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SYNTHESIS OF 3'-(L-2-AMINO-3-PHENYLPROPYL)AMINO-3'-DEOXY-N^6,N^6-DIMETHYLADENOSINE - A NEW ANALOG OF PUROMYCIN

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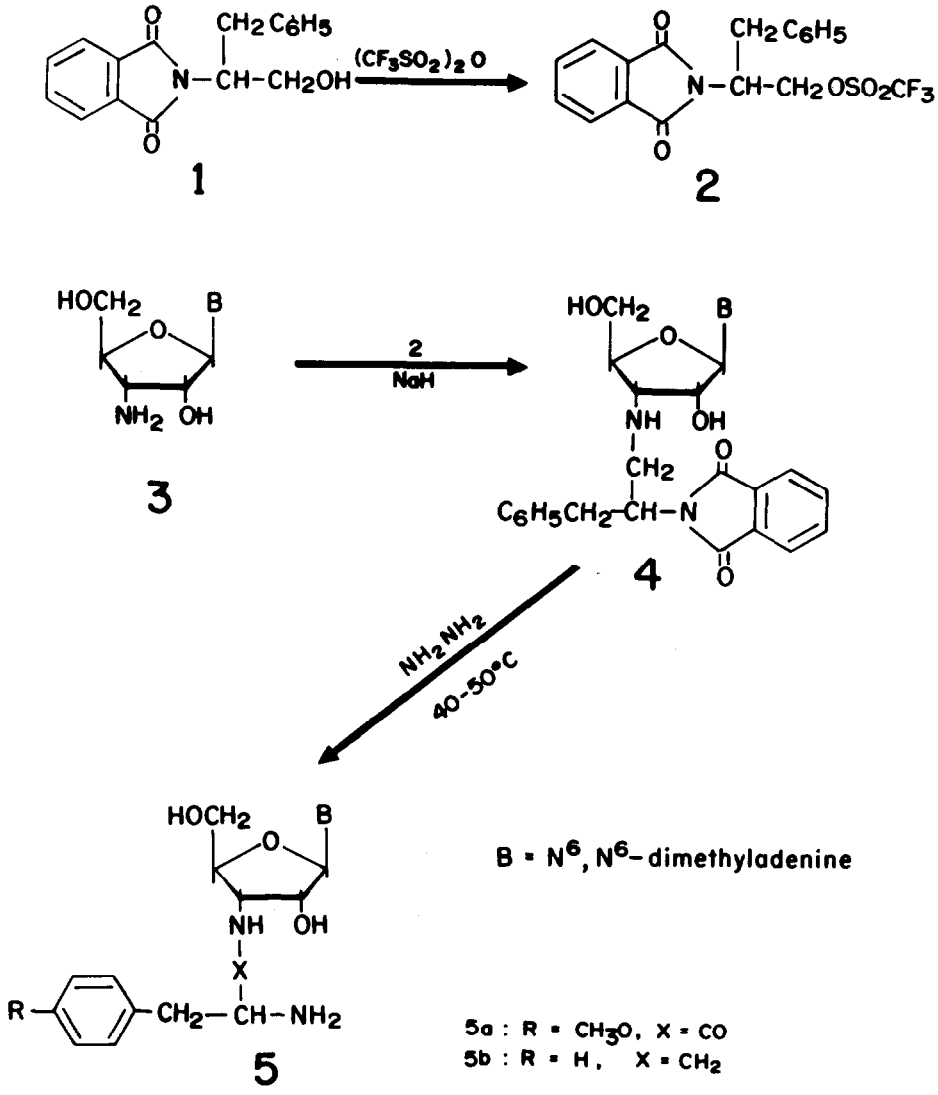
The nucleoside antibiotic puromycin (5a) is a powerful inhibitor of protein synthesis which exhibits distinct anticancer activity.[1] Analogs of puromycin (5a) wherein the carbonyl group of amino acid moiety has been reduced to a methylene group are of interest because such a modification would not increase the size of the molecule but would enhance its resistance towards chemical and enzymic hydrolysis. Such a compound would also address an important problem of the mechanism of ribosomal protein synthesis - requirement for a carbonyl group (amide or ester) in the acceptor substrate.[2,3] Similar analogs of some peptides have found use in structure - activity studies.[4,5]

We now wish to report the synthesis of compound (5b) using a novel selective alkylation procedure (see Scheme 1). Thus, L-3-phenyl-2-phthalimido-1-propanol (1) obtained by a method used for the corresponding racemic compound[6] gave on reaction with trifluoromethanesulfonic anhydride in the presence of pyridine[7] in CH_2Cl_2 trifluoromethanesulfonate 2. The interaction of 2 with puromycin aminonucleoside 3 using NaH in dimethylformamide (DMF) - dioxane mixture afforded the N-phthaloyl derivative 4. The structure of 4 was confirmed by negative ninhydrin and $NaIO_4$-benzidine[8] tests. The deblocking of 4 required the treatment with hydrazine in ethanol for 5 h at 40-50°C to afford the target compound 5b characterized as a hydrochloride salt. Product 5b gave a violet coloration with ninhydrin but it did not react with $NaIO_4$-benzidine reagent.

Although alkylation of simple amines with esters of trifluoromethanesulfonic acid is documented[9] the present report is the first application to sterically hindered esters and complex polyfunctional amines. The presence of trifluoromethanesulfonyloxy group as an effective leaving group in 2 is essential for the success of the procedure. Thus, the corresponding methanesulfonyl derivative of 1 failed to react with aminonucleoside 3 under a variety of conditions.

Preliminary tests in a cell-free *E. coli* ribosomal system using N-acetyl-L-phenylalanyl-tRNA as a peptide donor showed that compound 5b at concentration 1×10^{-3}M is not capable of accepting N-acetyl-L-phenylalanyl residue from N-acetyl-L-phenylalanyl-tRNA and also it does not inhibit the puromycin reaction in the same system.[10] Further biological testing is in progress.

Scheme 1


CH2C6H5
N–CH–CH2OH
(CF3SO2)2O
CH2C6H5
N–CH–CH2OSO2CF3
1
2
HOCH2
B
O
NH2 OH
3
2
NaH
HOCH2
B
O
NH OH
CH2
C6H5CH2–CH–N
O
O
4
NH2NH2
40-50°C
HOCH2
B
O
NH OH
X
R
CH2–CH–NH2
5
B = N6, N6-dimethyladenine
5a : R = CH3O, X = CO
5b : R = H, X = CH2

L-3-Phenyl-2-phthalimido-1-trifluoromethanesulfonyloxypropane-(2).[11]

A solution of compound 1 (ref. 6, 0.47 g, 1.7 mmol) and trifluoromethanesulfonic anhydride (0.47 g, 1.7 mmol) in CH_2Cl_2 (10 ml) was stirred 1 h at 0°C and 1 h at room temperature. The solvent was evaporated, the residue was washed with $CHCl_3$ (5 ml), the solution was filtered, the filtrate was evaporated and crude 2 was crystallized from 2-propanol, 0.5 g (73%), mp. 85-86°C; NMR ($CDCl_3$) δ, 3.25 (m, 2, CH_2 of benzyl), 4.71 (m, 1, CH), 5.01 (m, 2, CH_2O), 7.19 (s, 5, C_6H_5), 7.73 (m, 4, phthaloyl); mass spectrum: m/e 413 (M^+).

3'-Deoxy-N^6,N^6-dimethyl-3'-(L-3-phenyl-2-phthalimidopropyl)aminoadenosine (4).

A suspension of aminonucleoside 3 (20 mg, 68 μmol) in DMF-dioxane (1:1, 4 ml) was stirred with NaH (2 mg, 83 μmol) for 30 min. at room temperature. Reagent 2 (28 mg, 68 μmol) was then added and the stirring continued for 17 h. The insoluble portion was filtered off, the filtrate was evaporated and the residue was chromatographed on a loose layer of silica gel[12] in CH_2Cl_2-CH_3OH (93:7). The faster moving band was eluted, the eluate was evaporated and crude 4 was crystallized from 2-propanol or ethyl acetate, 21 mg (55%), mp. 202-203°C; UV_{max}^{EtOH} 267 nm (ε 17 300), shoulder 283 nm (ε 15 600); NMR (CD_3SOCD_3 + D_2O) δ, 3.50 (s, 6, $(CH_3)_2N$), 6.11 (d, $J_{1',2'}$ 3 Hz, 1, $H_{1'}$), 7.18 (s, 5, C_6H_5), 7.73 (m, 4, phthaloyl), 8.31 (s, 1, H_2), 8.46 (s, 1, H_8); mass spectrum: m/e 557 (M^+). $[\alpha]_D^{24}$ - 6.2° (c 0.15, ethanol).

3'-(L-2-Amino-3-phenylpropyl)amino-3'-deoxy-N^6,N^6-dimethyladenosine (5b).

A mixture of compound 4 (20 mg, 36 μmol), hydrazine hydrate (1 ml) and ethanol (4 ml) was heated for 5 h at 40°-50°C. After evaporation of solvents the residue was chromatographed on a loose layer of silica gel[12] in CH_2Cl_2-CH_3OH (4:1). The major UV absorbing band was eluted, the eluate was evaporated, product was dissolved in methanol (20 ml), the solution was saturated with HCl and then it was kept at -10°C for 3 days. The insoluble portion was filtered off, the filtrate was evaporated and the residue was crystallized from 80% ethanol, 11 mg (66%, hydrochloride); mp. 223-227°C; UV_{max}^{EtOH} 275 nm (ε 13 600); NMR (CD_3SOCD_3 + D_2O) δ, 3.46 (s, 6, $(CH_3)_2N$), 5.99 (d, $J_{1',2'}$ 3 Hz, 1, $H_{1'}$), 7.25 (s, 5, C_6H_5), 8.21 (s, 1, H_2), 8.40 (s, 1, H_8). $[\alpha]_D^{24}$ - 9.8° (c 0.12, H_2O).

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11. All new compounds gave satisfactory C, H, N analyses and they were homogeneous on TLC.[12] NMR spectra were measured on FT spectrometer JEOL FX 100 and mass spectra on JEOL JMS 01SG-2. Tetramethylsilane was used as an internal standard with $CDCl_3$ and sodium 2, 2-dimethyl-2-silapentane-5-sulfonate with CD_3SOCD_3. Evaporations were carried out on a rotary evaporator at 30°C. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected.
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