Synthesis of a Model Depsipeptide Lactone Related to the Quinoxaline Antibiotics

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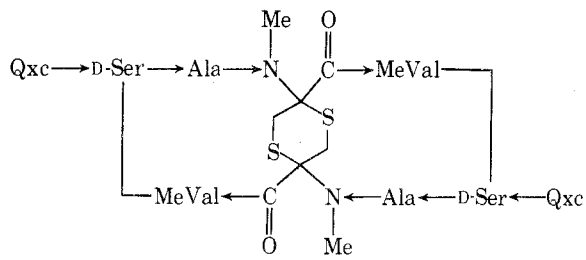
The depsipeptide lactone, *N*-benzyloxycarbonyl-L-seryl-L-alanyl-5-aminovaleryl-L-valine (serine hydroxyl) lactone (**2**), has been synthesized as a simple synthetic model for a portion of the depsipeptide lactone moiety common to the quinoxaline antibiotics. Synthesis involved condensation of *N*-benzyloxycarbonyl-L-serine 2,4-dinitrophenyl ester with L-alanine 4-(methylthio)phenyl ester to give dipeptide **6**. Depsipeptide bond formation in the preparation of tridepsipeptide **7** was effected using *N,N'*-dicyclohexylcarbodiimide in pyridine. Condensation of deblocked **7** with *N-tert*-butyloxycarbonyl-5-aminovaleric acid gave tetradepsipeptide **8**. Cyclization to give depsipeptide lactone **2** was effected by oxidation of **8** to the 4-(methylsulfonyl)phenyl active ester, deprotection, and cyclization under conditions of high dilution.

The quinoxaline antibiotics[1] are a group of bicyclic depsipeptide antibiotics that have been reported active against gram-positive bacteria[2] and certain tumors,[3] and to inhibit RNA synthesis.[4] Echinomycin (**1**), a representative



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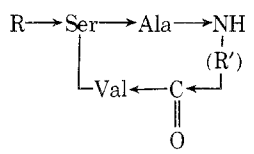
Qxc = 2-quinoxalinecarbonyl



2, R = carbobenzoxy; R' = $-(CH_2)_4-$

3, R = Qxc; R' = 1,4-cyclohexylene

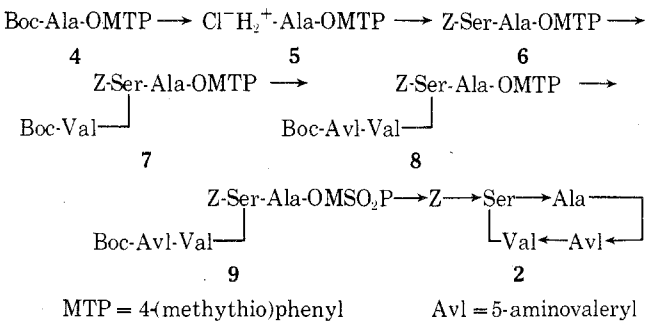
member of the above antibiotics, originally was reported[1a] to possess two 16-membered peptide lactone rings composed of a unit each of L-alanine, D-serine, and L-*N*-methylvaline and interconnected by a 1,4-dithiane amino acid moiety formally derivable from two *N*-methyl-L-cysteine residues; the lactone bonds are found to occur between the serine and valine residues. The structure of echinomycin recently has been revised[5] in which a thioacetal group is present rather than the dithiane moiety.

Pursuant to the synthesis of echinomycin, the depsipeptide lactone, *N*-benzyloxycarbonyl-L-seryl-L-alanyl-5-aminovaleryl-L-valine (serine hydroxyl) lactone (**2**), has been prepared as a simple synthetic model for a portion of the depsipeptide sequence common to the quinoxaline antibiotics.

An initial goal was to incorporate *cis*-4-aminocyclohexanecarboxylic acid[6] into a model system (**3**) representing hemiechinomycin. However, attempts to do so were not successful and 5-aminovaleric acid was used, therefore, in place of the above cyclohexane amino acid to provide a model system containing the same ring size as well as the tridepsipeptide sequence of *O*-(valyl)serylalanyl present in hemiechinomycin. The model lactone **2** includes substitution of L-serine for D-serine, and absence of *N*-methylamino acids and of the 2-quinoxalinecarbonyl function as normally found in the quinoxaline antibiotics.

N-tert-Butyloxycarbonyl-L-alanine was converted to the 4-(methylthio)phenyl ester **4** by condensation with 4-(methylthio)phenol[7] using *N,N'*-dicyclohexylcarbodiimide. The rationale[8] for use of the 4-(methylthio)phenyl ester as a carboxyl protective group relates to the fact that this group subsequently can be activated to the 4-(methylsulfonyl)phenyl active ester for use in the final cyclization step.

Deprotection of **4** with hydrogen chloride in acetic acid yielded L-alanine 4-(methylthio)phenyl ester hydrochloride (**5**) in a yield of 85%. Coupling of **5** with the known[9] 2,4-dinitrophenyl ester of *N*-benzyloxycarbonyl-L-serine furnished dipeptide **6** in 85% yield.



MTP = 4-(methythio)phenyl Avl = 5-aminovaleryl

MSO_2P = 4-(methylsulfonyl)phenyl

Formation of the depsipeptide bond in **7** was effected in 95% yield by condensation of dipeptide **6** with an excess of *N-tert*-butyloxycarbonyl-L-valine using *N,N'*-dicyclohexylcarbodiimide in pyridine.[10] Attempts at depsipeptide bond formation employing the carbonyldiimidazole or the mixed anhydride methods were not successful.

The *tert*-butyloxycarbonyl group in tridepsipeptide **7** was selectively removed with 70% trifluoroacetic acid,[11] followed by condensation with *N-tert*-butyloxycarbonyl-5-aminovaleric acid via the carbodiimide method to give tetradepsipeptide **8** in 63% yield. Oxidation[12] of the 4-(methylthio)phenyl ester in **8** with *m*-chloroperoxybenzoic acid gave in 91% yield the 4-(methylsulfonyl)phenyl ester **9**. Treatment of **9** with trifluoroacetic acid for 0.5 hr was followed by cyclization in chloroform containing 2% triethylamine to give cyclic depsipeptide **2** in 79% yield. The overall yield of depsipeptide **2** from L-alanine 4-(methylthio)phenyl ester **5** was 37%.

These studies provide a model for approaches to the synthesis of the quinoxaline antibiotics. The tridepsipeptide **7** should prove to be a key intermediate in future studies. Thus, incorporation into **7** of an appropriate cystine derivative would provide an approach to the triostin family of the above antibiotics, while incorporation of other amino

acid moieties would allow preparation of analogs and of other model systems that may be of interest.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian A-60 or XL-100 spectrometer. Infrared spectra were recorded on a Beckman IR-20A spectrophotometer. Solvents were removed in vacuo on a Buchler rotary evaporator. Thin layer chromatography was performed on commercially available silica gel plates with or without fluorescence indicator; components were located under ultraviolet irradiation and with iodine vapors. The solvent system used was chloroform–methanol–acetic acid (85:10:5). Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

***N*-*tert*-Butyloxycarbonyl-L-alanine 4-(Methylthio)phenyl Ester (4).** Using the method reported by Johnson and Trask,[7] 7.56 g (40 mmol) of *N*-*tert*-butyloxycarbonyl-L-alanine was dissolved in 80 ml of methylene chloride, following which 8.64 g (42 mmol) of *N,N'*-dicyclohexylcarbodiimide was added. After stirring for 10 min at room temperature, 5.88 g (42 mmol) of 4-(methylthio)phenol was added and the reaction mixture was stirred overnight at room temperature. The dicyclohexylurea was removed by filtration and washed with methylene chloride. The filtrate was washed with 10% sodium bicarbonate and water and the solid obtained was recrystallized from ethyl acetate–hexane to give 8.9 g (72%) of **4**: mp 93–95°; TLC R_f 0.83; $[\alpha]^{20}D$ −56° (*c* 1.5, EtOH); NMR ($CDCl_3$) δ 7.1 (q, 4 H, *S*-phenyl), 5.2 (d, 1 H, NH), 4.5 (m, 1 H, α-H), 2.5 (s, 3 H, *S*-methyl), 1.5 (d, 12 H, alanyl methyl, *tert*-butyl), Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.9; H, 6.79; N, 4.49. Found: C, 58.05; H, 6.81; N, 4.36.

L-Alanine 4-(Methylthio)phenyl Ester Hydrochloride (5). *N*-*tert*-Butyloxycarbonyl-L-alanine 4-(methylthio)phenyl ester (**4**, 7.0 g, 22.5 mmol) was dissolved in 50 ml of saturated hydrogen chloride in glacial acetic acid and allowed to stand overnight at room temperature. Addition of dry ether precipitated the hydrochloride, which was recrystallized from methanol–diethyl ether to yield 4.7 g (85%) of **5**: mp 180–182°; TLC R_f 0.31; $[\alpha]^{20}D$ +4° (*c* 1.5, EtOH); NMR (trifluoroacetic acid) δ 7.4 (m, 4 H, phenyl), 4.6 (m, 1 H, α-H), 2.5 (s, 3 H, *S*-methyl), 1.9 (d, 3 H, alanyl methyl). Anal. Calcd for $C_{10}H_{14}ClNO_2S$: C, 48.5; H, 5.69; N, 5.66; Cl, 14.33. Found: C, 48.35; H, 5.70; N, 5.51; Cl, 14.49.

***N*-Carbobenzoxy-L-seryl-L-alanine 4-(Methylthio)phenyl Ester (6).** To a solution of 4.72 g (19 mmol) of L-alanine 4-(methylthio)phenyl ester hydrochloride (**5**) in 120 ml of chloroform was added 2.04 g (20 mmol) of triethylamine and 7.70 g (19 mmol) of *N*-carbobenzoxy-L-serine 2,4-dinitrophenyl ester.[9] The reaction mixture was stirred overnight at room temperature, during which time the product precipitated from the solution. The precipitate was filtered and washed with ethyl acetate to give 5.03 g of white solid, mp 169–170°. The filtrate was evaporated in vacuo and the residue was washed with 10% sodium bicarbonate, water, and 10% citric acid and triturated with ether to give 2.65 g of a white solid, mp 167–168°. Both solids were combined and recrystallized from ethyl acetate–ethanol to yield 7.0 g (85%) of product. It was observed that the above 2,4-dinitrophenyl ester, and on occasion **5**, showed a second component on TLC analysis. However, use of these less pure materials did not affect the yield or purity of **6**: TLC R_f 0.76; $[\alpha]^{20}D$ −35° (*c* 1.5, DMF); NMR (Me_2SO-d_6) δ 7.2 (q, 9 H, benzyl aromatic and *S*-phenyl), 5.2 (s, 2 H, benzyl), 5.0–4.0 (m, 2 H, α hydrogens), 3.7 (d, 2 H, seryl methylene), 3.5 (s, 1 H, OH), 2.5 (s, 3 H, *S*-methyl), 1.4 (d, 3 H, alanyl methyl). Anal. Calcd for $C_{21}H_{24}N_2O_6S$: C, 58.3, H, 5.61; N, 6.48. Found: C, 58.45; H, 5.43; N, 6.45.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-L-valyl)-L-alanine 4-(Methylthio)phenyl Ester (7).** To a precooled solution of *N*-carbobenzoxy-L-seryl-L-alanine 4-(methylthio)phenyl ester (**6**, 7.68 g, 17.7 mmol) and *N*-*tert*-butyloxycarbonyl-L-valine (6.41 g, 29.5 mmol) in 100 ml of anhydrous pyridine was added 6.46 g (31.3 mmol) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred for 4 hr at 0° and then overnight at room temperature. The solvent was removed in vacuo; ethyl acetate was added to the residue and precipitated dicyclohexylurea was removed by filtration. The filtrate was evaporated in vacuo and the material obtained was recrystallized from ethyl acetate–petroleum ether (bp 60–90°) to afford 10.58 g (95%) of **7**: mp 128–130°; TLC R_f 0.92; ir (film) carbonyl absorption at 1740, 1690, 1670 cm^{-1}; $[\alpha]^{20}D$ −32° (*c* 1.5, EtOH); NMR ($CDCl_3$) δ 7.3 (m, 10 H, NH, *S*-phenyl, and benzyl aromatic), 6.0 (d, 1 H, NH), 5.2–3.8 (m, 8 H, NH, benzyl, α hydrogens, seryl methylene), 2.4 (s, 3 H, *S*-methyl), 2.3–1.7 (m, 1 H, valyl methine), 1.5 (d, 12 H, alanyl methyl and *tert*-butyl), 0.8 (q, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{31}H_{41}N_3O_9S$: C, 58.9; H, 6.55; N, 6.65. Found: C, 58.99; H, 6.41; N, 6.64.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-alanine 4-(Methylthio)phenyl Ester (8).** *N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-L-valyl)-L-alanine 4-(methylthio)phenyl ester (**7**, 8.0 g, 12.7 mmol) was dissolved in 50 ml of 70% aqueous trifluoroacetic acid and the solution was allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in 100 ml of ethyl acetate. The ethyl acetate solution was washed three times each with cold 10% sodium bicarbonate solution and saturated sodium chloride solution and was dried over anhydrous sodium sulfate. Evaporation in vacuo gave 4.96 g of a white solid which was dissolved in 90 ml of methylene chloride. The reaction mixture was cooled to 0° and 2.16 g (9.9 mmol) of *N*-*tert*-butyloxycarbonyl-5-aminovaleric acid[13] and 2.03 g (9.9 mmol) of *N,N'*-dicyclohexylcarbodiimide were added. The reaction mixture was stirred at 0° for 1 hr and then at room temperature overnight. The dicyclohexylurea was removed by filtration and washed with methylene chloride. The filtrate was evaporated in vacuo and the residue was crystallized from chloroform–petroleum ether (bp 90–120°) to yield 5.86 g (63%) of product, mp 157–160°. The product was recrystallized from chloroform–ether: mp 163–166°; TLC R_f 0.62; $[\alpha]^{23}D$ −20° (*c* 1.5, DMF(: NMR ($CDCl_3$) δ 7.7 (d, 1 H, NH), 7.1 (q, 9 H, *S*-phenyl and benzyl aromatic), 6.3 and 5.9 (two d, 2 H, NH), 5.1 (s, 2 H, benzyl), 4.9–4.0 (m, 5 H, α hydrogens and seryl methylene), 3.1 (m, 2 H, valeryl H-5), 2.5 (s, 3 H, *S*-methyl), 2.4–1.2 (m, 19 H, valeryl H-2 to 4, alanyl methyl, valyl methine), 0.8 (d, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{36}H_{50}N_4O_{10}S$: C, 59.2; H, 6.89; N, 7.66. Found: C, 59.40; H. 6.82; N, 7.74.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(Methylsulfonyl)phenyl Ester (9).** To a solution of 5.60 g (7.7 mmol) of *N*-carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(methylthio)phenyl ester (**8**) in 90 ml of dioxane was added 4.10 g (23.8 mmol) of *m*-chloroperoxybenzoic acid. After stirring overnight at room temperature, the solvent was removed in vacuo. The residue was dissolved in 90 ml of chloroform and washed with cold 10% sodium bicarbonate and cold saturated salt-solution. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed in vacuo to give 5.29 g of white solid, which was recrystallized from chloroform–petroleum ether (bp 60–90°) to yield 5.10 g (91%) of **9**: mp 133–136°; TLC R_f 0.65; $[\alpha]^{23}D$ −14° (*c* 1.5, DMF); NMR ($CDCl_3$) δ 8.1–7.2 (m, 10 H, *S*-phenyl and benzyl aromatic), 6.4 and 5.9 (two d, 2 H, NH), 5.1 (s, 2 H, benzyl), 4.9–4.0 (m, 5 H, α hydrogens and seryl methylene), 3.05 (m, 5 H, *S*-methyl and valeryl H-5), 2.5–1.1 (m, 19 H, valeryl H-2 to 4, valyl methine, alanyl methyl, *tert*-butyl), 0.9 (d, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{36}H_{50}N_4O_{12}S$: C, 56.7; H, 6.60; N, 7.34. Found: C, 56.58; H, 6.70; N, 7.14.

***N*-Carbobenzoxy-L-seryl-L-alanyl-5-aminovaleryl-L-valine (Serine Hydroxyl) Lactone (2).** *N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(methylsulfonyl)phenyl ester (**9**, 5.0 g, 6.6 mmol) was dissolved in 22 ml of trifluoroacetic acid. After standing for 0.5 hr, the solvent was removed in vacuo. The residue was dissolved in 60 ml of chloroform and this solution was added dropwise over a period of 4 hr to a stirred solution of 2% triethylamine in chloroform (900 ml). After stirring for 2 days, the chloroform solution was washed with 10% sodium bicarbonate, saturated sodium chloride solution, and 10% citric acid solution. The solution was dried over anhydrous sodium sulfate and evaporated in vacuo to give 2.8 g of white solid. The product was recrystallized from chloroform–ether to yield 2.55 g (79%) of **2**: mp 262–264°; TLC R_f 0.45, 0.76 (EtOH–H_2O, 80:20), 0.67 (*n*-BuOH–AcOH–H_2O, 4:1:1); $[\alpha]^{23}D$ −57 (*c*, 1.5, DMF); ir (film) carbonyl absorption at 1725, 1685, 1635, and 1530 cm^{-1}; NMR (trifluoroacetic acid) δ 7.8 (d, 4 H, NH), 7.4 (s, 5 H, benzyl aromatic), 5.3 (s, 2 H, benzyl), 4.8 (s, 5 H, α hydrogens and seryl methylene), 3.3–1.3 (m, 12 H, valeryl, alanyl methyl, and valyl methine), 1.1 (d, 6 H, valyl isopropyl hydrogens); mol wt (osmometry) 486 ± 20 (DMF, 37°). Anal. Calcd for $C_{24}H_{34}O_7N_4$: C, 58.8; H, 6.98; N, 11.4. Found: C, 58.5; H, 6.98; N, 11.0.

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Registry No.—**2**, 56411-59-7; **4**, 56411-60-0; **5**, 56411-61-1; **6**, 56411-62-2; **7**, 56411-63-3; **8**, 56411-64-4; **9**, 56411-65-5; *N*-*tert*-butyloxycarbonyl-L-alanine, 15911-69-0; 4-(methylthio)phenol, 1073-72-9; *N*-carbobenzoxy-L-serine 2,4-dinitrophenyl ester, 5249-65-0; *N*-*tert*-butyloxycarbonyl-L-valine, 13734-41-3; *N*-*tert*-butyloxycarbonyl-5-aminovaleric acid, 27219-07-4; *m*-chloroperoxybenzoic acid, 937-14-4.

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Structures of the 1:1:1 Adducts of the "Nitroso–Isonitrile–Isocyanate" Reaction. Possible Intermediacy of a Carbodiimide *N*-Oxide[1]

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Reaction of a nitrosoalkane with an isonitrile in the presence of an isocyanate affords 1:1:1 adducts, $RR'R''C_2N_3O_2$. Adducts **1** (R = R′ = R″ = *tert*-butyl) and **2** (R = *tert*-butyl; R′ = R″ = phenyl) are substituted 3-imino-1,2,4-oxadiazolidin-5-ones (C), proved by synthesis from the corresponding carbodiimides. Adducts **3** (R = *tert*-butyl; R′ = isopropyl; R″ = phenyl) and **4** (R = R′ = *tert*-butyl; R″ = phenyl) are assigned as substituted 2-imino-1,3,4-oxadiazolidin-5-ones (D) based on acid-catalyzed conversion to **13a** and **13b** (assigned as 3-amino-1,3,4-oxadiazolin-5-ones) and on base-catalyzed isomerization to substituted 1,3,4-triazolidine-2,5-diones (F, **16a**, **16b**), proved by synthesis. Adduct **5** is assigned as a substituted 3,5-diimino-1,4,2-dioxazolidine (A) on the basis of thermal isomerization to **4** and decomposition to di-*tert*-butyldiaziridinone (**19**, R = R′ = *tert*-butyl) and phenyl isocyanate. The relation of these structures to the course of the "nitroso–isonitrile–isocyanate" reaction is discussed. The results are in good agreement with the earlier suggestion of the intermediacy of a carbodiimide *N*-oxide (from RNO + RNC) and trapping of this species by the isocyanate. Adduct **1** loses carbon dioxide at 150°, affording tri-*tert*-butyldiaziridinimine (**10**), providing a new entry to this novel small-ring heterocyclic system.

Some years ago we described a novel route to a small-ring heterocyclic system: reaction of a nitrosoalkane with an isonitrile to give a diaziridinone (diazacyclopropanone) (Scheme I). Several lines of evidence pointed to an intermediate. In the presence of R″NCO (the best trapping agents were alkyl or aryl isocyanates), no diaziridinone was observed; instead, adducts of composition RNO + R′NC + R″NCO were formed. The rate of disappearance of RNO and R′NC was independent of the concentration of R″NCO. The intermediacy of a carbodiimide *N*-oxide was suggested. Heterocycles of type A and C (Scheme I) seemed the best candidates for the 1:1:1 adducts. In this paper, the structures of several of the adducts are established, both supporting Scheme I and providing some unexpected extensions.

Results

The adducts **1–5** are listed in Table I. Adducts **1–4**, although showing some differences in the infrared carbonyl region, were generally similar in mass spectra (primary fragmentation patterns are loss of carbon dioxide and isobutylene units),[2] in thermal stability (decomposition at 120°), and in sensitivity to acid. Adduct **5**, a much more labile material, differed from **1–4** in the infrared (e.g., compare the similarly substituted **3** vs. **5**), and in mass spectra (loss of R′NCO, no primary loss of carbon dioxide). Thermal decomposition of **5** at 80° afforded a mixture of **4**, diaziridinone, and phenyl isocyanate.[2] Our hypothesis early in the present study was that adducts **1–4** were heterocycles of type C (Scheme I) (3-imino-1,2,4-oxadiazolidin-5-one) and that adduct **5** was of type A (3,5-diimino-1,4,2-dioxazolidine). This hypothesis, shown to be correct for **1** and **2**, facilitated establishment of structure C for these adducts. As will be shown later in the paper, adducts **3** and **4** do *not* possess structure C. Structure A remains the best formulation for **5**.

Table I
1:1:1 Adducts, Composition $RR'R''C_2N_3O_2$ (RNO + R′NC + R″NCO)

Compd	R	R′	R″	Ir, cm^{-1}
1	*t*-Bu	*t*-Bu	*t*-Bu	1789, 1700
2[a]	*t*-Bu	C_6H_5	C_6H_5	1804, 1687
3	*t*-Bu	*i*-Pr	C_6H_5	1809, 1717
4	*t*-Bu	*t*-Bu	C_6H_5	1811, 1710
5	*t*-Bu	*t*-Bu	C_6H_5	1775, 1700

[a] Minor one of three adducts (**2**, **4**, and **5**) isolated from reaction of $(CH_3)_3CNO$, $(CH_3)_3CNC$, and C_6H_5NCO (see ref 2).

Adducts 1 and 2. Concentrated hydrochloric acid effected rapid loss of a *tert*-butyl group. The structures of the new products, **6a** and **6b**, were established by synthesis in high yield from the carbodiimides **7a** and **7b** (Scheme II). Assignment of the endocyclic C=N structure to **6** rather than the tautomeric exocyclic C=N form is based on the