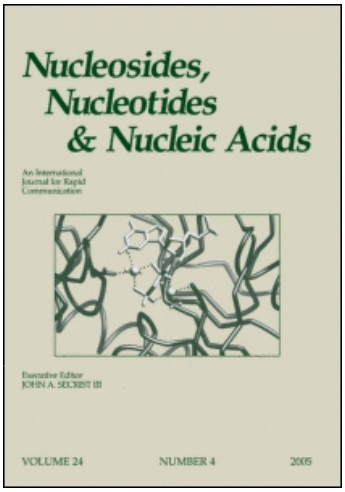

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ACETYLATION OF NUCLEOSIDES BY ACETYLSALICYLIC ACID (ASPIRIN)[1]

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Abstract: Acetylsalicylic acid (aspirin) reacted with adenosine, cytidine, guanosine and their 2'-deoxynucleosides to give acetylated nucleosides. Cytidine and 2'-deoxycytidine gave N^4-acetylated nucleosides in nitromethane while in pyridine fully acetylated products were obtained. Adenosine and 2'-deoxyadenosine also gave fully acetylated products. However, guanosine and 2'-deoxyguanosine gave 2',3',5'-tri-O-acetylribosyl and 3',5'-di-O-acetyl-2'-deoxyribosyl nucleosides, respectively. The corresponding aglycons also gave acetylated heterocycles under various conditions.

Aspirin is a well known but poorly understood teratogen in animals[2,3] and non-human primates.[4] Despite the fact that aspirin is the most frequently used drug in human pregnancy[5,6], the data are equivocal with respect to its teratogenic potential to human.[7]

Inhibition of prostaglandin synthesis by aspirin as an antiinflammatory agent is well documented.[8] Over the several years the beneficial action of aspirin has focused on its potential preventive effects against subsequent myocardial infarction after the initial episode.[9] More recently, however, aspirin has drawn attention as a possible causative agent in Reye's Syndrome.[10]

Chemically aspirin is a labile compound. Aspirin has been known to acetylate biopolymers such as serum proteins, enzymes, RNA, DNA, etc.[11,12]

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Using whole-body autoradiography and liquid scintillation counting techniques, Rainsford and co-workers[12] found that the acetyl group of ^{3}H-or ^{14}C-acetyl labelled aspirin became bounded to a wide variety of proteins, glycoproteins and lipids of the glandular and non-glandular region of the stomach, kidney, liver and to a lesser extent bone marrow, i.e. organs in which side effects are frequently encountered. Therefore, they suggested that the acetylation of biomolecules may be a major factor in the development of side-effects in these organs and in addition to acetylation of prostaglandin synthetase, the acetylation of enzymes and other biomolecules may have a much wider bearing on the biochemical changes underlying the development of these side-effects. However, the biological implications of its chemical lability has not been studied extensively relative to the molecular mechanism of teratogenesis and other untoward effects such as hypersensitivity, Reye's Syndrome, etc. This report deals with preliminary chemical model reactions of aspirin to determine the reactivity toward various nucleosides in order to understand the molecular mechanism of the side effects of aspirin. Additionally, it is of interest to determine whether the acetylating capability of aspirin can be utilized as a general acetylating agent for nucleosides.

Thus, various ribo- and 2'-deoxyribo-nucleosides as well as their corresponding heterocyclic moieties were reacted with an excess (5 to 6 molar equivalent) acetylsalicylic acid under various conditions (Table I). Cytidine and 2'-deoxycytidine gave selectively N^4-acylated nucleosides 2 and 4 , respectively, in nitromethane. Excess reagent and by-product, salicylic acid could be removed by triturating with ether after evaporation of the solvent used for the reaction. In the case of 2'-deoxycytidine, reaction temperature should be maintained below 85°C in order to avoid deglycosylation. In pyridine, however, both cytidine and 2'-deoxycytidine gave fully acetylated products 3 and 5 , respectively. This reaction, in general, gave cleaner product than in nitromethane. Cytosine also reacted with an excess of aspirin in pyridine or DMF to give N^4-acetylcytosine (1) in good yield. Both adenosine and 2'-deoxyadenosine gave fully acetylated nucleosides 7 and 8 , respectively. However, in the case of 2'-deoxyadenosine the reaction temperature should be maintained below 75°C due to the instability of the deoxynu-

TABLE I - Reaction of Nucleosides with Acetylsalicylic Acid (aspirin).

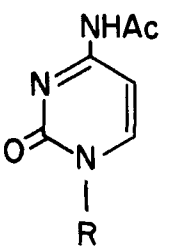
Starting Materials	Reaction Conditions(°C)	Products[a]	Isolated Yields	References
Cytosine	DMF or pyridine 110-20 (1 h)	1 R = H	88	15
Cytidine	CH_3NO_2 95-100 (4 h)	2 R = ribosyl	69	13
	Pyridine 85-90 (15 h)	3 R = 2',3',5'-tri-O-acetylribosyl	72	16,17
2'-deoxy-cytidine	CH_3NO_2 80-85 (15 h)	4 R = 2'-deoxy-ribosyl	24	14
	Pyridine 85-90 (15 h)	5 R = 2'-deoxy-3',5'-di-O-acetylribosyl	61	18
Adenine	Pyridine or DMA 100 (2 h)	6 R = H	86	19
Adenosine	Pyridine 100 (15 h)	7 R = 2',3',5'-tri-O-acetyl-ribosyl	81	20
2'-deoxy-adenosine	Pyridine (20 h)	8 R = 2'-deoxy-3',5'-di-O-acetylribosyl	72	21
Guanine	DMA 150-160 (15 h)	9 R_1 = H, R_2 = Ac	84	22
Guanosine	DMA-pyridine 95-100 (15 h)	10 R_1 = 2',3',5'-tri-O-acetylribosyl, R_2 = H	64	23
2'-deoxy-guanosine	Pyridine (15 h) 75	11 R_1 = 2'-deoxy-3',5'-di-O-acetylribosyl, R = H	30	24

[a]Identification of products has been made on the basis of spectroscopic and physical data in comparison with the authentic samples prepared by the literature methods shown or purchased (Compound 7 and 10)

cleoside. Adenine also reacted with aspirin to give a high yield of N^6-acetyladenine (6). Although guanosine did not react with the reagent in DMF or pyridine, probably due to its poor solubility in the solvents, it reacted readily in a mixture of pyridine-DMF (2:1.5) to give an O-acylated product 10. In order to prevent deglycosylation, 2'-deoxyguanosine was reacted with aspirin below 75°C. However, guanine afforded the N^2-acetylated product 9 after treatment with aspirin in dimethylacetamide (DMA) at high temperature (150-160°C).

All the naturally occurring nucleosides as well as their corresponding aglycons reacted with acetylsalicylic acid under various conditions. Thus, acetylsalicylic acid may serve as a general acetylating agent and this method can be used as an alternative to the known method of acetylation (acetic anhydride/pyridine or acetic anhydride/MeOH or EtOH) of nuleosides although it requires more stringent conditions.

Although the biological implications of this model chemical reaction remain to be the future subject of study, it is possible to speculate that the direct acylating ability might be related to the teratogenesis and other untoward effects of aspirin. Further chemical and biological studies toward the understanding of molecular mechanism of aspirin are warranted.



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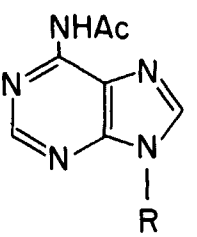

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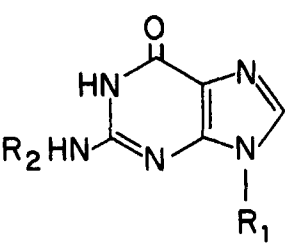

9-11

EXPERIMENTAL

General procedure for acetylation (see TABLE I for the individual reaction condition).

A mixture of nucleoside or heterocyclic base (0.002 mole) and acetylsalicylic acid (0.01 to 0.012 mole) in a solvent or a mixture of

solvents (5-10 ml) was heated at the designated temperature range until all the starting material disappeared, which was monitored by tlc (chloroform/methanol (10:1) for 3, 5, 7, 8, or isopropanol/ethylacetate/H_2O (3/9/0.5) for 1, 2, 4, 6, 9-11). After heating the solvent was evacuated in vacuo to syrup which was triturated with ether or acetone and then decanted the solvent. This was repeated several times until an excess acetylsalicylic acid and salicylic acid were removed. In the case of cytidine and 2'-deoxycytidine in nitromethane, short silica gel columns with the same solvent systems for tlc were used for purification of the products.

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