PRODUCT DISTRIBUTION IN THE RIBOSYLATION REACTIONS OF ADENINE AND 1-DEAZAPURINE IN THE PRESENCE OF STANNIC CHLORIDE [1]

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Product distribution has been examined in the ribosylation of adenine and 1-deazapurine as well as their trimethylsilyl derivatives in the presence of stannic chloride. It was found that each of the reaction parameters (the presence or absence of trimethylsilyl protection, reaction time, and the amount of stannic chloride) exerts a profound influence on the product distribution. Reaction conditions favorable to the formation of otherwise quite inaccessible 7-ribosyladenines were developed.

For the synthesis of purine nucleosides several procedures using 1-acyloxy-sugars rather than less stable glycosyl halides have been worked out, e.g., acid-catalyzed or autocatalyzed fusion reactions [2,3] and condensation with trimethylsilylated (TMS) heterocycles by Friedel-Crafts catalysts. [4-6] Out of these, the TMS-procedure using stannic chloride has been widely applied to the synthesis of natural nucleosides and their analogs and generally may give satisfactory to excellent results. On application to unexplored nitrogenous

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heterocycles where many possible ribosylation sites exist, it is always necessary to determine the site of ribosylation. This procedure will be more useful if we were able to predict a possible product distribution. To achieve this, it is prerequisite to closely examine the product distribution of this ribosylation. Systematic investigation of the product distribution, however, is limited although a few papers have appeared dealing with this problem [7] and also some scattered data concerning the product distribution are available in a number of papers. [8]

The present paper deals with some interesting observations regarding the product distributions in ribosylation reaction of imidazo[4,5-b]pyridine (1-deazapurine, 1) and adenine as well as their TMS derivatives in the presence of stannic chloride.

The ribosylation of imidazo[4,5-b]pyridine (1) by the chloromercuri-procedure has already been reported, [9] 68% yield of 3-β-D-ribosyl derivative (5) (R=benzoyl) being obtained along with a trace (3.3%) of 1-β-D-ribosyl derivative (6) (R=benzoyl). On the other hand, as shown in Table I, the ribosylation of 1 with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (3) catalyzed by an equimolar amount of stannic chloride in acetonitrile gave at room temperature rise to 3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (5, R=acetyl) as a sole product in 57% yield. The structure of the latter was confirmed by its conversion to a known nucleoside, 3-β-D-ribofuranosyl-3H-imidazo[4,5-b]-pyridine (5, R=H), [9] suggesting that stannic chloride may attach to the position 4 of 1 (the highest nucleophilic nitrogen) and the ribosylation may take place at other nitrogens. In sharp contrast, when trimethylsilylated imidazo-[4,5-b]pyridine (2) [10] was used and the reaction time was no longer than 5 hr, a new nucleoside, 4-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4H-imidazo[4,5-b]-pyridine (4, R=acetyl) was obtained as a major product (60-70% yield). The

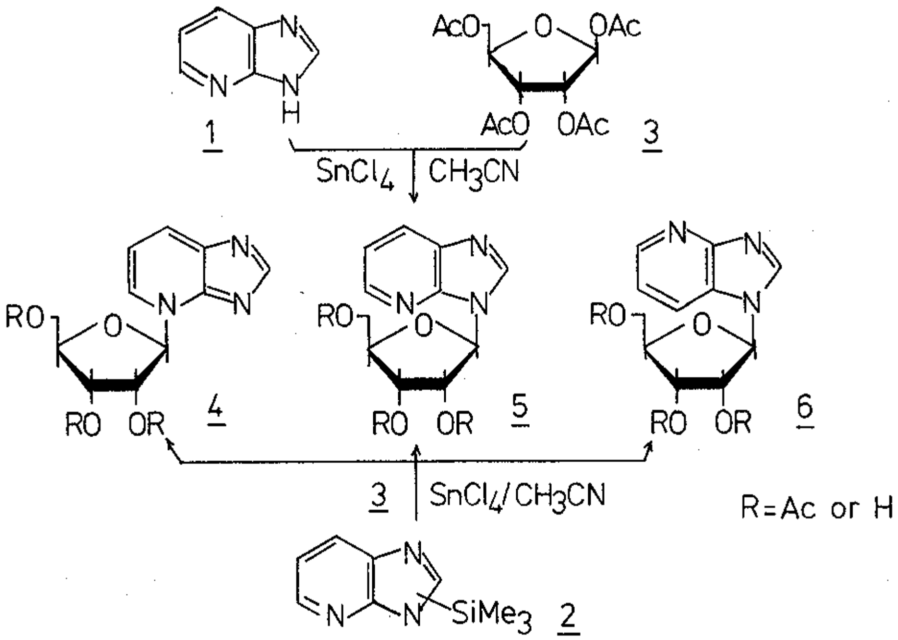


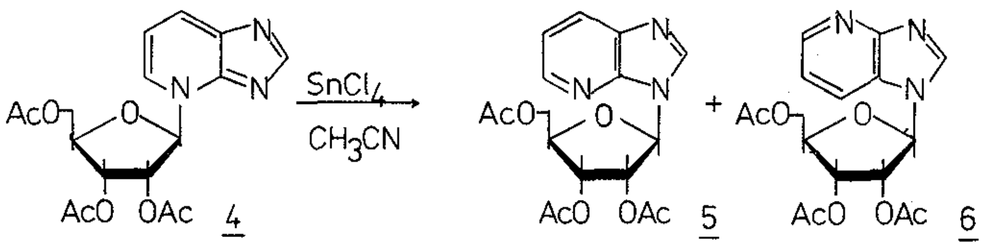
Table I. Product Distribution in Ribosylation Reaction with Imidazo-[4,5-b]pyridine

Base	Sugar 3	$SnCl_4$	Reaction time at room temperature	Yield (%) 4	5	6
1	1*	1.1	10	trace	57	
2	1	0.8	5	59.2	13.9	
	1	1.1	5	70.4	16.5	
	1	2.5	5	59.6	24.3	trace
	1	0.8	30	52.6	19.5	8.5
	1	1.1	30	62.0	16.2	11.2
	1	3.6	30	15.0	42.3	25.7

* Amount of reagent is expressed on the molar basis.

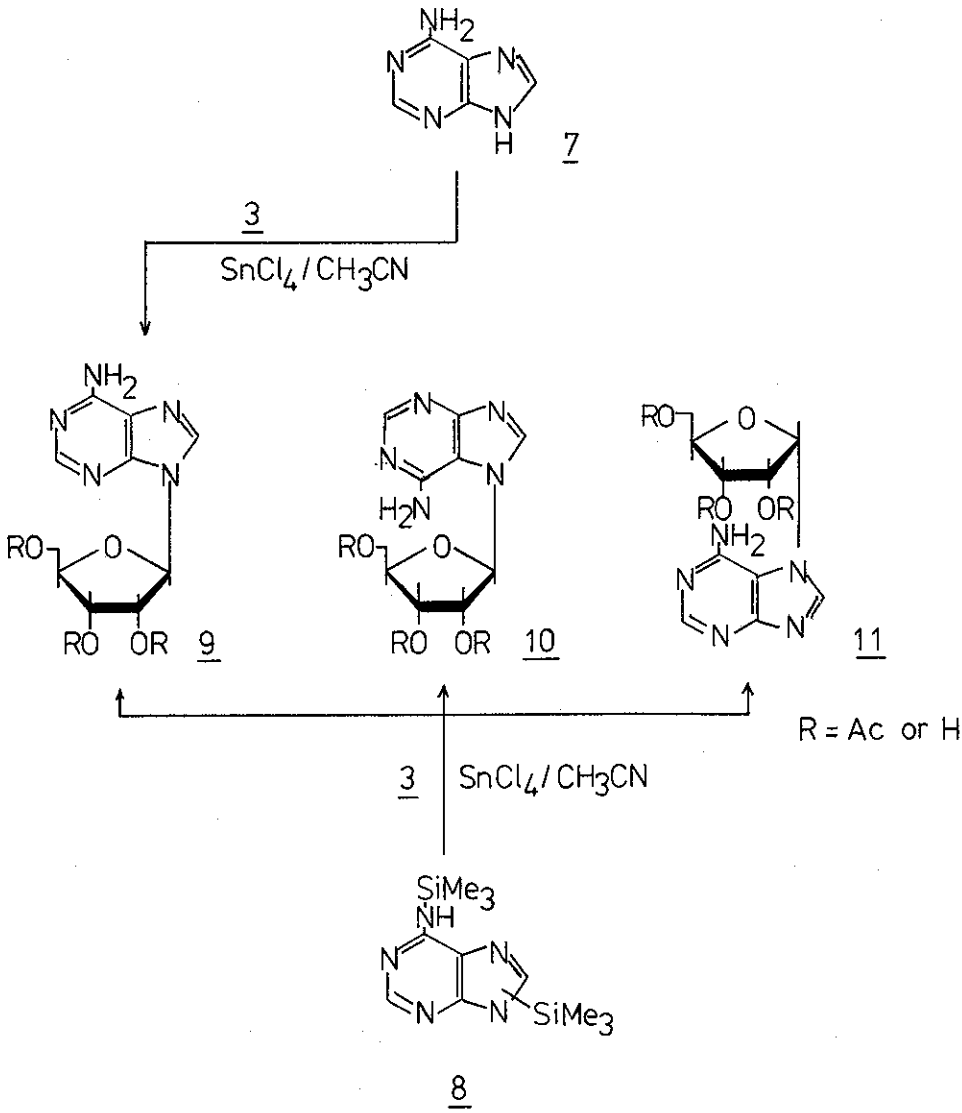
structure of the new compound was determined as follows. The blocked nucleoside (4, R=acetyl) was treated with methanolic ammonia to give a free nucleoside (4, R=H); m.p. 169-71^{o} Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.55; H, 5.22; N, 16.73. Found: C, 52.30; H, 5.10; N, 16.70. The site of the ribosylation was elucidated by comparison of its absorption maxima [λ_{max}^{pH1} 266, 296 nm] with those of 4-methyl-4H-imidazo[4,5-b]pyridine [11] and the anomeric configuration was established to be β according to "the isopropylidene rule" ($\Delta\delta_{CH_3}$ = 0.28 ppm). [12] When the reaction was performed for prolonged period (30 hrs) in the presence of excess stannic chloride, the yield of the 4-isomer (4) was reduced and yields of the 3-isomer (5, 42%) and 1-isomer (6, 25%) increased.

Treatment of the purified 4-isomer (4, R=acetyl) with an equimolar amount of stannic chloride gave rise to the compounds (5, R=acetyl) and (6, R=acetyl) in 39.5% and 25% yield, respectively. These data clearly show that the 4-isomer (4) may be a kinetically controlled product, which in turn rearranged to equilibrium products, 1- or 3-isomer under more vigorous condition. [13]



Quite recently Watanabe, Hollenberg, and Fox have proposed a possible mechanism for the TMS ribosylation reaction and stressed a similarity in the mechanism to other glycosylation reactions. [14]

It is now generally accepted that purine nucleoside formation by the mercuri


NH2
7
3
SnCl4 / CH3CN
NH2
RO
O
RO OR
9
H2N
10
11
R = Ac or H
SiMe3
NH
SiMe3
8

method may proceed via the initial N(3)-glycosylation, followed by rearrangement of the sugar moiety to N(9) or N(7).[15] Many attempts at isolation of 3-glycosyl derivatives in the ribosylation of purines by the TMS procedure have failed. The fact that the 4-isomer(4, an 1-deaza-analog of 3-glycosylpurines) was successfully isolated strongly suggests that initial ribosylation of TMS-purines also occurs at N(3).

Ribosylation of adenine (7) with 1,2,3,5-tetra-O-acetyl-β-D-ribose (3) in the presence of stannic chloride in acetonitrile gave rise to a quantitative yield of 2',3',5'-tri-O-acetyladenosine (9) (R=acetyl).[3b] With TMS-adenine (8),[16] a number of products were detected on thin layer chromatography in the earlier stage of the reaction (2 hr). After 20-hr period of reaction at room temperature, the most abundant products were 7-β-(10, 25%),[17] 7-α-(11, R=H, 18%)[18] and 9-β-(9, R=H, 20%) (structural elucidation of each product was carried out after column chromatographic separation, followed by deacetylation).

To our knowledge this is the first case where trimethylsilylated adenine has been used in the ribosylation and, in addition, 7-substituted adenine[17,18] which are usually quite inaccessible were isolated as main products.

Further studies on the mechanism of the TMS procedure and application of this reaction to the preparation of 7-glycosyladenines of biological interest are now under way in our laboratory.

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13 Transglycosylation using 4 was further studied. Thus, treatment of 4 with $SnCl_4$ or $HgCl_2$ in refluxing acetonitrile for a week gave rise to the 1- and 3-ribosyl derivatives (6 and 5, respectively) in the ratio 2:3, whereas more than 85% yield of 5 as well as a small amount of 6 were formed in refluxing toluene, suggesting that the 1-isomer (6) was thermodynamically stabilized to more extent in acetonitrile than in toluene.

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