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A NEW ROUTE TO 7-DEAZAGUANINE DERIVATIVES

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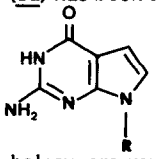
Abstract : The synthesis of 2-amino-4,6-dichloro-5-(2,2-diethoxyethyl) pyrimidine 7 has been performed in four steps starting from guanidine and diethylallylmalonate. 7 is a new key intermediate for the synthesis of 7-alkyl-2-amino-3,4-dihydro-7H-pyrrolo [2,3-d] pyrimidin-4-ones.

The synthesis of 7-deazaguanine (1a) has been reported by Davoll in 1960[1].

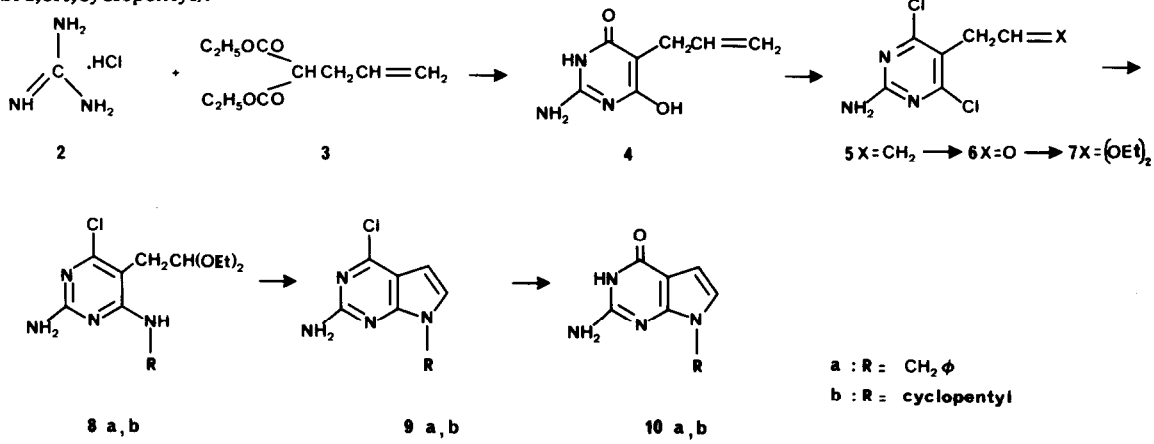


1 a : R= H
b : R= ribofuranosyl
c : R= arabinofuranosyl

Direct substitution of 1a with 1-halosugars usually results in N-1 and N-3 glycosylation products[2]. The synthesis of 7-deazaguanosine (1b) and its arabinosyl analogue (1c) has been carried out by glycosylation of 4-methoxy-2-methylthio-7H-pyrrolo [2,3-d] pyrimidine (itself prepared in a multistep sequence) and involves five further steps[2]. The carbocyclic analogues of 7-deazaguanosine cannot be prepared by this route since the different 3-halogeno-5-hydroxymethyl-1,2-cyclopentanediols are not yet known. As several carbocyclic analogues of guanine or 8-azaguanine nucleosides show significant activity against herpes simplex virus[3-5], the synthesis of carbocyclic analogues of 7-deazaguanosine seemed of interest and we sought a route to these compounds from the known 3-amino-5-hydroxymethyl-1,2-cyclopentanediols[6-8]. This communication deals with the synthesis of 2-amino-4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine, a key intermediate for the synthesis of 9-alkyl-7-deazaguanines.

Guanidine hydrochloride (2) reacted in absolute ethanol with 1 equiv. of diethylallylmalonate (3) in the presence of sodium ethoxyde (r.t., 18 h) to afford the pyrimidine 4 64 % yield, m.p. 272°C, ^{1}H NMR[9] δ 6.37 (s,2H,NH_2), 5.80 (m,1H,CH), 5.00 (m,1H,CH_2), 4.84 (m,1H,CH_2), 3.33 (brd NH,OH,DOH), 2.90 (dt,2H,CH_2). This 5-allyl-2-amino-4,6-dihydroxypyrimidine (4) was converted to the 4,6-dichloroderivative 5 by treatment with $POCl_3/PCl_5$/diethylaniline (4 h, 120°C) in 57 % yield, m.p. 182°C, UV[10] λ_{max} 305, 237 nm (4500,19700), ^{1}H NMR δ 7.36 (s,2H,NH_2), 5.88 (m,1H,CH), 5.03 (m,2H,CH_2), 3.45 (m,2H,CH_2).
Ozonolysis of 5 in ethylacetate-methanol at -78°C followed by the reduction of the ozonide by NaI-CH_3CO_2H afforded after extraction (CH_2Cl_2) and crystallization (toluene) the aldehyde 6 70 % yield, m.p. 180-182°C, UV λ_{max} 304, 237 nm (3700,15200), ^{1}H NMR δ 9.70 (s,1H,CH), 7.50 (s,2H,NH_2), 3.93 (s,2H,CH_2). The diethylacetal derivative 7 of 6 had then to be prepared in order to perform a clean monosubstitution on the pyrimidine by a primary amine. Therefore 6 was refluxed in absolute ethanol in the presence of catalytic amount of NH_4Cl for 3 h. After work up and recrystallization from hexane, 7 was obtained in 77 % yield,

m.p. 146-149°C, UV λ_{max} 304, 238 nm (4500,18300), ^{1}H NMR δ 7.36 (s,2H,NH_2), 4.68 (t,1H,CH), 3.54 (m,4H,OCH_2), 2.93 (d,2H,CH_2), 1.08 (t,6H,CH_3). The monosubstitution of (7) was carried out with 1 eq of two different alkylamines, in 1-butanol under argon atmosphere in the presence of triethylamine for 2 days at 100°C to provide 8 as oils after flash chromatography in toluene. Cyclisations of 8 into 9 could then be performed in aqueous 0.2 N HCl (r.t., 3d.). An excess of NH_4OH was added and after evaporation to dryness, the residue was washed with water and recrystallized from ethanol in the case of 9a (R = $CH_2\phi$) yield 70 % (from 7), m.p. 184°C, ^{1}H NMR δ 7.27 (m,5H,ϕ), 7.23 (d,1H,H-6), 6.64 (s,2H,NH_2), 6.37 (d,1H,H-5,J_{5-6} = 3.6 Hz). 9b (R = cyclopentyl) was recrystallized from cyclohexane ; yield 79 %, m.p. 92°C, ^{1}H NMR δ 7.27 (d,1H,H-6), 6.60 (s,2H,NH_2), 6.33 (d,1H,H-5,J_{5-6} = 3.8 Hz), 5.02 (m,1H,H-1'), 1.80 (m,8H,cyclopentyl). The pyrimidinones 10 were then obtained by hydrolysis of the chlorine atom 4 in 1N HCl-ethanol for 6 h under reflux. The mixture was neutralized and evaporated to dryness. 10a was purified by flash chromatography in AcOEt and crystallized from ethanol, yield 52 %, m.p. > 250°C, ^{1}H NMR δ 10.25 (s,1H,NH), 7.38-7.12 (m,5H,ϕ), 6.76 (d,1H,H-6), 6.29 (d,1H,H-5,J_{5-6} = 3.5 Hz), 6.21 (s,2H,NH_2), 5.18 (s,2H,CH_2). The same work-up as for 10a gave 10b after chromatography and crystallization from ethanol, yield 62 %, m.p. > 250°C, ^{1}H NMR δ 10.24 (s,1H,NH), 6.80 (d,1H,H-6), 6.26 (d,1H,H-5,J_{5-6} = 3.5 Hz), 4.80 (s brd,1H,H-1'), 1.78 (m brd,8H,cyclopentyl).



2 3 4 5 X=CH_2 → 6 X=O → 7 X=$(OEt)_2$

8 a,b 9 a,b 10 a,b

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9. Proton NMR spectra were obtained with a Varian XL100 (100 MHz) spectrometer in DMSO d_6.
10. Ultra Violet (UV) spectra were recorded in ethanolic solutions with a Cary 118 spectrophotomer.

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