containing 1.00 mmol of palladium(II) acetate in 1 mL of acetonitrile. The reaction was stirred for 24 h and yielded 23% of 3 by quantitative high-pressure LC.

Registry No. 1, 2566-22-5; 2, 21453-79-2; 3, 842-74-0; 4, 72659-38-2; 2-(*p*-nitrophenyl)-4-benzylidene-2-oxazolin-5-one, 15601-50-0; 2-(*p*-methoxyphenyl)-4-benzylidene-2-oxazolin-5-one, 34108-13-9; *N*-(*p*-nitrobenzoyl)phenylalanine, 24758-96-1; *N*-(*p*-methoxybenzoyl)phenylalanine, 59490-31-2.

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Preparation of Muconic Acid Anhydrides. Characterization of the 1-Oxacyclohepta-3,5-diene-2,7-dione Structure

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Several muconic acid anhydrides have been prepared from the corresponding *o*-benzoquinones by oxidation with monoperphthalic acid.[1-3] These species are synthetically useful intermediates for the formation of muconic acid derivatives by a simple hydrolytic ring opening.[2] There is a lack of information on the isolation and characterization of these cyclic anhydrides, presumably because of their tendency to undergo this facile ring cleavage to the open-chain systems. During our studies on the proposed new route to caprolactam involving the copper(II)-induced oxidation of phenol,[4,5] we uncovered carbon-carbon bond cleavage reactions that may proceed via muconic acid anhydride intermediates. In order to test this possibility we required pure samples of the substituted 1-oxacyclohepta-3,5-diene-2,7-dione derivatives 2, 4, and 6. In this report we describe a general method for preparation and isolation of these anhydrides and briefly discuss their structural features and several typical chemical transformations.

Results and Discussion

The required anhydrides were prepared simply by addition of a slight molar excess (10%) of *m*-chloroperbenzoic acid to a solution of the corresponding *o*-benzoquinones in dry methylene chloride at 0 °C. The oxidations were completed in 5-10 min as indicated by the initial deep-red clear solution turning to a heterogeneous light-yellow mixture. The majority of the generated *m*-chlorobenzoic

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