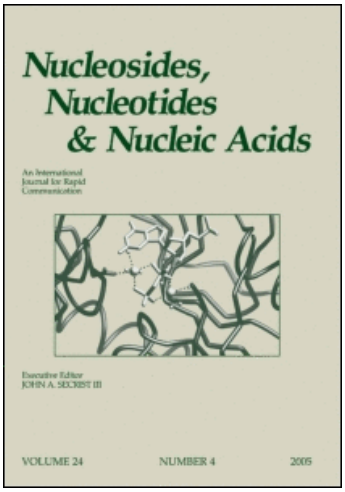

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Ukken O. Cheriyan[a]; Kelvin K. Ogilvie[a]
[a] Department of Chemistry, McGill University Montreal, Quebec, Canada

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PREPARATION OF 9-β-D-ARABINOFURANOSYLGUANINE (araG)

Ukken O. Cheriyan and Kelvin K. Ogilvie*

Department of Chemistry, McGill University
Montreal, Quebec, Canada, H3A 2K6

Abstract - A convenient practical synthesis of araG is described.

As part of our ongoing research program on the chemical and biological properties of natural nucleosides and their analogues we recently required araG in some quantity. The reported methods for the synthesis of araG did not provide practical routes to this compound.

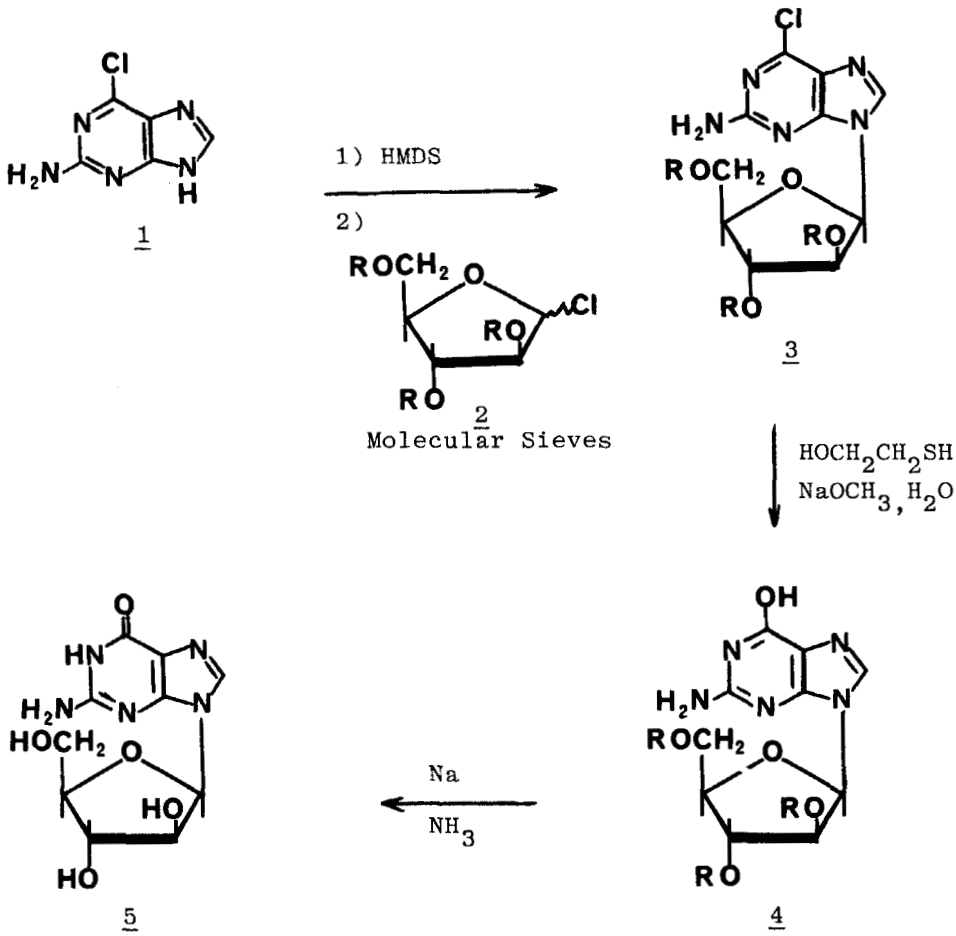
AraG was first synthesized by Reist and Goodman[1] by initial condensation of 2,6-dichloropurine with xylofuranose tetraacetate followed by transformation of the resulting tetraacetate. Ikehara and coworkers[2a], as well as Chattopadhyaya and Reese[2b], converted guanosine into araG via an anhydronucleoside. Attempts to prepare araG by the Lewis acid catalyzed coupling of tetra-O-acetyl-D-arabinose with N^2-acylguanines resulted in the formation of mostly the α-anomer.[3]

We first attempted to prepare araG *via* the condensation of silylated 2-amino-6-chloroguanine (1) with 2,3,5-tri-O-benzyl-α,D-arabinofuranosyl chloride (2) in the presence of mercuric cyanide.[4] As described,[4] nearly equal amounts of the α- and β-anomers were obtained. This mixture was successfully converted into the araG anomers. However, we found the separation of these anomers to be quite difficult and only the α-anomer was obtained pure by fractional crystallization.

Recently molecular sieves have been used[5] to condense 2 with silylated pyrimidines yielding exclusively the β-anomer. In fact, molecular sieves have been used to condense 2,6-diacetamido-purine with 2 giving moderate

yields of product.[6] The product after deacylation was converted to araG by enzymatic deamination in unspecified yield.[6]

We wish to report that silylation of 2-amino-6-chloro-purine followed by condensation with 2 in the presence of molecular sieves provides a good route to the β-anomer. The condensation was conducted in 1,2-dichloroethane as solvent over a five-day period. The β-anomer (3) was isolated as the sole product in 33% yield. The 6-chloro compound (3) was converted to the 6-hydroxy derivative (4) by refluxing 3 in methanol containing sodium methoxide, mercaptoethanol and a trace of water.[4] The product 4 was debenzylated with sodium in liquid ammonia to give 9-β-D-arabinofuranosylguanine (5).



1 2 3 4 5

R= ϕCH_2-

FIGURE 1

Experimental

2-Amino-6-chloro-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)9H-purine (3)

2-Amino-6-chloropurine (6 g, 35.3 mmole) was heated at reflux in hexamethyldisilazane (70 ml) in the presence of ammonium sulfate (100 mg) until a clear solution was obtained. The solvent was then removed at reduced pressure to leave a white solid. To a suspension of this solid in 1,2-dichloroethane (150 ml) were added molecular sieves (Linde 3A, 24 g) and a solution of 2[7] (35.1 mmole) in 1,2-dichloroethane (150 ml). The mixture was stirred at room temperature for five days. Dichloromethane (800 ml) was added and the solution was filtered through celite. The filtrate was washed successively with aqueous sodium carbonate and saturated salt solution and then dried over sodium sulfate. Removal of the solvent left a dark yellow solid (18 g) which was flash chromatographed on silica gel (230-400 mesh, Merck 60) using hexane-ethyl acetate (45:55). The product 3 was obtained, after evaporation of the appropriate fractions, as a white foam (6.6 g, 33%). The compound showed a λmax at 261, 322 nm (pH1), 260 and 322 nm (pH7), and 250, 315 nm (pH13). The 200 MHz spectrum in $CDCl_3$ showed absorption at δ = 3.64 (2H, d), 4.22 (3H, m), 4.56 (6H, d), 5.10 (2H, b.s., exchangeable with D_2O), 6.30 (1H, d), 6.96 (2H, m), 7.30 (13H, m), and 8.10 (1H, s). The compound had an R_f of 0.30 in hexane-ethyl acetate (45:55).

9-(2,3,5-Tri-O-benzyl-β-D-arabinofuranosyl)guanine (4)

To a solution of 3 (5.8 g, 10.1 mole) in methanol (100 ml) was added mercaptoethanol (4 ml), methanolic sodium methoxide (1 m, 40 ml), and water (0.3 ml) and the solution was heated at reflux for 6 h. On cooling to room temperature the solution was acidified with acetic acid and the solvents were removed at reduced pressure. The residue was triturated with dichloromethane and the solution collected by filtration. On removal of the solvents a viscous oil was obtained that was kept under reduced pressure (1 m m Hg) for 8 h. The solid foam obtained was purified by chromatography over silica gel (Merck 60, 230-400 mesh, 8.5 x 11 cm) using methanol-ethyl acetate (7.5:92.5). A total of 3.6 g of 4 (64%) was obtained. The product showed λmax at 252 and 274 nm in ethanol and 256, 274 (s)(pH1), 254, 270 (s)(pH7), and 257, 268 (pH13). The 200 MHz spectrum in $CDCl_3$ showed protons at δ = 3.64 (2H, d), 4.20 (3H, m), 4.52 (6H, m), 6.26 (1H, d), 6.40 (2H, b.s., exchangeable in D_2O), 7.00 (2H, m), 7.25 (13H, m), and 7.82 (1H, s). Compound 4 has an R_f of 0.35 in methanol-ethyl acetate (1:9).[8]

Anal. Calc. for $C_{31}H_{31}N_5O_5$: C, 67.26; H, 5.64; N, 12.65. Found: C, 67.21; H, 5.73; N, 12.76.

9-β-D-Arabinofuranosylguanine (5)

A solution of 4 (3.5 g, 6.3 mmole) in THF (25 ml) was added to liquid ammonia (150 ml) at -60° C with stirring, under a stream of nitrogen. The temperature of the bath was allowed to rise to -40° C and sodium was added in small quantities until a permanent blue color was obtained. After the addition was complete, stirring was continued for 15 min. The temperature of the bath was then lowered to -60° C and ammonium chloride was added in small quantities until the blue color was discharged. Ammonia and THF were evaporated under a stream of nitrogen. The white solid remaining was triturated with benzene and filtered. The residue was dissolved in water (50 ml) and the solution acidified with acetic acid. The white precipitate obtained was crystallized from water to give 1.4 g (78%) of ara G (mp; dec > 290° C, $[\alpha]_D^{25}$ + 29° (water, 1 mg/10 ml) λmax 255, 275 nm (pH1), 252, 270 nm (pH7), 255, 265 nm (pH13)). The 200 MHz spectrum in DMSO-d6 showed protons at δ = 3.60 (2H, m), 3.76 (1H, m), 4.01 (2H, m), 5.05 (1H, t, CH_2OH), 5.47 (1H, d, CHOH), 5.59 (1H, d, CHOH), 5.98 (1H, d, H_1'), 6.44 (2H, b.s., NH_2) and 7.73 (1H, s, H-8). Ara G had an R_f of 0.39 in 2PrOH:NH_4OH:H_2O (55:35:10).[8] These properties are in agreement with those of an authentic sample.[2]

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42,41; H, 4.63; N, 24.72. Found: C, 42.47; H, 4.72; N, 24.61.

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