hydride, 108-24-7; benzoyl chloride, 98-88-4; acrylic anhydride, 2051-76-5; 2-oxocyclopentane-1-carboxanilide, 4874-65-1; 2-oxocyclohexane-1-carboxanilide, 51089-06-6; 2-oxocyclohexane-1-*N*-ethylcarboxanilide, 64163-89-9; 1-*N*-morpholinocyclohexene, 670-80-4; ethyl isocyanate, 109-90-0; 3-chloropropenoyl chloride, 3721-36-6; 2-aminocyclohexene-1-*N*-ethylcarboxamide, 64163-90-2; *N,N*-diethylacetoacetamide, 2235-46-3; β-amino-*N,N*-diethylcrotonamide, 64163-91-3.

Supplementary Material Available. Further synthetic details (7 pages) plus amplified mass spectral data and interpretation (16 pages). Ordering information is given on any current masthead page.

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(25) Acylation of the enamino nitrogen of a cis vinylogous urea should enhance existing chelation when possible in the vinylogous ureide product.
(26) Some reversion of the original deuteration of **12f** occurred in the mass spectrometer and could not be prevented even by deuterating the probe. Correcting for natural isotopic abundances, the actual molecular ion mass ratios for "dideuterio" **12f** were 0.08:0.52:1.00 for *m/e* values 210 (**12f**), 211 (**12f-d_1**), and 212 (**12f-d_2**), respectively. Observed mass ratios of 1.00:1.18:0.13 (corrected as above) for *m/e* values 165 (**17f**), 166 (**15f** and **17f-d_1**), and 167 (**15f-d_1**) respectively, agree quite well with those calculated, assuming the deuterium atoms in a sample of **12f-d_1** are divided equally between the two nitrogen atoms, and only a statistical preference exists between N–H and C–H cleavage when ethylamine is ejected by molecular ion **12f.**
(27) No irregularities are apparent in the 100-MHZ NMR spectrum of **12f** in $CDCl_3$, and it includes signals at δ 12.7 (s, 1 H, chelated) and 6.10 (t, J = 7 Hz, 1 H).

A New Reaction of Amino Acids: Conversion to Benzoxazoles

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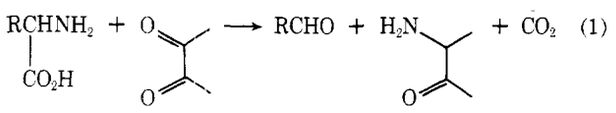
Reaction of α-amino acids with *o*-benzoquinones of type **3** is unique in that the expected Strecker degradation does not occur. We have observed that a decarboxylative condensation reaction takes place affording benzoxazoles. The new reaction appears to be general for α-amino acids and specific for quinones of type **3**.

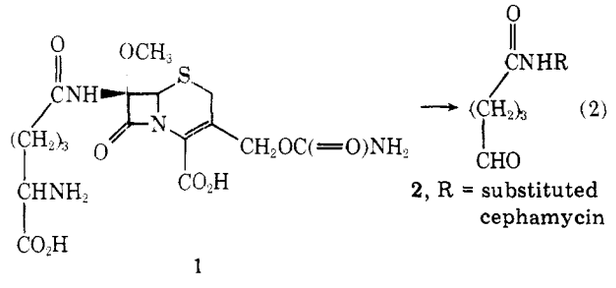
It has been reported that several diones (including *o*-quinones) oxidize α-amino acids to aldehydes while being reduced to α-amino carbonyls[1] (see eq 1). This reaction has been



(1)

termed[1] the "Strecker degradation" in honor of this discoverer.[2]

We were interested in oxidizing the antibiotic α-amino acid **1** to the corresponding aldehyde **2** (eq 2). The Strecker degradation appeared to be the most suitable method since the complexity and sensitivity of **1** warrants mild handling. Furthermore, the use of commercially available 3,5-di-*tert*-butylbzoquinone (**3**) appeared to be the most suitable dione since the steric bulk of the *tert*-butyl groups would prevent undesirable 1,4 addition of the amino acid, and the formation of an aromatic moiety (the reduced α-amino carbonyl now being an *o*-aminophenol) would provide a driving force for the oxidation–reduction process.



1 **2**, R = substituted cephamycin (2)

Results and Discussion

Amino acid **1** required 2 equiv of quinone **3** for complete reaction. However, instead of isolating the desired aldehyde **2** and the *o*-aminophenol, the benzoxazole **4** and catechol **5** were obtained (eq 3).

This oxidation reaction appears to be general for α-amino acids since alanine, α-aminoadipic acid, and phenylalanine all yielded the corresponding benzoxazoles[3] when treated with 2 equiv of **3**. The reaction with phenylalanine is complicated by a few minor side reactions; however, fair to good yields of pure products may be isolated by chromatography (see Experimental Section).

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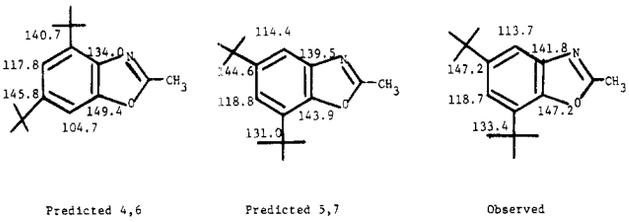
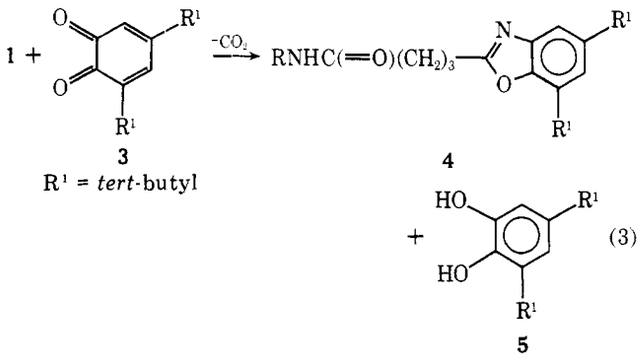
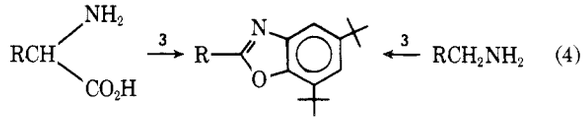


Figure 1. Predicted ^{13}C chemical shift values for 4,6- and 5,7-disubstituted benzoxazoles.[5] Experimental values for 6.



This unique reaction appears to be specific for 3,5-disubstituted quinones since complex mixtures were obtained with other diones (2,3-butanedione, 1,2-cyclohexanedione, 1,2-naphthoquinone, 9,10-phenanthroquinone, *o*-benzoquinone, and 4-*tert*-butylbenzoquinone). Furthermore, we were unable to obtain any evidence for oxazole formation with the above diones and alanine. The normal Strecker degradation occurs to some extent with these diones as indicated by the formation of some phenylacetaldehyde when phenylalanine was used. We feel that the propensity for amino acids to react in a 1,4 fashion with unsubstituted quinones removes the possibility for benzoxazole formation, which requires a 1,2 addition. Scheme I provides a suitable explanation for the formation of benzoxazoles from amino acids and *o*-quinones.

Benzoxazoles have also been prepared from primary amines of the type RCH_2NH_2[4] and quinone **3**. Thus, the reaction described herein establishes an analogy between certain primary amines and α-amino acids when reacted with quinone **3** (see eq 4). When **3** was allowed to react with either alanine or ethylamine, the same benzoxazole was obtained (**6**, R = CH_3) as shown by thin-layer chromatography, mass spectroscopy, and nuclear magnetic resonance spectroscopy, which also proves 5,7 disubstitution (see Figure 1).

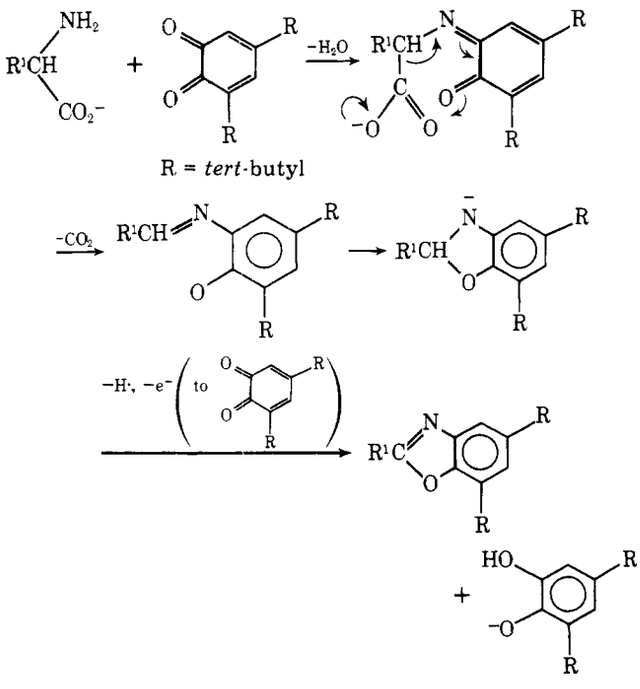


6

The reaction may be simplified by using 1 equiv of catechol in the presence of an oxidizing agent. In this manner alanine was converted in good yield to 2-methyl-5,7-di-*tert*-butylbenzoxazole by treatment of its tetraethylammonium salt with 1 equiv each of 3,5-di-*tert*-butylcatechol and manganese dioxide in acetonitrile for 20 min at room temperature. This modification avoids the necessity of performing the quinone and removing the equivalent of catechol formed from the oxidation of the intermediate (see Scheme I). Furthermore, the manganese dioxide is not necessary since stirring an acetonitrile solution of the amino acid salt and quinone in an open vessel for three days affords good yields of substituted benzoxazoles (see Experimental Section).

This new reaction of α-amino acids thus constitutes a viable method for preparing disubstituted (and higher) benzoxazoles.

Scheme I



Experimental Section

2-Methyl-5,7-di-*tert*-butylbenzoxazole (6). A solution of 0.445 g (5.00 mmol) of alanine and 2.95 g (5.00 mmol) of tetraethylammonium hydroxide, 25% aqueous solution, was concentrated at reduced pressure until about 180 mg of water remained. To the concentrate were added 50 mL of acetonitrile and 1.10 g (5.00 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone. The dark colored solution, after being stirred 3 days unstoppered, was concentrated at reduced pressure. The residue was taken up in diethyl ether and extracted twice with H_2O, once with dilute HCl (aqueous), twice with H_2O, and twice with saturated NaCl (aqueous). The ether solution was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to give 1.09 g (80%) of **6**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.39 (d, J = 2 Hz, 1 H), 7.20 (d, J = 2 Hz, 1 H), 2.55 (s, 3 H), 1.46 (s, 9 H), 1.37 (s, 9 H); mass spectrum, *m/e* 245 (M^+, 17), 230 (1000, 174 (15).

2-Benzyl-5,7-di-*tert*-butylbenzoxazole (7). A solution of 0.540 g (8.88 mmol) of 88.8% sodium methoxide and 1.467 g (8.88 mmol) of β-phenylalanine in 60 mL of methanol was concentrated at reduced pressure to 16 mL. 3,5-Di-*tert*-butyl-*o*-benzoquinone (1.954 g, 8.88 mmol) was added, and the reaction mixture was stirred for 18 h. The reaction was partitioned between ice water and diethyl ether, the layers were separated, and the organic phase was extracted twice with 1 N NaOH, twice with H_2O, and once with saturated NaCl (aqueous). the organic phase was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was taken up in hexane and chromatographed on silica gel (hexane–Et_2O, 20:1) to give 0.451 g (32%) of **7**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.44 (d, J = 2 Hz, 1 H), 7.26 (broad s, 6 H), 4.25 (s, 2 H), 1.41 (s, 9 H), 1.34 (s, 9 H).

5,7-Bis(*tert*-butyl)-2-benzoxazolylbutanoic Acid (8). To a solution of 243 mg (4 mmol) of 88.8% sodium methoxide and 322 mg (2 mmol) of aminoadipic acid in 10 mL of methanol was added 441 mg (2 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone. After 15 min, the dark blue solution was concentrated at reduced pressure. The residue was partitioned between ice water and diethyl ether, the layers were separated, and the aqueous phase was further extracted until the ether layer was colorless. The aqueous phase was adjusted to pH 2.5 and extracted twice with diethyl ether. The latter ether extracts were dried ($MgSO_4$), filtered, and concentrated at reduced pressure to afford 330 mg (52%) of **8**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.50 (d, J = 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 3.69 (s, 3 H), 2.99 (broad t, J = 7 Hz, 2 H), 1.90–2.60 (complex m, 4 H), 1.45 (s, 9 H), 1.34 (s, 9 H); mass spectrum, *m/e* 331 (M^+, 14), 316 (22), 299 (22), 258 (100), 232 (45).

7-[5,7-Bis(*tert*-butyl)-2-benzoxazolyl]butyramido-3-hydroxymethyl-7-methoxy-3-cephem-4-carboxylic Acid Carbamate (4). A solution of 1.22 g (20 mmol) of 88.8% sodium methoxide in 150 mL of methanol was cooled to −5 °C and charged with 10.0 g (20

mmol) of 1. Upon dissolution, 4.41 g (20 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone was added, the reaction stirred 1 h, an additional 4.41 g (20 mmol) of the quinone added, and stirring continued for 30 min. The reaction was partitioned between ice water and diethyl ether, the pH was adjusted to 8, the layers were separated, and the aqueous phase was extracted three more times with ether. The combined ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to yield 8.07 g (67%) of 4:[3] NMR (acetone-d_6, internal Me_4Si) δ 8.27 (broad s, 1 H), 7.48 (d, J = 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 5.91 (broad s, 2 H), 5.12 (s, 1 H), 4.86 (AB center, J = 13 Hz, 2 H), 3.82 (s, 3 H), 3.48 (broad s, 5 H), 3.07 (broad t, 2 H), 2.16–2.75 (complex m, 4 H), 1.47 (s, 9 H), 1.35 (s, 9 H); mass spectrum (methyl ester), *m/e* 616 (M^+, 11), 615 (26), 555 (61), 554 (100).

Registry No.—**1**, 64162-09-0; **3**, 3383-21-9; **4**, 64130-72-9; **6**, 64130-73-0; **7**, 64147-38-2; **8**, 64130-74-1; alanine, 56-41-7; β-phenylalanine, 63-91-2; aminoadipic acid, 542-32-5.

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(5) The ^{13}C NMR chemical shifts and ^1H–^{13}C coupling constants of **6** allow unequivocal assignment of the substitution pattern. Although substituent effects are not strictly additive, especially when ortho groups are present, the predicted chemical shifts using benzoxazole and *tert*-butylbenzene as models correlated well for a 5,7-disubstituted benzoxazole when used in conjunction with ^1H–^{13}C coupling data. Long-range ^1H–^{13}C coupling constants can be structurally useful especially in aromatic systems where the most significant long-range coupling is via a three-bond pathway.[6] In **6**, the aromatic carbons bearing hydrogen (113.7 and 118.7 ppm) can easily be determined from the large one-bond couplings, and they each exhibit a single three-bond coupling. The carbon resonanances at 147.2 and 133.4 ppm must be assigned to those bearing *tert*-butyl groups, due to long range couplings with the *tert*-butyl hydrogens. Of the two remaining aromatic signals, the one at 141.8 ppm shows no long-range coupling, while the signal at 147.2 ppm is a triplet ($J \cong$ 10 Hz), demanding two ring hydrogens which are at a distance of three bonds. The predicted chemical shift values (see Figure 1) clearly support the 5,7 isomer while ruling out 4,6 disubstitution.
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Photoproducts of Thymine and Uracil. Syntheses of the Four Bipyrimidine Combinations

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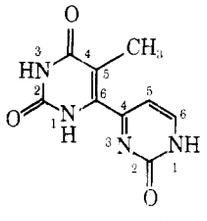
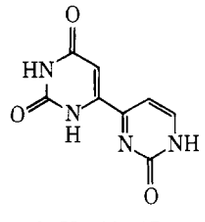
Convenient first syntheses have been devised for the following bipyrimidines: 6-(2-hydroxypyrimidin-4-yl)thymine, Thy(6-4)Pyo (**1**); 6-(2-hydroxypyrimidin-4-yl)uracil, Ura(6-4)Pyo (**2**); 6-(2-hydroxy-5-methylpyrimidin-4-yl)thymine, Thy(6-4)m^{5}Pyo (**3**); and 6-(2-hydroxy-5-methylpyrimidin-4-yl)uracil, Ura(6-4)m^{5}Pyo (**4**). The first three of these are among the non-cyclobutane photoproducts resulting from DNA or from frozen aqueous solutions of thymine, thymidine, uracil, or uridine under appropriate conditions. The synthetic methodology involved (1) the combination of 6-lithiopyrimidines with β-alkoxyacroleins, (2) oxidation to the corresponding masked β-dicarbonyl intermediates, (3) condensation of these with guanidine carbonate to form substituted aminobipyrimidines, and (4) diazotization and hydrolysis to furnish the desired products **1–4**. The spectroscopic properties, especially the ultraviolet excitation and fluorescence emission, are of special interest within the series and in comparison with the photoproducts of natural origin.

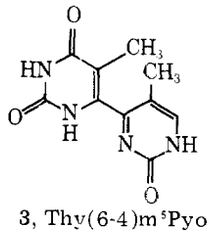
Considerable interest has been displayed in the isolation and identification of photoproducts of DNA as a means of investigating possible photobiological implications. Along with the familiar pyrimidine photodimers of the cyclobutane structure,[1] a series of bipyrimidine photoproducts has been accumulated by Wang and Varghese, exemplified by formulas **1–3**.[2] (As drawn, these formulas are not intended to portray a preferred torsional geometry.) The first of these, Thy(6-4)Pyo (**1**),[3] was identified as a product from the trifluoroacetic acid hydrolysates of DNA irradiated with far-UV light[4–6] and from photolysis of a frozen solution of thymine and uracil.[7] Ura(6-4)Pyo (**2**) was isolated from the UV irradiation of uracil in frozen aqueous solution[8] and from the acid hydrolysates of uridine irradiated in frozen aqueous solution.[9] Thy(6-4)-m^{5}Pyo (**3**) was obtained from the UV irradiation of frozen solutions of thymine[10,11] and of thymidine,[12] followed by acid treatment.



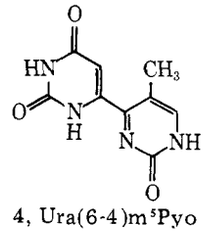
1, Thy(6-4)Pyo



2, Ura(6-4)Pyo



3, Thy(6-4)m^{5}Pyo



4, Ura(6-4)m^{5}Pyo

As part of our continuing interest in the structure determination and synthesis of nucleic acid radiation products,[13–17] we have devised unequivocal syntheses of compounds **1–3** which also provide independent confirmation of their assigned structures. We have also synthesized Ura(6-4)m^{5}Pyo (**4**) as a potential photoproduct which is theoretically accessible by a photoadduction pathway similar to that suggested for Ura(6-4)Pyo.[9]

An examination of the literature discloses several synthetic routes to bipyrimidines. Symmetrical 2,2′-, 4,4′-, and 5,5′-bipyrimidines have been obtained via an Ullmann or a Busch coupling reaction.[18,19] Symmetrical 4,4′- and 5,5′-bipyrimidines have also been prepared via construction of the carbon backbone followed by condensation with 2 equiv of a urea derivative.[20–23] Unsymmetrical 2,2′- and 2,4′-bipyrimidines

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