Communications to the Editor

[Chem. Pharm. Bull. 31(2) 787—790 (1983)]

A SIMPLIFIED SYNTHESIS OF 8-SUBSTITUTED PURINE NUCLEOSIDES VIA LITHIATION OF 6-CHLORO-9-(2,3-O-ISOPROPYLIDENE-β-D-RIBOFURANOSYL)PURINE

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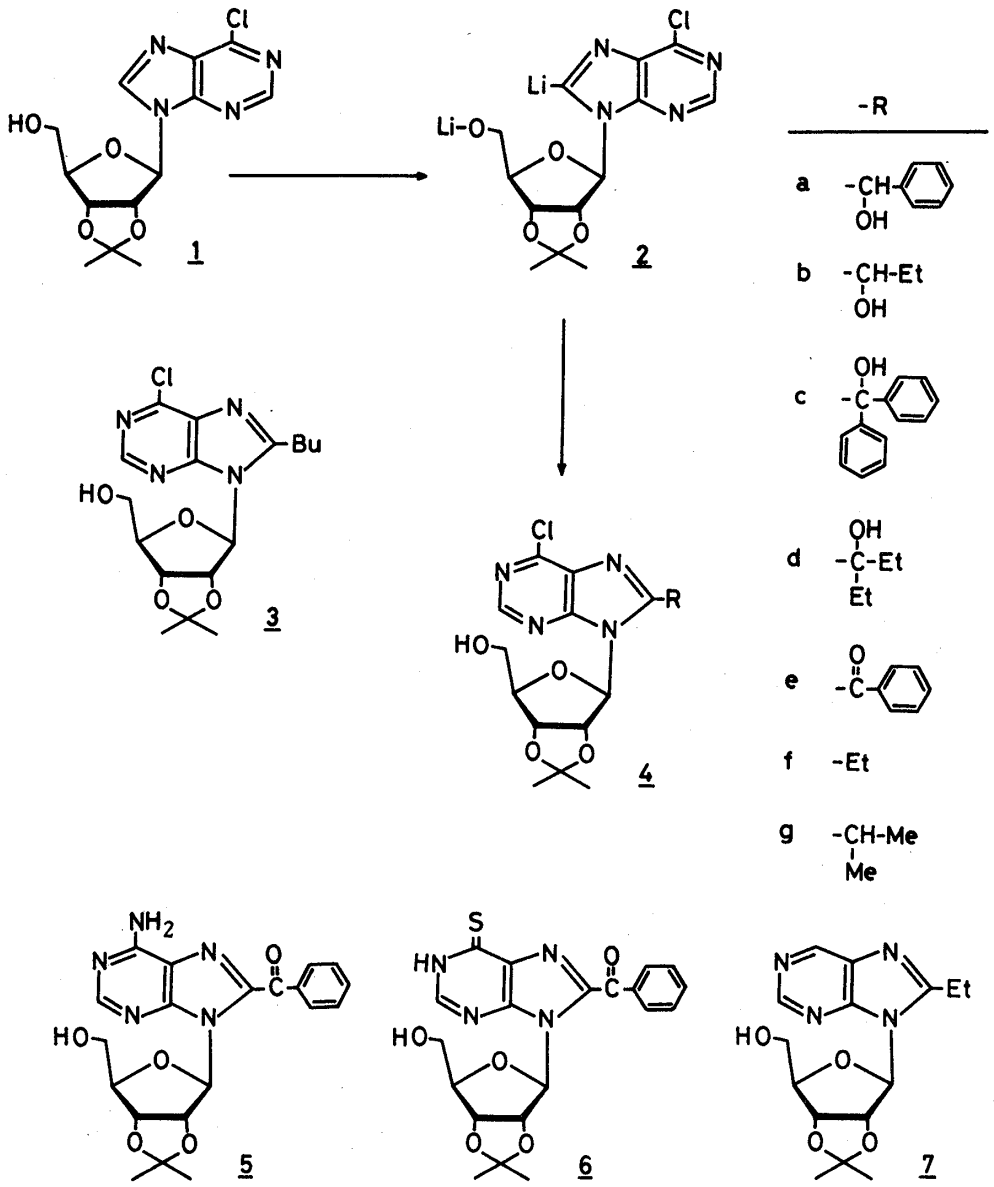
6-Chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine (1) was found to be a suitable substrate for the preparation of C-8 substituted purine nucleosides. Thus, upon lithiation of 1 with LDA and successive reaction with various types of electrophiles, the C-8 substituted products were obtained. The C-6 chlorine atoms in these products were readily replaced by an amino group, a mercapto group, or hydrogen, providing a facile preparation of 8-substituted adenosines, 6-thioinosines, or nebularines.

KEYWORDS—— 8-substituted purine nucleoside; lithiation; LDA; 6-chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine; adenosine derivative; 6-thioinosine derivative; nebularine derivative

Most earlier methods for the preparation of purine nucleosides bearing a carbon functionality at the C-8 position involved either nucleophilic displacement[1,2] or a homolytic reaction.[3] An apparent synthetic limitation of the above reactions lies in their lack of generality. In contrast to these methods, the reaction of a C-8 lithiated purine nucleoside derivative with various types of electrophiles provides a simple and general entry to the C-8 substituted purine nucleosides, as already shown in the synthesis of 6-substituted uridines.[4]

In our studies on the conversion of naturally occurring nucleosides to physiologically active derivatives, a method was needed for synthesizing 8-substituted adenosines, 6-thioinosines, and nebularines. In this communication, we describe a simple and effective method for synthesizing these 8-substituted purine nucleosides on the basis of lithiation.[5]

Recently, Barton et al. reported[6] that N^6-methyl-2',3'-O-isopropylideneadenosine, when treated with butyllithium followed by CH_3I, gave a 35% yield of N^6,N^6-dimethyl-8-methyl-2',3'-O-isopropylideneadenosine. Since the low yield of this reaction could be attributed to the insufficient solubility of the corresponding N^6,8,5'-trilithio derivative, 6-chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine (1), which has only one dissociable proton in its base moiety, was selected as a starting material in our experiment. The choice of 1 is further motivated by the following considerations: 1 is easily accessible from inosine and the



C-6 chlorine atom in 1 is convertible by nucleophilic substitution.

Treatment of 1 with 2.5 eq of LDA in THF below -70°C gave an orange coloured solution of 2. After the solution was quenched with CD_3OD below -70°C, the PMR spectrum of the deuterated 1 (recovery: 93.4%) showed that the lithiation took place exclusively at the C-8 position.[7] The extent of deuterium incorporation was estimated at 80.7%. It should be emphasized that, in the above reaction, no protection of the 5'-hydroxyl group in 1 was necessary to provide good solubility to the lithiated species, and that neither nucleophilic attack of the lithiating agent on the C-6 position nor lithium-halogen exchange was observed to any appreciable extent.

On the other hand, similar treatment of 1 with butyllithium followed by CD_3OD gave a complex mixture of products, from which 8-butyl-6-chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine (3)[8] was isolated. The isolation of 3 indicated that, under these conditions, lithium-chlorine exchange had occurred to generate butyl chloride. Thus, while Leonard and Bryant reported[9] the C-6 chlorine atom in 6-chloro-9-(tetrahydropyran-2-yl)purine to be compatible to the lithiation with butyllithium, it is unlikely that this reagent is suitable in our case.

When 2 was allowed to react with benzaldehyde (2.0 eq) below -70°C for 1 h, the 8-phenylhydroxymethyl derivative (4a, probably an epimeric mixture) was isolated as a foam (M^+ m/z: 432 and 434) in 71.4% yield after quenching with AcOH followed by chromatographic purification on a silica gel column (benzene:AcOEt= 3:1). The PMR spectrum of 4a in $CDCl_3$ (δ 8.68, 1H, H-2; δ 7.35, 5H, phenyl; δ 6.28, 1H, CHOHPh; δ 6.10, 1H, H-1'; δ 4.44, 1H, CHOHPh) was in good agreement with its structure. Under similar conditions, propionaldehyde and benzophenone worked equally well to give the corresponding 4b (isolated as diacetate, an epimeric mixture, 61.5%, syrup, M+1 m/z: 469 and 471) and 4c (60.6%, foam, M^+ m/z: 508 and 510). When the electrophile used was an enolizable ketone, the yield of the product decreased as in the case of diethyl ketone (yield of 4d: 38.6%, foam, M+1 m/z: 413 and 415). The 8-benzoyl derivative (4e, foam, M^+ m/z: 430 and 432) was prepared in 86.5% by oxidation of 4a with activated MnO_2 (in $CHCl_3$, room temperature, overnight). The reaction of 2 with CH_3I (2.0 eq, below -70°C, 3 h) produced a 21.2% yield of the 8-ethyl derivative (4f, foam, M+1 m/z: 355 and 357) together with a small amount of the 8-isopropyl derivative (4g, syrup, M^+ m/z: 368 and 370) and most of 1 was left unchanged. We were unable to detect the 8-methyl and 5'-O-methylated products even in trace amounts by careful PMR and TLC examination of the reaction mixture.

The common intermediate 4 can be treated in a number of ways to reach other types of purine nucleosides. We demonstrated this using 4e and 4f. When a THF solution of 4e containing 28% aq-NH_4OH was heated in a sealed tube (90°C, 1 h), 8-benzoyl-2',3'-O-isopropylideneadenosine (5, mp 176∿178°C, M^+ m/z: 411) was obtained in 83.8% yield. The corresponding 6-thioinosine derivative (6, mp 197∿200°C, M^+ m/z: 428) was prepared from 4e in 77.8% yield by using NaSH (in DMF, room temperature, 1 h). Hydrogenolysis of 4f over 5% Pd-C (in Et_3N/aq-EtOH, 3 atm of H_2, room temperature, 1 h) afforded the 8-ethylnebularine derivative (7, 91.9%, syrup, M+1 m/z: 321).

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8) Compound 3 was isolated as a foam. Physical data of 3 are as follows: MS m/z: 382 and 384 (M^+), 210 and 212 (B+1). PMR ($CDCl_3$) δ: 1.00 (3H, t, $CH_2CH_2CH_2$-CH_3), 1.26∿2.03 (4H, m, $CH_2CH_2CH_2CH_3$), 1.39 (3H, s, isop.Me), 1.66 (3H, s, isop.Me), 2.94∿3.11 (2H, m, $CH_2CH_2CH_2CH_3$), 3.72∿4.06 (2H, m, CH_2-5'), 4.53 (1H, m, H-4'), 5.12 (1H, dd, H-3'), 5.26 (1H, t, H-2'), 5.95 (1H, d, J= 4.9 Hz, H-1'), 8.66 (1H, s, H-2).
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(Received January 20, 1983)