بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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Zagazig University
Faculty of Science

Synthesis of some modified nucleosides

A Thesis
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Of
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The Index Content

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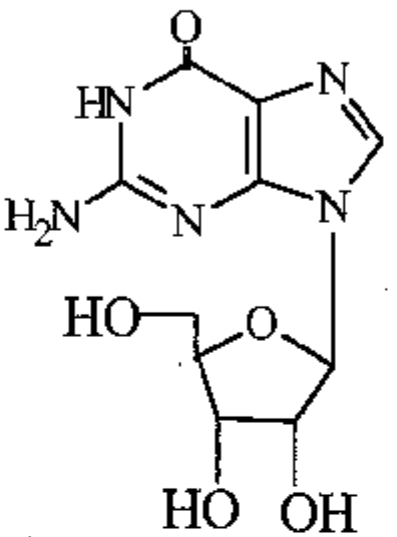
NOTE

Beside the work carried out in this thesis the candidate has attended post graduate courses in organic chemistry ,covering the following topics :

- Mechanism of organic chemistry reactions .
- Heterocyclic compounds .
- Microanalysis of organic compounds .
- Spectroscopy (U.V. ,I.R. ,N.M.R. ,M.S.) .
- Synthesis reactions .
- Free radical reactions .
- Carbohydrates .
- Deutsch language .

Summary

In this thesis some of the guanosine derivatives which are belong to the nucleosides and its structure consists of purine ring connected with sugar residue at position 9 .



The synthesized compounds include amino and amino acids residues ,also some of the synthesized derivatives had a biological activity since it had the ability to interfere into the DNA of the cell .Such that modified nucleosides are derivatives from the normal nucleosides which had an important role in biological activity especially the binding between tRNA and mRNA . They had an important role in protein biosynthesis. Some of these nucleosides used as antibiotics and can be prepared in laboratory which are resemble in the structure of the nucleosides which are present in DNA . Also it can be used as antitumor , antifungs , inhibitor for virus and used as therapy for both of rheumatic arthritis and increasing uric acid in blood .

8-Bromoguanosine was used as a suitable substrate and it was easily prepared by reacting guanosine with bromine in presence of water.Then it was used as a substrate to prepare many derivatives by nucleophillic substitution

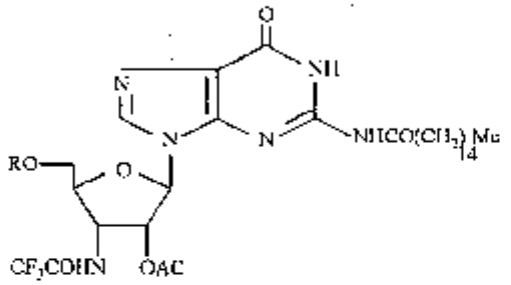
of bromine at position 8 of the purine ring with some aromatic and aliphatic amine and amino acids , such as diphenyl amine , ethylhydrazinoformate ,serine,proline ,glycine and others. It was prepared 4-thionederivative **96** by replacement of oxygen atom with sulfur at C-4. Also some other products such as dinucleoside derivative were prepared , and the reaction of uridine with the maleic anhydride was also described .Beside to that the cyclonuleoside derivative **93** was prepared . This compound has an important role in preparation of some other derivatives especially by functionalizing the reaction at position $5^{\backslash}$ of the ribose residue after protection the positions $2^{\backslash}$ and $3^{\backslash}$.

Finally, the structure of these derivatives was proved and elucidated by the physical and spectral analysis such as IR. ,NMR. ,UV., and MS ., and the micro analysis was also performed . Furthermore the biological evaluation of some of the synthesized derivatives was achieved by detection their effect on both of some of the gram positive and the gram negative bacteria.

Introduction

Visser *et al*[1] reported a synthesis of 3`- amino - 3`- deoxy guanosine 5`- triphosphate. Trimethylsilylation of $N^2$- palmitoylguanine followed by glycosylation with 1,2 - di-O-acetyl -O- benzoyl-3- trifluoroacetamido -3`- deoxy-D-ribofuranose gave nucleoside **1**. The DNA binding of 2-benzidine azo dyes, congored and direct blue 6 was compared in rat liver by **Kennely and co-workers[2]**, both dyes showed binding consequent upon metabolism to benzidine and in each case hydrolysis of the liver DNA yielded N- (Deoxy guanosine - 8- yl) -N`- acetylbenzidine. **Hering[3]** described a new preparation and properties of chloro - N, N-dialkylamino - 2,2,2- tirchloro ethoxy - and chloro-N,N-dialkylamino 2,2,2-trichloroethoxy and chloro-N,N,-dialkylamino2,2,2-trichloro -1,1-dimethylethoxyphosphines and thier deoxy nucleoside phosphitamidates. Deoxy nucleoside phosphitetamidates were building blocks for DNA synthesis. **Yankanagouda and co-workers[4],** showed that annelation of guanosine by reaction with methyl -N-cyanomethanimidate and sodium methoxide to give a tricyclic flourescent analog of adenosine. The tricyclic N- ribonucleoside **2** thus formed ressemble adenosine in its periphery and is an inhibitor of adenosine deaminase. 1-Ethyl-3-methyl isoguanosine **3** was prepared by **Hae Y. *et al*[5]**, on reacting of ribofuranosylimidazole with EtNCO in DMF and treating the product with NH_4 OH. **Gordeeva *et al*[6]**, reported a nucleotides labeled with tritium in the 5- position of the pyrimidine ring or the 8 position of the purine rings which prepared by direct bromination followed by catalytic dehalogenation with tritium gas.A series of 8-substituted guanosine and 2`-deoxyguanosine derivatives were tested as inducers for the differentiation of friend murine erythroleukemia cells in culture.[7]

Vasu *et al*[8] reported a reproducible and highly efficient synthesis of isoguanosine starting from guanosine and is described in which the key step is the photo induced hydration of 2 - iodoadenosine . **P.C chaeles *et al*[9]** reported a high temperature glycosylation of 3,6-dibromoallopurinol with1-O-acetly-2,3,5,tri-O- benzoyl - D ribofuranose in the presence of BF_3OEt_2 followed by ammonolysis to provide nucleoside **4**. Similar glycosylation of either3-bromo-4(5H)- oxopyrazolo (3,4-d) pyrimidine-6-ylmethylsulphoxide and subsequent ammonolysis also gave nucleoside **4**. Application of this glycosylation procedure to 6-(methylthio)-4(5H)-oxopyrazolo[3,4-d] pyrimidine -3- carboxamide gave the corresponding N-1 glycosyl derivative **5**. Consequently **Wang[10]** prepared isoguanosine by a one - potreaction involving a condensation of 5-amino-1- (β - D - ribofuranosyl) imidazole - 4 - carboxamide with benzoylisothiocyanate. Treatment of the resulting thiourea derivation with N, N- dicyclohexyl carbdiimide Furnished imidazole carbonitrile which was then annulated with ethanolic ammonia to afford isoguanaosine.The reaction of deoxy guanosine derivative **6** with $Cl(CH_2)_2OH$ in MeCN in the presence of DBU gave 70 % tricyclic nucleoside **7**, this reaction was prepared by **Maggio A. F. *et al*[11]** It is noteworthy that a method for the synthesis of O^6-alkylated guanosine and deoxygunosine phosphoramidates was described by **Schulz B.S[12]**. Furthermore **John M.*et al*[13]** investigated the reactions of the genotoxin 2 - bromoacroline with DNA, the aldehyde was treated with 2- deoxyguanosine to give isomeric adducts. **Chung and co- workers [14]** reported the reactions under mild conditions of deoxy gunaosine with the mutagenic, α, β- unsaturated carbonyl compounds. The structures of the adducts were characterized by U.V, proton NMR, and Mass spectra and compared to those formed from



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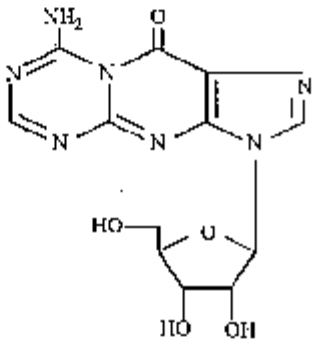

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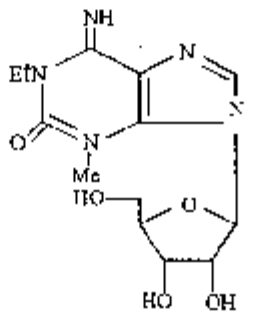

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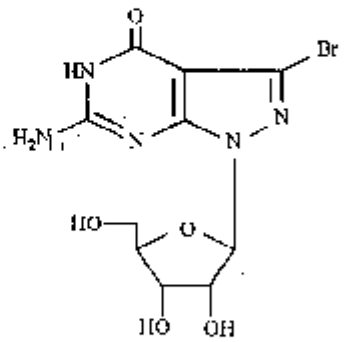

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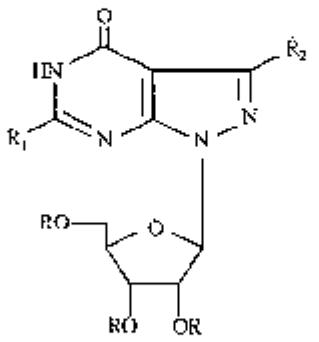
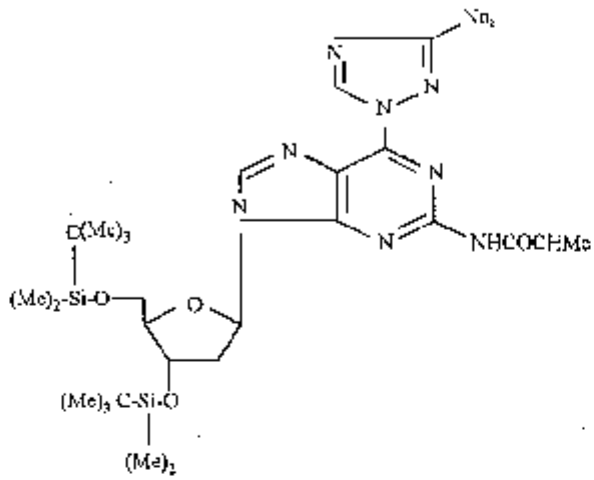


5 (R= Bz, R_1=SMe, R_2=$CONH_2$)



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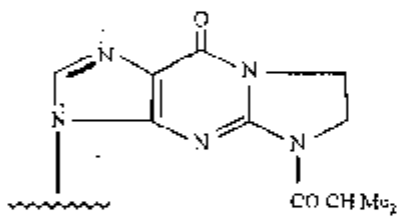

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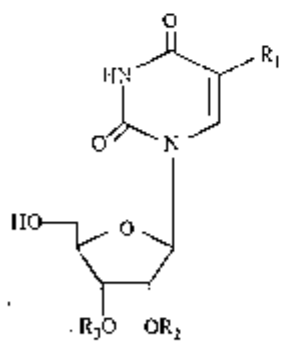

8 (R_1 = Br, R_2, R_3 = Me, C)

11 (R_1 = P (O) (OEt)$_2$, R_2 = R_3 = H)

acrolein and crotonaldehyde with deoxyguanosine. A potochemical reaction[15] of bromo nucleosides **8** , **9** and **10** with P (OEt)$_3$ in DMF and MeCN followed by deprotection gave the representively diethylphosphonate derivatives **11**, ***12*** and **13** .

K. Ganesh *et al* [16] showed that a trimethylsilyation of 2- chloro – 7- methylpurine-6,8-dione with hexamethyldisilazane followed by glycosylation with 1- O - acetyl- 2,3,5 - tri-O-benzoyl - D - ribofuranose gave 84.7 % nucleoside derivative **14**, which on treatment with NaOH/ MeOH gave 87% **15** which on amination with NH_3 gave 60% guanosine dertivative **16**. The adenosine and guanosine compounds[17] were deuterated at C (8) by refluxing in D_2O then back-exchange with boiling H_2O. **Anthony and co- workers**[18], suggested a practical synthesis of 7-iodo - 2`,3`-dideoxy -7- deazaguanosine **17** and 7- iodo - 2`,3`- dideoxy - 7- deazadenosine **18** from 2– (methylthio) -6- methoxy -7- deazapurine and 1-chloro-2-deoxy-3,5-di-O-p.toluoyl-α-D-erythro-pentofuranose and nucleoside **19**.On the other hand **Hroyoshi *et al***[19] prepared a nucleoside derivatives **20** as antiviral agents and deoxynucleoside derivatives **21** . **Yoshifumi *et al***[20] showed that treatment with N- halosuccinimides in AcOH, Nucleosides **22** undergo an intramolecular cyclization leading to the corresponding 5`-O,8-cyclopurine nucleosides **23** which strongly suggests that the initial attack of a halogenium ion occurs at the N (7) - position rather than the C (8) position in the purine ring under the conditions employed furtheremore, the synthesis of compound **24** from **25** by a five-step deoxygenation route was described[21]. Amino (deoxytoluoyl pentofuranosly) methoxy pyrazolopyrimidine **26**, the precursor of nucleoside **25**, was prepared by solid - liquid phase transfer glycosylation which gave higher yields (57%) than the liquid - liquid method.