

## Approaches for the Synthesis of D-Arabinosyl Nucleosides and their Derivatives

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### Introduction

The D-Arabinosyl nucleosides (spongocnucleosides) were first isolated by Werner Bergman from a sea sponge "*Cryptotetha crypta*" in shallow waters of Florida<sup>1</sup>, and later from other sea shores. Bergman had sought the presence of these arabinonucleosides in 16 other different species of sponge, but only *C. crypta* was found to contain arabinosyl nucleosides. They are also termed as spongocnucleosides due to their isolation and extraction from sea sponge. They have an arabinose sugar instead of ribose.

Bergman extracted the sponge from acetone in a Soxhlet apparatus; crystalline material was isolated from boiling solvent and arabinosylthymine (I, R'=H, R=CH<sub>3</sub>) was obtained on recrystallization. It was observed that the nucleoside did not complex with borate, indicating the absence of a cis diol system<sup>2</sup>. Reduction of the nucleoside with sodium in a mixture of dry liquid ammonia in ethanol and hydrolysis of the reduced pyrimidine nucleoside indicated the presence of D-arabinose as the sole carbohydrate constituent by paper chromatography in different solvent systems. The spongocnucleoside proved to be 1-β-D-arabinofuranosylthymine (I, R'=H, R=CH<sub>3</sub>). Later spongouridine was isolated from sea sponge and was identified as 1-β-D-arabinofuranosyluracil (I, R,R'=H). 1-β-D-Arabinofuranosylcytosine (II, R,R', R''=H) has not yet been isolated as a natural constituent of a sponge, but it is entirely a product of chemical synthesis.

### Chemical Synthesis of D-Arabinosyl Nucleosides

D-Arabinosyl nucleosides can be synthesized chemically by two different routes:-

(i) Condensation of protected 1-halo sugars with substituted pyrimidines. However this approach leads to a problem that the condensation product can be an α-nucleoside instead of β-anomer<sup>3</sup>. Vörbruggen and co-workers in Germany have made an improvement in the condensation method and have shown that if the carbonyl groups are protected by silylation prior to condensation (as the 2,4-bis silyl derivative of the pyrimidine) then the condensation products were obtained in very good yields<sup>4</sup>.

(ii) Nucleoside Transformation: This method is more commonly applied than the condensation method as the problem of α- and β-anomers does not arise. The normal nucleoside (With D-ribose sugar) is subjected to a series of chemical changes, which mostly involve the prior protection of 3,5'-hydroxy groups and then introducing a suitable leaving group at position 2' of the ribose moiety (Scheme 1). The product would undergo 2,2'-anhydronucleoside formation (under mild basic conditions) yielding the corresponding D-arabinosyl nucleoside. This approach was initially used by Todd and co-workers<sup>5</sup>, who used tosyl group as a leaving group at 2' position of the ribose unit (XVII). Methanesulphonyl group was used by Fox and co-workers<sup>6</sup> for the synthesis of arabinosylthymine (I, R'=CH<sub>3</sub>) and 2,4-dinitrobenzoyl group has been used in our laboratory for the synthesis of arabinosyl cytosine<sup>7</sup> (Scheme 2).

Another convenient method for these arabinosyl nucleosides *via* nucleoside transformation involves the preparation of the 2',3'-cyclic phosphates<sup>8</sup> or 2',3'-cyclic carbonates<sup>9</sup> of the nucleosides and opening of the ring would then afford, the corresponding arabinosyl nucleoside. 2',3'-epoxide formation can also be used to prepare the arabinosyl nucleosides, but the experimental conditions have to be carefully controlled as this approach gives a mixture of lyxo and arabino nucleosides.

### Synthesis of D-Arabinosyl Pyrimidine Nucleoside & their Derivatives

D-Arabinosylthymine (I, R'=H ; R=CH<sub>3</sub>) was one of the earliest pyrimidine nucleosides synthesized *via* nucleoside transformation by Fox and co-workers<sup>6</sup>, methanesulphonyl group being used as a leaving group at position 2' of the ribose moiety. They have also reported the synthesis of D-arabinosyluracil (I, R,R'=H) from 5-O-trityluridine with thiocarbonyldiimidazole in refluxing pyridine<sup>10</sup>.

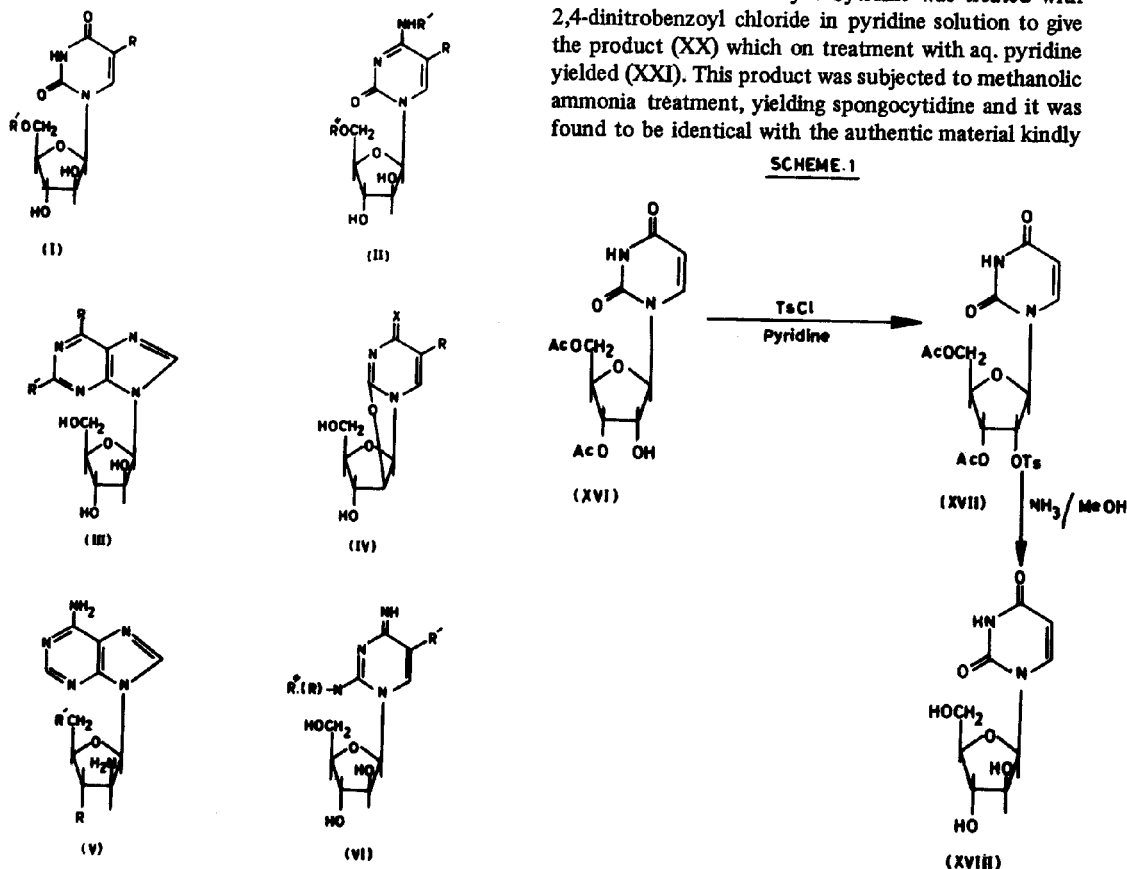
D-Arabinosylcytosine (II, R,R', R''=H) is the most important among all the arabinosyl nucleosides due to its importance in chemotherapy. It has been found to be effective against *Ehrlich* carcinoma and prolongs the

survival of mice infected with L-1210 leukemia<sup>11</sup>. It antagonizes the action of 2-deoxycytidine. The mechanism of lethal action of D-arabinosylcytosine and D-arabosyladenine (III, R'=H; R=NH<sub>2</sub>) in animal cells and viruses has been reviewed by Samuel Cohen. Due to its importance in chemotherapy several groups of workers have made different approaches to synthesize this compound and also to prepare its different derivatives with a view to study their biological activity. It was initially synthesized by Walwick<sup>13</sup> by treating cytidine (XIX) with polyphosphoric acid to yield 3,5-diphosphate of 2,2'-anhydrocytidine. It was subsequently dephosphorylated and hydrolyzed to give D-arabosylcytosine. This method was further improved by Dekkar<sup>14</sup>. This approach was also adopted by Cohen to prepare D-arabosyluracil. A simple one step synthesis of arabosylcytosine was achieved by Beranek in 1978, by treating cytidine with diphenyl carbonate in DMF; the separation of cytidine and arabosyl cytidine

was brought about by borate formation on an ion exchange resin<sup>9</sup>. In 1966, arabosylcytosine synthesis via N<sup>4</sup>, 2',3',5',-di-O-acetyl 2,2'-anhydronucleoside intermediate was studied<sup>16</sup>. Another convenient route for arabosylcytosine was studied by T.Kanai and co-workers in Japan; they treated 2',3'-lyxo-β-D-arabinofuranosylcytosine under mild basic conditions and obtained spongocytidine in satisfactory yield. A group of Chinese workers<sup>17</sup> in 1974 reported the synthesis of this compound via 2,2'-anhydronucleoside formation by treating cytidine with phosphorus oxychloride and ammonia<sup>17</sup>. Hessler<sup>18</sup>, in 1976, reported the synthesis of this compound by condensation of cis-β-trimethylammonium acrylonitrile tosylate with 2-amino β-D-arabinofurano (1':2', 4:5) -O-oxazoline, resulting in the formation of the desired cyanovinyl adduct, which was converted into arabosylcytosine.

A synthetic route for spongocytidine has also been studied in our laboratory<sup>7</sup>. Cytidine was treated with 2,4-dinitrobenzoyl chloride in pyridine solution to give the product (XX) which on treatment with aq. pyridine yielded (XXI). This product was subjected to methanolic ammonia treatment, yielding spongocytidine and it was found to be identical with the authentic material kindly

SCHEME. 1



supplied to us by Ichino<sup>19</sup>, who prepared this compound by the action of cytidine with partially hydrolyzed  $\text{POCl}_3/\text{H}_2\text{O}$  followed by alkaline hydrolysis, yielding (XXII) in 62.9% yield. A year later Ichino<sup>20</sup> stated another route for arabinosylcytosine synthesis. It was observed that when cytidine (XIX) was treated with chloromethylene dimethylammonium chloride at room temperature for 5 hours the reaction mixture after work up yielded arabinosylcytosine in 70% yield.

The interconversion of arabinosyl nucleosides has also been achieved. D-arabinsyluracil was converted into D-arabinsylcytosine by Hunter<sup>21</sup>, 2',3',5'-Tri-O-acetyl-D-arabinsyluracil (XXIII)– was thiated at position 4 of uracil by  $\text{P}_2\text{S}_5$  in pyridine yielding the corresponding 4-thio derivative (XXIV). The later on treatment with methanolic ammonia gave spongocytidine. Another approach was adopted by Kaneko and Shimizu<sup>22</sup> by halogenation of 2',3',5'-tri-O-benzoyl chloride with *N,N*-diethylaniline and  $\text{POCl}_3$  in ethyl acetate; the product was dissolved in chloroform and subsequently treated with ammonia with cooling until the volume was doubled. It was then debenzoylated to give arabinosyl cytosine (II,  $\text{R}, \text{R}', \text{R}''=\text{H}$ ) in good yield. Some important properties of these arabinosyl nucleosides are given in Table 1.

Since arabinosylcytosine is of considerable importance in chemotherapy, therefore the synthesis of its derivatives have attracted the attention of different groups of workers with a view to studying their biological activity.

Nagev and West<sup>23</sup> have prepared the arabinosylcytosine conjugates of cortisone and cortisol. 5' (cortisol 21-phosphoryl) arabinosylcytosine were prepared by treating *N*<sup>4</sup>,2',3',-tri-O-acetyl arabinosylcytosine-5'-phosphate with cortisone and cortisol in DCC at room temperature, followed by 2*N* methanolic ammonia treatment. Both the compounds increased the survival time by 240-280% in L-1210 leukemia implanted mice at 5 doses of 50 mg./kg., which was significantly higher when compared to the activity of arabinosylcytosine (at 5 doses of 25 mg /day and 50 mg /kg. increased the survival time by 127% and 110% respectively).

The hydrochloride salt of 2,2'-anhydroarabinosylcytosine (IV;  $\text{R}=\text{H}; \text{X}=\text{NH}\cdot\text{HCl}$ ) was injected (200mg./kg.) to L-1210 leukemia in mice. It was observed that

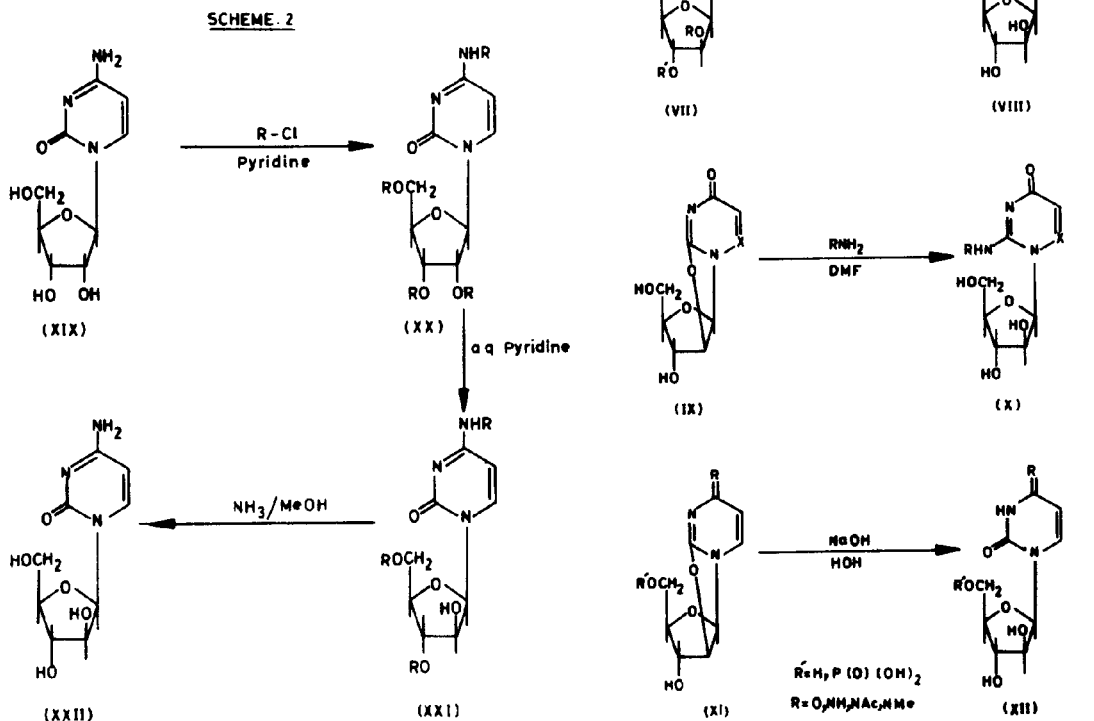


Table 1. Some Properties of D-Arabinosyl Nucleosides

S. No.	Compound	M.P. (°C)	Specific Rotation		Spectra in acid			Spectra in Alkali		
			$[\alpha]_R$	Temp. (°C)	$\lambda_{\max.}$ , $\mu$	$\Sigma_{\max.}$	pH	$\lambda_{\max.}$ , $\mu$	$\Sigma_{\max.}$	pH
1.	Spongouridine	220-221	+131	20	262.5	10,500	6	—	—	—
2.	Spongothymidine	246-247	+ 93	24	268.5	10,000	1	268.5	7,870	12
3.	Spongocytidine	212-213	+158	38	279	13,400	2	273	9,500	12
4.	Spongoadenosine	257-258	-5	27	257.5	12,700	1	259	14,000	13
5.	Spongoguanosine	300	+28	24	256	12,600	1	256	11,600	13

the compound induced a 46% increase in the life span of mice after 24 hours of tumor inoculation<sup>24</sup>.

Kondo and co-workers<sup>25</sup> have recently synthesized an active antiviral agent; the product was the hydrochloride salt of arabinosylcytosine with N-benzylamino group at 2-position of the pyrimidine ring.

In order to study the physiological activity, Kodama and his collaborators<sup>26</sup> prepared N<sup>4</sup>-dialkylamino-methylene arabinosylcytosine (VIII); it was prepared by the action of arabinosylcytosine with R<sub>2</sub>N CH(OR)<sub>2</sub> in DMF at room temperature. A series of N<sup>4</sup>-acyl D-arabinosylcytosine derivatives were synthesized by a group of Japanese workers. Twelve different compounds were synthesized (II, R,R'' =CH<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>.CO- where n=7,9,11,13,15,17,19,21,23,25,27,29). All these compounds were prepared in 90-99% yield by treating the arabinosylcytosine with [Me (CH<sub>2</sub>)<sub>n</sub> CO]<sub>2</sub> O, at 80°C. Treatment of mice containing implanted leukemia tumor with 50 mg of R= R=CH<sub>3</sub> (CH<sub>2</sub>)<sub>7</sub>.CO- and oleoyl showed a 190 and 300 survival rate (in mice) of these two compounds and on leave beans gave 100% bean mite larva mortality<sup>27</sup>. An interesting piece of work was carried out by Wetchner and Kelly<sup>28</sup> who prepared a series of derivatives of arabinosylcytosine (II, R'=H, CCl<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>C<sub>2</sub>-; R=H; and R''=H, Ph<sub>3</sub>C, Me<sub>3</sub>-CCO, BZ, AC, tosyl, octanyl and cyclohexylcarbonyl.) Most of these compounds were found to possess immunosuppressant activity and were found useful in the treatment of rheumatoid arthritis and leukemia. Various other derivatives in which the arabinose sugar has been modified were also prepared by different groups of workers. O-Alkylation of the arabinose sugar in spongocytidine was carried out with dimethyl sulphate/diethylsulphate in KOH (VII, R,R', R=H, Me, Et.) followed by basic ion exchange column. All the possible O-Et and O-Me derivatives of arabinosylcytosine were obtained<sup>29</sup>. These derivatives were converted into the O-alkyl derivatives of arabinosyluracil by deamination in IM acetic acid. 2'-Halo 2'-deoxy-arabinosylcytosine derivatives were also prepared and characterized<sup>30,31</sup>.

Holly in Czechoslovakia prepared the 5'-O-carboxy-

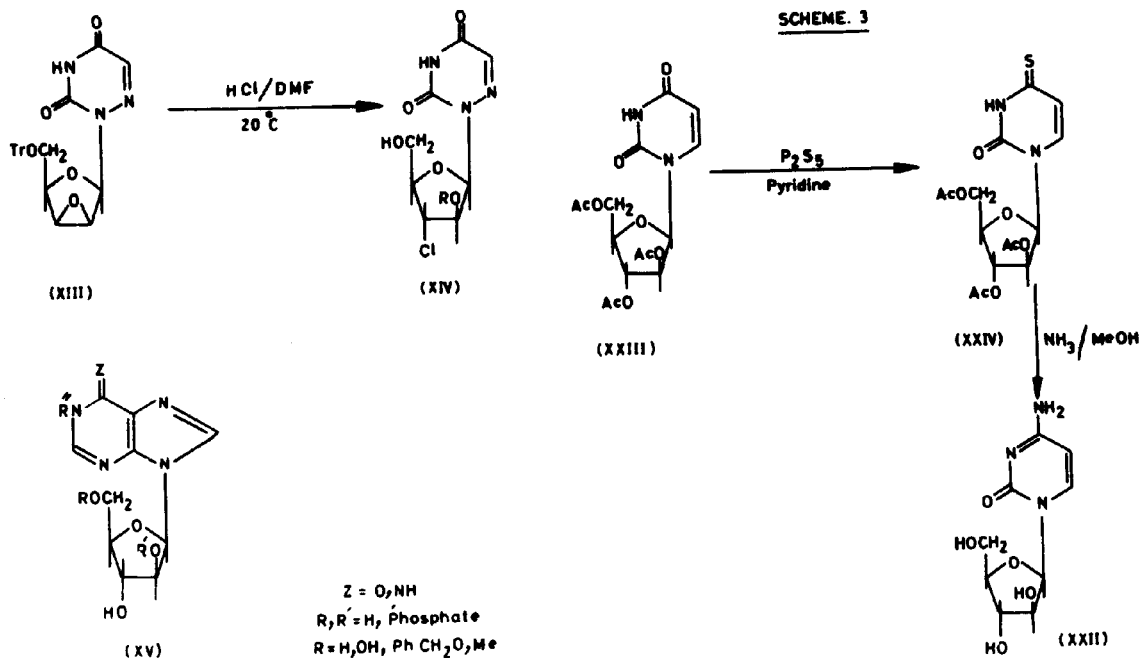
methyl arabinosylcytosine<sup>32</sup> and the compound was found to possess immunosuppressant activity. 5-Dithiocarbamate derivative of arabinosylcytosine were prepared and characterized (II; R,R'=H; R''=S(S). NCR<sub>2</sub>) and was found to possess antitumor properties<sup>35</sup>.

A research group working in Japan, substituted the N<sup>4</sup>-amino group of cytosine (II R'', R=H, and R''=stearyl, caproyl, valeryl and propionyl) These compounds were found to be anticarcinogen<sup>34</sup>. The same team a year later, prepared another series of compounds (II, R,R''=H, R''=Ac, butryl, succinyl, stearyl, arachidonyl). Arabinosylcytosine was treated with the corresponding acid anhydride in aq. dioxane at 60-80°C. Compound II (R=butryl) showed 100% mortality against mite larva on green beans and gave a survival rate of 180% at a dose of 50 mg/kg for mice infected with leukemia tumor cells<sup>35</sup>. Eleven different arabinosylcytosine esters were prepared by Wetcher and Warner (VII, R', R', R''=H and/or palmitoyl, stearyl, PhCO, CH<sub>3</sub>COO), these types of compounds were found to be useful as immunosuppressant, antineoplastic and anti-leukemic drugs<sup>36</sup>.

The disubstituted cytosine bases at C-5 and at C-2 were prepared by Ichino and co-workers<sup>37</sup> (VI, R'-H, Cl, Br, I; R,R''= and C<sub>1</sub>-C<sub>5</sub> alkyl). They also reported the synthesis of 5-amino and 5-hydroxy cytosine derivatives with arabinose sugar. These compounds were prepared from the corresponding 2', 3'-epoxides.

In 1973, Suzuki et al<sup>38</sup> prepared the N-substituted arabinosyl nucleosides from the corresponding 2,2'-anhydronucleosides by ring cleavage with aq. sodium hydroxide (XI and XII). The corresponding nucleotides with N-acetyl and N-methyl groups were also prepared. Some new antitumor agents with a long carbon chain at N<sup>4</sup>-position of arabinosylcytosine were synthesized (II, R',R''=H; R''=stearyl, palmitoyl, oleoyl). Different compounds were prepared by treating arabinosylcytosine with fatty acids reactive derivative e.g. thiolstearic acid or fatty acids in the presence of a condensing agent i.e. Bu<sub>3</sub>P-N-methylmorpholine-CBr<sub>4</sub><sup>39</sup>

Marsh and co workers<sup>40</sup> have investigated the chem-



otherapeutic properties of 5'-phosphate ester of arabinosylcytosine. The desired compound (II,  $R, R' = H$ ;  $R'' = \text{phosphate}$ ) was prepared by the action of cytidine with  $POCl_3$  in  $(EtO)_3PO$  at  $0^\circ C$ . The reaction mixture was adjusted to pH2, and extracted with dichloromethane. The aq. phase was separated, dried and crystals of arabinosylcytosine-5'-phosphate were obtained. The compound was found to be an antiviral agent. Arabinosyl 6-azacytosine was found to be virucide and neoplasm inhibitor in doses of 50-500 mg/kg of the body weight<sup>41</sup>. Arabinosyl isocytosine ( $X, X = CH$ ) and arabinosyl azaisocytosine were prepared and characterized ( $X, R = Bu, \text{alkyl}, PhCH_2, \text{cyclohexyl}$  and  $X = N$ ). Some of these compounds were found to possess distinct antiviral properties. In 1973, Nagyvary<sup>42</sup> stated the conversion of cytidylic acid into arabinosylcytosine 3'-phosphate. The triethylammonium salt of 5'-O- $N^4$ -diacetylcytidine 2',3'-cyclic phosphate with an activating group (toluene-p-sulphonyl chloride) in dioxan (with tert-butylamine) yielded 5'-O- $N^4$ -diacetyl arabinosylcytosine 3-phosphate, which was deacetylated with methanolic ammonia.

Arabinosyluracil ( $I, R, R' = H$ ) was not found to be a

biologically active compound; however it was synthesized initially by Brown & Todd<sup>5</sup>, by treating 3',5'-di-O-acetyl 2'-O-tosyluridine (XVII) under basic conditions, where upon the compound underwent cyclization i.e. 2,2'-anhydronucleoside formation, yielding spongouridine (XVIII). It was observed by Fox and Wempen<sup>43</sup> that uridine on treatment with thiocarbonyldimidazole in refluxing toluene for 45 minutes, yielded 2,2'-anhydrouridine (IV,  $R = H$ ;  $X = O$ ) via 2',3'-thionocarbonate as the intermediate. Treatment of the latter with dilute alkali at room temperature yielded arabinosyluracil ( $I, R, R' = H$ ); In contrast to arabinosyluracil, the 5-fluoro derivative ( $I, R = H; R' = F$ ) has shown distinct biological activity; it has been found to be as good a chemotherapeutic agent as 5-fluoro 2'-deoxyuridine in the treatment of leukemia, but the dosage has to be increased four times<sup>12</sup>. This compound was prepared from 5-flourouridine via the formation of 5'-O-trityl-2'-O-tosyl derivative. It underwent cyclization under mild basic conditions yielding 5-fluoro arabinosyluracil. Ozaki further extended this work and stated that when 5-fluoro spongouridine ( $I, R' = H; R = F$ ) was heated with diphenyl carbonate in DMF with little sodium bicarbonate it afforded 5-fluoro 2,2'-anhydrouridine<sup>44</sup> ( $IV; R = F; X = O$ ).

Halogens have also been introduced to the sugar moiety of arabinosyluracil by 2',3'-epoxide formation. In this connection 3'-fluoro 3'-deoxyarabinosyluracil was prepared from the 2',3'-epoxy precursor with HF in dioxan. The quantity of the arabino nucleoside formed was double that of the lyxo isomer<sup>45</sup>. In addition to fluoro, the chloro derivatives were also prepared with azauracil base. 3'-Chloro 3'-deoxy-arabinosyl 6-azauracil (XIV) was prepared in an analogous way from the corresponding 2',3'-epoxy nucleoside<sup>46</sup> with 5'-O-trityl group (XIII). Hunter has reported the remaining 5-bromo-, 5-chloro-, and 5-iodo derivatives of arabinosyluracil (I; R'=H; R=Cl, Br, I) by direct halogenation of arabinosyluracil<sup>47</sup>.

In order to study the antiviral activity and anti cell growth, Mineo and Nakayama<sup>48</sup> prepared the 5-methyl-, 5-propyl and 5-butyl arabinosyluracil (I; R'=H; R=Me, Et, Pr). 5-Ethyl arabinosyluracil was also prepared separately by Sugar and co-workers<sup>49</sup> by condensation method i.e. condensation of sugar halide with 5-ethyluracil; the compound showed marked activity against primary rabbit kidney and human fibroblast cell system but was totally ineffective against vaccinia viruses.

Ueda et al<sup>50</sup> introduced the arabinosyl S-alkylthiouracil derivatives (I; R'=H; R=SEt, SPr, SMe) from uridine. One of the compounds (I; R'=H; R=SMe) showed distinct activity against the herpes simplex virus. Among the other investigated derivatives of spongouridine include the 3'-amino 3'-deoxy arabinosyl 6-azauracil<sup>51</sup>, arabinosyl 4-thiouracil<sup>52</sup> and arabinosyluracil 5'-phosphate (XII; R=O; R'=phosphate).

#### Arabinosyl Purine Nucleosides & their Derivatives

Arabinosyladenine (III; R'=R=NH<sub>2</sub>) has been found to be effective against ascite tumor cells<sup>53</sup>. It inhibits the incorporation of alanine and lysine in the protein synthesis of ascite cells in tumor bearing mice. It was initially by Lee and Benitz<sup>54</sup> in 1960 by the rearrangement of 9-β-D-xylofuranosyladenine, producing 2',3'-epoxide, which cleaved to form 9-β-D-arabinofuranosyladenine (III; R'=H; R=NH<sub>2</sub>). Bergman attempted the synthesis of this compound by condensation method i.e. protected D-arabinose sugar was condensed with substituted purine, but led to the formation of α-nucleoside instead of β-anomer. Another attempt was made by Fletcher and Baker<sup>55</sup> to synthesize this compound by condensation. 2',3',5'-Tri-O-benzoyl/arabinofuranosyl-chloride was condensed with N-benzoyl adenine giving the condensation product in 46% yield, the debenzoylation resulted in the formation of the β-nucleoside as the major product with very little α-anomer being formed. Ikehara and co-workers<sup>56</sup> prepared this compound by the ring opening of 8,2'-anhydro 8-oxo 9-β-D-arabinosyladenine. This approach was further extended for

the preparation of the corresponding 3',5'-phosphate of arabinosyladenine<sup>57</sup>.

In 1977, its synthesis via 8,2'-cyclonucleoside formation was also studied<sup>58</sup>. It was observed that when 8,2'-cycloadenosine was treated with hydrazine, it yielded the corresponding hydrazine derivative (III; R=NH<sub>2</sub>, R'=NH.NH<sub>2</sub>) which on Hg<sub>2</sub>O<sub>3</sub> oxidation gave 93.5% of arabinosyl adenine (III; R'=H; R=NH<sub>2</sub>). A year later this approach was modified by Ikehara<sup>59</sup> who cleaved 8,2'-anhydroadenine by H<sub>2</sub>S and then desulfurized the product to give arabinosyladenine in good yield. They have also phosphorylated the arabinosyladenine at 5'-phosphate ester of arabinosyladenine was prepared by Mengel<sup>60</sup>. Arabinosyladenine was also synthesized by condensation method<sup>61</sup>; thioxazolide was condensed with 4-amino 6-chloro 5-nitropyrimidine in the presence of mercuric bromide and sodium hydride. The condensation product was subjected to a catalytic hydrogenation followed by desulphurization gave 9-β-D-arabinosylcytosine.

Various other derivatives of arabinosyladenine were prepared with a view to study their biological activity. 2'-Deoxy 2'-amino arabinosyladenine (R,R'=OH) was prepared by the hydrogenolysis of the corresponding azide or by ring cleavage of the aziridine<sup>62</sup>. Different disubstituted purine derivatives of arabinosyladenine were prepared. (III, R=NH<sub>2</sub>, SH, SMe, OH; and R'=NH<sub>2</sub>, OH) by Burroughs Wellcome Co. and five different compounds were found to possess distinct antiviral and immune response-suppressing activity<sup>63</sup>. Ranganathan and Larwood<sup>64</sup> introduced 2'-mercapto and 2'-amino derivatives of arabinosyladenine using different experimental conditions. It was observed that when adenosine was treated with acetic anhydride or (EtCO)<sub>2</sub> Co in pyridine solution, it yielded the respective O-acyl derivatives. These compounds were found to be virucide<sup>65</sup>. In 1974, Tolman and co-workers prepared 10 different nucleoside derivatives (XV) of arabinosyladenine and most of them were found to possess antiviral activity<sup>66</sup>. 2'-Deoxy-2'-amino derivatives of spongoadenosine and spongoguanosine were prepared by a group of Japanese workers<sup>67</sup> from the corresponding azide. The azide was obtained by nucleophilic substitution of tosyloxy group of 2'-O-tosyladenine and guanosine respectively. Their antitumor activity against Sarcoma-180 solid tumor and cytotoxic activity against He La-S<sub>3</sub> cells were determined. 9-β-D-Arabinofuranosyl 8-azaadenine was synthesized by cyclization of triazole as a precursor. It has a virus rating of 0.8 against herpes Simplex by method of Sidwell<sup>68</sup>.

Arabinosylguanaine (III; R=OH; R'=NH<sub>2</sub>) is not as effective biologically as arabinosyladenine is effective. It was initially synthesized by Reist and Goodman<sup>69</sup> via the conversion of D-xylosyladenine to arabinosyladenine. Ikehara synthesized this compound the same way as they had syn-

thesized arabinosyladenine via 8,2'-cyclonucleoside transformation. Ring cleavage by  $H_2S$  and reduction of the mercapto derivative yielded arabinosylguanine<sup>70</sup>.

2'-Azido 2'-deoxy and 2'-amino 2'-deoxy derivatives of arabinosylguanine were prepared by Bobek<sup>71</sup> and their biological activities have been examined.

### Conclusions

Arabinosyl nucleosides were initially isolated from a sea sponge and then synthesized chemically by different groups of workers. Among these arabinosylcytosine has been found to be most important as an antiviral and an antitumor agent. Different types of derivatives of these spongonucleosides have been prepared and characterized. A brief account of these derivatives has been described above. In some derivatives, the pyrimidine or purine base has been substituted by another group or atom while in other derivatives the hydroxygroups of the arabinose sugar have been replaced by other substituents. Some derivatives with modified base and sugar unit have also been synthesized. Several hundred of these arabinosyl nucleoside derivatives have been prepared and characterized. Some of these have been found to be biologically active compounds. Although compounds like 4-thiospongouridine and 5-fluoro-spongouridine have been synthesized but it will be interesting to synthesize compounds like 5-fluoro 2,4-dithiospongouridine or 5-iodo 2-thiospongocytidine or 5-bromo 2,4-dithiospongouridine. Although one cannot anticipate their biological actions but their activity in various tumor cells may prove to be promising.

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