Selective Protection of Polyamines: Synthesis of Model Compounds and Spermidine Derivatives

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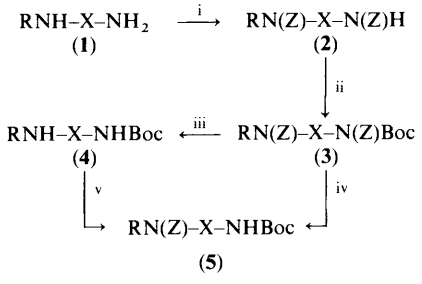
A general procedure for the selective protection of mixed primary–secondary (poly)amines, based on t-butoxycarbonylation of carbamate groups (exhaustive t-butoxycarbonylation) derived from the primary amino functions only, is reported. In most cases to be described, benzyl (poly)carbamates are used for this purpose. Subsequent removal of all benzyloxycarbonyl (Z) groups from the resulting intermediates by catalytic hydrogenolysis liberates the secondary amino functions, while t-butoxycarbonyl (Boc) is retained on the primary ones. Alternatively, selective removal of Z only from amino functions protected by both Z and Boc, which can be accomplished by base-catalysed methanolysis, results in protected (poly)amines with Boc and Z on their primary and secondary amino groups, respectively. The new reactions have been studied with two unsymmetrical derivatives of ethylene- and *p*-phenylene-diamine as model substances. The yields of most intermediates and the products were high. Additional experiments have been performed with spermidine to give N^1,N^8-Boc_2-spermidine. Finally, by virtue of the non-equivalence of the two primary amino groups in this molecule, the synthesis of N^8-Boc-N^1-Z-spermidine by the same approach is presented.

Naturally occurring polyamines such as putrescine, spermidine, and spermine have been widely studied; nevertheless their specific biological functions are in many respects still obscure.[1] Some novel aspects of the chemistry of these compounds have recently been reviewed.[2] In addition to their occurrence in native form, these substances form conjugates with other types of compounds such as sugars, steroids, phospholipids, and peptides, and they also furnish precursors for the biosynthesis of numerous substances such as alkaloids and siderophores.[2] All three amines, after suitable transformations, provide valuable starting materials for synthetic work. Owing to the presence of two non-equivalent primary amino groups in addition to a secondary one, spermidine constitutes a particular challenge in this context and a great deal of effort has been aimed at its selective modification.[3]

Monoacylation even of diamines, in high yield, poses considerable difficulties.[4] No wonder, therefore, that many different procedures have been studied for selective protection of various polyamines.[2,3] Recently, however, two acylation methods were reported with chemoselectivity for primary amino groups.[5,6] Both gave N^1,N^8-bisacylspermidines in better than 90% yield.

We recently approached the problem of selective protection of mixed primary–secondary amines from a different direction and proposed a procedure which we believe is of considerable scope in this context.[7] It is based on t-butoxycarbonylation of carbamates derived from primary amines and can be accomplished under surprisingly mild conditions with the aid of di-t-butyl dicarbonate[8] (Boc_2O) in the presence of 4-dimethylaminopyridine (DMAP) as a catalyst.[9] This paper gives examples of selective protection of model mixed primary–secondary (di)amines as well as spermidine, by use of the convenient and well established protecting groups for amino functions benzyloxycarbonyl (Z) and Boc, and describes in detail our experimental approach. The new procedure thereby provides a simple three-step synthesis of N^1,N^8-Boc_2-spermidine[10] in high overall yield. Furthermore, the non-equivalence of the primary amino groups of this triamine is exploited in a five-step synthesis of N^8-Boc-N^1-Z-spermidine,[11] also in high overall yield.

Selective Protection of Two Model Compounds (**1a** *and* **b**).—As a simple aliphatic model substance for studying selective protection of mixed primary–secondary polyamines, we first chose N^1-ethylethylenediamine (**1a**); most of our experiments with this compound are summarized in Scheme 1.

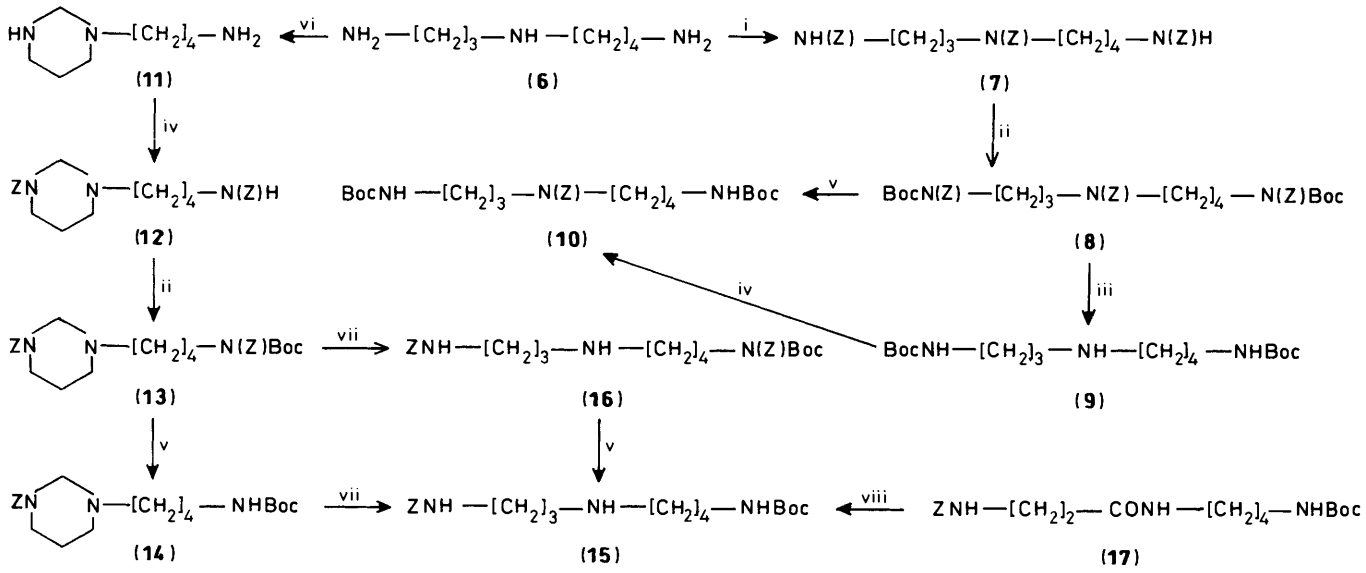


a; R = Et, X = CH_2CH_2 **b**; R = Me, X = *p*-C_6H_4

Scheme 1. *Reagents:* i, ZCl (pyridine or aq. Na_2CO_3); ii, Boc_2O, DMAP (MeCN, room temp.); iii, (**3a**), HCO_2NH_4, Pd–C (80% HOAc, room temp.); (**3b**), H_2, Pd–C (MeOH); iv, TMG (MeOH, room temp.); v, (**4a**), Z_2O (CH_2Cl_2); (**4b**), ZCl (pyridine)

Thus, the straightforward reaction of substance (**1a**) with a slight excess of ZCl furnished the biscarbamate (**2a**) nearly quantitatively. The key step, its transformation into (**3a**) by using Boc_2O with DMAP as a catalyst, also proceeded essentially quantitatively, although in this case a modest excess of acylating reagent was required to complete the reaction. The two Z groups were removed by catalytic transfer hydrogenolysis, and the resulting product (**4a**) turned out to be crystalline in contrast to the intermediates (**2a**) and (**3a**) which were both oils. The overall yield of the selectively protected compound (**4a**) from the corresponding unprotected amine (**1a**) was 78%. However, crystalline derivatives were obtained when *p*-nitrobenzyloxycarbonyl[12] [Z(NO_2)] was substituted for Z (see Experimental section). It should be stressed in this context that a Z group occupying the same nitrogen atom as a Boc group retains its well known lability to hydrogenolysis,[7] which has been the basis for much synthetic work in the past, particularly in the field of peptide synthesis, although in that area Z and Boc are used to protect different amino groups.

More important, compound (**3a**) could also be debenzyloxy-



Scheme 2. *Reagents:* i, ZCl (aq. Na_2CO_3); ii, Boc_2O, DMAP (MeCN, room temp.); iii, HCO_2NH_4, Pd–C (80% aq. HOAc, room temp.); iv. Z_2O (CH_2Cl_2, room temp.); v, TMG (MeOH, room temp.); vi, HCHO; vii, malonic acid, pyridine (MeOH, reflux); viii, $NaBH_4$, CF_3CO_2H (tetrahydrofuran, 40 °C)

carbonylated essentially selectively on the originally primary amino group by tetramethylguanidine(TMG)-catalysed methanolysis.[7] The ^{1}H n.m.r. spectrum of crude (**5a**) indicated the presence of only trace amounts (<1%) of the anomalous cleavage product (**2a**). This finding was unexpected in the light of the rather low selectivity obtained in the aminolysis of a similar compound.[13] This new cleavage reaction is the key step in our synthesis of N^8-Boc-N^1-Z-spermidine (**15**) described later.

Moreover, since selective diacylation of spermidine until recently[5,6] was difficult to accomplish,[14] an attempt at direct mono-t-butoxycarbonylation of (**1a**) was made. This experiment, however, gave the Boc_2 derivative as the major product (not described in the Experimental section).

As a simple model substance for exploratory experiments with a mixed primary–secondary aromatic diamine according to Scheme 1, we chose N^1-methyl-*p*-phenylenediamine (**1b**). In this series too, all the three steps leading to compound (**4b**) proceeded smoothly and no evidence for the formation of a by-product was noticed. This is reflected in the high overall yield (80%) of product (**4b**) from (**1b**). Furthermore, on TMG-catalysed methanolysis, the intermediate (**3b**) was cleaved selectively to give (**5b**), in essentially quantitative yield. Less than 2% of the undesired by-product (**2b**) could be detected in crude (**5b**) (^{1}H n.m.r.). A few minor modifications were made in the experimental procedures used in this reaction sequence as compared with those applied to the corresponding ethylenediamines. Thus, pyridine was used as solvent in the preparation of (**2b**) instead of aqueous dioxane. Although catalytic transfer hydrogenolysis was applied to obtain (**4a**), it gave a less pure product than ordinary catalytic hydrogenolysis in the case of (**4b**). Finally, all four compounds (**2b**)—(**5b**) were crystalline.

Analogous Experiments with Unsubstituted Spermidine.—Our various experiments aimed at protection of spermidine (**6**) are summarized in Scheme 2. Among these is a three-step sequence, analogous to those described in the preceding paragraph, leading to N^1,N^8-Boc_2-spermidine (**9**).[10] Triacylation of (**6**) was accomplished in aqueous dioxane essentially as for (**1a**) and gave compound (**7**) as an oil in 84% yield after chromatography. t-Butoxycarbonylation of the latter in the presence of DMAP according to our general procedure[9c] furnished compound (**8**) in 92% yield after chromatography, also as an oil, which on catalytic transfer hydrogenolysis gave solid (**9**). The overall yield of N^1,N^8-Boc_2 spermidine from spermidine was 56%. Furthermore, TMG-catalysed methanolysis of (**8**) yielded (**10**), which could also be obtained from (**9**) by benzyloxycarbonylation on N^4. Thus, the various reactions took place as easily on spermidine as on the model compounds discussed previously.

Experiments with the Spermidine–Formaldehyde Condensation Product (**11**).—The procedure outlined in the present paper up to this point exploited the difference between primary and secondary amino groups. However, with the spermidine–formaldehyde condensation product (**11**)[15] a further discrimination between the two primary amino groups of spermidine could be accomplished by the same approach. The major experiments are summarized in the reaction sequence (**11**) ⟶ (**15**) in Scheme 2.

The crude formaldehyde adduct (**11**), easily obtained in quantitative yield as stated in ref. 15*b*, was benzyloxycarbonylated on N^1 and N^8, this time with Z_2O,[16] to give (**12**). On treatment of this substance with Boc_2O-DMAP further substitution took place on N^8, giving rise to compound (**13**) with one Z and one Boc group on this nitrogen atom. Thus again we could apply TMG-catalysed methanolysis to remove the Z group on N^8 selectively, to furnish compound (**14**) as an oil in 88% yield after chromatography. On treatment with malonic acid in pyridine,[10c] the substance (**15**) was obtained as a solid in 78% yield after chromatography. This substance could also be obtained from (**13**) *via* (**16**), *i.e.* by performing the TMG-catalysed methanolysis and the cleavage by malonic acid in the reversed order, although the total yield then was lower. The overall yield of compound (**15**) in this five-step route from spermidine was 45%.

The structure of compound (**15**) was confirmed by an independent synthesis. Thus the amide (**17**), readily available from 1-Boc-tetramethylenediamine and Z-βAla-ONp, afforded (**15**) upon reduction with $NaBH_4$–TFA[10b] in modest yield. In addition to being susceptible to selective derivatization on N^4, compound (**15**), with its two orthogonal protecting groups, should, when needed, be well suited for conversion into related triprotected spermidine derivatives.

Discussion

Groups of carbamate or amide type are generally used in the protection of amino functions in synthetic work.[17] With the advent of a method of converting carbamates and amides into Boc derivatives[9] as well as additional procedures for subsequent cleavage,[9,13] the stage was set for application to the polyamine field of the orthogonal Boc/Z set of protecting groups, previously elaborated in the synthesis of peptides. Although in principle both Boc and Z are labile to acid, it is normally possible to remove Boc selectively with HCl in organic solvents or with TFA; Z, on the other hand, is preferentially removed by catalytic hydrogenolysis.

As demonstrated with the model substances (**1a** and **b**), sterically non-hindered aliphatic and aromatic, primary as well as secondary amino groups can be converted into benzyl carbamates in essentially quantitative yields. This is a prerequisite of their application as temporary protecting groups for polyamines, at the same time allowing discrimination in the next step between their primary and secondary amino functions. Benzyloxycarbonylation of amines is well documented,[17,18] particularly for amino acids, and will therefore not be further discussed here. The chemistry behind the next step, the t-butoxycarbonylation of various acylated amines,[9c] was recently discussed in detail and so was the cleavage of the products.[13] In this context we will therefore only stress that, for selective cleavage of Z from amino functions also carrying a Boc group, a much smaller amount of TMG is required than that originally used,[13] although slightly longer reaction times are needed as a result. This is illustrated in the synthesis of compounds (**5a**), (**14**), and (**15**).

In its application to the protection of spermidine, it should be noted how well the foregoing procedure worked for compound (**9**). The first synthesis of this derivative, characterized as its hydrochloride,[10a] seems to have been partly overlooked in the literature. It was accomplished from N^4-benzylspermidine, which in turn was obtained from the corresponding dinitrile. Sundaramoorthi *et al.*[10b] made (**9**) in 4—5 steps starting from 4-Boc-aminobutyric acid and 3-amino-1-chloropropane, whereas Nagarajan and Ganem[10c] made use of the spermidine–formaldehyde adduct (**11**) (see Scheme 2), which for the first time furnished a crystalline product.

While compound (**9**) was an ideal derivative for the synthesis of agrobactin A[19] and various N^4-cinnamoylated spermidine derivatives,[10b] as well as for photoaffinity labelling at this nitrogen atom,[10c] other work[20] required access to derivatives with three different protecting groups on the nitrogen atoms, and in that context N^8-benzyloxycarbonyl-N^1-phthaloyl-N^4-tosylspermidine[20] and N^4-benzyl-N^1-t-butoxycarbonyl-N^8-trifluoroacetylspermidine[21] were prepared. The first of these requires at least 6 steps for its preparation, and rather drastic deprotection conditions (*e.g.* liquid ammonia) for liberation afterwards, whereas the second requires 5 steps. The spermidine derivative (**15**), previously generated from two fragments *in situ* by Borowski *et al.*,[11] should complement the two compounds mentioned, but its prior preparation seems to have been completely overlooked in the chemical literature. We obtained it from Ganem's spermidine–formaldehyde adduct (**11**)[15] in a satisfactory overall yield. Compound (**15**) requires an additional step for protection at N^4, if it is going to be used for substitution elsewhere. Deprotection at N^1 as well as N^8 can be accomplished specifically under rather mild conditions.

Thus, the procedure outlined for selective protection of mixed primary–secondary amines, as described for the two model compounds, works well for spermidine, too. With respect to the general scope of this reaction, however, it should be pointed out that the Boc group is rather bulky and that cases are known when, for steric reasons, it cannot be introduced at all or only with difficulty.[9c] Therefore, for sterically hindered di- or polyamines, cases can be envisaged, when the procedure is not going to work satisfactorily. Also other functional groups present in the molecule might give rise to additional complications.

Experimental

All m.p.s were recorded on a Gallenkamp apparatus. All solvents applied as reaction media were of analytical grade and were dried for several days over a molecular sieve (4 Å). The spermidine used in this work was obtained from Fluka AG (purum quality). The ZCl was 86% w/w as measured by ^{1}H n.m.r. and the quantities applied were corrected accordingly; the remainder was benzyl chloride which did not interfere in these reactions. Unless otherwise stated, all organic extracts were repeatedly washed in turn with half their volumes of aqueous 1M $KHSO_4$, aqueous 1M $NaHCO_3$, and saturated aqueous NaCl, and dried over anhydrous $MgSO_4$ (for amines Na_2SO_4). T.l.c. analyses were performed on 0.25 mm thick precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}), eluted with (A) PhMe–MeCN (2:1). (B) light petroleum–ether (2:1), (C) CH_2Cl_2–ether (12:1), (D) CH_2Cl_2–Me_2CO–HOAc (5:5:1), (E) EtOAc–Me_2CO–HOAc–H_2O (5:3:1:1), (F) CH_2Cl_2–MeOH–HOAc (18:2:1), (G), (H), and (K) CH_2Cl_2–Me_2CO (4:1, 9:1, and 20:1). Spots were located under u.v. light at 254 nm, by exposure to iodine vapour or, after brief heating, by exposure to Cl_2 followed by dicarboxidine spray[22] (violet-blue spots). N.m.r. spectra were routinely recorded for solutions in $CDCl_3$ with a JEOL FX90Q instrument at 90 MHz (^{1}H) or 22.5 MHz (^{13}C). The ^{13}C signals were assigned by comparing chemical shifts and peak shapes, and are tentative. Elemental analyses of selected derivatives were carried out by Mikro Kemi AB, Uppsala, Sweden.

N^1-*Ethyl*-N^1,N^2-Z_2-*ethylenediamine* (**2a**).—An ice-cold solution of (**1a**) (4.41 g, 50.0 mmol) in aqueous 2M Na_2CO_3–dioxane (4:1; 250 ml) was treated dropwise with vigorous stirring with ZCl (24.1 g, 122 mmol) dissolved in dioxane. Simultaneously aqueous 2M NaOH (62 ml) was added under temperature control (≤8 °C). Cold water (total 100 ml) was introduced to facilitate stirring for 16 h at 4 °C. Most of the dioxane was stripped off at room temperature and the remaining suspension (*ca.* 0.4 l) was extracted with ether (200 ml + 2 × 100 ml). The combined extracts were washed and dried according to the general procedure already outlined. Evaporation to complete dryness and meticulous drying under low pressure at 50 °C for several hours afforded an almost colourless oil (16.6 g). This crude product contained *ca.* 3% (w/w) of benzyl alcohol (^{1}H n.m.r.) and was suitable for further work. The crude yield was 90%. An analytical specimen could readily be obtained by column chromatography on silica: neat CH_2Cl_2 eluted traces of non-polar contaminants whereas CH_2Cl_2–Me_2CO (16:1) furnished pure (**2a**) as a colourless oil, showing one spot on t.l.c. (A or B); δ_H 7.33 (s, 10 H, ArH), 5.38 (br s, *ca.* 1 H, NH), 5.10 and 5.08 (2 s, 4 H, CH_2Ph), 3.19—3.37 (complex, 6 H, 6 methylene H), and 1.11 (t, 3 H, CH_2CH_3); δ_C 156.5 (both CO), 136.5, 128.5, 128.0, and 127.8 (ArC), 67.1 and 66.7 (CH_2Ph), 46.5 (NCH_2CH_3), 42.7 ($CH_2NCH_2CH_3$), 40.1 ($CH_2CH_2NCH_2CH_3$), and 13.8 (NCH_2CH_3).

Similarly, from $Z(NO_2)Cl$ and (**1a**), N^1-ethyl-N^1,N^2-$[Z(NO_2)]_2$-ethylenediamine was prepared. The yield of crude product containing 16% of contaminating *p*-nitrobenzyl carbonate (^{1}H n.m.r.) was 6.14 g (64% corrected for impurity). Chromatography on silica with CH_2Cl_2–Et_2O (20:1) as eluant afforded the pure compound as a yellow oil which solidified. The chromatographed material was dissolved in ether (160 ml g^{-1}), and the solution filtered and concentrated to one tenth of the volume. Cooling induced precipitation of tiny pale yellow crystals, which were collected, rinsed with cold ether and dried

in vacuo. T.l.c. (A or C) gave one spot; m.p. 104.5—105 °C; δ_H 8.20 and 7.50 (A_2B_2q, 8 H, ArH), 5.46 (br s, *ca.* 1 H, NH), 5.23 and 5.18 (2 s, 4 H, $CH_2C_6H_4NO_2$), 3.24—3.51 (complex, 6 H, all methylene H), and 1.16 (t, 3 H, NCH_2CH_3); δ_C 155.9 (both CO), 147.5, 144.0, 128.0, and 123.7 (ArC), 65.6 and 65.2 ($CH_2C_6H_4NO_2$), 46.7 (NCH_2CH_3), 42.7 ($CH_2NCH_2CH_3$), 40.3 ($CH_2CH_2NCH_2CH_3$), and 13.9 (NCH_2CH_3).

N^1-*Methyl*-N^1,N^4-Z_2-1,4-*phenylenediamine* (**2b**).—Crude, finely ground dihydrochloride of compound (**1b**) (7.80 g, 40.0 mmol) was suspended in dry pyridine (250 ml) and the resulting light brown mixture was chilled in ice. This stirred slurry was then treated during *ca.* 1 h dropwise with ZCl (30.2 g, 150 mmol) below 8 °C. The brownish turbid mixture was stirred at room temperature for 20 h. Most of the solvent was removed by evaporation at reduced pressure below 30 °C, and the remaining dark sludge was partitioned between EtOAc (1.0 l) and aqueous 2M HCl (0.5 l). The brown aqueous phase was discarded and the organic extract was washed in turn with aqueous 2M HCl, aqueous 1M $NaHCO_3$, and saturated aqueous NaCl (3 × 250 ml each), dried (Na_2SO_4), and treated with decolourizing carbon. Evaporation to dryness afforded an almost colourless oil which soon solidified. The white solid was thoroughly triturated with cold light petroleum (100 ml) and the insoluble residue repeatedly rinsed with cold light petroleum (3 × 10 ml). The yield of crude product, homogeneous by t.l.c. (C), was 15.3 g (98%). Recrystallization from light petroleum–EtOAc (2:1; 25 ml g^{-1}) gave, after cooling, white *needles* (*ca.* 14 g); m.p. 119—119.5 °C; δ_H 6.99—7.36 (complex *ca.* 15 H, ArH + NH), 5.18 and 5.13 (2 s, 4 H, CH_2Ph), and 3.26 (s, 3 H, NCH_3); δ_C 155.5 and 153.3 (CO), 138.3, 136.4, 135.9, 128.5, 128.4, 128.2, 127.8, 127.6, 126.2, and 119.0 (ArC), 67.2 and 66.9 (CH_2Ph), and 37.8 (NCH_3) (Found: C, 70.7; H, 5.4; N, 7.4. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.7; N, 7.2%).

N^2-*Boc*-N^1-*ethyl*-N^1,N^2-Z_2-*ethylenediamine* (**3a**).—A solution of the crude compound (**2a**) (2.92 g, 8.19 mmol) and DMAP (205 mg, 1.68 mmol) in dry acetonitrile (30 ml) was treated with Boc_2O (1.97 g, 9.02 mmol) in one portion with agitation. Gas was evolved and the brandy-coloured mixture was stirred at room temperature. After 1 h, t.l.c. (A) showed that starting material still remained in the mixture and more Boc_2O (1.0 g, 4.5 mmol) was introduced. The reaction was essentially complete after 4–5 h and the mixture was left overnight to decompose the excess of Boc_2O. Most of the solvent was stripped off at room temperature and the brownish, oily residue was partitioned between ether (200 ml) and aqueous 1M $KHSO_4$ (100 ml). The dark aqueous phase was discarded and the pale yellow ethereal extract worked up as already described. After treatment with decolourizing carbon, the extract was taken to dryness and the residual yellow oil was dried under high vacuum at 50 °C to remove traces of Boc_2O. The yield of essentially pure (**3a**) was 3.44 g (92%). The analytical specimen was readily obtained by chromatography on silica with CH_2Cl_2–Et_2O (10:1) as eluant. Pure (**3a**) was obtained as a pale yellow viscous syrup. T.l.c. (A, B, or C) displayed one spot only; δ_H 7.33 (s, 10 H, ArH), 5.21, 5.10, and 5.08 (3 s, 4 H, CH_2Ph), 3.81 (perturbed m, 2 H, $BocNHCH_2CH_2$), 3.41 (t, 2 H, NCH_2CH_3), 3.25 (perturbed signal, 2 H, $CH_2NCH_2CH_3$), 1.45 [s, 9 H, $C(CH_3)_3$], and 1.07 (t, 3 H, NCH_2CH_3); δ_C 155.7, 153.5, and 151.8 (CO), 136.8, 135.4, 128.5, 128.3, and 127.8 (ArC), 83.1 [$C(CH_3)_3$], 68.4 and 67.0 (CH_2Ph), 45.8/44.9 (NCH_2CH_3, two conformers), 44.6 ($BocNHCH_2$), 42.7 ($CH_2NCH_2CH_3$), 27.9 [$C(CH_3)_3$], and 13.8/13.1 (NCH_2CH_3, two conformers).

N^2-Boc-N^1-ethyl-N^1,N^2-$[Z(NO_2)]_2$-ethylenediamine was obtained analogously. The yield of crude Boc analogue, obtained as a yellow oil was 91%, essentially pure by t.l.c. (A). The analytical specimen was obtained by dissolving this crude material in ether (100 ml g^{-1}). After concentration to one tenth of the volume and chilling to −20 °C overnight, a light yellow crystal mass precipitated (>80% crystallization yield); m.p. 109—109.5 °C; δ_H 8.22 (perturbed d, 4 H, ArH), 7.47—7.65 (complex, 4 H, ArH), 5.33, 5.27, 5.21, and 5.20 (four signals, 4 H, $CH_2C_6H_4NO_2$), 3.88 (t, 2 H, CH_2NBoc), 3.48 (t, 2 H, $CH_2NCH_2CH_3$), 3.33 (q, 2 H, NCH_2CH_3), 1.50 [s, 9 H, $C(CH_3)_3$], and 1.14 (t, 3 H, NCH_2CH_3); δ_C 155.5/155.2 and 153.6 ($CO_2CH_2C_6H_4NO_2$, two conformers), 151.4 [$CO_2C(CH_3)_3$], 147.7, 147.5, 144.1, 142.7, 142.5 128.2, 127.9, and 123.7 (ArC), 83.6 [$C(CH_3)_3$], 66.9 and 65.6 ($CH_2C_6H_4NO_2$), 45.8/44.4 (NCH_2CH_3, two conformers), 44.8 (CH_2NBoc), 42.9 ($CH_2NCH_2CH_3$), 27.9 [$C(CH_3)_3$], and 13.9/13.1 (NCH_2CH_3, two conformers).

N^4-*Boc*-N^1-*methyl*-N^1,N^4-Z_2-1,4-*phenylenediamine* (**3b**).—To a slurry of finely ground (**2b**) (3.90 g, 10.0 mmol) in dry acetonitrile (40 ml) was added DMAP (244 mg, 2.00 mmol) followed by Boc_2O (2.40 g, 11.0 mmol) in one portion with shaking. Evolution of gas commenced and after a few min stirring a clear, slightly coloured solution was obtained. T.l.c. (C) indicated complete reaction after 3 h at room temperature. Removal of the solvent left a syrupy residue, which was partitioned between ether (200 ml) and aqueous 1M $KHSO_4$ (100 ml). The brownish aqueous phase was discarded and the almost colourless ethereal extract was worked up as usual. After treatment with decolourizing carbon, the extract was taken to dryness, leaving a yellow oil which was thoroughly dried *in vacuo* at 50 °C. The yield of crude (**3b**) containing traces (*ca.* 1%) of Boc_2O was 4.43 g (90%). Recrystallization from light petroleum–ether (4:1; 40 ml g^{-1}) gave, after cooling to −70 °C for 3 days, a white crystalline *precipitate* (>90% crystallization yield); m.p. 75—76 °C; δ_H 7.06—7.34 (complex, 14 H, ArH), 5.19 and 5.17 (2 s, 4 H, CH_2Ph), 3.33 (s, 3 H, NCH_3), and 1.39 [s, 9 H, $C(CH_3)_3$]; δ_C 155.2, 152.8, and 151.2 (CO), 142.5, 136.3, 136.1, 135.3, 128.4, 128.1, 127.9, 127.7, and 125.8 (ArC), 83.4 [$C(CH_3)_3$], 68.1 and 67.3 (CH_2Ph), 37.6 (NCH_3), and 27.8 [$C(CH_3)_3$] (Found: C, 68.4; H, 6.0; N, 5.9. $C_{28}H_{30}N_2O_6$ requires C, 68.6; H, 6.2; N, 5.7%).

N^2-*Boc*-N^1-*ethylethylenediamine* (**4a**).—Into a solution of crude (**3a**) (1.05 g, 2.30 mmol) in aqueous 80% HOAc (30 ml) was introduced ammonium formate (1.20 g, 18.5 mmol). When all had dissolved, a slurry of Pd–C (10%; 0.40 g) in aqueous 80% HOAc (10 ml) was added in small portions with rapid stirring under nitrogen at room temperature. After 3 h stirring under nitrogen, t.l.c. (D or E) still indicated the presence of starting material, and more ammonium formate (1.20 g, 18.5 mmol) was added. After a further 2 h stirring, the reaction was complete and the catalyst was filtered off and rinsed with aqueous 80% HOAc. Evaporation of the colourless filtrate furnished an oily residue, which was partitioned between ether (80 ml) and aqueous 30% K_2CO_3 (80 ml). The aqueous phase was further extracted with ether (2 × 40 ml) and the combined colourless extracts were washed with saturated aqueous NaCl (2 × 40 ml). After drying ($MgSO_4$), the colourless extract was evaporated to dryness, leaving a light yellow oil which slowly solidified. The yield of crude, essentially pure (**4a**) was 405 mg (94%; the product was somewhat volatile and excessive drying at low pressure caused losses). T.l.c. (D or E) showed largely one spot. Crystallization of the crude material from light petroleum (15 ml g^{-1}; decolourizing carbon) furnished very pure (**4a**) as white *needles* (*ca.* 85% crystallization yield) after chilling to −20 °C; m.p. 54.5—55 °C; δ_H 5.03 (br s, *ca.* 1 H, amide NH), 3.23 (q, 2 H, $BocNHCH_2$), 2.73 (t, 2 H, CH_2NEt), 2.65 (q, 2 H, NCH_2CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 1.26 (br s, *ca.* 1 H, amine NH), and 1.10 (t, 3 H, NCH_2CH_3)]; δ_C 156.1 (CO), 79.1 [$C(CH_3)_3$], 49.0 (NCH_2CH_3), 43.7 (CH_2NEt), 40.4 ($BocNHCH_2$), 28.4

[$C(CH_3)_3$], and 15.4 (NCH_2CH_3) (Found: C, 56.9; H, 10.5; N, 14.7. $C_9H_{20}N_2O_2$ requires C, 57.4; H, 10.7; N, 14.9%).

N^4-*Boc*-N^1-*methyl*-1,4-*phenylenediamine* (**4b**).—Crystallized (**3b**) (490 mg, 1.00 mmol) was dissolved in methanol (40 ml) and hydrogenolysed (1 atm; room temperature) in the presence of Pd–C (5%; 112 mg). After 2 h, t.l.c. (C) indicated complete reaction and the catalyst was filtered off. The colourless filtrate was taken to dryness and the residue dried *in vacuo* at 40 °C to remove contaminating benzyl alcohol. The yield of crude (**4b**), obtained as a colourless viscous oil, was 217 mg (98%). This product was homogeneous by t.l.c. (C) and solidified slowly during several days in the cold. Recrystallization from light petroleum–ether (40 ml g^{-1}; decolourizing carbon) furnished a white crystalline *solid* after cooling at −70 °C for a few days; m.p. 62—62.5 °C; δ_H 7.15 and 6.55 (A_2B_2q, *J* 8.8 Hz, 4 H, ArH), 6.31 (br s, *ca.* 1 H, amide NH), 3.48 (br s, *ca.* 1 H, amine NH), 2.80 (s, 3 H, NCH_3), and 1.50 [s, 9 H, $C(CH_3)_3$]; δ_C 153.4 (CO_2Bu^t), 145.7, 128.6, 121.2, and 112.9 (ArC), 79.9 [$C(CH_3)_3$], 31.2 (NCH_3), and 28.4 [$C(CH_3)_3$] (Found: C, 65.0; H, 8.0; N, 12.6. $C_{12}H_{18}N_2O_2$ requires C, 64.8; H, 8.2; N, 12.6%).

N^2-*Boc*-N^1-*ethyl*-N^1-*Z*-*ethylenediamine* (**5a**).—(A) *Methanolysis of* (**3a**) *in the presence of catalytic amounts of TMG.* A mixture of (**3a**) (288 mg, 0.50 mmol) and TMG (11.5 mg, 0.10 mmol) in methanol (1 ml) was left at room temperature for 24 h. The mixture was partitioned between ether (40 ml) and aqueous 1M $KHSO_4$ (20 ml). The ethereal extract was washed as usual and taken to dryness, and the residual oil was dried under high vacuum to remove benzyl alcohol. The yield of crude product was essentially quantitative (163 mg). Only traces (≤1%) of (**2a**) could be detected by inspection of the ^1H n.m.r. spectrum. Recrystallization from light petroleum (15 ml g^{-1}) gave after chilling to −20 °C and seeding, white crystals which were rinsed with a little cold light petroleum and dried *in vacuo* over paraffin; m.p. 47.5—48 °C; δ_H 7.35 (s, 5 H, ArH), 5.13 (s, 2 H, CH_2Ph), 4.90 (br s, *ca.* 1 H, NH), 3.22—3.44 (complex cluster, 6 H, all methylene H), 1.43 [s, 9 H, $C(CH_3)_3$], and 1.13 (t, 3 H, NCH_2CH_3); δ_C 156.8 and 156.0 (CO), 136.6, 128.5, 128.0, and 127.8 (ArC), 79.3 [$C(CH_3)_3$], 67.1 (CH_2Ph), 46.7/46.0 (NCH_2CH_3, two conformers), 42.7 (CH_2NEt), 39.5 ($BocNHCH_2$), 28.4 [$C(CH_3)_3$], and 13.9/13.4 (NCH_2CH_3, two conformers).

(B) *From* (**4a**). To an ice-cold solution of crystallized (**4a**) (376 mg, 2.00 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a solution of Z_2O (572 mg, 2.00 mmol) in dry CH_2Cl_2, with vigorous stirring. The clear, colourless mixture was stirred for 1 h in ice and overnight at room temperature, and then applied to a silica column packed in CH_2Cl_2. Elution with this solvent removed contaminating benzyl alcohol, and switching to CH_2Cl_2–Me_2CO (9:1) afforded the desired product (634 mg, 98%) as a colourless oil which became solid in the cold. T.l.c. (C) gave one spot. The recrystallized sample was identical with the product obtained by procedure (A) (m.p., t.l.c., and ^1H n.m.r.).

N^4-*Boc*-N^1-*methyl*-N^1-*Z*-1,4-*phenylenediamine* (**5b**).—(A) *Methanolysis of* (**3b**), *with an excess of TMG.* Finely ground compound (**3b**) (245 mg, 0.50 mmol) was suspended in methanol (2.0 ml) and treated with TMG (94 μl, 0.75 mmol) with rapid stirring at room temperature. The mixture became clear within a few min, but after 1 h a precipitate reappeared. The thick sludge was stirred overnight and then partitioned between EtOAc (50 ml) and aqueous 1M $KHSO_4$ (25 ml). The colourless extract was treated as usual and evaporated to dryness, affording a white solid [176 mg, 99%; ^1H n.m.r. indicated <2% of (**2b**)]. Recrystallization from heptane–EtOAc (10:1) (100 ml g^{-1}) furnished white crystals; m.p. 171.5—172 °C; δ_H 7.08—7.39 (s + A_2B_2q, *J* 9.0 Hz, 9 H, ArH), 6.59 (br s, *ca.* 1 H, NH), 5.14 (s, 2 H, CH_2Ph), 3.27 (s, 3 H, NCH_3), 1.51 [s, 9 H, $C(CH_3)_3$]; δ_C 155.6 and 152.7 (CO), 138.1, 136.6, 136.4, 128.4, 127.9, 127.7, 126.4, and 118.4 (ArC), 80.6 [$C(CH_3)_3$], 67.2 (CH_2Ph), 37.9 (NCH_3), and 28.3 [$C(CH_3)$].

(B) *From compound* (**4b**). A solution of (**4b**) (222 mg, 1.00 mmol) in dry pyridine (2 ml) was slowly treated with ZCl (200 mg, 1.00 mmol), with rapid stirring at room temperature. When the addition was complete (*ca.* 15 min), the resulting brownish sludgy mixture was stirred overnight at room temperature. Most of the solvent was stripped off below 30 °C and the tan, semisolid residue was partitioned between EtOAc (40 ml) and aqueous 1M $KHSO_4$ (20 ml). The extract was washed and dried as before. Removal of the solvent left a pale yellow powder, which was thoroughly triturated with cold ether (3 ml). The insoluble solid was filtered off, rinsed with small portions of cold ether (3 × 1 ml) and dried *in vacuo*. The yield of crude (**5b**), homogeneous by t.l.c. (C), was 233 mg (65%). The crystallized specimen was identical with the product prepared according to procedure (A).

N^1,N^4,N^8-Z_3-*Spermidine* (**7**).—This compound was prepared from spermidine on a 10 mmol scale essentially as described for (**2a**). The yield of chromatographed material, obtained as a pale yellow oil, pure by t.l.c. (H), was 4.6 g (84%). The product solidified after several weeks in the refrigerator; δ_H 7.31 (s, 15 H, ArH), *ca.* 5.6 (br s, *ca.* 2 H, NH), 5.08 and 5.06 (2 s, 6 H, CH_2Ph), 2.98—3.38 (m, 8 H, CH_2N), and 1.48—1.71 (m, 6 H, CCH_2C); δ_C 156.4 (CO), 136.0, 128.5, 128.4, 128.0, 127.9, 127.4, and 126.9 (ArC), 67.1 and 66.6 (CH_2Ph), 46.4 and 44.1 (CH_2NCH_2), 40.5 and 37.7 (CH_2NHZ), and 28.9, 28.2, 27.2, and 25.5 (CCH_2C).

N^1,N^8-Boc_2-N^1,N^4,N^8-Z_3-*spermidine* (**8**).—The t-butoxycarbonylation of compound (**7**) was achieved as described for (**2a**). The crude product was chromatographed on silica (CH_2Cl_2–Et_2O, 20:1) to give Boc_2-Z_3-spermidine (**8**) as a pale yellow oil (7.6 g, 92%); pure by t.l.c. (A or H); δ_H 7.34 and 7.31 (2 s, 15 H, ArH), 5.20 (s, 4 H, $BocNCO_2CH_2Ph$), 5.10 (s, 2 H, third CH_2Ph), 3.56—3.62 [m, 4 H, $CH_2NZ(Boc)$], 3.16—3.28 (m, 4 H, CH_2NCH_2), and 1.71—1.94 (m) and 1.45 (s) (together 24 H, CCH_2C + CH_3); δ_C 155.9, 153.8, 153.6, 152.0, and 151.8 (CO), 136.8, 135.5, 128.5, 128.3, 128.2, 127.8, and 127.7 (ArC), 82.8 and 82.7 (CMe_3), 68.2 ($BocNCO_2CH_2Ph$), 66.9 (third CH_2Ph), 46.7, 46.1, and 44.4 (NCH_2C), 27.9 [$C(CH_3)_3$], and 26.2 and 25.4 (CCH_2C).

N^1,N^8-Boc_2-*spermidine* (**9**).—To fully protected compound (**8**) (8.7 g, 12 mmol), dissolved in 80% aqueous acetic acid (200 ml) and kept under N_2, was added ammonium formate (13 g, 200 mmol), followed by 5% Pd–C (4.0 g), and the mixture was stirred for 1 h. The catalyst was filtered off and the filtrate concentrated under reduced pressure. After addition of aqueous 30% K_2CO_3 (250 ml) the product was extracted with ether (3 × 300 ml). The combined organic layers were washed with saturated aqueous NaCl (2 × 50 ml), dried (Na_2SO_4), and evaporated to give a yellow oil which soon solidified. Recrystallization from light petroleum (100 ml g^{-1}) afforded the Boc_2-spermidine (**9**), homogeneous by t.l.c. (E), as a white *solid* (2.9 g, 72%); m.p. 85.5—86.5 °C (lit.,[10c] 79—80 °C); δ_H *ca.* 5.2 and 4.8 (2 br s, *ca.* 2 H, amide NH), 3.20 (q, 4 H, CH_2NHBoc), 2.67 (m, CH_2NCH_2), and 1.52—1.79 (m) and 1.44 (s, together 25 H, CCH_2C, CH_3, and amine NH); δ_C 156.1 and 156.0 (CO), 79.0 (CMe_3), 49.4 and 47.7 (CH_2NCH_2), 40.5 and 39.2 (CH_2NH-Boc), 29.8, 27.9, and 27.3 (CCH_2C), and 28.5 [$C(CH_3)_3$] (Found: C, 59.0; H, 10.1; N, 12.2. $C_{17}H_{35}N_3O_4$ requires C, 59.1; H, 10.2; N, 12.2%).

N^1,N^8-*Boc*$_2$-N^4-*Z-spermidine* (**10**).—(A) *Methanolysis of* (**8**), *with an excess of TMG*. The Z groups on N^1 and N^8 were removed with TMG as in the synthesis of (**5b**). The residue was worked up as usual to give a pale yellow oil, which was chromatographed on silica with CH_2Cl_2–Me_2CO (20:1) as eluant to give compound (**10**) as a chromatographically pure oil (ether or K) (725 mg, 80%); δ_H 7.34 (s, 5 H, ArH), 5.12 (s, 2 H, CH_2Ph), 3.08—3.30 (m, 8 H, CH_2NHBoc and CH_2NZCH_2), and 1.47—1.74 (m) and 1.43 (s) (together 24 H, CCH_2C and CH_3); δ_C 155.9 (CO), 136.6, 128.5, 128.2, 128.0, and 127.8 (ArC), 79.2 and 79.1 (CMe_3), 67.1 (CH_2Ph), 46.4 and 44.3 [$CH_2N(Z)CH_2$], 40.2 and 37.5 (CH_2NHBoc), 28.4 (CH_3), and 28.4, 27.3, and 25.6 (CCH_2C).

(B) *From compound* (**9**). The structure (**10**) was confirmed by an alternative synthesis from compound (**9**) according to the procedure described for (**5a**) [procedure (B)] to afford, after column chromatography (ether), an oil in 77% yield, with ^1H and ^{13}C n.m.r. spectra in agreement with the data given under (A).

N^1,N^4-*Methylenespermidine* (**11**).—This compound was prepared according to a previously described procedure,[15b] using fresh formaldehyde solution. The yield of essentially pure (**11**), obtained as a colourless oil which soon solidified, was 95%; δ_H 3.38 (s, 2 H, NCH_2N), 2.51—2.88 (m, 6 H, CH_2N), 2.17—2.33 (m, 2 H, CH_2NH_2), and 1.40—1.73 (m, together 8 H, CCH_2C and NH_2); δ_C 69.9 (NCH_2N), 55.4 and 53.1 ($NCH_2CH_2CH_2N$), 45.2 and 42.1 (CH_2N), and 31.8, 27.2, and 24.3 (CCH_2C).

N^1,N^4-*Methylene*-N^1,N^8-Z_2-*spermidine* (**12**).—A solution of Z_2O (12 g, 42 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise to a cooled solution of compound (**11**) (3.0 g, 19 mmol) in dry CH_2Cl_2 (15 ml), and the resulting mixture was stirred for 3 h. The solvent was removed under reduced pressure and the colourless residue was chromatographed on silica (CH_2Cl_2–Me_2CO, 4:1) to afford chromatographically essentially pure (G) product (**12**) as a pale yellow oil (6.1 g, 76%); δ_H 7.34 (s, 10 H, ArH), 5.12 and 5.08 (2 s, 4 H, CH_2Ph), 4.14 (s, 2 H, NCH_2N), 3.53 (t, 2 H) and 3.13—3.23 (m, 2 H) (CH_2NZ), 2.71 (t, 2 H), and 2.29—2.53 (m, 2 H) (CH_2N), and 1.33—1.74 (m, 6 H, CCH_2C); δ_C 156.4 and 155.0 (CO), 136.6, 128.4, and 128.0 (ArC), 67.0 and 66.4 (CH_2Ph), 65.0 (NCH_2N), 52.4 and 52.2 (2 × NCH_2), 43.8 and 40.8 (2 × $ZNCH_2C$), and 27.6, 24.4, and 22.9 (CCH_2C).

N^8-*Boc*-N^1,N^4-*methylene*-N^1,N^8-Z_2-*spermidine* (**13**).—To a stirred solution of compound (**12**) (4.4 g, 10 mmol) in dry MeCN (20 ml) was added DMAP (128 mg, 1.03 mmol), followed by Boc_2O (2.5 g, 11 mmol). When the starting material had been consumed [t.l.c. (G)] the solvent was evaporated under reduced pressure and the brownish residue was chromatographed (silica; ether) to give pure (A and G) compound (**13**) as a yellow oil (4.9 g, 90%); δ_H 7.35 and 7.33 (2 s, 10 H, ArH), 5.20 [s, 2 H, $PhCH_2O_2CN(Boc)$], 5.12 (s, 2 H, CH_2Ph), 4.12 (s, 2 H, NCH_2N), 3.35—3.62 [m, together 4 H, CH_2NZ and $CH_2NZ(Boc)$], 2.67 (t, 2 H) and 2.38 (t, 2 H) (CH_2N), and 1.46—1.72 (m) and 1.46 (s) (together 15 H, CCH_2C and $C(CH_3)_3$]; δ_C 154.8, 153.6, and 151.8 (CO), 136.5, 135.3, 128.3, 128.0, and 127.7 (ArC), 82.5 (CMe_3), 68.0 [$PhCH_2O_2CN(Boc)$], 66.9 (CH_2Ph), 65.2 (NCH_2N), 52.2 and 51.6 (CH_2N), 46.2 and 43.6 (CH_2NZ), 27.8 (CH_3), and 26.6, 24.2, 22.9, and 22.5 (CCH_2C).

N^8-*Boc*-N^1,N^4-*methylene*-N^1-*Z-spermidine* (**14**).—A stirred solution of compound (**13**) (3.67 g, 6.98 mmol) in dry methanol (40 ml) was treated with TMG (402 mg, 3.50 mmol) at room temperature for 2 days. The solution was evaporated under reduced pressure and the residue was chromatographed (silica; CH_2Cl_2–Me_2CO, 4:1) to afford the chromatographically pure (G) product (**14**) as a yellow oil (2.42 g, 88%); δ_H 7.34 (s, 5 H, ArH), 5.13 (s, 2 H, CH_2Ph), *ca.* 4.9 (br s, *ca.* 1 H, NH), 4.13 (s, 2 H, NCH_2N), 3.53 (t, 2 H, CH_2NZ), 2.96—3.13 (m, 2 H, CH_2NHBoc), 2.70 (t, 2 H) and 2.17—2.40 (m, 2 H) (CH_2N), and 1.34—1.75 (m) and 1.44 (s) [together 15 H, CCH_2C and $C(CH_3)_3$]; δ_C 155.9 and 155.0 (CO), 136.6, 128.4, 128.0, and 127.9 (ArC), 78.9 [$C(CH_3)_3$], 67.1 (CH_2Ph), 65.1 (NCH_2N), 52.6 and 52.2 (CH_2N), 43.8 CH_2NZ), 40.4 (CH_2NHBoc), 28.4 [$C(CH_3)_3$], and 27.7, 24.5, and 22.8 (CCH_2C).

N^8-*Boc*-N^1-*Z-spermidine* (**15**).—(A) A solution of compound (**14**) (2.4 g, 6.1 mmol) in dry methanol (50 ml) was refluxed with pyridine (1.5 g, 19 mmol) and malonic acid (2.3 g, 22 mmol) with stirring for 2 h. The solvent was evaporated under reduced pressure and after addition of aqueous 30% K_2CO_3 (30 ml) the product was extracted with $CHCl_3$ (3 × 60 ml). The combined organic layers were washed with saturated aqueous NaCl (2 × 30 ml), dried (Na_2SO_4), and evaporated to afford a crude oil which was chromatographed (silica; CH_2Cl_2–MeOH–HOAc, 18:2:1). The appropriate fractions were collected and again neutralized as for the crude product to give a yellow oil which was triturated with light petroleum to afford the Boc-Z-spermidine (**15**) as a white *solid* (1.8 g, 78%); pure by t.l.c. (E or F). An analytical specimen was obtained by recrystallization from heptane–ether (2:1; 100 ml g^{-1}); m.p. 63—64 °C; δ_H 7.34 (s, 5 H, ArH), *ca.* 5.65 (br s, *ca.* 1 H, amide NH), 5.09 (s, 2 H, CH_2Ph), *ca.* 4.80 (br s, *ca.* 1 H, amide NH), 3.06—3.30 (m, together 4 H, CH_2NHZ and CH_2NHBoc), 2.51—2.74 (m, 4 H, CH_2N), and 1.49—1.79 (m) and 1.43 (s) (together *ca.* 16 H, CCH_2C, CH_3, and amine NH); δ_C 156.5 and 156.0 (CO), 136.7, 128.4, and 128.0 (ArC), 79.0 [$C(CH_3)_3$], 66.4 (CH_2Ph), 49.3 and 47.7 (CH_2N), 40.4 and 39.9 (CH_2NHBoc and CH_2NHZ), 29.5 (CCH_2C), 28.4 [$C(CH_3)_3$], and 27.8 and 27.2 (CCH_2C) (Found: C, 63.3; H, 8.6; N, 11.3. $C_{20}H_{33}N_3O_4$ requires C, 63.3; H, 8.8; N, 11.1%).

(B) *From compound* (**16**). A stirred solution of compound (**16**) (281 mg, 0.550 mmol) (see later) in dry methanol (2.5 ml) was treated with TMG (32.0 mg, 0.280 mmol) at room temperature for about 2 days. The solvent was removed under reduced pressure and the residue chromatographed and worked up as under (A) to afford compound (**15**) (135 mg, 65%); m.p. and ^1H and ^{13}C n.m.r. spectra were in agreement with the foregoing data.

N^8-*Boc*-N^1,N^8-Z_2-*spermidine* (**16**).—To a solution of the N^1,N^4-methylenespermidine derivative (**13**) (2.0 g, 3.8 mmol) in dry methanol (35 ml) were added pyridine (94 mg, 12 mmol) and malonic acid (1.4 g, 14 mmol). The mixture was refluxed with stirring for 2 h, then worked up as described for (**15**) except that the crude product was chromatographed with CH_2Cl_2–Me_2CO–HOAc (5:5:1) to furnish essentially pure (D or E) compound (**16**) as a yellow oil (0.9 g, 48%); δ_H 7.35 and 7.33 (2 s, 10 H, ArH), 5.65 (br s, *ca.* 1 H, amide NH), 5.20 (s, 2 H, $PhCH_2O_2CNBoc$), 5.08 (s, 2 H, CH_2Ph), 3.63 [t, 2 H, $CH_2NZ(Boc)$], 3.24 (m, 2 H, CH_2NHZ), 2.60 (q, 4 H, CH_2N), and 1.46—1.77 (m) and 1.46 (s) (together *ca.* 16 H, CCH_2C, CH_3, and amine NH); δ_C 156.5, 153.9, and 152.1 (CO), 136.7, 135.5, 128.5, 128.2, and 128.0 (ArC), 82.7 (CMe_3), 68.2 ($PhCH_2O_2CNBoc$), 66.4 (CH_2Ph), 49.4 and 47.6 (CH_2NCH_2), 46.3 [$CH_2NZ(Boc)$], 39.9 (CH_2NH), 29.6 (CCH_2C), 28.0 (CH_3), and 27.0 and 26.6 (CCH_2C).

N^4-*Boc*-N^1-(*Z*-β*Ala*)-*tetramethylenediamine* (**17**).—To a solution of N^1-Boc-tetramethylenediamine[11] (1.13 g, 6.00 mmol) in dry acetonitrile (20 ml) Z-βAla-ONp (1.72 g, 5.00 mmol) dissolved in dry acetonitrile (20 ml) was added dropwise with vigorous stirring during 15 min. The mixture immediately became bright yellow, and after 1 h agitation at room temperature a precipitate appeared. More acetonitrile (10 ml)

was added to facilitate stirring, which was continued overnight (20 h). The thick sludge was filtered by suction and the collected white solid was thoroughly triturated repeatedly with cold acetonitrile (3 × 5 ml) and sucked dry. The crude yield of chromatographically pure (**17**) was 1.82 g (92%). Recrystallization from acetonitrile (30 ml g^{-1}) gave, after cooling for a few days, a white fluffy crystalline solid (90% crystallization yield); t.l.c. (E or F) gave one spot; m.p. 133—134 °C; δ_H 7.33 (s, 5 H, ArH), 6.10 (br s, *ca.* 1 H, CCONH), 5.62 (br s, *ca.* 1 H, ZN*H*), 5.09 (s, 2 H, CH_2Ph), 4.68 (br s, *ca.* 1 H, BocN*H*), 3.46 (perturbed t, 2 H), 3.18 (perturbed m, 2 H), and 3.13 (perturbed signal, 2 H) (3 × NCH_2), 2.39 (t, 2 H, COCH_2), *ca.* 1.49 (m, 4 H, CCH_2CH_2C), and 1.43 [s, 9 H, C(CH_3)$_3$]; δ_C 171.3 (CH_2CONH), 156.5 and 156.1 (2 × OCONH), 136.5, 128.4, 128.0, and 127.9 (ArC), 79.2 [*C*(CH_3)$_3$], 66.6 (CH_2Ph), 40.1 and 39.1 (CH_2NHCO$_2$), 37.2 and 35.9 (CH_2CONHCH_2), 28.4 [C(CH_3)$_3$], and 27.5 and 26.5 (CCH_2CH_2C).

Independent Synthesis of Compound (**15**) *by Reduction of the Amide* (**17**).– The amide (**17**) was reduced on a 1 mmol scale with $NaBH_4$–CF_3CO_2H, essentially as outlined in ref. 10*b* (footnote 9), and purified as described here to give a waxy solid (88 mg, 23%). A recrystallized sample was identical with compound (**15**) as obtained earlier.

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