A Short Synthesis *via* a Common Intermediate of N^1- and N^8-Monoacylspermidine Conjugates

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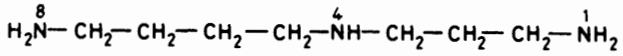
N^1- and N^8-Substituted spermidine (**1**) conjugates formed with different oxygenated cinnamic acids occur in many higher plants and also in some micro-organisms. A short and efficient synthetic route to such compounds (**14**)—(**17**), (**21**), and (**22**) is described by way of the suitably protected spermidine derivative (**2**) which undergoes selective deprotection and monoacylation.

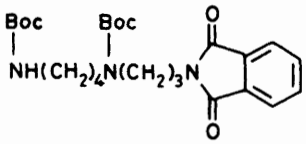
The common aliphatic di- and poly-amines (such as putrescine, cadaverine, spermine, and spermidine) often occur conjugated with variously substituted cinnamic acids in many higher plants[1] and micro-organisms.[2] These cinnamamides are of interest because of their diverse biochemical profiles. The general occurrence and physiology of hydroxycinnamamides in *Nicotiana tabacum* has been studied intensively in recent years.[3] Thus, several amides of hydroxycinnamic acids (*e.g. p*-coumaric, caffeic, and ferulic acids) formed with putrescine and spermidine, generally known as the phenolamides, have been detected in the reproductive organs of tobacco and several other plant species.[1,3] Whereas the structural proof of the monoacylated putrescines is unambiguous, full structural determinations of the monoacylated spermidines may remain uncertain as it is often difficult to determine which of the three amine functions of spermidine [*N*-(3-aminopropyl)butane-1,4-diamine] (**1**), N^1, N^4, and N^8, is acylated. Their synthesis is therefore important as a proof of structure, and also because it makes these substances available in sufficient quantities for biological study. However, the monosubstitution of spermidine with phenolic acids is still difficult. Although it was possible to protect the aminopropane moiety alone using formaldehyde,[1a] no general method is available for the selective monoacylation of each amino group. Starting from 4-aminobutyric acid, a readily available, inexpensive material, we have developed an efficient synthesis of the fully protected spermidine (**2**) which can serve as a suitable intermediate for the acylation at the N^1 or the N^8 position depending on the deprotection conditions employed.

Several recently described methods[1,4] could have been used to synthesize N^1- and N^8-monoacylated spermidines. However, unlike our method none of these would have provided, in a few steps, a spermidine derivative with readily removable protecting groups, as in (**2**), which could serve as a common intermediate for the synthesis of the desired N^1- and N^8-phenolamides in good to excellent yields.

Treatment of 4-aminobutyric acid with di-t-butyl dicarbonate[5] provided 4-t-butoxycarbonylaminobutyric acid in almost quantitative yield. This was then treated with ethyl chloroformate, and the resulting mixed anhydride treated with 3-amino-1-chloropropane to give the amide (**3**) in 80% yield (Scheme 1). It is generally acknowledged that amides can be selectively reduced to amines in the presence of a t-butoxycarbonyl group by various reagents.[6,7] However, in our hands, the reduction of compound (**3**) with borane–methyl sulphide complex (BMS) followed by reflux in methanolic hydrochloric acid provided both compound (**4**) and its *N*-methyl derivative (**5**), which arose *via* carbamate reduction. Similarly the reaction of compound (**3**) with sodium trifluoroacetoxyborohydride in tetrahydrofuran (THF) at room temperature, as reported by Coward *et al.*,[7] gave the desired amine $BocNH(CH_2)_4NH(CH_2)_3Cl$ in only 30% yield, and above 60 °C the *N*-methyl derivative (**5**) (as the free base) was obtained exclusively. It was,



(**1**)



(**2**)

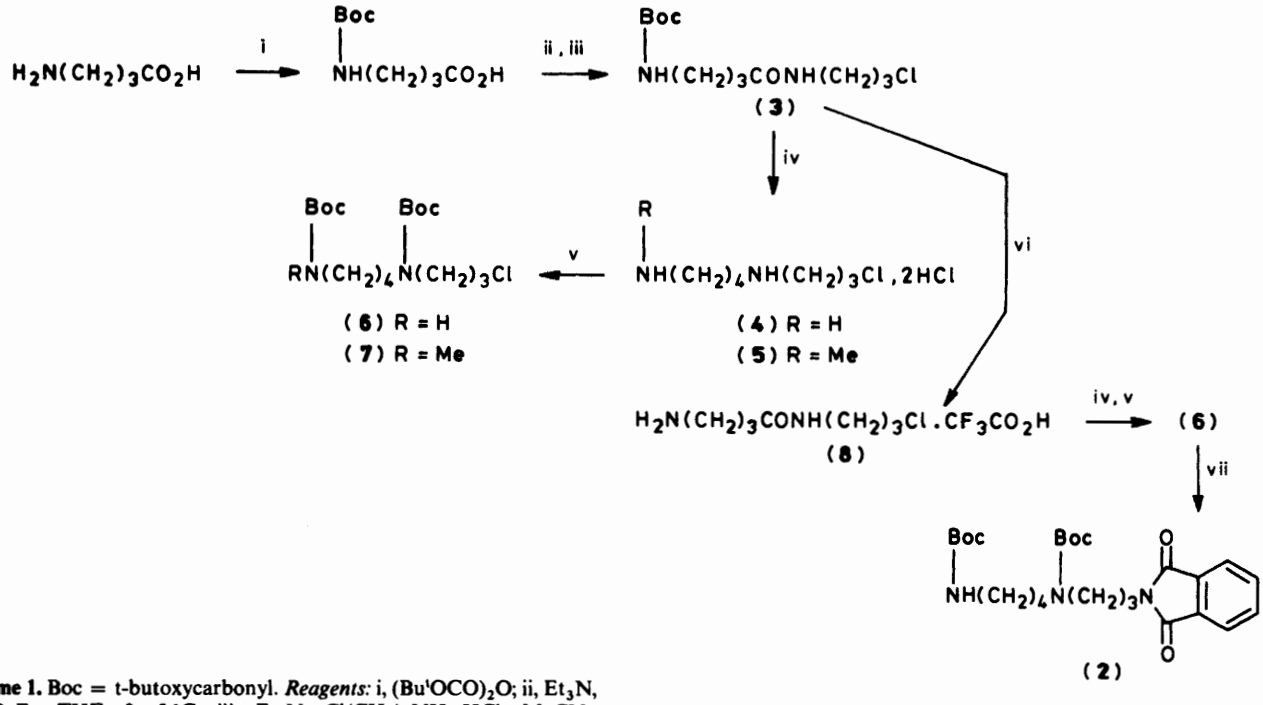
however, observed that sodium trifluoroacetoxyborohydride reduced $BocNH(CH_2)_3CONH(CH_2)_3NHBoc$ to $BocNH(CH_2)_4NH(CH_2)_3NHBoc$. In view of these results, compound (**3**) was first deprotected with trifluoroacetic acid–diethyl ether to the amide (**8**), and then reduced with borane–methyl sulphide (BMS) complex[6] and subsequently refluxed with methanolic hydrochloric acid to give the amine (**4**); this, without isolation, was treated with di-t-butyl dicarbonate to yield compound (**6**) (68%). Subsequent reaction of (**6**) with the sodio derivative of phthalimide in dimethylformamide (DMF) in the presence of a catalytic amount of sodium iodide afforded in 85% yield the fully protected derivative (**2**) of spermidine.

The conversion of this derivative (**2**) into various N^1- or N^8-substituted cinnamoylspermidines was accomplished in the following manner. Hydrazine hydrate treatment of compound (**2**) in ethanol provided the N^1-free spermidine derivative (**9**) which was acylated (Scheme 2) quantitatively (95—100%) either with the *p*-nitrophenyl esters of the *O*-acetylated derivatives of *p*-coumaric,[8] ferulic,[9] sinapinic,[9] and caffeic[10] acids (4-hydroxy-, 4-hydroxy-3-methoxy-, 4-hydroxy-3,5-dimethoxy-, and 3,4-dihydroxy-cinnamic acids) or with the *O*-acetylated *p*-coumaroyl,[8] feruloyl,[9] sinapinoyl,[9] and cafeoyl[10] chlorides, respectively. Deprotection of the resulting N^1-cinnamoylspermidines (**10**)—(**13**) by successive treatment with methanol–ammonia and trifluoroacetic acid provided the phenolamides (**14**)—(**17**),* respectively.

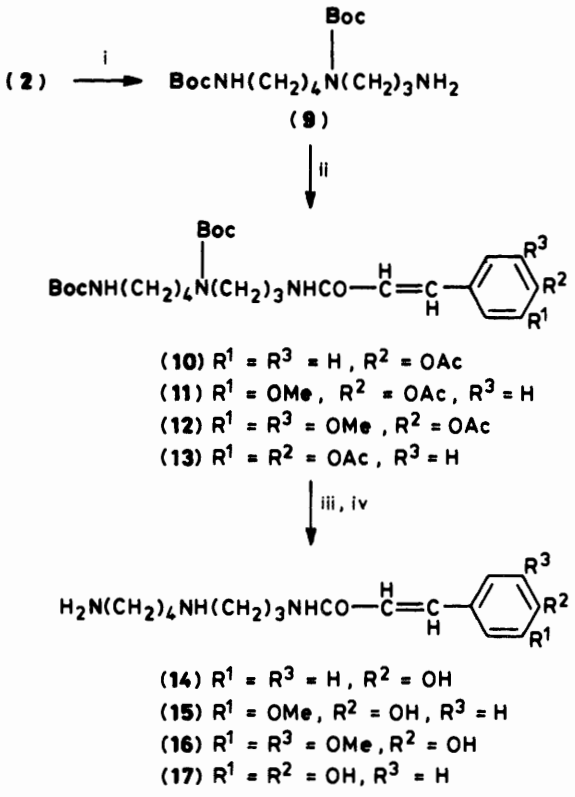
Alternatively, treatment of compound (**2**) with trifluoroacetic acid followed by selective acylation at the primary amino group with the activated *p*-nitrophenyl esters of *O*-acetylferulic acid and *O*-acetylsinapinic acid gave the corresponding N^8-cinnamoyl-N^1-phthaloylspermidine (**19**) and (**20**) in an overall yield of 55—60% (Scheme 3). Complete deprotection of compounds (**19**) and (**20**) by treatment with hydrazine hydrate gave the phenolamides (**21**) and (**22**), respectively.

It is worth mentioning that the N^1-substituted phenolamides, *viz.* (**14**)—(**17**), had an R_F value (0.33) (solvent B, see

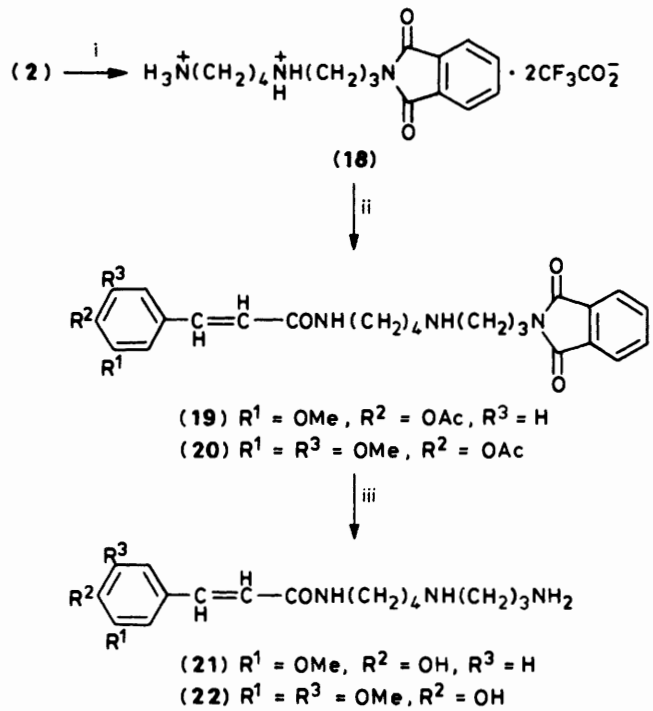
* Compound (**17**) could not be purified as it was very unstable.



Scheme 1. Boc = t-butoxycarbonyl. *Reagents:* i, $(Bu^tOCO)_2O$; ii, Et_3N, $ClCO_2Et$, THF, 0—5 °C; iii, Et_3N, $Cl(CH_2)_3NH_2$·HCl, MeCN–CH_2Cl_2, 20 °C, 4 h; iv, BMS, THF, 80 °C, 1.5 h, N_2, MeOH–HCl; v, $(Bu^tOCO)_2O$, Na_2CO_3, dioxane–H_2O (2:1), 20 °C, 16 h; vi, CF_3CO_2H, Et_2O; vii, NaH, phthalimide, DMF, NaI, 60 °C, 16 h, N_2



Scheme 2. Boc = t-butoxycarbonyl. *Reagents:* i, NH_2NH_2·H_2O, EtOH, 80 °C, 1 h; ii, Et_3N, CH_2Cl_2, *p*-nitrophenyl ester of *O*-acetylated *p*-coumaric, ferulic, sinapinic, or caffeic acid, 16 h, 20 °C; iii, MeOH, NH_3, 20 °C, 5 h, N_2; iv, CF_3CO_2H, Et_2O



Scheme 3. *Reagents:* i, CF_3CO_2H, Et_2O; ii, Et_3N, *p*-nitrophenyl ester of *O*-acetyl-ferulic or -sinapinic acid, CH_2Cl_2, N_2, 16 h; iii, NH_2NH_2·H_2O, EtOH, 80 °C, N_2, 40 min

Experimental section), which differed from that of the N^8 derivative, *viz.* (**21**) and (**22**) (R_F 0.42).

In conclusion, the easily accessible intermediate (**2**) should be useful for the regioselective preparation of the N^1- or N^8-

monoacylated spermidines and also for the preparation of *N*-acylated spermine derivatives.

Experimental

M.p.s were determined with a Reichert hot-stage microscope and are uncorrected. U.v. spectra were obtained in methanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^{1}H N.m.r. spectra were measured on Bruker Spectrospin WP 80 (80 MHz) and WP 200 SY (200 MHz) spectrometers using tetramethylsilane as the internal standard. ^{13}C N.m.r. spectra were recorded on a Bruker spectrospin WP 200 SY spectrometer operating at 50.30 MHz in the pulsed F.T. mode. Electron impact (E.I.), chemical ionization (C.I.; isobutane as reactant gas) and fast atom bombardment (FAB; with xenon on glycerol matrix) mass spectra, were determined on AEI MS50, AEI MS9, and KRATOS MS80 instruments, respectively. Tetrahydrofuran and ether were distilled prior to use from sodium benzophenone. Dichloromethane and triethylamine were distilled from calcium hydride and stored over molecular sieves (Linde 3 Å). Purified products were shown to be homogeneous by t.l.c. on Merck aluminium-backed plates with a 0.2-mm layer of Kieselgel 60 F_{254}, with visualization by ninhydrin solution. Solvent systems used were, solvent A: dichloromethane–methanol (100:5), and solvent B: dichloromethane–methanol–ammonia (2:2:1). Medium pressure liquid chromatography (m.p.l.c.) was performed using glass columns of different dimensions packed with silica gel 60 (0.040—0.63 mm) and monitored with a u.v. detector (254 nm). The organic solvents after extraction of the products were dried over anhydrous Na_2SO_4 unless stated otherwise in the text. Ether refers to diethyl ether.

N-(3-*Chloropropyl*)-4-*t*-*butoxycarbonylaminobutyramide* (**3**).—4-Aminobutyric acid (10 g, 97 mmol) was treated with di-t-butyl dicarbonate (22 g, 100 mmol) according to the procedure of Moroder *et al.*[5] to provide 4-*t*-*butoxycarbonylaminobutyric acid* (15.2 g, 99%), m.p. 50 °C (hexane), R_F 0.45 (solvent A) (Found: C, 53.3; H, 8.5; N, 7.0. $C_9H_{17}NO_4$ requires C, 53.20; H, 8.37; N, 6.90%); δ_H (80 MHz; $CDCl_3$) 1.40 (9 H, s, CMe_3), 1.82, 2.26, and 3.08 (6 H, 3 m, CH_2 × 3), 4.67 (1 H, br s, NHBoc), and 10.10 (1 H, s, CO_2H); *m*/*z* (C.I.) 204 (MH^+).

To a well-stirred solution of 4-t-butoxycarbonylaminobutyric acid (10.15 g, 50 mmol) and triethylamine (9 ml, 50 mmol) in THF (50 ml) maintained at 0—5 °C was added a solution of ethyl chloroformate (4.7ml, 50 mmol) in THF (10 ml) during 30 min. The resulting mixture was stirred for a further 30 min and filtered. The residue was washed with THF (3 × 10 ml). To the combined filtrates was added triethylamine (18 ml, 100 mmol) followed by a solution of 3-chloropropylamine hydrochloride (9.75 g, 75 mmol) in dichloromethane–acetonitrile (1:1; 250 ml) dropwise. The resulting mixture was stirred at room temperature for 4 h after which the solvent was evaporated under reduced pressure. To the residue was added water (250 ml) and dichloromethane (200 ml). The organic layer was separated, washed, dried, and evaporated to leave a pale yellow solid (10.1 g, 81%), m.p. 73—74 °C (from ethyl acetate–hexane); R_F 0.48 (solvent A) (Found: C, 51.5; H, 8.2; N, 10.0. $C_{12}H_{23}ClN_2O_3$ requires C, 51.69; H, 8.31; N, 10.05%); δ_H (80 MHz; $CDCl_3$) 1.50 (9 H, s, CMe_3), 1.73, 2.43, and 3.50 (12 H, 3 m, CH_2 × 6), 4.93 (1 H, br s, NH), and 6.59 (1 H, br s, NH); *m*/*z* (E.I.) 278, 280 ($M^{+\bullet}$ ^{35}Cl, ^{37}Cl), 243 ($M^{+\bullet}$ − Cl$^\bullet$).

N^1-(3-*Chloropropyl*)-N^1,N^4-*bis*(*t*-*butoxycarbonyl*)*butane*-1,4-*diamine* (**6**).—The above amide (**3**) (5 g, 18 mmol) was taken up in trifluoroacetic acid (7 ml) and stirred at room temperature for 2.5 h after which dry ether (75 ml) was added and the mixture was cooled. The separated solid was filtered, repeatedly washed with dry ether to remove any traces of acid, and dried *in vacuo* for 3 h to yield the trifluoroacetate salt (**8**). To a well-stirred, boiling solution of (**8**) in THF (20 ml) under N_2 was added a solution of borane–methyl sulphide (BMS) in THF (2M; 16—17 ml) dropwise during 25 min and the refluxing was continued for 1.5 h. The solvent and dimethyl sulphide were removed under reduced pressure. To the residue was added THF (5 ml), and then, very slowly, methanol (10 ml) saturated with dry HCl gas. The borane–amine complex decomposed with vigorous evolution of H_2. The addition of acid was complete in 30 min, after which the mixture was stirred for 1 h at 20 °C. Dry ether (75 ml) was added and the mixture was stirred at 0 °C for a further 15 min. The separated solid was rapidly filtered and washed with ether (3.92 g), m.p. 210 °C; *m*/*z* (C.I.) 165 (MH^+). The solid was used as such without purification for the next step. The residue was taken in saturated sodium hydrogencarbonate (3.8 ml; pH 8) and dioxane (20 ml), water (10 ml), di-t-butyl dicarbonate (5.82 g), and sodium carbonate (4.3 g) then added, and the mixture was stirred for 16 h at 20 °C. Excess of dioxane was removed under reduced pressure and the solution was acidified to pH 2 with a saturated solution of $KHSO_4$ and extracted with dichloromethane. The organic layer was washed, dried, and evaporated to yield the *diamine* (**6**) as a colourless gum (4.50 g, 68%) which was purified by passage through a short column of silica gel using dichloromethane as eluant; R_F 0.82 (solvent A); δ_H (80 MHz; $CDCl_3$), 1.45 (18 H, s, CMe_3 × 2), 2.07, 3.30, and 3.52 (14 H, 3 m, CH_2 × 7), and 4.75 (1 H, br s, NH) (Found: $M^{+\bullet}$ (E.I.; ^{35}Cl), 364.2132; $C_{17}H_{33}{}^{35}ClN_2O_4$ requires *M*, 364.2129).

Borane–Methyl Sulphide (*BMS*) *Reduction of the Amide* (**3**).—The amide (**3**) (2.5 g) was reduced with BMS complex and then refluxed with methanolic hydrochloric acid according to the procedure of Brown and Choi[6] to yield a white powder (1.6 g) consisting of a mixture of the hydrochlorides (**4**) and (**5**); *m*/*z* (C.I.) 165 and 179, corresponding to MH^+ (^{35}Cl) of (**4**) and (**5**), respectively. Treatment of compounds (**4**) and (**5**), without separation, with di-t-butyl dicarbonate gave the bis(t-butoxycarbonyl) derivatives (**6**) and (**7**) (total 2.2 g), separated by chromatography on a column of silica gel, using hexane–ethyl acetate (80:20) as eluant and collecting 50-ml fractions. Fractions 8—10 gave N^1-(3-*chloropropyl*)-N^4-*methyl*-N^1,N^4-*bis*(*t*-*butoxycarbonyl*)*butane*-1,4-*diamine* (**7**) (650 mg, 29%) as a colourless oil; R_F 0.82 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.50 (18 H, s, CMe_3 × 2), 2.08, 3.30, and 3.52 (14 H, 3 m, CH_2 × 7), and 2.83 (3 H, s, NMe); δ_C($CDCl_3$) 25.20, 25.80, 28.54, 31.71, 34.21, 42.54, 44.86, 47.41, 48.45, 79.37, 150.05, and 155.81 p.p.m.; *m*/*z* (E.I.) 378, 380 ($M^{+\bullet}$ ^{35}Cl, ^{37}Cl). Fractions 13—15 gave compound (**6**) (1 g, 67.9%); spectral data as described above.

N^1-*Phthaloyl*-N^4,N^8-*bis*(*t*-*butoxycarbonyl*)*spermidine* (**2**).—NaH (50% emulsion in oil, 618 mg, 25 mmol) was washed well with dry toluene (3 × 5 ml) under N_2 and covered with dry DMF (10 ml). To this was added slowly a solution of phthalimide (3.71 mg, 25 mmol) in DMF (20 ml). To the resulting sodio derivative was added dropwise a solution of the chloride (**6**) (4.48 g, 12 mmol) and sodium iodide (0.36 mg, 6 mmol) in DMF (20 ml). The mixture was stirred at 60 °C for 16 h under N_2. The solution was poured into ice–water (150 ml) containing $KHSO_4$. The aqueous layer was repeatedly extracted with dichloromethane (3 × 100 ml); the organic layer was washed, dried, and evaporated to yield a gum (5.6 g) which was chromatographed on a column of silica gel (150 g) using dichloromethane as the eluting solvent; 100-ml fractions were collected. Fractions 21—30 gave the desired *compound* (**2**) (4.86 g, 95%) as a colourless gum; R_F 0.76 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.55 (18 H, s, CMe_3 × 2), 1.99, 3.29, and 3.73 (14 H, 3 m, CH_2 × 7), 4.88 (1 H, br s, NH), and 7.68 (4 H, m, ArH); *m*/*z*

(C.I.) 476 (MH^+) [Found: $M^{+\cdot}$ (E.I.) 475.2679. $C_{25}H_{37}N_3O_6$ requires M, 475.2682].

General Method of Preparation of N^1-*Acylated*-N^4,N^8-*bis*(*t-butoxycarbonyl*)*spermidines* (**10**)—(**13**).—To compound (**2**) (1 g, 4.2 mmol) in ethanol (10 ml) was added hydrazine hydrate (98%; 1 ml) and the mixture was refluxed at 80 °C for 1 h. The reaction mixture was cooled and the phthaloyl hydrazide was filtered off and repeatedly washed with cold ethanol (3 × 20 ml). The combined filtrates were evaporated under reduced pressure. The residue was suspended in a saturated solution of sodium chloride (40 ml) and extracted with dichloromethane (3 × 50 ml). The dichloromethane layer was washed with brine, dried, and evaporated to yield N^4,N^8-bis(t-butoxycarbonyl)-spermidine (**9**) in the form of a gum (748 mg); *m/z* (C.I.) 345 (MH^+); R_F 0.03 (solvent A).

To the above gum (**9**) (345 mg, 1 mmol) in dichloromethane (5 ml) was added triethylamine (0.5 ml) followed by a solution of the *p*-nitrophenyl esters † of each of the *O*-acetyl derivatives of the substituted cinnamic acids (1.25 mmol) in dichloromethane (10 ml) and the mixture was stirred at 20 °C for 16 h. The reaction mixture was evaporated to dryness and the residue was taken up in water and repeatedly extracted with dichloromethane (3 × 50 ml). The organic extract was washed with water, dried ($MgSO_4$) and evaporated to yield a yellow gum (923 mg) which was chromatographed by m.p.l.c. (3 × 30 cm column) using dichloromethane as solvent; 25-ml fractions were collected. Each of the amides (**10**)—(**13**) was worked up as follows.

N^1-(4-*Acetoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)-*spermidine* (**10**). Fractions 8—13 yielded the starting ester (72 mg), while fractions 16—20 yielded the desired N^1-*amide* (**10**) (498 mg, 94%) as a colourless gum; R_F 0.53 (solvent A); δ_H (200 MHz; $CDCl_3$) 1.42 and 1.43 (18 H, 2 s, CMe_3 × 2), 1.60 and 3.23 (14 H, 2 m, CH_2 × 7), 2.30 (3 H, s, COMe), 4.85 (1 H, br s, NHBoc), 6.46 and 7.63 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 7.09 and 7.53 (4 H, ABq, *J* 8 Hz, ArH), and 7.26 (1 H, br s, NHCO) [Found: $M^{+\cdot}$ (E.I.), 533.3106. $C_{28}H_{43}N_3O_7$ requires *M*, 533.3101].

N^1-(4-*Acetoxy*-3-*methoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)*spermidine* (**11**). Fractions 8—13 yielded the starting ester (68 mg), while fractions 18—28 yielded the desired N^1-*amide* (**11**) (502 mg, 95%) as a colourless gum; R_F 0.53 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.42—1.80 (24 H, CMe_3 × 2 and CH_2 × 3), 2.31 (3 H, s, COMe), 3.28 and 3.47 (8 H, 2 m, CH_2 × 4), 3.81 (3 H, s, OMe), 4.71 (1 H, br s, NH), 7.36 and 7.49 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.99 (3 H, ArH) [Found: $M^{+\cdot}$ (E.I.), 563.3197. $C_{29}H_{45}N_3O_8$ requires *M*, 563.3206].

N^1-(4-*Acetoxy*-3,5-*dimethoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)*spermidine* (**12**). After purification by m.p.l.c. *compound* (**12**) was obtained as a colourless foam (372 mg, 74%); R_F 0.53 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.40 and 1.48 (24 H, s, CMe_3 × 2 and CH_2 × 3), 2.91 and 3.41 (8 H, 2 m, CH_2 × 4), 3.82 (6 H, s, OMe × 2), 6.32 and 7.45 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.17 (2 H, s, ArH) [Found: $M^{+\cdot}$ (E.I.), 593.3318. $C_{30}H_{47}N_3O_9$ requires *M*, 593.3312].

N^1-(3,4-*Diacetoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)-*spermidine* (**13**). After purification by m.p.l.c., *compound* (**13**) was obtained as a pale yellow foam [295 mg, 100% from 0.5 mmol of the starting amine (**9**)]; R_F 0.53 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.48—1.80 (24 H, CMe_3 × 2 and CH_2 × 3), 2.26 (3 H, s, COMe), 3.19 (8 H, m, CH_2 × 4), 4.70 (1 H, br s, NH), 6.33 and 7.45 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 7.08 (1 H, ABq, *J* 8 Hz, ArH), and 7.25 (2 H, ArH); *m/z* (FAB) 592 (MH^+) [Found: $M^{+\cdot}$ (E.I.), 591.3158. $C_{30}H_{45}N_3O_7$ requires *M*, 591.3155].

De-O-*acetylation of Compounds* (**10**)—(**13**).—To the *O*-acetyl derivative (0.5 mmol) in methanol (5 ml) under N_2 was added an aqueous solution of NH_3 (27% v/v; 1.8 ml). After the mixture had been stirred for 5 h at 20 °C, the solvent was evaporated under reduced pressure. The residue was taken up in dichloromethane (50 ml), dried ($MgSO_4$), and evaporated. The spectral data of the phenolamides are as follows.

N^1-(4-*Hydroxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)-*spermidine* was obtained as a foam (261 mg, 100%); R_F 0.43 (solvent A); δ_H (200 MHz; $CDCl_3$) 1.43 (18 H, s, CMe_3 × 2), 1.68, 3.13, and 3.33 (14 H, 3 m, CH_2 × 7), 4.73 (1 H, br s, NHBoc), 6.26 and 7.54 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 6.86 and 7.31 (4 H, ABq, *J* 8 Hz, ArH), 8.87 (1 H, br s, OH), and 7.06 (1 H, br s, CONH); *m/z* (FAB) 492 (MH^+).

N^1-(4-*Hydroxy*-3-*methoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)*spermidine* was obtained as a colourless foam (227 mg, 98%); R_F 0.43 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.45—1.67 (24 H, CMe_3 × 2 and CH_2 × 3), 3.21 and 3.47 (8 H, 2 m, CH_2 × 4), 3.87 (3 H, s, OMe), 4.69 (1 H, br s, NH), 6.25 and 7.48 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.93 (3 H, m, ArH) [Found: $M^{+\cdot}$ (E.I.), 521.3112. $C_{27}H_{43}N_3O_7$ requires *M*, 521.3101].

N^1-(4-*Hydroxy*-3,5-*dimethoxycinnamoyl*)-N^4,N^8-*bis*(*t-butoxycarbonyl*)*spermidine* was obtained as a colourless foam [148 mg, 100%, from 0.25 mmol of (**12**)]; R_F 0.43 (solvent A); δ_H (80 MHz; $CDCl_3$) 1.50—1.80 (24 H, CMe_3 × 2 and CH_2 × 3), 3.10 and 3.50 (8 H, 2 m, CH_2 × 4), 3.91 (6 H, s, OMe × 2), 4.62 (1 H, br s, NH), 6.30 and 7.50 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.73 (2 H, s, ArH) [Found: $M^{+\cdot}$ (E.I.), 551.3212. $C_{28}H_{45}N_3O_8$ requires *M*, 551.3206].

N^1-(3,4-Dihydroxycinnamoyl)-N^4,N^8-bis(t-butoxycarbonyl)spermidine was obtained as a yellow foam; *m/z* (E.I.) 507 ($M^{+\cdot}$) which was immediately converted into compound (**17**).

Deprotection of the t-Butoxycarbonyl Group.—To the above phenolamide (100 mg) in dichloromethane (0.5 ml) was added trifluoroacetic acid (0.1 ml). After the mixture had been stirred for 1.5 h at 5 °C under N_2 the solvent was evaporated under reduced pressure. The residue was dried *in vacuo* after the traces of acid had been removed by adding dry ether and decanting. The spectral data of each of the phenolamides (**14**)—(**17**) are as follows.

N^1-(4-*Hydroxycinnamoyl*)*spermidine* (**14**) *bistrifluoroacetate*, colourless gum (92 mg, 98%); R_F 0.33 (solvent B); $\lambda_{max.}$(MeOH) 232, 300, and 314 nm (log ε 3.76, 4.06, and 4.08); δ_H (200 MHz; CD_3OD), 1.59, 2.86, and 3.33 (14 H, 3 m, CH_2 × 7), 6.36 and 7.39 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.69 and 7.29 (4 H, ABq, *J* 8 Hz, ArH); δ_C(CD_3OD) 24.17, 25.45, and 27.64 (CCH_2C), 36.63, 39.94, 46.30, and 48.13 (CCH_2N), 116.85, 127.44, 130.66, and 160.79 (Ar*C*), 117.78, 142.50 (CH=CH), and 170.14 p.p.m. (CONH); *m/z* (FAB) 292 (MH^+) [Found: $M^{+\cdot}$ (E.I.; free base), 291.1942. $C_{16}H_{25}N_3O_2$ requires *M*, 291.1947].

N^1-(4-*Hydroxy*-3-*methoxycinnamoyl*)*spermidine* (**15**) *bistrifluoroacetate*, yellow gum (95 mg, 100%); R_F 0.33 (solvent B); $\lambda_{max.}$(MeOH) 240, 297, and 320 nm (log ε 3.85, 3.83, and 3.98); δ_H (200 MHz; CD_3OD + $CDCl_3$) 1.88 and 2.96 (14 H, 2 m, CH_2 × 7), 3.90 (3 H, s, OMe), 6.38 and 7.55 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.85 and 7.03 (3 H, m, ArH); δ_C(CD_3OD) 24.18, 25.48, 27.67 (CCH_2C), 36.98, 40.00, 46.35, and 48.13 (CCH_2N), 111.72, 116.56, 123.49, 128.16, 149.34, and 150.03 (ArC), 118.19, 142.71 (CH=CH), 170.27 (CONH), and 56.50 p.p.m. (OMe); *m/z* (FAB) 322 (MH^+) [Found: $M^{+\cdot}$ (E.I.; free base), 321.2046. $C_{17}H_{27}N_3O_3$ requires *M*, 321.2052].

N^1-(4-*Hydroxy*-3,5-*dimethoxycinnamoyl*)*spermidine* (**16**) *bistrifluoroacetate*, yellow gum [42 mg, 95% from 50 mg of

† The active *p*-nitrophenyl esters of different cinnamic acids were prepared following the procedure of H. Ito, *Synthesis*, 1979, 465.

(**12**)]; R_F 0.33 (solvent B); $\lambda_{max.}$(MeOH) 240 and 320 nm (log ε 4.03 and 4.03); δ_H (200 MHz; $CDCl_3$ + CD_3OD) 1.80 and 2.95 (14 H, 2 m, CH_2 × 7), 3.90 (6 H, s, OMe × 2), 6.46 and 7.50 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.83 (2 H, s, ArH); δ_C(CD_3OD) 24.20, 25.51, and 27.71 (CCH_2C), 37.04, 40.01, 46.41, and 48.15 (CCH_2N), 106.80, 127.13, and 142.86 (Ar*C*), 118.71 and 142.86 (*C*H=*C*H), 170.12 (CONH), and 56.95 p.p.m. (OMe); *m/z* (FAB) 352 (MH^+) [Found: $M^{+\cdot}$ (E.I.; free base), 351.2170. $C_{18}H_{29}N_3O_4$ requires *M*, 351.2158].

N^1-(3,4-*Dihydroxycinnamoyl*)*spermidine* (**17**) *bistrifluoroacetate*. This compound was not obtained in a pure form but its presence could be ascertained from the FAB mass spectrum [*m/z* 308 (MH^+)] and also from the ^{13}C n.m.r. data; δ_C(CD_3OD) 24.12, 25.41, and 27.59 (CCH_2C), 36.90, 39.95, 46.28, 48.11 (CCH_2N), 115.2, 116.57, 122.36, 128.13, 146.58, and 146.72 (Ar*C*), 117.82 and 142.81 (CH=CH), and 170.26 p.p.m. (CONH).

N^8-(4-*Acetoxy*-3-*methoxycinnamoyl*)-N^1-*phthaloylspermidine* (**19**) *and* N^8-(4-*Acetoxy*-3,5-*dimethoxycinnamoyl*)-N^1-*phthaloylspermidine* (**20**).—To compound (**2**) (750 mg, 1.58 mmol) was added trifluoroacetic acid (0.75 ml) and the mixture was stirred at 20 °C for 1 h under N_2. Then dry ether (75 ml) was added and the solution was cooled. The white solid that separated was rapidly filtered off and washed with ether to remove any traces of the acid to give (**18**) (702.9 mg); *m/z* (C.I.) 276 (MH^+). This compound was used for subsequent acylation reactions.

To the above residue (350 mg, 1.27 mmol) was added dichloromethane (7 ml) and triethylamine (175 μl) followed by *p*-nitrophenyl 4-acetoxy-3-methoxycinnamate (448 mg, 1.38 mmol) in dichloromethane (5 ml) and triethylamine (175 μl). The mixture was stirred under N_2 for 16 h at 20 °C and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5 ml) and passed through a short column of silica gel (finer than 200 mesh, 2 × 10 cm); 10-ml fractions were collected. Fractions 1—3 were eluted with dichloromethane and contained the active ester (84 mg), while fractions 5—8 were eluted with dichloromethane–methanol (100:1) and gave the desired amide (**19**) contaminated with *p*-nitrophenol and triethylamine. The mixture was rechromatographed [m.p.l.c., 1 × 30 cm column, dichloromethane–methanol–ammonia (2:1:1), lower layer, as the solvent]; 25-ml fractions were collected. Fractions 1—7 gave the desired *amide* (**19**) (331 mg, 53%) as a colourless foam; R_F 0.94 (solvent B); δ_H (80 MHz; $CDCl_3$) 1.67 (6 H, m, CH_2 × 3), 2.40 (3 H, s, COMe), 3.05 (8 H, m, CH_2 × 4), 3.83 (3 H, s, OMe), 6.40 and 7.55 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 7.06 (3 H, m, ArH), and 7.46 (4 H, m, ArH) [Found: $M^{+\cdot}$ (E.I.), 493.2212. $C_{27}H_{31}N_3O_6$ requires *M*, 493.2213].

In a similar way, reaction of the amine (**18**) (350 mg, 1.27 mmol) with the active *p*-nitrophenyl 4-acetoxy-3,5-dimethoxycinnamate (644 mg, 1.38 mmol) followed by purification by m.p.l.c., yielded *compound* (**20**) (301 mg, 47%) as a colourless foam; R_F 0.94 (solvent B); δ_H (80 MHz; $CDCl_3$) 1.80, 2.72, and 3.43 (14 H, 3 m, CH_2 × 7), 2.36 (3 H, s, COMe), 3.83 (6 H, s, OMe × 2), 6.28 and 7.30 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 6.63 (2 H, s, ArH), and 7.68 (4 H, m, ArH) [Found: $M^{+\cdot}$ (E.I.), 593.3302. $C_{30}H_{47}N_3O_9$ requires *M*, 593.3311].

N^8-(4-*Hydroxy*-3-*methoxycinnamoyl*)*spermidine* (**21**) *and* N^8-(4-*Hydroxy*-3,5-*dimethoxycinnamoyl*)*spermidine* (**22**).—A mixture of compound (**19**) (211 mg, 0.43 mmol), ethanol (3 ml), and hydrazine hydrate (98%; 43.5 μl, 0.85 mmol) was refluxed at 80 °C under N_2 for 40 min and then cooled. After 40 min, the solid that separated was filtered and the residue was washed with cold ethanol (2 × 5 ml). The combined ethanolic solution was evaporated to dryness and the residue was converted into the bistrifluoroacetate salt (methanolic trifluoroacetic acid: 1M; 0.1 ml). The resulting gum was chromatographed twice by m.p.l.c. (30 × 2 cm column, dichloromethane–methanol–ammonia, 2:2:1, as solvent); 25-ml fractions were collected. Fractions 1—4 yielded the phthaloyl hydrazide (42 mg), and fractions 5—8 yielded the *phenolamide* (**21**) (62.4 mg) which was immediately converted into its bistrifluoroacetate salt (82.4 mg, 61%); R_F 0.42 (solvent B); $\lambda_{max.}$(MeOH) 240, 297, and 320 nm (log ε 4.03, 4.1, and 4.19); δ_H (200 MHz; $CDCl_3$ + CD_3OD) 1.73 and 2.10 (14 H, 2 m, CH_2 × 7), 3.90 (3 H, s, OMe), 6.51 and 7.46 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), 6.72 (1 H, s, ArH), and 7.06 (2 H, m, ArH); δ_C(CD_3OD) 24.35, 25.22, 27.46 (CCH_2C), 39.46, 37.86, 45.75, and 48.58 (CCH_2N), 111.55, 116.52, 123.34, 128.28, 149.26, and 149.74 (Ar*C*), 118.83, 142.03 (CH=CH), 169.47 (CONH), and 56.46 p.p.m. (OMe); *m/z* (FAB) 322 (MH^+) [Found: $M^{+\cdot}$ (E.I.; free base), 321.2048. $C_{17}H_{27}N_3O_3$ requires *M*, 321.2052].

In a similar way hydrazinolysis of compound (**20**) (200 mg, 0.385 mmol) followed by its conversion into the bistrifluoroacetate salt yielded *compound* (**22**) (82.5 mg, 47%); R_F 0.42 (solvent B); $\lambda_{max.}$(MeOH) 240 and 320 nm (log ε 4.17 and 4.17); δ_H (200 MHz; $CDCl_3$ + CD_3OD) 1.72 and 2.12 (14 H, 2 m, CH_2 × 7), 3.90 (6 H, s, OMe × 2), 6.48 and 7.46 (2 H, ABq, *J* 16 Hz, *trans*-cinnamic H), and 6.83 (2H, s, ArH); δ_C(CD_3OD) 24.46, 25.34, and 27.58 (CCH_2C), 37.91, 39.45, 45.79, and 49.84 (CCH_2N), 106.73, 127.25, 149.56 (Ar*C*), 119.21, 142.37 (CH=CH), 169.34 (CONH), and 56.95 p.p.m. (OMe); *m/z* (FAB) 352 (MH^+) [Found: $M^{+\cdot}$ (E.I.; free base), 351.2161. $C_{18}H_{29}N_3O_4$ requires *M*, 351.2158].

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