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SYNTHESIS OF N^4-ACYLSPERMIDINES

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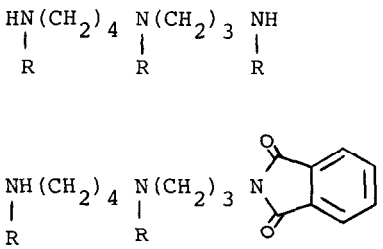
Abstract : N^4-Acylspermidines have been synthesised in good yields from γ-aminobutyric acid and from spermidine.

The di- and polyamine conjugates of various hydroxycinnamic acids, generally known as phenolamides, have been found to occur in several plant species and in some micro-organisms[1,2]. Because of their diverse biochemical profiles as well as for the purpose of their unambiguous identification, these compounds have been the subject of many synthetic efforts in recent years. The regioselective monoacylation of spermidine (1a) with different hydroxycinnamoyl groups (or any other acyl group) is of significance in this context.

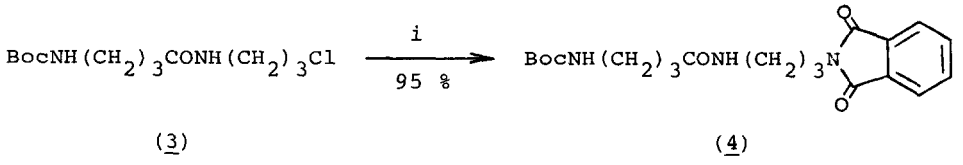
Several synthetic routes giving access to N^1- or N^8-acylspermidines are now available[1,3]. Our own efforts in this area resulted in the synthesis of N^1 and N^8 acylated spermidines from an easily accessible common intermediate (2) by way of regioselective deprotection and acylation reactions[4].



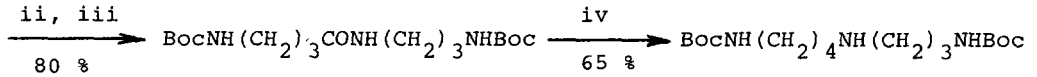
(1a) R = H
(1b) R = Boc

(2) R = Boc

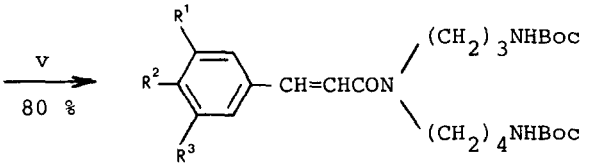
In the initial stage of the synthesis of the fully protected spermidine derivative (2) from γ-aminobutyric acid, compound (3) was smoothly prepared by reacting 4-N-tert-butoxycarbonylaminobutyric acid with ethyl chloroformate followed by treatment of the resulting mixed anhydride with 3-amino-1-chloropropane in 80 % yield. We now illustrate that the intermediate (3) can also be utilised for the preparation of N^1,N^8-di-tert-butoxycarbonylspermidine (6) which we required for the synthesis of N^4-acylspermidines such as (11), (12), (13) and (14). Alternatively, the suitably protected spermidine derivative (6)



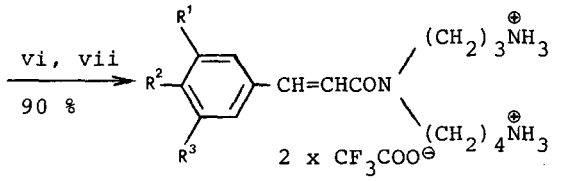
(3) (4)



(5) (6)



(7) R^1= R^3= H; R^2= OAc
(8) R^1= OMe; R^2= OAc; R^3= H
(9) R^1= R^3= OMe; R^2= OAc
(10) R^1= R^2= OAc; R^3= H



(11) R^1= R^3= H; R^2= OH
(12) R^1= OMe; R^2= OH; R^3= H
(13) R^1= R^3= OMe; R^2= OH
(14) R^1= R^2= OH; R^3= H

i. NaH, phthalimide, NaI, DMF, 60°C, 16 h; ii. $NH_2NH_2.H_2O$, EtOH, 80°C, 40 min; iii. (t-BuOCO)$_2$O, Na_2CO_3, dioxane-H_2O, 16 h; iv. $Na(CF_3COO)BH_3$, THF, 20°C, 5 h; v. substituted cinnamoyl chloride, CH_2Cl_2, 20°C, 16 h; vi. MeOH-NH_3, 20°C, 5 h; vii. CF_3COOH, Et_2O

was obtained in 85 % yield from N^1,N^4,N^8-tri-tert-butoxycarbonylspermidine (1b)[5] by preferential deprotection at the N^4 position[6] using either MeLi or n-BuLi in tetrahydrofuran at -20°C.

Compound (3), when allowed to react with the sodio derivative of phthalimide in the presence of a catalytic amount of sodium iodide, afforded (4)[7] which after hydrazinolysis followed by treatment with di-tert-butyl dicarbonate yielded (5)[8]. Reduction of (5) with sodium borohydride-trifluoroacetic acid in tetrahydrofuran generated the secondary amine (6)[9]. Acylation of (6) with the corresponding acyl chloride of 4-acetoxycinnamic acid [10], 4-acetoxy-3-methoxycinnamic acid[11], 4-acetoxy-3,5-dimethoxycinnamic acid[11] and 3,4-diacetoxycinnamic acid[12] produced (7)[13], (8)[14], (9)[15] and (10)[16], respectively. Removal of the protecting groups by sequential exposure to base (NH_3-MeOH) and acid (CF_3COOH in Et_2O) gave the trifluoroacetate salts of the N^4-acylspermidines (11)[17], (12)[18], (13)[19] and (14)[20].

In conclusion, compound (6) should be a useful precursor for N^4-acylspermidines which might be elaborated to other structures containing a spermidine framework. The methodology described here for the preparation of (6) starting with γ-aminobutyric acid as well as with spermidine itself offers an efficient alternative to the recently described route[21] to similar spermidine derivatives such as N^1,N^8-dibenzyloxycarbonylspermidine from spermidine.

Acknowledgements

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References and Notes

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7. (4), white solid, m.p. 104-105°C ($CHCl_3$/hexane) ; EIMS : m/z 389 ($M^{+\cdot}$) ; δH (80 MHz, $CDCl_3$) 1.50 (18H, s, t-Bu x 2), 1.85, 2.23, and 3.25 (10H, m x 3, $-CH_2$ x 5), 3.78 (2H, t, $-CH_2N<$), 4.80 (1H, br s, -NHBoc), 6.52 (1H, br s, CONH), 7.82 (4H, ArH).
8. (5), white solid, m.p. 135°C ($CHCl_3$/hexane) ; EIMS : m/z 359 ($M^{+\cdot}$) ; δH (80 MHz, $CDCl_3$) 1.37 (18H, s, t-Bu x 2) 1.70, 2.16, and 3.13 (12H, m x 3, $-CH_2$ x 6) 4.93, and 6.60 (2H, br s x 2, -NHBoc x 2).
9. Procedures for the preparation of (6) : To sodium borohydride (190 mg, 5 mmol) in THF (5 ml) was added trifluoroacetic acid (0.385 ml, 5 mmol). After stirring for 30 min at 20°C the amide (5) (359 mg, 1 mmol) in THF (10 ml) was added and the reaction was continued for 16 h. The usual work up and purification by chromatography gave (6) (222 mg, 65 %). In a second procedure, the amide (1b) (445 mg, 1 mmol) dissolved in THF (10 ml) was treated with a solution of n-butyllithium (10 ml, ca. 16 mmol) at -20°C and the mixture was stirred at the same temperature for 5 h. After usual work up and chromatography (6) was obtained as a gum (293 mg, 85 %). EIMS : m/z 345 ($M^{+\cdot}$) ; CIMS : m/z 346 (MH^+).
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13. (7), pale yellow foam ; EIMS : m/z 533 ($M^{+\cdot}$) ; δH (200 MHz, $CDCl_3$) 1.43 (18H, s, t-Bu x 2), 1.59, 3.13, and 3.43 (14H, m x 3, $-CH_2$ x 7), 2.26 (3H, s, -COMe), 5.00, and 5.66 (2H, br s x 2, -NHBoc x 2), 6.83, and 7.66 (2H, ABq, J 16 Hz, olefinic H), 7.13, and 7.56 (4H, ABq, J 8 Hz, ArH).
14. (8), pale yellow foam; EIMS : m/z 563 ($M^{+\cdot}$) ; δH (80 MHz, $CDCl_3$) 1.50 (24H, s & m, t-Bu x 2 and $-CH_2$ x 3), 2.30 (3H, s, -COMe), 3.17, and 3.55 (8H, m x 2, $-CH_2$ x 4), 3.92 (3H, s, -OMe), 4.70, and 5.42 (2H, br s x 2, -NHBoc x 2), 6.33, and 7.73 (2H, ABq, J 16 Hz, olefinic H), 7.13 (3H, ArH).
15. (9), pale yellow foam ; EIMS : m/z 593 ($M^{+\cdot}$) ; δH (200 MHz, $CDCl_3$) 1.42, and 1.43 (18H, s x 2, t-Bu x 2), 2.33 (3H, s, -COMe), 1.63, 3.13, and 3.45 (14H, m x 3, $-CH_2$ x 7), 3.90 (6H, s, -OMe x 2), 4.73, and 5.54 (2H, br s x 2, -NHBoc x 2), 6.76 (3H, ArH and olefinic H), 7.59 (1H, d, J 16 Hz, olefinic H).
16. (10), pale yellow gum ; FABMS : m/z 592 (MH^+) ; δH (200 MHz, $CDCl_3$) 1.42 (18H, s, t-Bu x 2), 2.31 (6H, s, -COMe x 2), 1.73, 3.14, and 3.43 (14H, m x 3, $-CH_2$ x 7), 4.79, and 5.51 (2H, br s x 2, -NHBoc x 2), 6.73, and 7.59 (2H, ABq, J 16 Hz, olefinic H), 7.26 (3H, m, ArH).
17. (11), pale yellow foam ; FABMS : m/z 292 (MH^+) ; δH (200 MHz, CD_3OD) 1.80, 2.83, and 3.41 (14H, m x 3, $-CH_2$ x 7), 6.69, 7.36 (2H, ABq, J 16 Hz, olefinic H), 6.69, and 7.56 (4H, ABq, J 8 Hz, ArH), 7.91 (1H, br s, -OH) ; $\delta^{13}C$ (50.3 MHz) 25.74, 26.84, 27.37, 38.15 (2 x C), 40.43, 44.05, 114.32, 116.85, 127.77, 130.96, 145.19, 160.79, and 170.14.
18. (12), pale yellow foam ; CIMS : m/z 322 (MH^+) ; δH (200 MHz, CD_3OD) 1.88, 2.70, and 3.46 (14H, m x 3, $-CH_2$ x 7), 3.80 (3H, s, -OMe), 6.69, and 7.42 (2H, ABq, J 16 Hz, olefinic H), 6.60, and 6.90 (3H, ArH) ; $\delta^{13}C$ (50.3 MHz) 25.76, 26.91, 27.41, 38.16 (2 x C), 40.43, 44.06, 56.68, 112.58, 114.62, 116.61, 123.51, 128.38, 145.48, 149.34, 150.26, and 170.14.
19. (13), pale yellow foam ; FABMS : m/z 352 (MH^+) ; δH (200 MHz, CD_3OD) 1.57, 2.84, and 3.47 (14H, m x 3, $-CH_2$ x 7), 3.82 (6H, s, -OMe x 2), 6.66, and 7.44 (2H, ABq, J 16 Hz, olefinic H), 6.78 (2H, s, ArH) ; $\delta^{13}C$ (50.3 MHz) 25.76, 27.07, 27.28, 38.34 (2 x C), 40.52, 44.15, 57.26, 107.62, 115.55, 127.56, 139.63, 145.4, 149.62, and 170.0.
20. (14), pale yellow foam ; FABMS : m/z 308 (MH^+). This compound could not be obtained pure as it was very unstable.
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