was evaporated and chromatographed on 40 g of alumina. Methylene chloride fractions (500 mL) gave 0.84 g (15%) of **29** as yellow solid: mp 202–204 °C (lit.[22] mp 191 °C); NMR (CD_3CN) δ 5.80 (br, 2 H, exchange with D_2O), 7.15 (m, 3 H, *m*- and *p*-H), 7.50 (m, 2 H, *o*-H), 8.01 (s, 1 H, NCH).

Reaction of DISN with Norbornadiene. A solution of 32 g (0.30 mol) of DISN and 50 g of freshly distilled norbornadiene in 320 mL of CH_3CN was stirred at 25 °C under nitrogen for 7 days and evaporated. The black gummy solid was extracted with four 150-mL portions of hot CH_2Cl_2. The insoluble gummy solid was recrystallized from CH_3CN and identified as 1,4-diamino-1,2,5-tricyano-3,6-diazahexatriene 17[2c] by IR.

The CH_2Cl_2 extracts gave upon concentration 3.23 g of a greenish yellow solid, which was recrystallized twice from ethyl acetate to give 1-substituted 1,4,4a,5,8,8a-hexahydro-5,8-methanoquinoxaline-2,3-dicarbonitrile **31**: UV (C_2H_5OH) 395 nm (ε 15 700), 320 (11 000), 240 sh (9750); IR (KBr) 3425, 3330, 3200, 2220, 2200, 1605, 1565 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 1.40 (AB, 2 H, CH_2), 3.15 (m, 2 H), 4.02 (d, 1 H), 4.38 (d, 1 H), 6.41 (m, 2 H, olefinic).

Anal. Calcd for $C_{17}H_{14}N_{10}$: C, 56.97; H, 3.94; N, 39.09. Found: C, 57.23; H, 3.71; N, 39.14.

The above CH_2Cl_2 filtrate was evaporated, and ether-insoluble solid was filtered, 3.58 g, mp 134–135 °C (from CCl_4), identical with an authentic sample of 2,3-dicyanopyrazine (**32**).[2a]

The ether-soluble fraction, 6.5 g, was chromatographed on 60 g of silica. Benzene fractions (200 mL) gave 2.26 g of crude **32**, which gave 1.64 g of colorless crystals, mp 133–135 °C.

The column was further eluted with benzene (450 mL) and CH_2Cl_2 (700 mL). The combined material was rechromatographed on 50 g of alumina. Benzene fractions gave 422 mg of a solid, which was triturated with cold ether to give 214 mg of 2,5-diazatricyclo[6.2.1.$0^{2,6}$]undeca-3,5,9-triene-3,4-dicarbonitrile (**33**) as colorless crystals. An analytical sample was prepared by a recrystallization from CCl_4–ether: mp 120–122 °C; NMR ($CDCl_3$) δ 2.08 (d, J = 12 Hz, 1 H), 2.50 (d × t, J = 12 and 4 Hz, 1 H), 3.05 (m, 1 H), 3.30 (d, J = 14.5 Hz), 3.34 (m), together 2 H, 5.05 (m, 1 H), 6.40 (m, 2 H); UV (C_2H_5OH) 255 nm (ε 10 400); IR (KBr) 2235, 1504, 1415, 1304 cm^{-1}.

Anal. Calcd for $C_{11}H_8H_4$: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.43; H, 4.01; N, 28.48.

Further elutin with CH_2Cl_2 gave 460 mg of a solid, which was triturated with cold ether to give 349 mg of 3-aza-3-(2-amino-1,2-dicyanovinyl)tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**30**). An analytical sample was prepared by a recrystallization from benzene–hexane: mp 122–124 °C; NMR ($CDCl_3$) δ 1.80 (m, 2 H, CH_2), 2.97 (m, 4 H, CH), 5.89 (t, 2 H, olefinic), 4.42 (br, 2 H, NH_2); UV (C_2H_5OH) 303 nm (ε 14 000); IR (KBr) 3400, 3310, 3205, 2227, 2217, 1635, 1597 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.66; H, 5.10; N, 28.22.

1-(1,2-Diimino-2-cyanoethyl)-1,4,4a,5,6,7,8,8a-octahydro-5,8-methanoquinoxaline-2,3-dicarbonitrile (38). A solution of 3.0 g of DISN and 5 g of norbornene in 40 mL of CH_3CN was refluxed under nitrogen for 30 h, treated with charcoal, and evaporated. The gummy solid was recrystallized from ethyl acetate to give 657 mg of yellow crystals. A recrystallization from CH_3CN gave an analytical sample, which decomposed above 250 °C without melting: NMR (Me_2SO-d_6) δ 1.17 (m, 2 H, CH_2), 1.52 (m, 4 H, CH_2), 2.44 (m, 2 H, CH), 4.10, 4.36 (d, J = 7.6 Hz, 2 H, CH), 7.64 (s, 2 H, NH), 8.55 (s, 1 H, NH); UV (C_2H_5OH) 398 nm (ε 11 700), 317 (8560); IR (KBr) 3380, 3300, 3190, 2205, 1603, 1560 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}N_7$: C, 60.20; H, 4.69; N, 35.11. Found: C, 60.57; H, 4.69; N, 35.37.

4,5-Dimethylpicolinonitrile (39). To a solution of 3.0 g of DISN in 30 mL of CH_3CN was added 16 mL of 2,3-dimethylbutadiene dropwise over a period of 20 min and stirred for 4 h at 22–33 °C; no DISN remained. The solvent was evaporated under vacuum. The yellow-orange oil turned black at room temperature within a few hours, and 840 mg of DAMN was isolated by filtration of $CHCl_3$ solution. The filtrate was chromatographed on alumina. A benzene fraction (270 mL) gave 1.21 g of colorless crystals contaminated with a yellow oil. Three recrystallizations from ether–hexane gave an analytical sample: 676 mg, of **39**, mp 76–78 °C; NMR ($CDCl_3$) δ 2.35 (s, 6 H), 7.49 (s, 1 H), 8.44 (s, 1 H); UV (C_2H_5OH) 328 nm (ε 15), 275 (2840), 267 (3300), 230 (11 400); IR (KBr) 2230, 1587, 1560 cm^{-1}.

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.19. Found: C, 72.41; H, 5.96; N, 21.32.

Registry No. **3a**, 88548-87-2; **3b**, 88548-88-3; **4**, 13481-25-9; **5a**, 4231-26-9; **5b**, 4231-35-0; **6a**, 72113-14-5; **6b**, 88548-89-4; **7**, 88548-90-7; **8**, 88548-91-8; **9**, 88548-92-9; **11**, 88548-93-0; **12a**, 100-42-5; **12b**, 1073-67-2; **12c**, 405-99-2; **12d**, 637-69-4; **12f**, 622-97-9; **13a**, 88548-94-1; **13b**, 88548-95-2; **13c**, 88548-96-3; **13d**, 88549-04-6; **13f**, 88548-98-5; **14d**, 37494-42-1; **14e**, 37494-43-2; **15d**, 67170-60-9; **15e**, 72545-80-3; **15f**, 67823-06-7; **16**, 1187-42-4; **17**, 88548-97-4; **18**, 88548-99-6; **19**, 88549-00-2; **20**, 88549-01-3; **21a**, 873-66-5; **21b**, 766-90-5; **22a**, 88549-03-5; **22b**, 88588-22-1; **27**, 59574-37-7; **29**, 56029-18-6; **30**, 88549-07-9; **31**, 88549-05-7; **32**, 13481-25-9; **33**, 88549-06-8; **38**, 88549-08-0; **39**, 24559-31-7; DISN, 28321-79-1; *cis*-dimethoxyethylene, 7062-96-6; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; 2-(*p*-tolyl)propene, 1195-32-0; *trans*-anethole, 4180-23-8; 5-methyl-6-*p*-anisylpyrazine-2,3-dicarbonitrile, 88549-02-4; 2-vinylfuran, 1487-18-9; diazomethane, 334-88-3; cycloheptatriene, 544-25-2; norbornadiene, 121-46-0; norbornene, 498-66-8; 2,3-dimethylbutadiene, 513-81-5.

Retro-Inverso Isomerization of Peptides: Side Reactions in the Synthesis of *N,N'*-Diacyl-1,1-diamino-2-phenylethane Derivatives

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In general, the synthesis of retro-inverso peptides requires the formation of diacylated *gem*-diaminoalkyl structures. One way to prepare these *gem*-diaminoalkyl residues involves the Curtius rearrangement of the N-acylated amino acid hydrazides to the corresponding *N*-acyl-α-aminoalkyl isocyanates which are subsequently trapped by an alcohol. We have found that the side reactions associated with alcohol addition to the isocyanate vary with the nature of the N-acylating group on the α-amino function and the ratio of alcohol to isocyanate. These side reactions can be minimized by using only small excesses of alcohol over isocyanate or by performing the Curtius rearrangement on hydrazides derived from *N*-acetyl residues rather than on *N*-alkoxycarbonyl amino acids.

In the course of our studies on linear, retro-inverso peptide isomers, we have incorporated 1,1-diaminoalkyl and malonyl residues as basic structural units into the modified peptide backbone.[2] This modification, which

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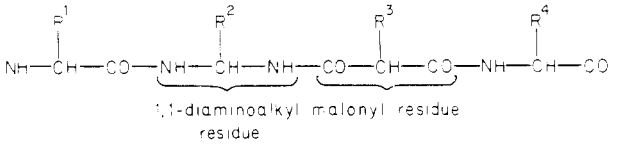
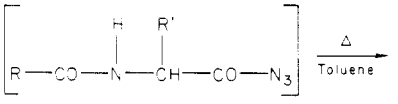


produces topochemical analogues represents an attempt to construct biologically active peptides with altered properties.[3] The *N,N'*-diacylated-1,1-diaminoalkanes (**3**) required for this transformation were prepared from the corresponding *N*-acyl-α-aminoacyl azide (**1**) by the Curtius rearrangement.[4] The intermediary isocyante (**2**) was



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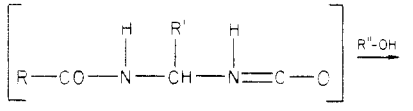

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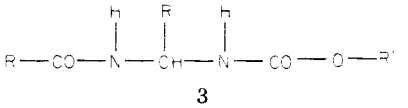

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trapped by an appropriate alcohol to yield a urethane protected amine at the α-carbon. This protecting group could be selectively removed to allow further synthetic elaboration of the liberated amino function.

In an attempt to optimize the yield of the desired product (**3**), we increased the ratio of alcohol to isocyanate. The addition of a large excess of alcohol did not increase the yield of **3** but rather resulted in a complex mixture of products including compounds such as α-hydroxy and α-alkoxy *N*-alkylamides. There are numerous methods reported in the literature that deal with the preparation[5-15] and synthetic applications[16-20] of such compounds. However, our interest is directed primarily at the preparation of appropriately substituted 1,1-diaminoalkanes (**3**) to be used in peptide synthesis. In this paper, we present a search for appropriate ratios between the isocyanate and alcohol reactants and compare the effect of changing the N-acylating group on the product distribution.

This is not a mechanistic study, rather we have analyzed the product composition obtained under various synthetic conditions after the isocyanate has been consumed. Benzyl alcohol and methanol were used to obtain urethane structures since they resemble practical protecting groups used in peptide synthesis or are model cases suitable for simple analysis of the reactions. An understanding of the variables which determine product distribution is essential to design of the optimum synthesis of *gem*-diaminoalkyl structures.

Results and Discussion

After allowing a 20-fold excess of methanol to react with *N*-(benzyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (**2a**), obtained from the Curtius rearrangement of *N*-(benzyloxycarbonyl)-L-phenylalanine azide (**1a**), we could isolate and characterize five different products: *N*-(benzyloxycarbonyl)-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (**3a**), *N*-(benzyloxycarbonyl)-1-amino-1-methoxy-2-phenylethane (**4a**), *N*-(benzyloxycarbonyl)-1-amino-*trans*-styrene (**5a**), bis[[1-(*N*-(benzyloxycarbonyl)amino)-2-phenylethyl]amino] ketone (**6a**), and methyl *N*-(*N*-(benzyloxycarbonyl)-1-aminophenethyl)-allophanate (**7a**). Scheme I shows the possbile routes leading to the five compounds noted above. All of these possible pathways arise from the isocyanate intermediate.

When a 2-fold excess of methanol was allowed to react with the same isocyanate (**2a**) only two products were isolated: the diacylated 1,1-diaminoalkyl compound (**3a**) and the allophanate (**7a**). The latter was a minor product (~2%).

Similar results were obtained upon trapping the isocyanate *N*-(*tert*-butyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (**2b**) formed by Curtius rearrangement of *N*-(*tert*-butyloxycarbonyl)-L-phenylalanine azide (**1b**) with methanol. With a 20-fold excess of methanol three isolated and identified products were obtained: the desired diacylated 1,1-diaminoalkyl compound (**3c**) and, as side products, the allophanate (**7c**) and the corresponding 1-amino-1-methoxyalkyl compound (**4c**). In this case the ratio of the desired material to side products was almost 1:1 (see Table I). When only a 2-fold excess of methanol was employed we could not detect any of the *N*-(*tert*-butyloxycarbonyl)-1-amino-1-methoxy-2-phenylethane (**4c**). The ratio of the desired product, diacylated 1,1-diaminoalkyl compound (**3c**), to the side product, allophanate (**7c**), increased to more than 10:1 along with almost a 2-fold increase in the total yield of the desired diacylated 1,1-diaminoalkyl compound. (See Table I). Figure 1 shows the ^{1}H NMR spectra of the three major products [**3c**, **4c**, and **7c**] obtained in the reaction of compound **2b** with a 20-fold excess of methanol.

As indicated in Table I, benzyl alcohol, which yields a common N-protecting group, i.e., benzyloxycarbonyl, gave

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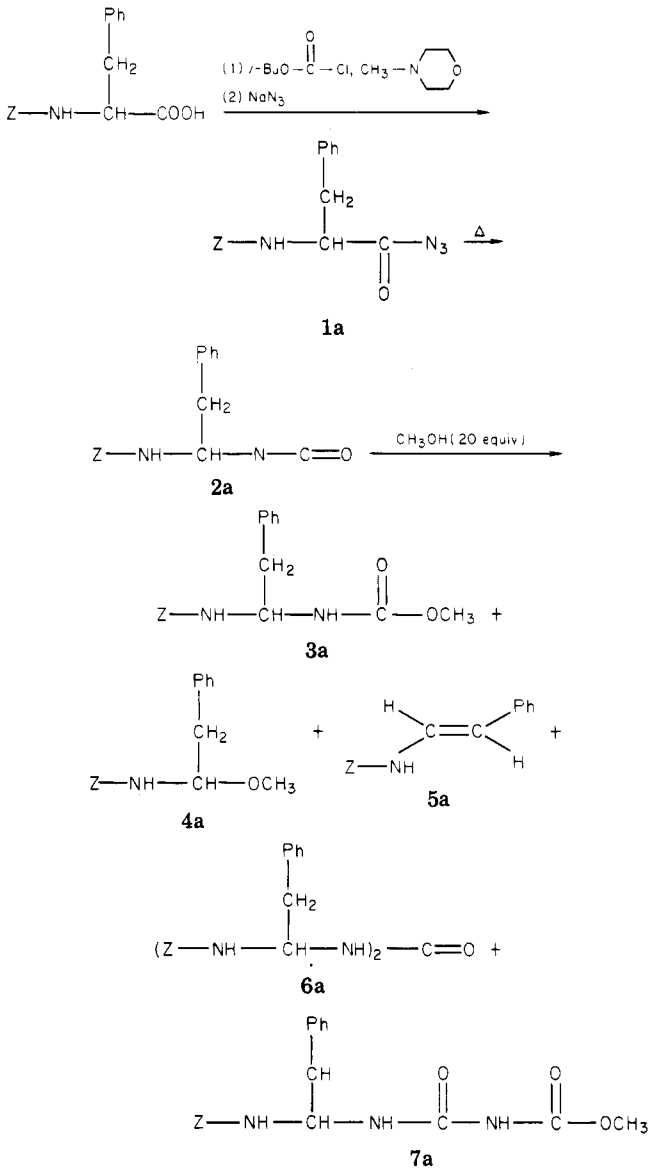


a product distribution similar to that observed for methanol. A large excess of benzyl alcohol to isocyanate (**2b**) (10-fold) gave almost equal yields of the three products **3b**, **4b**, and **7b**. Lowering the ratio of benzyl alcohol to isocyanate (**2b**) to 2:1 completely eliminated one of the side products, namely the 1-amino-1-(benzyloxy)alkyl compound (**4b**), and improved the ratio of desired material (**3b**) to side product from 1:2 with the 10-fold excess to almost 3:2. Also, the total yield of the diacylated 1,1-diamino alkane (**3b**) improved significantly under these conditions (see Table I).

Once the isocyanate (**2**) is formed, alcohol can react with it to produce the desired material, diacylated *gem*-diamine (**3**), or it can undergo other reactions. As the relative amount of alcohol increases, the reaction medium becomes more polar and heterolytic or displacement reactions lead to the remaining compounds shown in Scheme I. It is interesting to note that heating the *N*-(*tert*-butyloxycarbonyl)-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (**3c**) for 12 h at 80 °C in the presence of a large excess of methanol does not produce compound **4c** or any other product. Thus, once the diacylated 1,1-diaminoalkyl compound (**3**) is obtained, it is stable toward those conditions in which it is formed.

In scheme I, we indicate that the isocyanate group can act as a leaving group to yield the alkene derivative (**5**) or

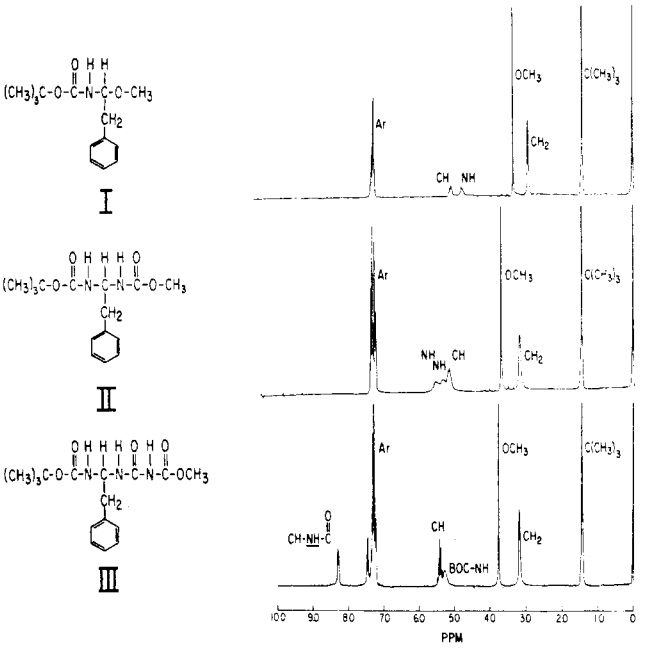
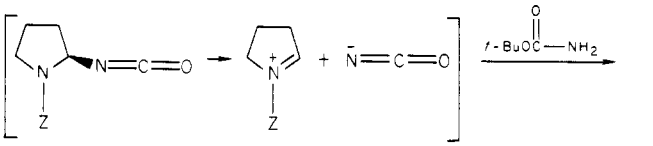


Figure 1. ^{1}H NMR spectra in $CDCl_3$ (Me_4Si as an internal reference) of products obtained in reacting *N*-(*tert*-butyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (**2b**) with excess methanol: (I) *N*-(*tert*-Butyloxycarbonyl)-1-amino-1-methoxy-2-phenylethane (**4c**). (II) *N*-(*tert*-Butyloxycarbonyl)-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (**3c**). (III) Methyl *N*-(*N*-(*tert*-butyloxycarbonyl)-1-amino-2-phenethyl)-allophanate (**7c**).

can be displaced to yield the acylated 1-amino-1-alkoxyalkane (**4**). It is also possible that the isocyanate ion, as a leaving group, can recombine with the implied carbonium ion to form a racemic diacylated 1,1-diamino alkane (**3**). In our hands, we have not observed the formation of a racemic diacylated 1,1-diamino alkane (**3**), either in the presence of a low or a high ratio of alcohol to isocyanate. However, Murato and co-workers observed the formation of racemic *N*-(benzyloxycarbonyl)-2-(*N*-(*tert*-butyloxycarbonyl)amino]pyrrolidine (**9**) from *N*-(benzyloxycarbonyl)-2-isocyanopyrrolidine (**8**) in the presence of *N*-*tert*-butylcarbamate. They proposed that heterolysis



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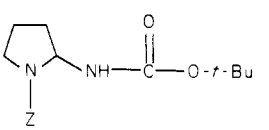

Racemic

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of **8** yielded the corresponding cyclic acyliminium ion and isocyanate anion. The reaction between the carbamate and the acyliminium ion yields the racemic diacylated 1,1-diaminoalkyl compound (**9**).[21] A similar heterolysis of isocyanate **2** will yield an ion pair. It is known that an increase in solvent polarity will favor ion pair formation and thus increase amounts of products **4** and **5** derived from the acylium and isocyanate ions **2'** and **2''**, respectively (see Scheme I).

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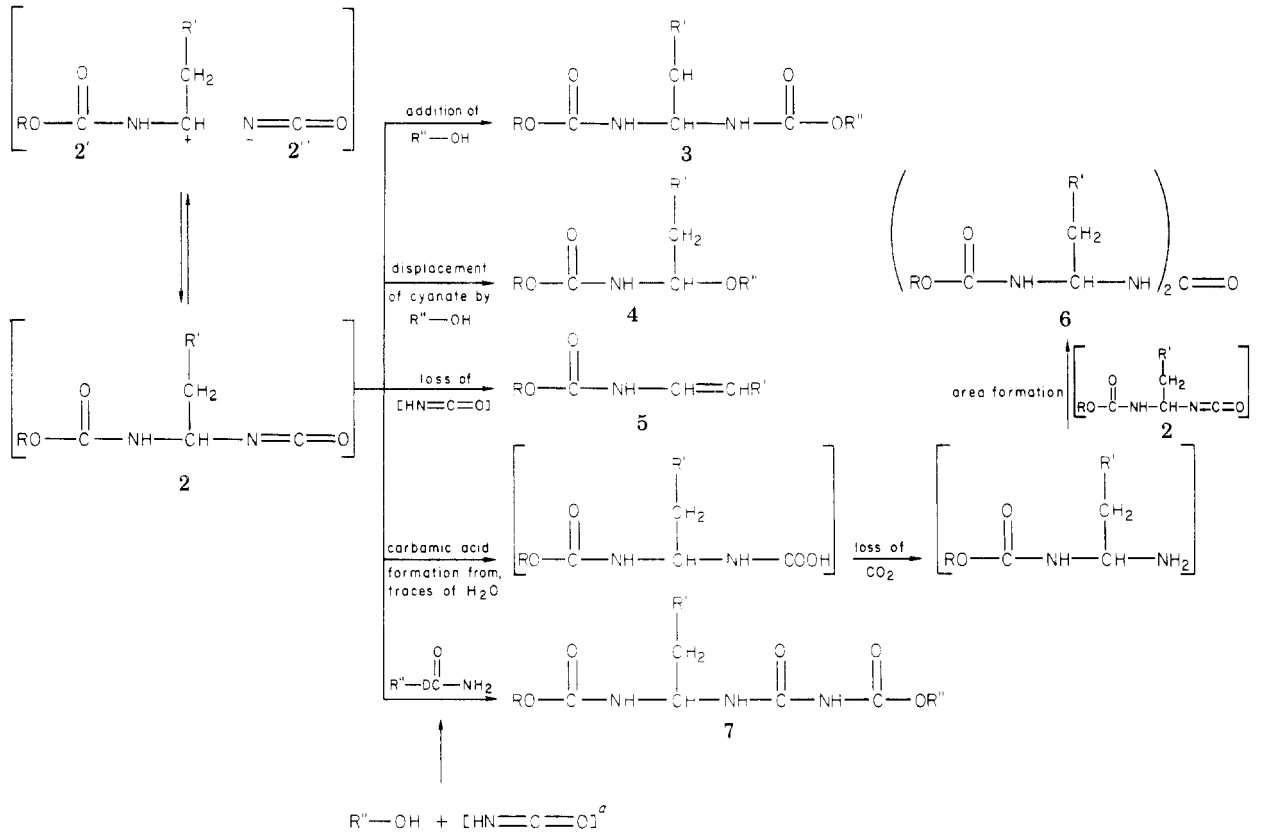
Scheme I



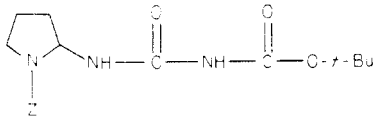
[a] From displacement reaction above.

Table I. Products Obtained from the Reaction of *N*-(Alkoxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (2a and 2b) with Alcohol

isocyanate derivative	alcohol, equiv	1-amino-1-alkoxyalkane[a] (4)	diacylated 1,1-diamino-alkane[a] (3)	allophanate[a] (7)
Z-Phe-OH[b] (2a)	MeOH 20	9%	49%	5%
	MeOH 2		65%	2%
Boc-Phe-OH (2b)	MeOH 20	44%	29%	12%
	MeOH 2		45%	4%
	$PhCH_2OH$ 10	18%	18%	20%
	$PhCH_2OH$ 2		31%	18%

[a] Isolated yield is based on starting amino acid. [b] The symmetrical urea and β-aminostyrene were also isolated.

The same investigators did not detect the formation of a 1-amino-1-alkoxy alkane when the isocyanate 8 was allowed to react with a large excess of *tert*-butyl alcohol. Under these circumstances only two products were isolated and characterized: the diacylated 2-aminopyrrolidine (**9**) and the corresponding allophante (**10**).[21] They also reported isolating a fast running chromatographic fraction which had only a urethane carbonyl in the IR (1720 cm^{-1}). However, the ^1H NMR spectrum possessed resonances that could be assigned to the pyrrolidine ring and the benzyl substituent; they did not see resonances corresponding to a *tert*-butyl group. From our experience, we expect that this fast running fraction is the 2-alkoxypyrrolidine compound. We have repeated the reaction as reported by Murato et al.[21] and have focused our efforts on the isolation and characterization of the previously unidentified fast moving fraction. As we anticipated, this material was *N*-(benzyloxycarbonyl)-2-(*tert*-butyloxy)pyrrolidine (**11**),



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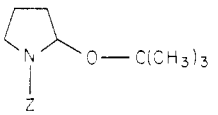

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which was confirmed by IR, ^1H NMR, and mass spectral analysis. The compound was not stable even when stored at −4 °C under a nitrogen atmosphere. As a result, a satisfactory microchemical analysis could not be obtained.

Table I shows that the product distribution obtained by the addition of methanol to *N*-(benzyloxycarbonyl)- or *N*-(*tert*-butyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (**2a** and **2b**, respectively) varies with the reaction conditions employed. The isocyanate **2b** is more prone to the displacement of the isocyanate anion by an alcohol than **2a**, which results in an increased yield of the corresponding 1-amino-1-methoxyalkyl compound (**4c**). In contrast, under identical conditions (20-fold excess), the isocyanate **2a** yields the corresponding diacylated 1,1-diaminoalkyl compound **3a** as the major product. At the present time, we are not in a position to explain the differences in the reactivity of these two isocyanates toward methanol.

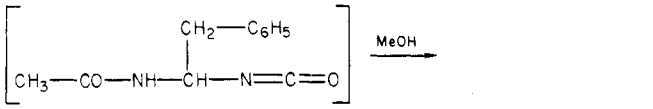
The replacement of the *N*-urethane-type protecting group in *N*-acyl-*N'*-carbonyl-1,1-diamino-2-phenylethane by an acetyl group, as in **2d**, led almost exclusively to the formation of the diacylated 1,1-diaminoalkane **3d** in high yield (70–80%). Regardless of the amount of methanol employed, only trace amounts of the 1-amino-1-methoxy-

Table II. Yield of Products Obtained from the Reaction of N-Acetyl-N'-carbonyl-1,1-diamino-2-phenylethane (2d) with a Large Excess of Methanol

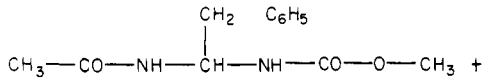
	products	
reaction conditions	1-amino-1-methoxyalkane[a] (4d)	diacylated 1,1-diaminoalkane[b] (3d)
10 equiv of MeOH	2%	78%
20 equiv of MeOH; 1 equiv of pyridine	1%	74%
20 equiv of MeOH; 0.1 equiv of p-toluenesulfonic acid	1%	73%
10 equiv of MeOH[c]	6%	73%
120 equiv of MeOH[d]	1%	80%

[a] Yield determined by 220-MHz NMR. [b] Isolated yield. [c] Rearrangement was run in dioxane. [d] The isocyanate-toluene solution was added to refluxing MeOH.

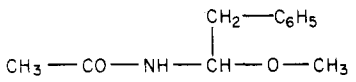
Scheme II



2d



3d



4d

alkyl compound **4d** could be obtained. We were able to isolate the compound after extensive column chromatography (see reaction sequence in Scheme II and Table II). Table II also shows that the yield of **4d** could not be improved by either acidic or basic catalysis. The differences observed between the N-urethane protected isocyanates (**2a** and **2b**) and the N-acetyl isocyanate (**2d**) can be related either to the relatively reduced tendency of isocyanate (**2d**) to undergo heterolysis to the N-acylium carbocation (see Scheme I) or to its lesser susceptibility to direct displacement by the alcohol. Proton NMR spectra of the two products are depicted in Figure 2. The relative ratio of diacylated 1,1-diaminoalkane (**3d**) to the N-acyl-1-amino-1-methoxyalkane (**4d**) was determined by comparing the integration of the two respective methoxy resonances (3.66 and 3.33 ppm).

Conclusions

From our studies it is apparent that a large excess of alcohol should not be used to convert the isocyanate derived from an N-urethane-type protected amino acid to the corresponding diacylated 1,1-diaminoalkane. The use of a large excess of alcohol decreases the yield of the product required for the synthesis of partially modified retroinverso peptide analogues and complicates the purification procedure. We have also shown that the conversion of acetyl-L-phenylalanine to its corresponding diacylated 1,1-diaminoalkyl compound is insensitive to the relative amounts of alcohol used. It therefore appears that acyl or peptidyl isocyanates represent preferred routes for the formation of peptide derivatives containing 1,1-diaminoalkyl residues. In those cases where this approach

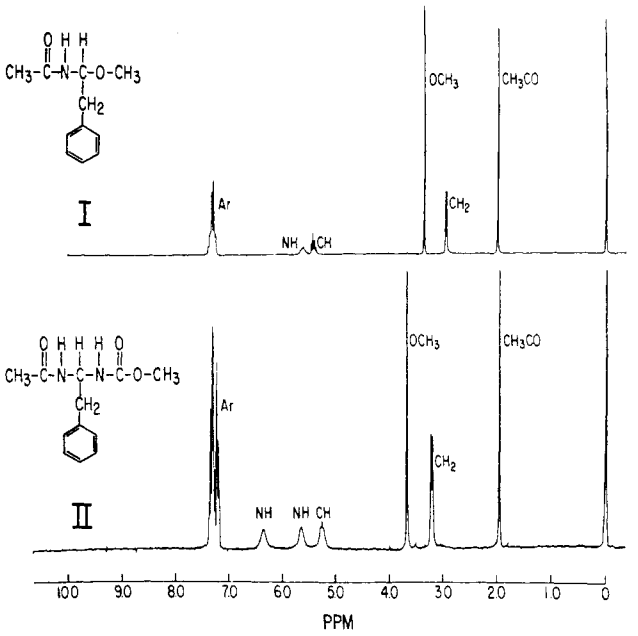


Figure 2. ^{1}H NMR spectra in $CDCl_3$ (Me_4Si as an internal reference) of products obtained in reacting N-acetyl-N'-carbonyl-1,1-diamino-2-phenylethane (**2d**) with a large excess of methanol: (I) N-acetyl-1-amino-1-methoxy-2-phenylethane (**4d**). (II) N-acetyl-N'-(methoxycarbonyl)-1,1-diamino-2-phenylethane (**3d**).

is not practical, the N-alkoxycarbonyl amino acid can be utilized if an excess of alcohol is avoided. Future studies will concentrate on possible routes[22] to catalyze the addition of alcohols to N-(alkoxycarbonyl)-N'-carbonyl-1,1-diaminoalkanes to maximize the yield of the desired diacylated 1,1-diaminoalkanes.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus; they are uncorrected. IR spectra were recorded on a Perkin-Elmer 180 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter with a 10-cm water-jacketed cell. High-resolution ^{1}H NMR spectra were obtained in the Fourier Transform (FT) mode by using a Varian HR-220 spectrometer at the University of California—San Diego. Peak assignment was done by homonuclear spin-decoupling experiments which were carried out in the FT mode by employing a double irradiation technique. All chemical shifts are reported in ppm downfield from Me_4Si. Mass spectra were determined on an LKB-9000A mass spectrometer. All elemental analyses were performed by Galbraith Laboratories, Knoxville, TN 37921. All of the amino acid derivatives are commercially available and are of the L configuration.

Analytical TLC plates were purchased from E. Merck: silica gel 60, F-254, glass-backed. The plates were developed with ninhydrin or visualized with UV light (254 nm). The following chromatography systems were used: (1) EtOAc, hexanes [1:1]; (2) $CHCl_3$, MeOH, H_2O [85:10:5]; (3) EtOAc. Column chromatography was performed on Brinkman silica gel 60 (70–270 mesh ASTM) and monitored with an ISCO UA-5 detector.

General Experimental Procedure. To a cold (−20 °C) 0.5 M solution of an N-protected amino acid in tetrahydrofuran (THF) were added 1 equiv of N-methylmorpholine and 1 equiv of isobutyl chloroformate. The mixture was stirred for 15 min and warmed to 0 °C and a 2 M aqueous solution of sodium azide (2 equiv) was added. After 30 min at 0 °C, the reaction was diluted with cold EtOAc and washed with several portions of cold brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to yield the azide (IR ~2120 cm^{-1}). The azide was dissolved in dry toluene and heated at 80 °C under N_2 until the rearrangement was complete (IR 2260 cm^{-1}), typically 5–10

(22) W. J. Bailey and J. R. Griffith, *J. Org. Chem.*, *43*, 2690 (1978).

min were needed for completion of rearrangement. Dry alcohol was added and the solution was heated at 80 °C until all of the isocyanate had been consumed.

Reaction of *N*-(Benzyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (2a) with Methanol. (a) Ratio of Isocyanate to Alcohol 1:20. The amino acid derivative Z–Phe–OH (20 mmol) was converted to the corresponding isocyanate (**2a**). Methanol (400 mmol) was added and the progress of the reaction was monitored by IR. Upon completion (~5 min) the solvent was removed under reduced pressure and the residue taken into hot EtOAc. The mixture was cooled to room temperature and filtered. A precipitate of the symmetrical urea formed, was collected, and washed thoroughly with EtOAc.

Bis[[1-(*N*-(benzyloxycarbonyl)amino)-2-phenylethyl]-amino] ketone (6a): the symmetrical urea; yield 1.1%; mp 210–211 °C dec; $[\alpha]^{23}_D$ −1.4° (c 0.5, Me_2SO); IR (KBr) 3320, 1693, 1510 cm^{-1}; NMR (Me_2SO-d_6) δ 7.70 (d, 1 H, C_α–NH–CO), 7.31–7.20 (m, 10 H, Ar), 6.49 (d, 1 H, Z–NH), 5.16 (m, 1 H, C_αH), 4.96 (s, 2 H, PhCH_2O–), 2.89 (d, 2 H, $C_\beta H_2$).

Anal. Calcd for $C_{33}H_{34}N_4O_5$: C, 69.95; H, 6.05; N, 9.89. Found: C, 69.73; H, 6.30; N, 9.78.

The filtrate was taken to dryness and the residue chromatographed on a silica gel column (2 × 30 cm) with a gradient of EtOAc (15% to 40%) in hexane. The products obtained are listed in order of their elution:

***N*-(Benzyloxycarbonyl)-1-amino-*trans*-styrene (5a)**: yield 6.3%; R_{f_1} 0.60; mp 93–94 °C; IR (KBr) 1710, 1657, 1516 cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5 H, Ar), 7.26 (m, 5 H, Ar), 7.18 (m, 1 H, *CH*–NH–Z), 6.61 (m, 1 H, NH), 5.96 (d, 1 H, J = 15 Hz, C= *CH*Ph), 5.20 (s, 2 H, PhCH_2O–).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.68; H, 6.29; N, 5.58.

***N*-(Benzyloxycarbonyl)-1-amino-1-methoxy-2-phenylethane (4a)**: yield 8.6%; R_{f_1} 0.54; mp 80 °C; $[\alpha]^{23}_D$ −3.4° (c 3.0, EtOH); IR (KBr) 1686, 1520 cm^{-1}; NMR ($CDCl_3$) δ 7.32 and 7.23 (m, 10 H, Ar), 5.14 (m, 1 H, C_αH), 5.08 (s, 2 H, PhCH_2O–), 4.97 (m, 1 H, NH), 3.34 (s, 3 H, CH_3), 2.93 (d, 2 H, J = 6.6 Hz, $C_\beta H_2$).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.71; H, 6.91; N, 4.97.

***N*-(Benzyloxycarbonyl)-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (3a)**: yield 48.6%; R_{f_1} 0.37; mp 148–150 °C $[\alpha]^{23}_D$ −3.3° (c 3.04, DMF); IR (KBr) 1705, 1550, 1505 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ar), 7.17 (m, 5 H, Ar), 5.50 (m, 2 H, *NH*–CH–*NH*), 5.22 (m, 1 H, Cαh), 5.09 (s, 2 H, PhCH_2O–), 3.66 (s, 3 H, CH_3), 3.17 (d, 2 H CβH_2).

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.58; N, 8.53; Found: C, 65.70; H, 6.58; N, 8.76.

Methyl *N*-(*N*-(Benzyloxycarbonyl)-1-aminophenethyl)-allophanate (7a): yield 4.6%; R_{f_1} 0.20; mp 187–188 °C; IR (KBr) 1745, 1720, 1700, 1540, 1508, 1490 cm^{-1}; NMR ($CDCl_3$) δ 8.35 (m, 1 H, C_αH–*NH*–CO), 7.32 (s, 5 H, Ar), 7.21 (m, 5 H, Ar), 7.10 (s, 1 H, CO–*NH*–CO_2CH_3), 5.50 (m, 2 H, C_αH and Z*NH*–), 5.09 (s, 2 H, PhCH_2O–), 3.75 (s, 3 H, CH_3), 3.18 (d, 2 H, $C_\beta H_2$).

Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.30; H, 5.89; N, 11.35.

(b) Ratio of Isocyanate to Alcohol 1:2. The amino acid derivative Z–Phe–OH (10 mmol) was converted to the corresponding isocyanate **2a** and allowed to react with dry methanol (20 mmol). After all the isocyanate had been consumed, the mixture was taken to dryness, washed repeatedly with water, and dried overnight in vacuo. The residue was chromatographed on a silic gel column (2 × 30) with a gradient of EtOAc (15% to 40%) in hexane. The products obtained are listed in order of their elution:

***N*-(Benzyloxycarbonyl)-*N'*-(methoxycarbonyl)-1,1-diamino-2-phenylethane (3a)**: yield 64.6%. Identical with the *gem*-diaminoalkyl compound described above.

Methyl *N*-(*N*-(Benzyloxycarbonyl)-1-amino-2-phenylethyl)allophanate (7a): yield 1.8%. Identical with the allophante compound described above.

Reaction of *N*-(*tert*-Butyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (2b) with Benzyl Alcohol. (a) Ratio of Isocyanate to Alcohol 1:2. The amino acid derivative Boc–Phe–OH (20 mmol) was taken through the general procedure to obtain the isocyanate **2b**. Dry benzyl alcohol (40 mmol) was added and the reaction monitored by IR until it reached completion. As the toluene solution cooled to room temperature, a white solid crystallized from solution. Filtration give diacylated *gem*-diaminoalkyl compound.

***N*-(*tert*-Butyloxycarbonyl)-*N'*-(benzyloxycarbonyl)-1,1-diamino-2-phenylethane (3b)**: yield 24.5%; R_{f_1} 0.57; mp 150–152 °C; $[\alpha]^{23}_D$ +4.6° (c 2.0, DMF); IR (KBr) 1700, 1540, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ar), 7.22 (m, 5 H, Ar), 5.52 (m, 1 H, C_αH), 5.29 (m, 2 H, *NH*–CH–*NH*), 5.09 (s, 2 H, PhCH_2O–), 3.13 (d, 2 H, $C_\beta H_2$), 1.42 (s, 9 H, $(CH_3)_3$C).

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.05;, H, 7.05; N, 7.52.

The mother liquor was diluted with hexane and cooled to initiate crystallization. The solid was removed by filtration and recrystallized from a small amount of toluene to yield the allophanate.

Benzyl *N*-(*N*-(*tert*-Butyloxycarbonyl)-1-aminophenethyl)allophanate (7b): yield 13%; R_{f_1} 0.44; mp 156–157 °C; $[\alpha]^{23}_D$ +11.9° (c 3.0, DMF); IR (KBr) 1715 (s), 1698, 1683, 1533, 1490 cm^{-1}; NMR ($CDCl_3$) δ 8.27 (d, 1 H, C_αH–*NH*–CONH). 7.35 (s, 5 H, Ar), 7.27 (m, 6 H, Ar and CO–*NH*–$CO_2C_7H_7$), 5.39 (m, 1 H, C_αH), 5.28 (m, 1 H, Boc–NH), 5.14 (s, 2 H, PhCH_2O–), 3.15 (d, 2 H, $C_\beta H_2$), 1.42 (s, 9 H, $(CH_3)_3$C).

Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.88; H, 6.56; N, 10.11.

The filtrate was taken to dryness and the residue chromatographed on a silica gel column with a gradient of EtOAc (15% → 40%) in hexane. The first fraction was the *gem*-diaminoalkyl derivative (**3b**) (6.5%) and the second was the allophanate (**7b**) (4.8%).

(b) Ratio of Isocyanate to Alcohol 1:10. The amino acid derivative Boc–Phe–OH (10 mmol) was converted to the corresponding isocyanate (**2b**) and allowed to react with benzyl alcohol (100 mmol). After the isocyanate had been consumed, the mixture was taken to dryness, washed repeatedly with water, and dried overnight in vacuo. The residue was chromatographed on a silica gel column (2 × 30 cm) with a gradient of EtOAc (15% → 50%) in hexane. The products obtained are listed in order of their elution:

***N*-(*tert*-Butyloxycarbonyl)-1-amino-1-(benzyloxy)-2-phenylethane (4b)**: yield 18.1% recrystallized from EtOH–H_2O; R_{f_1} 0.7; mp 76–77 °C; $[\alpha]^{23}_D$ 0.0 (c 3.0, EtOH); IR (KBr) 1690, 1510, 1495 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.27 and 7.25 (m, 10 H, Ar), 5.29 (m, 1 H, C_αH), 4.90 (m, 1 H, NH), 4.65 and 4.48 (q_{AB}, 2 H, J = 13.2 Hz, –OCH_2Ph), 2.96 (d, 2 H, J = 4.4 Hz, $C_\beta H_2$), 1.42 (s, 9 H, $(CH_3)_3$C).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.29; H, 7.79; N, 4.22.

***N*-(*tert*-Butyloxycarbonyl)-*N'*-(benzyloxycarbonyl)-1,1-diamino-2-phenylethane (3b)**: yield 17.88% recrystallized from EtOAc–hexanes. Identical with *gem*-diaminoalkyl compound described above.

Benzyl *N*-(*N*-(*tert*-Butyloxycarbonyl)-1-aminophenethyl)allophanate (7b): yield 19.8% recrystallized from EtOAc–hexanes. Identical with the allophanate described above.

Reaction of *N*-(*tert*-Butyloxycarbonyl)-*N'*-carbonyl-1,1-diamino-2-phenylethane (2b) with Methanol. (a) Ratio of Isocyanate to Alcohol 1:20. The amino acid derivative Boc–Phe–OH (20 mmol) was rearranged to the corresponding isocyanate **2b**. Methanol (400 mmol) was added and the progress of the reaction was monitored by IR. Upon completion, the mixture was taken to dryness and the residue chromatographed on a silica gel column (2 × 30 cm) with a gradient of EtOAc (5% → 50%) in hexane. The products obtained are listed in order of their elution:

***N*-(*tert*-Butyloxycarbonyl)-1-amino-1-methoxy-2-phenylethane (4c)**: yield 44%; R_{f_1} 0.62; mp 70–71 °C; $[\alpha]^{23}_D$ −0.27° (c 3.0, DMF); IR (KBr) 1720, 1500, 1490 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (m, 5 H, Ar), 5.06 (m, 1 H, C_αH), 4.78 (m, 1 H, NH), 3.36 (s, 3 H, –OCH_3), 2.90 (d, 2 H, $C_\beta H_2$), 1.41 (s, 9 H, $(CH_3)_3$C.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.08; H, 8.60; N, 5.57.

***N*-(*tert*-Butyloxycarbonyl)-*N'*-(methoxycarbonyl)-1,1-diamino-2-phenylethane (3c)**: yield 29%; R_{f_1} 0.55; mp 154–155 °C; $[\alpha]^{23}_D$ +2.0 (c, 3.0, DMF); IR (KBr) 1703, 1678, 1539, 1504 cm^{-1}; NMR ($CDCl_3$) δ 7.24 (m, 5 H, Ar), 5.50 and 5.33 (m, 2 H, *NH*–CH–*NH*), 5.13 (m, 1 H, C_αH), 3.66 (s, 3 H, OCH_3), 3.14 (d,

2 H, $C_\beta H_2$), 1.42 (s, 9 H, $(CH_3)_3C$).

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: 61.39; H, 7.68; N, 9.36.

Methyl *N*-(*N*-(*tert*-Butyloxycarbonyl)-1-amino-2-phenylethyl)allophanate (7c): yield 12%; R_{f_1} 0.26; mp 157-159 °C; $[\alpha]^{23}_D$ +12.0° (c 3.0, DMF); IR (KBr) 1733, 1692, 1557, 1498 cm^{-1}; NMR ($CDCl_3$) δ 8.29 (d, 1 H, $C_\alpha H$-N*H*-CO), 7.45 (s, 1 H, CO-NH-CO), 7.23 (m, 5 H, Ar), 5.41 (m, 1 H, $C_\alpha H$), 5.27 (m, 1 H, Boc-*NH*), 3.75 (s, 3 H, OCH_3), 3.15 (d, 2 H, $C_\beta H_2$), 1.42 (s, 9 H, $(CH_3)_3C$).

Anal. Calcd for $C_{16}H_{23}N_3O_5$: C, 56.96, H, 6.87; N, 12.45. Found: C, 57.00; H, 6.93; N, 12.50.

(b) Ratio of Isocyanate to Alcohol 1:2. The amino acid derivative Boc-Phe-OH (20 mmol) was converted to the corresponding isocyanate (**2b**). Dry methanol (40 mmol) was added. After complete disappearance of isocyanate the mixture was taken to dryness and the residue was chromatographed on a silica gel column (2 × 30 cm) as described above. The products obtained are listed in order of their elution.

***N*-(*tert*-Butyloxycarbonyl)-*N'*-methoxycarbonyl-1,1-diamino-2-phenylethane (3c)**: yield 44.7%. Identical with the *gem*-diaminoalkyl compound described above.

Methyl *N*-(*N*-(*tert*-Butyloxycarbonyl)-1-aminophenethyl)allophanate (7c): yield 3.8%. Identical with the allophanate described above.

Reaction of *N*-Acetyl-*N'*-carbonyl-1,1-diamino-2-phenylethane (2d) with Methanol. (a) Ratio of Isocyanate to Alcohol 1:10. The compound *N*-acetylphenylalanine[23] (10 mmol) was converted to azide **1d**, taken up in 10 mL of dioxane, and rearranged to the isocyanate **2d**. Methanol (10 equiv) was added and after 90 min all of the isocyanate was consumed. Upon cooling at room temperature, the urethane crystallized from solution. An analytical sample recrystallized from MeOH yielded the desired diacylated *gem*-diaminoalkyl compound.

***N*-Acetyl-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (3d)**: yield 70%; R_{f_2} 0.52; mp 202-203 °C; $[\alpha]^{23}_D$ +3.88° (c 1.1, DMF); IR (KBr) 3300, 1698, 1648, 1555 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ar), 6.35 (m, 1 H, NH) 5.65 (m, 1 H, NH), 5.25 (m, 1 H, $C_\alpha H$), 3.66 (s, 3 H, CO_2CH_3), 3.20 (d, 2 H, J = 6.6 Hz, $C_\beta H_2$), 1.94 (s, 3 H, CH_3CONH).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.96; H, 6.90; N, 11.94.

The filtrate was taken to dryness and the residue chromatographed on a silica gel column (2 × 30 cm) with EtOAc-hexanes (1:1). The products obtained are reported in order of their elution:

***N*-Acetyl-1-amino-1-methoxy-2-phenylethane (4d)**: yield 2%; R_{f_3} 0.33; mp 98-99 °C (after recrystallization from EtOAc-hexane); $[\alpha]^{23}_D$ -0.3 (c 2.02, EtOH); IR (KBr) 3300, 1655, 1540, 1115 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (m, 5 H, Ar), 5.58 (br d, 1 H, NH), 5.38 (m, 1 H, CH) 3.33 (s, 3 H, OCH_3), 2.92 (d, 2 H, J = 6.6 Hz, $PhCH_2$-), 1.96 (s, 3 H, CH_3CONH).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.18; H, 7.93; N, 7.08.

***N*-Acetyl-*N'*-(methyloxycarbonyl)-1,1-diamino-2-phenylethane (3d)**: Yield 6%. This material was identical with that obtained from the first crystallization.

(b) Ratio of Isocyanate to Alcohol 1:20. The substance *N*-acetylphenylalanine (10 mmol) was converted to the isocyanate **2d** by the general procedure already described and then subjected to one of the following conditions: 20 equiv of MeOH; 20 equiv of MeOH and 1 equiv of pyridine; 20 equiv of pyridine; 20 equiv of MeOH and 0.1 equiv of *p*-toluenesulfonic acid; 10 equiv of MeOH in dioxane; and the isocyanate solution in toluene added to refluxing MeOH (120 equiv). In all cases, the urethane crystallized from the reaction solution and was removed by filtration. The filtrate was taken to dryness and examined by Fourier Transform 220-MHz NMR to determine the extent of formation of 1-amino-1-methoxyalkyl compound (**4d**). These data are summarized in Table II.

***N*-(Benzyloxycarbonyl)-2-(*tert*-butyloxy)pyrrolidine (11).** The amino acid derivative Z-Pro-OH was converted to the corresponding isocyanate (**8**) and reacted with *t*-BuOH as described in the literature.[21] After 2 h of heating, all of the isocyanate was consumed (determined by IR). The solvent was removed under reduced pressure to yield a clear oil which was chromatographed on a silica gel column (2 × 30 cm) with EtOAc-hexane (1:1). The first fraction was obtained as a colorless oil: F_{f_1} 0.6; IR (neat) no NH, 1706 cm^{-1} (urethane C=O); NMR ($CDCl_3$) δ 7.34 (m, 5 H, Ar), 5.39 (br d, 1 H, $C_\alpha H$), 5.13 (m, 2 H, $PhCH_2O$-), 3.56 (m, 1 H, $C_\delta H$), 3.30 (m, 1 H, C-$C_\delta H$), 2.09 and 1.81 (m, 4 H, $C_\beta H_2$ and $C_\gamma H_2$), 1.28 and 1.13 (br d, br d, total of 9 H, 3:2, $(CH_3)_3C$); MS, *m/e* 277 (M^+), 221 ($M^+ - C_4H_8$), 205 ($M^+ - C_4H_8O$). The compound was not sufficiently stable to be sent for elemental analysis. The latter fractions were found to correspond to the gem-diaminoalkyl compound (**9**) and the allophanate (**10**) described by Murato et al.[21]

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Registry No. **1d**, 18934-58-2; **2a**, 88425-14-3; **2b**, 88425-15-4; **2d**, 88425-16-5; **3a**, 88425-17-6; **3b**, 88425-18-7; **3c**, 88425-19-8; **3d**, 88425-20-1; **4a**, 88425-21-2; **4b**, 88425-22-3; **4c**, 88425-23-4; **4d**, 88494-18-2; **5a**, 88425-24-5; **6a**, 88425-25-6; **7a**, 88425-26-7; **7b**, 88425-27-8; **7c**, 88425-28-9; **8**, 88425-29-0; **11**, 88425-30-3; (*Z*)-Phe-OH, 1161-13-3; Boc-Phe-OH, 13734-34-4; MeOH, 67-56-1; $PhCH_2OH$, 100-51-6; *N*-acetylphenylalanine, 2018-61-3.

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(2 + 2) Photocycloaddition of the Carbon-Nitrogen Double Bond of Quinoxalin-2(1*H*)-ones to Electron-Deficient Olefins

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The photochemical reactivity of the quinoxalin-2(1*H*)-ones **1a-i** with electron-deficient olefins such as acrylonitrile (**2a**), methacrylonitrile (**2b**), methyl acrylate (**2c**), methyl methacrylate (**2d**), and vinyl acrylate (**2e**) is described. Irradiation of the quinoxalin-2(1*H*)-ones **1a-f,i** in the presence of electron-deficient olefins (**2a-e**) gave the novel regiospecific (2 + 2) cycloadducts (**3-18**) of the carbon-nitrogen double bond of **1** and olefin **2**. The photoreaction of the quinoxalin-2(1*H*)-ones **1** with olefins **2** occurs from a triplet state.

(2 + 2) Photocycloaddition of olefins to carbon-carbon[1,2] and carbon-oxygen double bonds[2,3] has been extensively employed in organic synthesis; however, similar cycloadditions to the carbon-nitrogen double bond are less

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