Some Applications of the Curtius Rearrangement [1]

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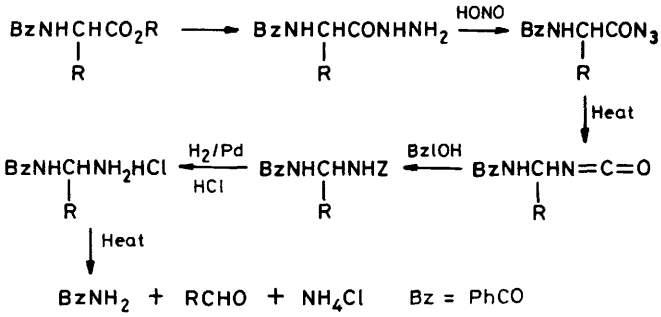
Pairs of optically pure enantiomers of substituted 1,1-diamines have been prepared from the azides of L-amino-acids *via* the Curtius rearrangement.

This synthesis is based on the interchange of two groups attached to the asymmetrically substituted tetrahedral α-carbon atom of the parent amino acid. Such an interchange occurs without the intermediate formation of a racemate. In addition, some side reactions of isocyanates of *N*-benzyloxycarbonyl-L-amino acids in aqueous acidic solution have been elucidated.

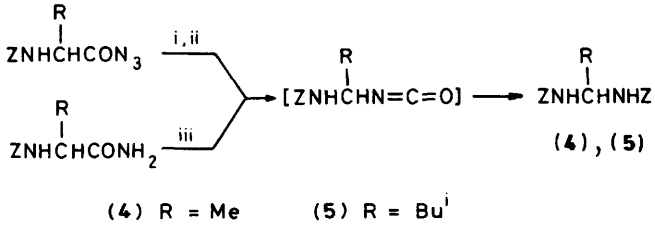
It is known that *N*-protected amino acid azides are subject to the Curtius rearrangement and that the resulting isocyanates can react with alcohols to give urethane derivatives. In 1936 Bergmann and Zervas [2] applied the so-called benzyloxycarbonyl stepwise degradation method to the elucidation of the primary structure of peptides (Scheme 1). Recently, the same series of



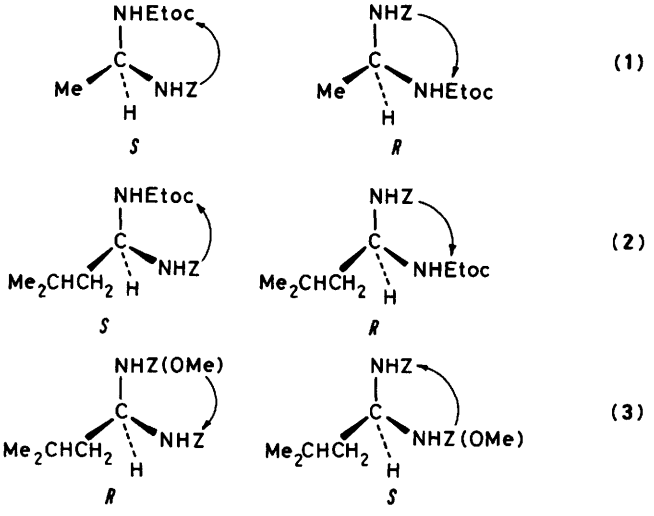
Scheme 1.

reactions have been used for the incorporation of *gem*-diamino compounds into synthetic retro-isomers of biologically active peptides.[3]

Here we describe the synthesis of the enantiomeric pairs (*R*,*S*) of the following compounds: *N*-benzyloxycarbonyl-*N'*-ethoxycarbonylethane-1,1-diamine (**1**); *N*-benzyloxycarbonyl-*N'*-ethoxycarbonyl-3-methylbutane-1,1-diamine (**2**); and *N*-benzyloxycarbonyl-*N'*-(*p*-methoxybenzyloxycarbonyl)-3-methylbutane-1,1-diamine (**3**). To the best of our knowledge, the whole synthesis is the second example of the principle first applied by Fischer[3a] who converted (+)-isopropylmalonamidic acid into its (−)-enantiomer. In addition, the isocyanates of *N*-benzyloxycarbonyl-L-alanine and *N*-benzyloxycarbonyl-L-leucine (formed in aqueous acidic solution) unexpectedly gave the symmetrical *gem*-diurethane *N*,*N'*-dibenzyloxycarbonylethane-1,1-diamine (**4**) and *N*,*N'*-dibenzyloxycarbonyl-3-methylbutane-1,1-diamine (**5**), respectively. A mechanism is proposed for the sequence of reactions outlined in Scheme 2.



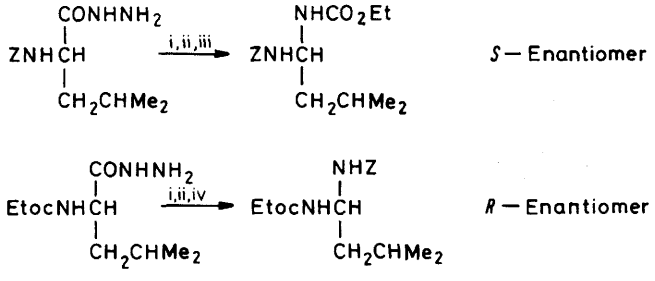
Scheme 2. *Reagents:* i, H_2O, H^+; ii, Heat; iii, $PhI(OCOCF_3)_2$ in MeCN–H_2O



Results and Discussion

The hydrazides of *N*-protected L-amino acids were converted into the corresponding azides under the conditions described by Honzl and Rudinger.[4] The application of the Curtius rearrangement, followed by reaction of the isocyanates formed with appropriate alcohols, gave optically pure enantiomers of *N*,*N'*-substituted-*gem*-diamines (assuming that no inversion or partial racemization occurs at the chiral centre which migrates from C to N; Scheme 3).

The pairs of enantiomers shown in the Table have been synthesized in a similar way. The desired azides, necessary



Scheme 3. *Reagents:* i, Bu'ONO, H^+; ii, Heat; iii, EtOH iv, BzlOH

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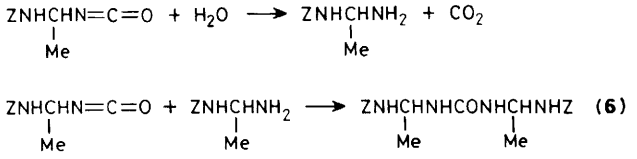
Table.

Starting material	Alcohol used	Final product	$[\alpha]_D$ Value	t/°C	c (g/100 ml)	M.p. (°C)
Z-L-Ala-$NHNH_2$	EtOH	(*S*)-(**1**)	+17.1°	25	1.05	143—146
Etoc-L-Ala-$NHNH_2$	BzlOH	(*R*)-(**1**)	−16°	25	0.9	143—145
Z-L-Leu-$NHNH_2$	EtOH	(*S*)-(**2**)	+12.4°	25	0.96	123—125
Etoc-L-Leu-$NHNH_2$	BzlOH	(*R*)-(**2**)	−12.4°	25	1.01	123—125
Z-L-Leu-$NHNH_2$	Bzl(OMe)OH	(*R*)-(**3**)	−1.8°	20	0.9	138—140
Z-L-Leu-OH[b]	Bzl(OMe)OH	(*R*)-(**3**)	−1.8°	20	0.9	138—140
Z(OMe)-L-Leu-$NHNH_2$	BzlOH	(*S*)-(**3**)	+1.75°	20	0.95	138—140

[a] In DMF. [b] Using DPPA.

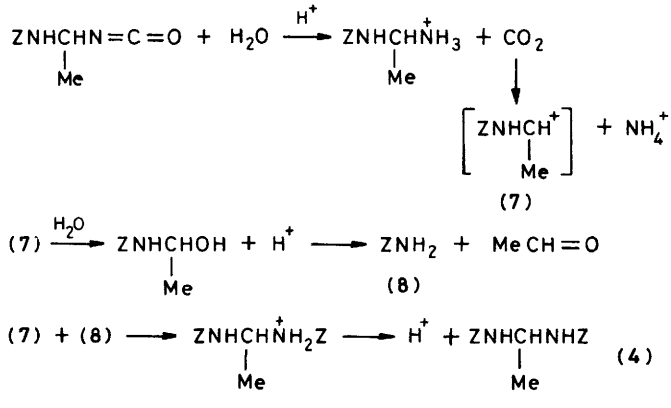
precursors for the *N*,*N*′-substituted *gem*-diamines, were, in some cases, also prepared directly from *N*-protected L-amino-acids by the use of diphenylphosphoryl azide (DPPA),[5] as indicated in the Table.

Primary alcohols, used as shown above, gave the best results with isocyanates. However, starting from Boc-L-Ala-$NHNH_2$ and using benzyl alcohol, we failed to obtain the *N*,*N*′-disubstituted *S*-enantiomer. This is possibly due to the decomposition[6] of the Boc-group on heating. We obtained the known *R*-enantiomer[3] from Z-L-Ala-$NHNH_2$ only in the presence of anhydrous Et_3N as a catalyst;[7] in the absence of Et_3N, depending upon the conditions, we isolated two other products [(**4**) in Scheme 2, and (**6**)]. The formation of the latter, a symmetrical urea derivative [*N*,*N*′-bis(1-benzyloxycarbonylaminoethyl) urea], can be explained by the reactions shown in Scheme 4.



Scheme 4.

Since the mixture was carefully dried, after the formation of the azide the necessary water for the above reaction could be derived from the dehydration[8] of Bu^{t}OH by the isocyanates. The other compound (**4**) was isolated in the presence of aqueous acid, *i.e.* either when the azide was insufficiently washed with aqueous $KHCO_3$, or was warmed in aqueous acid (1M HCl), or when *I*,*I*-bis(trifluoroacetoxy)iodobenzene (PIT)[9] was used in MeCN–H_2O for the degradation of Z-L-Ala-NH_2 to the corresponding *gem*-diamine (Scheme 2). This last reaction is considered also to occur *via* an isocyanate with simultaneous

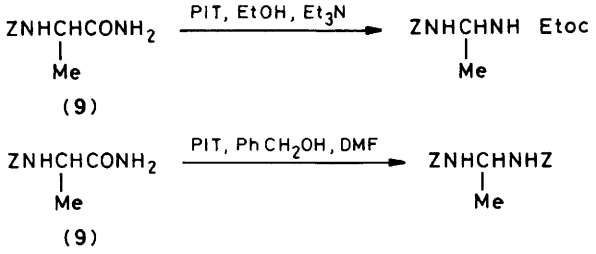


Scheme 5.

liberation of trifluoroacetic acid. We suggest the following mechanism for the formation of the unexpected compound (**4**) (Scheme 5).

As is shown in Scheme 2, the azide as well as the amide of *N*-benzyloxycarbonyl-L-leucine gave, under the same conditions, the unexpected symmetrical *gem*-diurethane (**5**). During all the aforementioned reactions we were able to detect (t.l.c.) the intermediate ZNH_2.

As regards the interaction of PIT with amides, we were able to prepare the desired *N*,*N*′-substituted-*gem*-diamines directly at room temperature, using PIT and *N*-benzyloxycarbonyl-L-alanine amide (**9**), in the presence of a base and the appropriate primary alcohol. Under these conditions, PIT did not oxidize the alcohols.[10]



Scheme 6.

The last two reactions constitute a new method for the preparation of *N*, *N*′-substituted *gem*-diamines.

Experimental

M.p.s were taken for samples in capillary tubes. Anhydrous solvents were used for the preparation of *gem*-diurethanes. Evaporations were carried out under reduced pressure at 35—40 °C, unless otherwise specified. When necessary, solutions in organic solvents were dried over sodium sulphate. Before analysis, compounds were dried over P_2O_5 at room temperature under high vacuum. R_F Values refer to t.l.c. on silica gel G (Fluka) containing 13% calcium sulphate in the following solvent systems (proportions by volume): (A) toluene–pyridine–acetic acid (80:10:1); (B) chloroform–methanol (9:1); (C) carbon tetrachloride–ethyl acetate (1:1); (D) chloroform–carbon tetrachloride–methanol (6:3:1); (E) butanol–acetic acid–water (10:1:3); (F) propanol–ammonia (67:33); (G) acetonitrile–water (3:1); (H) carbon tetrachloride–ethyl acetate (1:2); (J) ethyl acetate; (K) butanol–acetic acid–water–ethyl acetate (1:1:1:1).

Plates were developed with ninhydrin solution [0.5% in acetone–acetic acid–water (90:5:5)], with iodine, with ammonium sulphate solution (20% in 4% sulphuric acid) and heating, with u.v. light and, in the case of hydrazides, with potassium dichromate solution (1%). Light petroleum refers to the fraction b.p. (60—80 °C).

N-*Ethoxycarbonyl*-L-*alanine Hydrazide*.—A solution of L-alanine methyl ester hydrochloride[11] (2.8 g, 20 mmol) in chloroform (50 ml) was cooled to −5 °C and neutralized by the addition of triethylamine (2.8 ml, 20 mmol). To this mixture, ethoxycarbonyl chloride (1 ml, 10 mmol) followed by triethylamine (1.4 ml) was added twice in succession within 10 min. After being stirred for 1 h at room temperature, the mixture was washed with water, 5% sulphuric acid solution, water, 5% aqueous sodium hydrogen carbonate, and water (to neutral pH), and then dried and evaporated to dryness. The residual oil of *N*-ethoxycarbonyl-L-alanine methyl ester was homogeneous by t.l.c., R_F (B) 0.8. It was dissolved in methanol (20 ml), and hydrazine hydrate (3 ml) was added. After being stirred for 2 h at room temperature, the mixture was left overnight at 4 °C. The solvent was evaporated and the excess of hydrazine was removed in the dessicator over sulphuric acid. The product was precipitated by addition of ether. It was recrystallized from methanol–ether (3.4 g, 97%), m.p. 108—110 °C; $[\alpha]_D^{25}$ −30° (*c* 1 in 1M-hydrochloric acid); R_F (B) 0.6 (Found: C, 41.2; H, 7.5; N, 23.8. $C_6H_{13}N_3O_3$ requires C, 41.1; H, 7.5; N, 24.0%).

N-*Ethoxycarbonyl*-L-*leucine Hydrazide*.—This compound was prepared from *N*-ethoxycarbonyl-L-leucine methyl ester as described for *N*-ethoxycarbonyl-L-alanine hydrazide. The hydrazide, precipitated by addition of light petroleum, was recrystallized from ether–light petroleum (yield 90%), m.p. 56—59 °C; $[\alpha]_D^{23}$ −23.1° (*c* 1.9 in 1M-hydrochloric acid); R_F (B) 0.5 (Found: C, 49.7; H, 8.8; N, 19.1. $C_6H_{19}N_3O_3$ requiries C, 49.75; H, 8.8; N, 19.3%).

N-p-*Methoxybenzyloxycarbonyl*-L-*leucine Hydrazide*.—A suspension of *N*-*p*-methoxybenzyloxycarbonyl-L-leucine dicyclohexylammonium salt[12] (23.8 g, 50 mmol) in ether was shaken in a separatory funnel with 0.1M-sulphuric acid until it dissolved. The organic layer was washed with water (×3), dried, and evaporated. To the oily residue, dissolved in ether (150 ml), a cooled (0 °C) solution of diazomethane[13] in ether was added until no more bubbles were formed. Some drops of glacial acetic acid were added (to destroy any excess of diazomethane) and the ether solution was washed with water, 5% aqueous potassium hydrogen carbonate, and water (to neutral pH), then dried and evaporated. The residual oil of *N*-*p*-methoxybenzyloxycarbonyl-L-leucine methyl ester was homogeneous by t.l.c., R_F (B) 0.8.

To a solution of the above oily residue in methanol (100 ml) hydrazine hydrate (10 ml) was added. After being stirred for 3 h at room temperature, the mixture was set aside overnight at 4 °C. Upon addition of cold water, the hydrazide was precipitated and this was filtered off and recrystallized from ethanol (13.9 g, 90%), m.p. 122—123 °C; $[\alpha]_D^{20}$ −28.3° (*c* 1 in chloroform); R_F (B) 0.5, R_F (K) 0.6 (Found: C, 58.2; H, 7.5; N, 13.6. $C_{15}H_{23}N_3O_4$ requires C, 58.2; H, 7.5; N, 13.6%).

Preparation of the R *and* S *Enantiomers of* N,N-*Disubstituted* gem-*Diamines: General Procedure*.—A suspension of the pertinent hydrazide (10 mmol) in tetrahydrofuran (5 ml) was cooled to −15 °C using acetone–solid CO_2. Hydrogen chloride in ether (6.8 M; 3.7 ml) was added, followed by t-butyl nitrite (1.4 ml, 11 mmol). The mixture was stirred for about 30 min at −15 °C until a clear solution was obtained. After evaporation of the solvent, the residue was extracted with ether precooled to −10 °C, then washed with cold water, 5% aqueous sodium hydrogen carbonate, cold water, then dried. Into the dried ethereal solution of the azide, the appropriate alcohol (25 mmol) was added and the solvent was evaporated at 5–10 °C. The residual mixture of the azide and the alcohol was then dissolved in benzene (15 ml) and refluxed for 2—4 h. If ethanol was used, it replaced benzene.

N-*Benzyloxycarbonyl*-N′-*ethoxycarbonylethane*-1,1-*diamine* (**1**).—S-*Enantiomer*. (*a*) *N*-Benzyloxycarbonyl-L-alanine hydrazide[14] (2.4 g, 10 mmol) was converted into the corresponding azide as described in the general procedure. The mixture was refluxed for 2 h in ethanol after which it was evaporated to dryness. The oily residue was dissolved in ethyl acetate (5 ml) and light petroleum (50 ml) was added to slight turbidity; the mixture was then left for 24 h at 4 °C, whereupon the diamine crystallized out. Pure material was obtained by column chromatography on silica gel using carbon tetrachloride–ethyl acetate (1:1, v/v) as eluant, combining fractions containing the pure material (t.l.c.), and evaporating them to dryness. Pure *S*-enantiomer (0.4 g) was obtained by dissolving the residue in ethyl acetate and adding light petroleum; it had m.p. 143—146 °C; $[\alpha]_D^{25}$ +17.1° (*c* 1.05 in dimethylformamide); R_F (A) 0.5, R_F (B) 0.8, R_F (C) 0.7 (Found: C, 58.4; H, 6.7; N, 10.5. $C_{13}H_{18}N_2O_4$ requires C, 58.6; H, 6.8; N, 10.5%).

(*b*) *N*-Benzyloxycarbonyl-L-alanine amide (1.1 g, 5 mmol) was dissolved in ethanol (30 ml) and PIT (2.15 g, 5 mmol) was added. After 5 min, triethylamine (1.5 ml) was added dropwise with stirring into the mixture. After each drop, the solution turned yellow owing to formation of an unstable base–isocyanate complex. The colour persisted for a short time and then disappeared. After the addition of all the base, the mixture was warmed to 30 °C for 3 h. The solvent was evaporated off and the residue, dissolved in ethyl acetate, was washed with water, 5% aqueous potassium hydrogen carbonate, 5% aqueous sulphuric acid, and water, and it was then dried. The solution was concentrated to a small volume, light petroleum was added, and the crystalline *S*-enantiomer (0.2 g) separated out, m.p. 143—146 °C; $[\alpha]_D^{25}$ +17.05° (*c* 1 in dimethylformamide).

R-*Enantiomer*. *N*-Ethoxycarbonyl-L-alanine hydrazide (1.75 g, 10 mmol) was converted into the corresponding azide as described above in the general procedure. To the benzene solution of the azide, benzyl alcohol (1.1 ml) was added and the mixture was refluxed for 2 h. After the evaporation of the solvent, the residue was crystallized by addition of ethyl acetate (5 ml) and light petroleum (50 ml) with cooling. Purification was achieved as described for the *S*-enantiomer; yield 300 mg, m.p. 143—145 °C; $[\alpha]_D^{25}$ −16° (*c* 0.9 in dimethylformamide); R_F (A) 0.5, R_F (B) 0.8, R_F (C) 0.7.

N-*Benzyloxycarbonyl*-N′-*ethoxycarbonyl*-3-*methylbutane*-1,1-*diamine* (**2**).—S-*Enantiomer*. *N*-Benzyloxycarbonyl-L-leucine hydrazide[15] (5.6 g, 20 mmol) was converted into the corresponding azide; it was dissolved in ethanol and refluxed for 3 h. After the evaporation of the solvent, the residue was crystallized by addition of ethyl acetate, (5 ml) and light petroleum (70 ml) with cooling. The compound was purified by column chromatography over silica gel using carbon tetrachloride–ethyl acetate (1:1, v/v) as eluant. The fractions containing pure material (t.l.c.) were combined and concentrated to dryness. By dissolving the residue in ethyl acetate, and adding light petroleum, the pure product was obtained (2 g), m.p. 123—125 °C; $[\alpha]_D^{25}$ +12.4° (*c* 1 in dimethylformamide); R_F (B) 0.8, R_F (A) 0.5, R_F (C) 0.7.

R-*Enantiomer*. *N*-Ethoxycarbonyl-L-leucine hydrazide (4.35 g, 20 mmol) was converted into the corresponding azide. It was dissolved in benzene, benzyl alcohol (2.2 ml) was added, and the mixture was refluxed for 3 h. The title compound was isolated and purified as described for the *S*-enantiomer; yield 1.3 g, m.p. 123—125 °C; $[\alpha]_D^{25}$ −12.4° (*c* 1 in dimethylformamide); R_F (A) 0.5, R_F (B) 0.8, R_F (C) 0.7 (Found: C, 62.3; H, 7.8; N, 9.2. $C_{16}H_{24}N_2O_4$ requires C, 62.3; H, 7.8; N, 9.1%).

N-*Benzyloxycarbonyl*-N′-p-*methoxybenzyloxycarbonyl*-3-*methylbutane*-1,1-*diamine* (**3**).—R-*Enantiomer*. (*a*) *N*-Benzyloxycarbonyl-L-leucine hydrazide (2.8 g, 10 mmol) was

converted into the corresponding azide by the general procedure. From a benzene solution of the azide, the expected 1,1-diurethane was prepared after adding *p*-methoxybenzyl alcohol and refluxing for 3 h. Evaporation of the solvent, crystallization of the oily residue from ether, and recrystallization from ethanol yielded pure product (1.5 g), m.p. 138—140 °C; $[\alpha]_D^{20}$ −1.8° (*c* 0.9 in dimethylformamide); R_F (A) 0.6, R_F (B) 0.9, R_F (C) 0.7 (Found: C, 65.8; H, 7.0; N, 7.0. $C_{22}H_{28}N_2O_5$ requires C, 66.0; H, 7.05; N, 7.0%).

(*b*) *N*-Benzyloxycarbonyl-L-leucine[16] (1.3 g, 5 mmol) was dissolved in dioxane (20 ml) and neutralized with triethylamine (0.7 ml). After the addition of diphenylphosphoryl azide (1.4 g, 5.2 mmol) and *p*-methoxybenzyl alcohol (1.4 g, *ca.* 10 mmol), the mixture was refluxed for 3 h. The solvent was evaporated off and the residue was dissolved in ethyl acetate and the organic layer washed successively with 0.33M-citric acid, water, 5% aqueous potassium hydrogen carbonate, and water; it was then dried and evaporated to dryness. The product was precipitated by adding light petroleum and was purified after three recrystallizations from ethanol, yield 0.5 g, m.p. 138—140 °C; $[\alpha]_D^{20}$ −1.8° (*c* 0.9 in dimethylformamide).

S-*Enantiomer*. *N*-*p*-Methoxybenzyloxycarbonyl-L-leucine hydrazide (6.2 g, 20 mmol) was converted into the corresponding azide as described in the general procedure. To the benzene solution of the azide, benzyl alcohol (2.2 ml) was added and the mixture was refluxed for 3 h. Isolation and purification was achieved as described for the *R*-enantiomer; yield 4 g, m.p. 138—140 °C; $[\alpha]_D^{20}$ +1.75° (*c* 0.95 in dimethylformamide); R_F (A) 0.6, R_F (B) 0.9, R_F (C) 0.7.

N,N′-*Bis*(*benzyloxycarbonyl*)*ethane*-1,1-*diamine* (**4**).—(*a*) *N*-Benzyloxycarbonyl-L-alanine hydrazide (2.4 g, 10 mmol) was converted into the azide. It was dissolved in benzene, benzyl alcohol (1.1 ml) was added and the mixture was refluxed for 3 h. The solvent was evaporated and the product was precipitated by the addition of ether; it was recrystallized from acetonitrile, yield 1.2 g, m.p. 196—198 °C; R_F (A) 0.5, R_F (B) 0.8, R_F (C) 0.7 (Found: C, 65.7; H, 6.1; N, 8.7. $C_{18}H_{20}N_2O_4$ requires C, 65.8; H, 6.1; N, 8.5%).

(*b*) *N*-Benzyloxycarbonyl-L-alanine azide obtained from the corresponding hydrazide, according to the general procedure, was refluxed with 2M-hydrochloric acid. After 15 min, the symmetrical *gem*-diurethane separated out and was filtered off, triturated with ether, and recrystallized from acetonitrile; yield 48%, m.p. 196—198 °C.

(*c*) *N*-Benzyloxycarbonyl-L-alanine amide (1.1 g, 5 mmol) was dissolved in a solution of PIT (2.15 g, 5 mmol) in acetonitrile–water (1:1, v/v) and stirred at room temperature. Bubbles of carbon dioxide appeared almost immediately and after 10 min the symmetrical diurethane precipitated. It was filtered off, triturated with ether, and recrystallized from acetonitrile; yield 0.5 g, m.p. 196—198 °C.

(*d*) *N*-Benzyloxycarbonyl-L-alanine amide (1.1 g, 5 mmol) was dissolved in dimethylformamide (15 ml) and PIT (2.15 g, 5 mmol) was added. After 5 min, benzyl alcohol (1 ml) was also added and the mixture was heated at 40 °C for 3 h. The solvent was evaporated off and the residue, dissolved in ethyl acetate, was washed successively with 5% aqueous sulphuric acid, water, 5% aqueous potassium hydrogen carbonate, and water; the organic layer was then dried and evaporated. Precipitation from ether and recrystallization from acetonitrile afforded pure compound (150 mg), m.p. 196—198 °C.

The compounds prepared *via* all the above precedures were identical by melting point, mixed melting point, and i.r. spectra.

N,N′-*Bis*(*benzyloxycarbonyl*)-3-*methylbutane*-1,1-*diamine* (**5**).—*N*-Benzyloxycarbonyl-L-leucine amide[17] (2.6 g, 10 mmol) was dissolved in a solution of PIT (4.3 g, 10 mmol) in acetonitrile–water (1:1, v/v). After 3 min, the formation of carbamic acid benzyl ester [R_F (B) 0.6] (**8**) was detected by t.l.c.; the product had R_F (B) 0.8. The mixture was stirred for 4 h at room temperature, and was then extracted with ethyl acetate. The organic phase was washed with 5% aqueous sulphuric acid, 5% aqueous potassium hydrogen carbonate, and water, and then dried and evaporated. Precipitation from ether–light petroleum, followed by recrystallization from methanol, gave pure product; yield 0.4 g, m.p. 105—109 °C; R_F (A) 0.5, R_F (B) 0.8 (Found: C, 68.0; H, 7.1; N, 7.6. $C_{21}H_{26}N_2O_4$ requires C, 68.1; H, 7.1; N, 7.6%).

N,N′-*Bis*(1-*benzyloxycarbonylaminoethyl*)*urea* (**6**).—*N*-Benzyloxycarbonyl-L-alanine hydrazide (2.4 g, 10 mmol) was converted into the corresponding azide, dissolved in benzene (or toluene), and heated for 60 min at 70—80 °C. t-Butyl alcohol was then added, whereupon a white precipitate was formed. After 2 h, the solvent was evaporated off and the product was crystallized from ether and recrystallized from dimethylformamide–ether; yield 1.2 g, m.p. 225—228 °C (Found: C, 60.8; H, 6.3; N, 13.5. $C_{21}H_{26}N_4O_5$ requires C, 60.85; H, 6.3; N, 13.5%).

By dissolving the azide in t-butyl alcohol (instead of using benzene or toluene as solvent), the same compound was isolated.

N-*Benzyloxycarbonyl*-N′-*t-butyloxycarbonylethane*-1,1-*diamine*.— The azide, prepared from *N*-benzyloxycarbonyl-L-alanine hydrazide (2.4 g, 10 mmol), was dissolved in benzene (50 ml) and the solution was heated at 50 °C. After 10 min, t-butyl alcohol (20 ml) and triethylamine (2 ml) were added, and the mixture was refluxed for 2 h. The solvent was then evaporated off and the residue precipitated from light petroleum. The crude product was purified by column chromatography over silica gel using carbon tetrachloride–ethyl acetate (1:1, v/v) as eluant; yield 1 g, m.p. 148—150 °C (lit.,[3] m.p. 149—150 °C); $[\alpha]_D^{22}$ −12.7 (*c* 1 in chloroform); R_F (A) 0.6, R_F (B) 0.7.

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