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Synthesis of a New Bicyclic Guanidine Heterocycle as a Potential Anti HIV Agent

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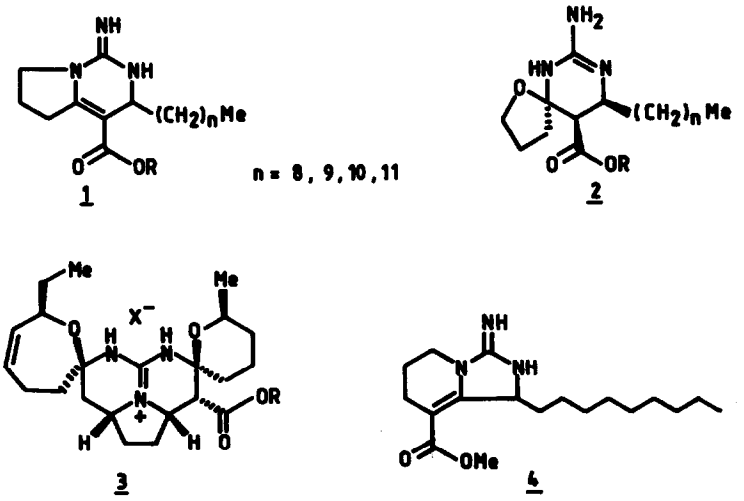
Abstract : Synthesis of a new and potential anti-HIV bicyclic guanidine heterocycle has been described by a novel and versatile protocol.

The 2',3'-dideoxynucleosides are the first group of anti-viral compounds utilised in the treatment of the dreadful AIDS disease[1]. Many new and structurally variant anti-viral natural products are currently undergoing extensive screening for HIV infections[2]. Marine natural products containing polycyclic guanidine skeleton and represented by crambine A (1) and B (2)[3] and ptilomycalin A (3)[4] are some of the outstanding anti-viral lead compounds[5]. To understand their structure to activity relationship and more importantly to derive their analogues that can antagonise HIV-infection more profoundly, we have undertaken a programme to synthesise new guanidine heterocyclic bases. This communication describes the synthesis of an unknown bicyclic guanidine moiety (4) that is structurally related to the acyl portion of crambine-A but for the placement of guanidine functionality which is integrated in a 5-membered ring (in 4) rather than in a 6-membered ring (in crambine-A) (scheme 1).

SCHEME-1



1 n = 8, 9, 10, 11 2

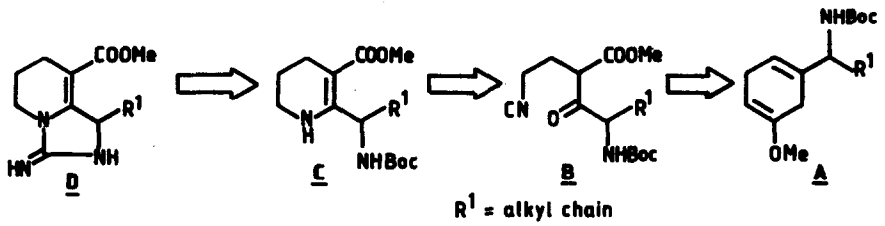
3 4

R = long alkyl chain

In contemplating the synthesis of this unknown polycyclic guanidine heterocycle (type D), we reasoned that the diamino derivative (C) would be an ideal precursor, the synthesis of which looked appealing by reductive dehydration[6] of the α-cyanoethyl-β-keto-ester derivative

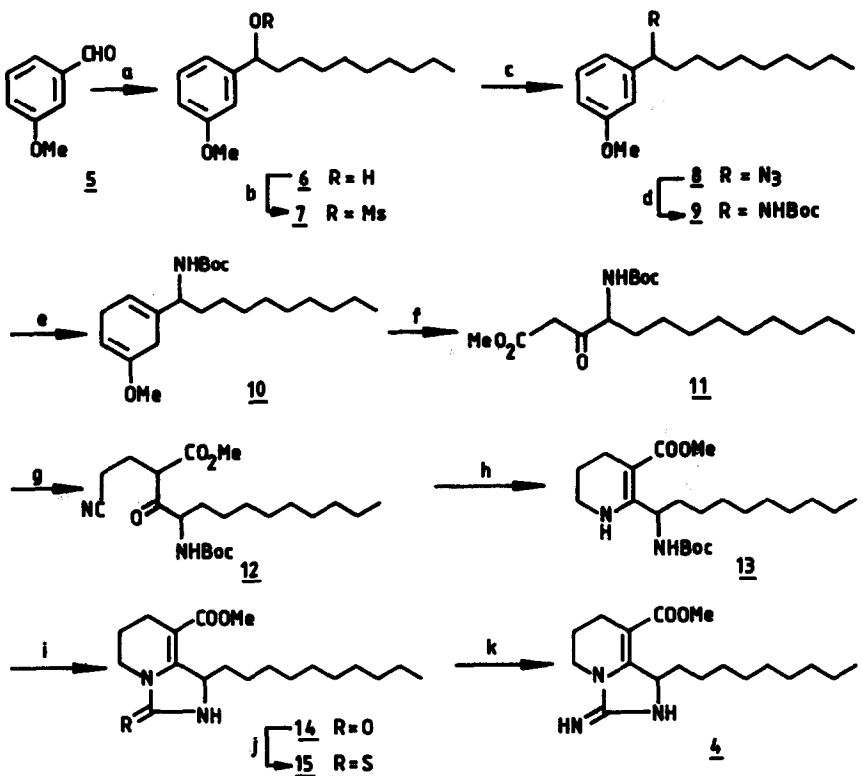
(B). We further envisioned that the preparation[7] of B from the 1,4-cyclohexadiene intermediate (A) should be a straight forward exercise (Scheme 2).

SCHEME-2



The benzylic alcohol derivative (6), obtained from the Grignard reaction of m-methoxy-benzaldehyde (5) and n-nonylmagnesiumbromide, was converted into the mesyl derivative (7) by reacting with MsCl-Et_3N. Subsequent nucleophilic displacement reaction of 7 with LiN_3

SCHEME-3



a) $C_9H_{19}MgBr$, THF, RT, 1h, 90%; b) MsCl, Et_3N, CH_2Cl_2, 0°-RT, 2h, 85%; c) LiN_3, DMF, 90°, 4h, 85%; d) i) Pd-C, H_2, MeOH, 1 atm, RT, 5h, 90%; ii) $(Boc)_2O$, 0.5N, aq. NaOH, dioxane, 0°-RT, 2h, 92%; e) Na, liq. NH_3, Et_2O, EtOH, -78°, 2h, 80%; f) O_3, EtOH, Pd-C, 95%; g) acrylonitrile, Triton B (40% solution in MeOH), dioxane, 50°, 2h, 35%; h) Raney-Nickel, H_2, EtOH, 70°, 70 psi, 2h, 85%; i) (i) HCl in dry Et_2O, RT, 2h, 86%; (ii) Triphosgene, pyridine, CH_2Cl_2, RT, 4h, 60%; j) Lawesson's reagent, dioxane, reflux, 12h, 75%; k) NH_3-$AgSO_3CF_3$, CH_2Cl_2,-10°-RT, 5h, 46%.

in DMF at 90° furnished **8**. Subsequent hydrogenation of **8** over 10% Pd-C in MeOH at normal pressure and temperature gave the free amine which was isolated as a N-Boc derivative (**9**) by the reaction with $(Boc)_2O$ in aqueous NaOH. The Birch reduction of **9** in the presence of Na in liq. NH_3 at -78° gave the 1,4-cyclohexadiene derivative (**10**) whose ozonolysis in EtOH at -78° followed by reductive work-up[7] furnished the β-keto-ester (**11**) (Scheme 3).

The next step of monocyanoethylation of **11** with acrylonitrile turned out to be a difficult proposition because of competitive dicyanoethylation reaction. However, best results[8] were achieved when **11** was treated with 1 eq. of freshly distilled acrylonitrile with Triton B (40% solution in MeOH) as a base at 50° affording **12** in 35% yield.

Reduction[6] of **12** in the presence of freshly prepared Raney nickel in an autoclave at 70° with 70 psi of hydrogen pressure for 2h gave the crude tetrahydropyridine derivative (**13**). Treatment of **13** with HCl in dry ether cleaved the N-Boc group which was followed by the treatment[9] with triphosgene in dry pyridine for 4h to provide the cyclic urea derivative (**14**). Compound **14** was then transformed into the thiourea derivative (**15**) by refluxing with Lawesson's reagent in dioxane.

The final conversion of **15** into the bicyclic guanidine derivative (**4**) was performed with NH_3-$AgSO_2CF_3$ in CH_2Cl_2 at -10° to room temperature[10]. The structure of **4** was based on the following spectral data : ^1H NMR ($CDCl_3$ + CD_3OD) δ 0.88 (t, 3H, J = 6.2 Hz), 1.3 (m, 14H), 1.70 (m, 1H), 1.84 (m, 1H), 2.00 (m, 2H), 2.32 (m, 1H), 2.48 (m, 1H), 3.46 (m, 1H), 3.70 (s, 3H), 5.58 (dd, 1H, J = 2.2, 8.0 Hz); Mass spectrum (m/z) 322 (M^++1), IR (Neat) 3350-3400, 2910, 1705, 1610, 1450, 1360 cm^{-1}.

The biological activity studies of **4** have been undertaken.

References and Notes

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11. Selective physical data for compounds **8**, **9**, **11**, **12**, **14** and **15**.
    Compound **8** ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.25 Hz), 1.25 (bs, 14H), 1.75 (m, 2H), 3.81 (t, 3H), 4.33 (t, 1H, J = 7.5 Hz), 6.83 (m, 3H), 7.27 (t, 1H, J = 8.3 Hz); IR (Neat) 2900, 2075, 1666, 1592, 1450, 1355, 1251 and 1160 cm^{-1}.

Compound **9**: ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 6.25 Hz), 1.20 (bs, 14H), 1.34 (s, 9H), 1.62 (bs, 2H), 3.74 (s, 3H), 4.58 (bs, 1H), 4.63 (bs, 1H), 6.70 (m, 3H), 7.14 (m, 1H).
Compound **11**: ^{1}H NMR ($CDCl_3$): 0.90 (t, 3H, J = 6.25 Hz), 1.28 (bs, 14H), 1.46 (s, 9H), 1.5-2.0 (m, 2H), 3.54 (ABq, 2H, J = 16.0 Hz), 3.74 (s, 3H), 4.32 (m, 1H), 5.02 (d, 1H, J = 8.0 Hz).
Compound **12** : ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 6.25 Hz), 1.29 (bs, 14H), 1.45 (s, 9H), 1.87 (m, 2H), 2.2 (m, 2H), 2.5 (m, 2H), 3.75, 3.79 (2s, 3H), 3.91 (dd, 1H, J = 6.25, 10.4 Hz), 4.2-4.5 (m, 1H), 4.81 (d, 1H, J = 8.2 Hz)., 4.91 (d, 1H, J = 8.7 Hz); IR (Neat) 3360, 2900, 2240, 1770-1700, 1500, 1450, 1360, 1250, 1165 cm^{-1}.
Compound **14** : ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 6.2 Hz), 1.27 (bs, 14H), 1.5-2.5 (m, 6H), 3.5-3.7 (m, 2H), 3.72 (s, 3H), 5.53 (dd, 1H, J = 2.1, 7.6 Hz); Mass spectrum (m/z) 323 (M^++1).
Compound **15** : ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.25 Hz), 1.4 (m, 14H), 1.6-2.6 (m, 6H), 3.6 (m, 1H), 3.71 (s, 3H), 3.9 (m, 1H), 5.75 (dd, 1H, J = 2.1, 8.0 Hz); Mass spectrum (m/z) 339 (M^++1); IR (Neat) 2900, 1694, 1637, 1373, 1262, 1168, 1133 cm^{-1}.

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