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SYNTHESIS OF SOME FLUORINATED PUTRESCINE ANALOGUES

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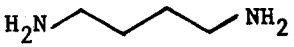
SUMMARY

Mono- and tetrafluoroputrescine were obtained in moderate yields from 2-hydroxy-1,4-dibromobutane and perfluorosuccinamide respectively.

Polyamines such as putrescine 1 (1,4-diaminobutane) are naturally occurring products known to be involved in the regulation of growth processes [1]. They have also been implicated, as useful diagnostic markers, in a number of diseases such as human malignancies [2]. Suitable methods for tumor localization using radiolabelled putrescine [3] and related compounds [4] are being investigated by us and other workers.



1 Putrescine

Our ultimate goal is the synthesis of fluorinated putrescine radiolabelled with positron-emitting radio-

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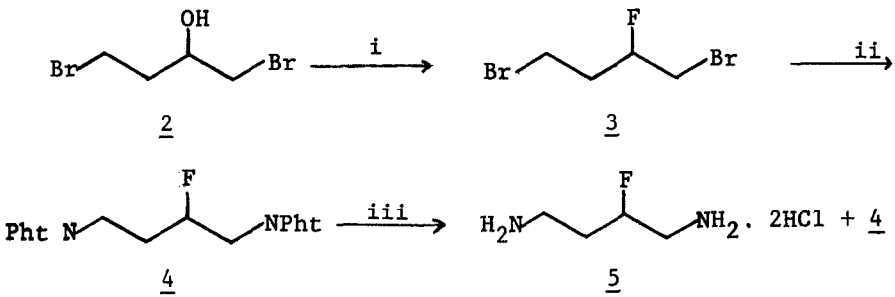
nuclides (fluorine-18; $t_{1/2}$ 109.7 min and carbon-11; $t_{1/2}$ 20.4 min) and their subsequent use in tumor localization in conjunction with positron-emission tomography. Since, to the best of our knowledge, fluorinated 1,4-diaminobutane derivatives have not been reported in the literature, the synthesis of unlabelled mono-5 and tetrafluoroputrescine 13 was undertaken. No attempts were made to optimize yields at that stage, however the interesting biological properties of such compounds [5] prompt us to report their preparation.

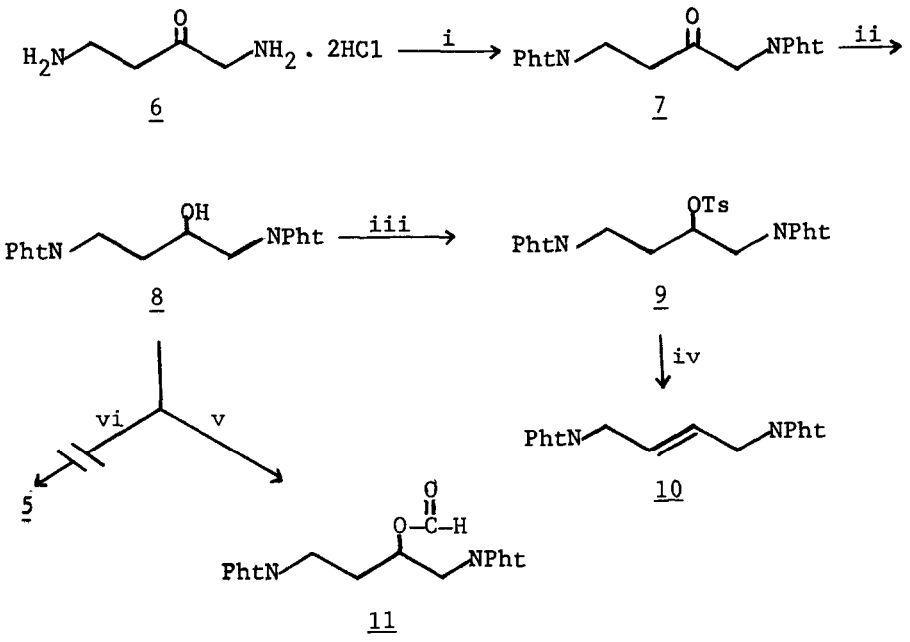
Fluorination of 2-hydroxy-1,4-dibromobutane (2) with diethylaminosulfur trifluoride (DAST) gave fluoro compound 3 (b.p. 93-96°/23 mm, 76%) [6,7] which was converted to its corresponding diphthalimide 4 (m.p. 222-223°, 52%) [7]. Compound 4 was found to be extremely resistant to acid hydrolysis. Deprotection of 4 by heating in concentrated hydrochloric acid for 3 days afforded the desired 2-fluoro-1,4-diaminobutane (5), as its dihydrochloride salt, in low yields (m.p. 220° dec., 8%) [7] and mostly unreacted starting material 4 (80%) (Scheme I). Prolonged heating of the diphthalimide 4 at 120° in acid for a week or in a sealed tube for 3 days did not improve the yield of 5, whereas heating in the presence of hydrazine gave 5 in 10% yield along with decomposition products.



i) DAST in CH_2Cl_2, - 78° RT, 16h then aqueous workup.
ii) PhtNK in DMF, 12h at 100°. iii) Conc HCl, 3d at 120°C.

Scheme I

Alternative routes for the preparation of monofluoroputrescine 5 were investigated (Scheme II). Protection of the diamine 6 to the diphthalamide 7 (m.p. 145-147°, 65% [7,8] followed by reduction gave the alcohol 8 (m.p.244-246° 72%) [7]. Alcohol 8 failed to react with sodium fluoride in hydrogen fluoride-pyridine (HFx/Py) and 8 was recovered unchanged. Furthermore, treatment of 8 with DAST in DMF afforded the corresponding formate 11 in almost quantitative yields (m.p. 172-173°) [7] instead of the desired fluoroputrescine 5. Compound 11 was identified by comparison with a sample prepared by formylation of alcohol 8.

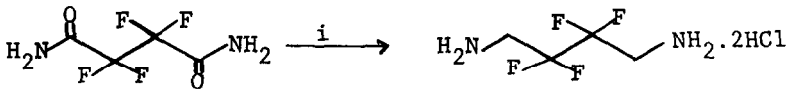


i) $NaHCO_3$ then $PhtNCO_2CH_3$, 16h at RT. ii) $NaBH_4$ in CH_3OH, 1h at RT. iii) TsCl in Py, 3h at 15°. iv) KF in diglyme, 200°. v) DAST in DMF, -30°→ RT, 16h then aqueous work-up or $HCO_2H/(CH_2CO)_2O$, 7d at RT. vi) NaF in HFx/Py, 2h at RT.

Scheme II

In another attempt to prepare compound 5, alcohol 8 was converted to its corresponding tosylate 9 (m.p. 201-203°, 90%) [7]. Treatment of 9 with tetrabutylammonium fluoride (Bu_4NF) in acetonitrile yielded the tosylate 9 unchanged. On the other hand, heating with potassium fluoride in diglyme resulted in dehydrofluorination of 9 to give the alkene 10 (m.p. 228-230°, 20%) [7,10] and unidentified decomposition products.

The second compound of interest, tetrafluoroputrescine 13 (2,2,3,3-tetrafluoro-1,4-diaminobutane) was prepared by reduction of perfluorosuccinamide 12 (commercially available) with BH_3/THF (Scheme III). Compound 12 was isolated as its dihydrochloride salt (m.p. 211-213°, 20%) [7,11]. Alternative synthetic pathways for the preparation of 5 and 13 are currently being investigated in view of their interesting biological properties [5].



12 13

i)BH_3/THF, 3h at 70° followed by acidic work-up.

Scheme III

ACKNOWLEDGEMENT

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