THE PREPARATION OF SOME POTENTIALLY POLYMERIZABLE DERIVATIVES OF URACIL AND 5-FLUOROURACIL

by

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ABSTRACT

THE PREPARATION OF SOME POTENTIALLY POLYMERIZABLE DERIVATIVES OF URACIL AND 5-FLUOROURACIL

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Potentially polymerizable derivatives of uracil and 5-fluorouracil were prepared using various isocyanates. These derivatives may, at some later date, find applications as antineoplastic, polymeric drugs with reduced toxic side effects. The products prepared in the reactions were: 1) 5-fluoro-N^1(N-ethylcarbamoyl) uracil; 2) 5-fluoro-N^1(N-allylcarbamoyl) uracil; 3) 5-fluoro-N^1(N-isopropylidenecarbamoyl) uracil; 4) 5-fluoro-N^1(N-vinylcarbamoyl) uracil; 5) N^1(N-ethylcarbamoyl) uracil and 6) N^1(N-vinylcarbamoyl) uracil. These compounds were all soluble in boiling chloroform. The assigned structures are supported by elemental analyses and infrared spectroscopy. They all showed amide III bands at 1300 cm^{-1} and double bonds in the 895-945 cm^{-1} region as would be expected for these structures. These compounds are the first reported 5-fluorouracil monomers.

While 5-fluorouracil reacted readily in benzene with all of the isocyanates used in this study, uracil reacted readily only with vinyl isocyanate. It was also found that a catalyst, triethylamine, was necessary for the reaction to proceed in all cases. Several factors are believed to be

responsible for this phenomenon and these include: 1) solvent polarity; 2) pKa (acidity); 3) conjugation and 4) steric factors. The fact that uracil reacted well only with the vinyl isocyanate in the non polar solvent, benzene, while it reacted with ethyl isocyanate and other isocyanates in the more polar solvent, dimethylsulfoxide, supports the presence of solvent effects in this reaction. The fact that 5-fluorouracil, with the lower pKa and hence more acidic nature, reacts better with all isocyanates than does uracil supports the possibility of pKa effects. Since uracil reacts readily with vinyl isocyanate in the non polar solvent, benzene, conjugation appears to have an important effect on this reaction. The fact that isopropylidene isocyanate, which is also conjugated, did not react readily with uracil and also produced the lowest yield in reaction with 5-fluorouracil supports the hypothesis that steric factors are important in this reaction. The vinylcarbamoyl derivative of 5-fluorouracil appears to polymerize when treated with boiling chloroform. The material becomes insoluble and the IR spectrum showed the dissappearance of the peak at 1540 cm^{-1} which was presumed due to a carbon-carbon double bond. Further studies are necessary.

Isopropylidene isocyanate was prepared for the first time and its structure was substantiated by its IR spectrum and its chemical reactions.

Some polymerization reactions have been run on the isopropylidene isocyanate derivative of 5-fluorouracil and

the vinyl derivative of uracil, but no polymer properties were studied.

ACKNOWLEDGEMENTS

I would like to dedicate this thesis to my loving wife Georgiann without whose love and complaisant kinship this work would not have been completed and to my advisor, Dr. Charles Gebelein, whose knowledge and understanding was inspiring and whose patience proved invaluable in the completion of this paper. I would also like to thank Dr. Thomas Dobbelstein and Dr. Irwin Cohen for alloting me their valuable time to read and appraise this paper.

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CHAPTER I

GENERAL INTRODUCTION AND HISTORICAL

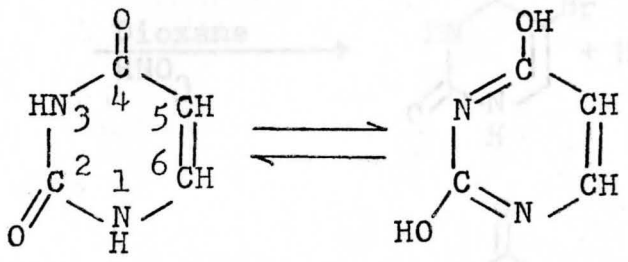
Polymers have been increasingly useful to society for many years from the viewpoint of cheaper, sturdier and safer materials. They have found applications in clothes, food wraps, dishes, etc. and the list will continue to grow as time goes on. However, the most important applications have been in the medical field where lives are at stake. Some of these biomedical uses are: 1) plasma expanders; 2) pseudoenzymes; 3) polyelectrolytes; 4) cardiac valves; 5) external organ prosthetics; 6) intravenous catheters; 7) false teeth; etc..

With todays increasing technology has come new variables which are spawning a great interest and concern in the causes and treatments of cancer. Surgery or radiological treatment, which have come to be recognized as the classical methods of cancer treatment, are localized treatments limited to the tumor mass and the immediate area. Because of this limitation cancer may remain undetected in other parts of the body, only to appear at a later time. In view of this disadvantage, the onset of chemotherapy came into being which affords the physician a much broader spectrum in the palliative treatment of metastatic disease. Many of these drugs are derivatives of the purines (eg. 6-mercaptopurine) or the

pyrimidines (eg. 5-fluorouracil) which interfere with the genetic duplication process. This work is concerned primarily with 5-fluorouracil.

Uracil (fig. 1) has been the subject of much research and study since its initial isolation in 1900 and was found to exist in two tautomeric forms with the lactam form being predominant at neutral pH. Uracil has been separated from many materials since that time, all of which contain polymeric ribonucleic acid (RNA), by a process of controlled hydrolysis. To date, the best synthetic routes to uracil are:[1]

1) Principal synthesis
   Formylacetic acid and urea in fuming sulfuric acid.
2) Treatment of 2-thiouracil with chloroacetic acid followed by acid hydrolysis.



Lactam Lactim

Figure 1. Structure of uracil demonstrating lactam-lactim tautomerization.

Being a pyrimidine (or more exactly a pyrimidinedione), uracil would be expected to undergo the same types of

reactions as would the parent compound, pyrimidine. Some of these reactions are summarized below and examples are shown in equations 1-7.[2]

1) Substitution Reactions

   a) substitution at C-5

   b) substitution at Nitrogen

2) Addition Reactions

   a) addition of hydrogen across 5,6 double bond.

   b) addition of oxygen at 5,6 double bond.

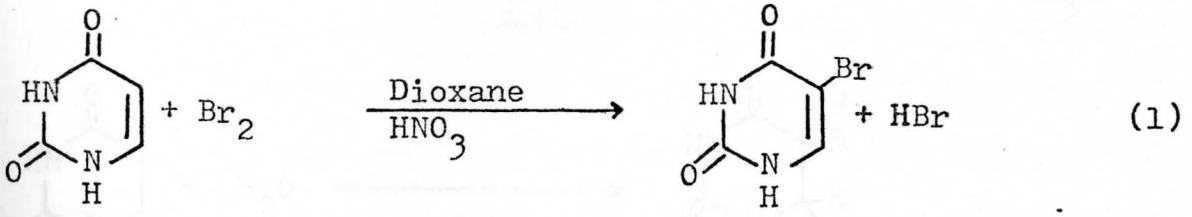
   c) addition of halogens

   d) addition of amides and carbodiimides.

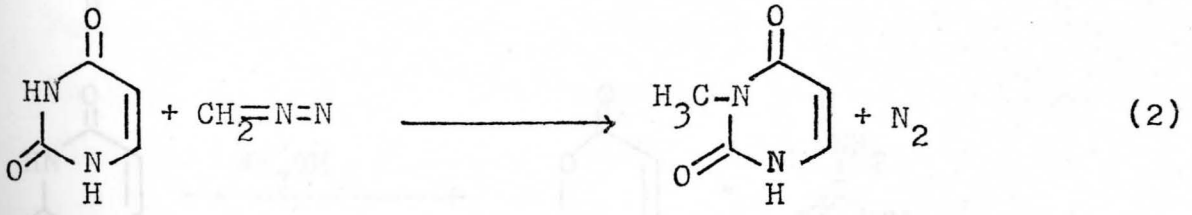
3) Photoaddition Reactions

4) Reactions of the Carbonyl Group

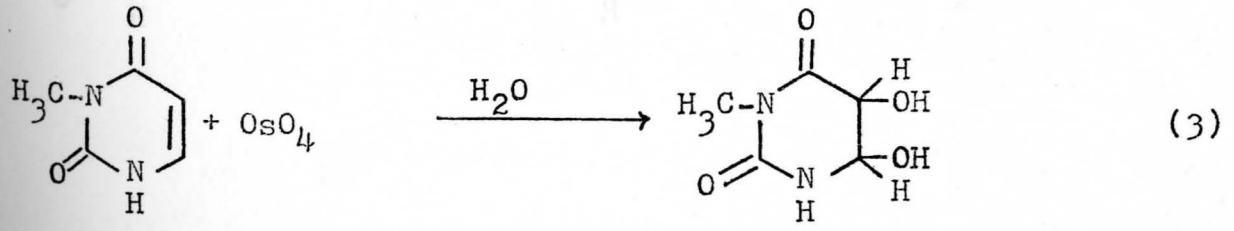
5) Ring Opening Reactions



(1)



(2)



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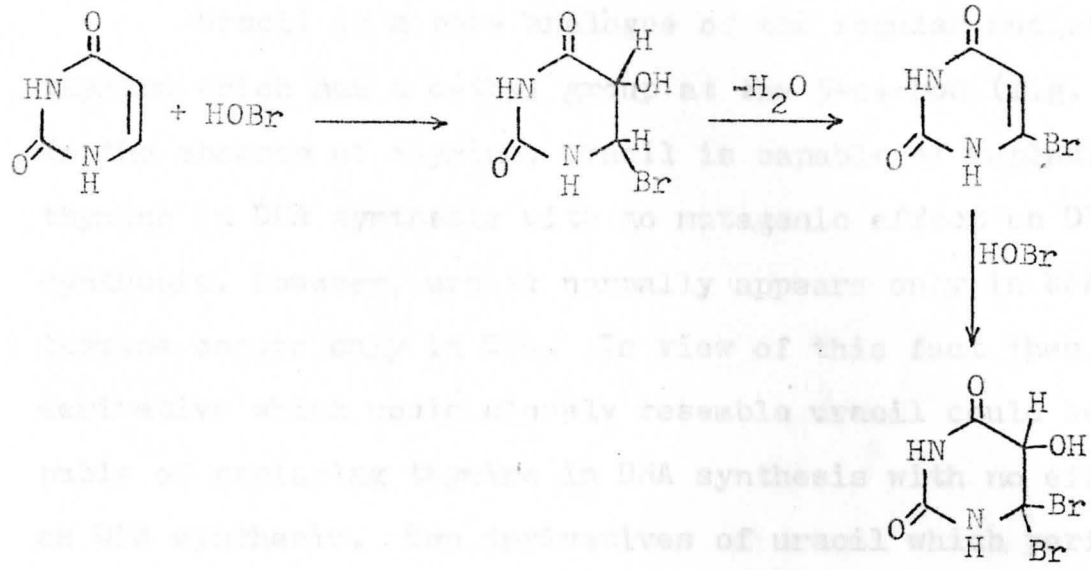

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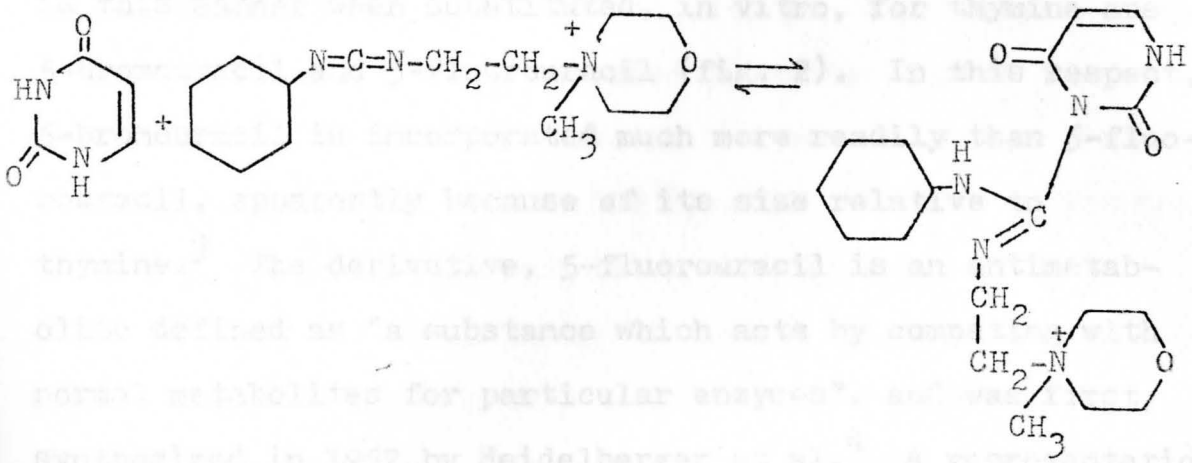

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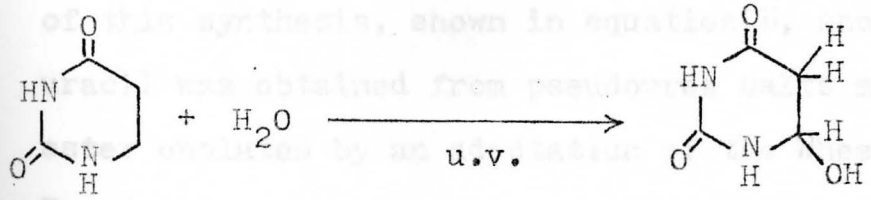

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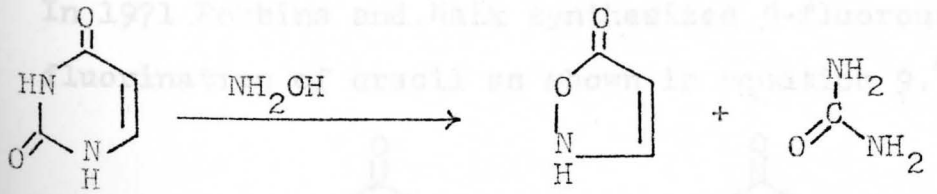


(7)

Uracil is a base analogue of the regular nucleotide thymine which has a methyl group at the 5-carbon (fig. 2). In the absence of thymine, uracil is capable of replacing thymine in DNA synthesis with no mutagenic effect on DNA synthesis, however, uracil normally appears only in RNA and thymine occurs only in DNA. In view of this fact then, any derivative which would closely resemble uracil could be capable of replacing thymine in DNA synthesis with no effect on DNA synthesis. Two derivatives of uracil which perform in this manner when substituted, in vitro, for thymine are 5-bromouracil and 5-fluorouracil (fig. 2). In this respect, 5-bromouracil is incorporated much more readily than 5-fluorouracil, apparently because of its size relative to thymine.[3] The derivative, 5-fluorouracil is an antimetabolite defined as "a substance which acts by competing with normal metabolites for particular enzymes", and was first synthesized in 1957 by Heidelberger et al.[4] A representation of this synthesis, shown in equation 8, shows that 5-fluorouracil was obtained from pseudourea salts and α-fluoro-β-keto ester enolates by an adaptation of the Wheeler synthesis. Pseudothiourea salts may also be used in this synthesis.[5] In 1971 Robbins and Naik synthesized 5-fluorouracil by direct fluorination of uracil as shown in equation 9.[6]

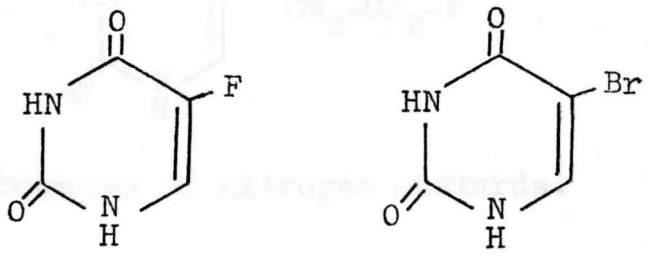
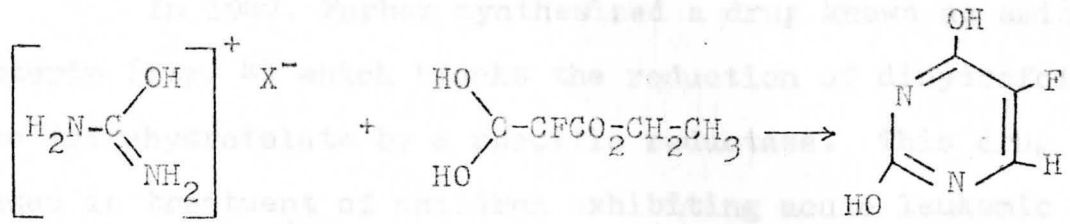


Figure 2. Structure of a) 5-fluorouracil and b) 5-bromouracil



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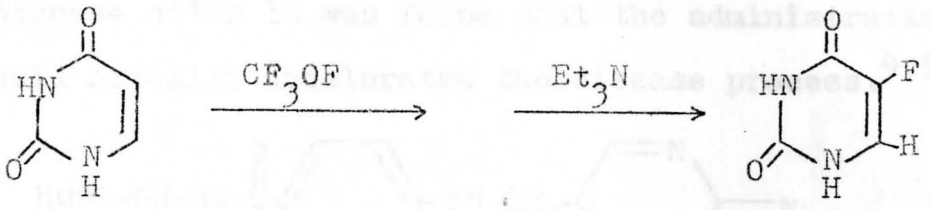


(9)

In 1957 Heidelberger et al described the biochemical mechanism of action and the first clinical trial of 5-fluoro-uracil as a tumor inhibitory agent in patients with advanced metastatic disease.[7] This however was not the first use of drugs as cancer chemotherapeutic agents. Cancer chemotherapy had its birth with compounds known as nitrogen mustards (fig. 3). These compounds may be considered the prototype of todays alkylating agents and their action was dependent on the electron releasing capacity of the nitrogen atom.[8]

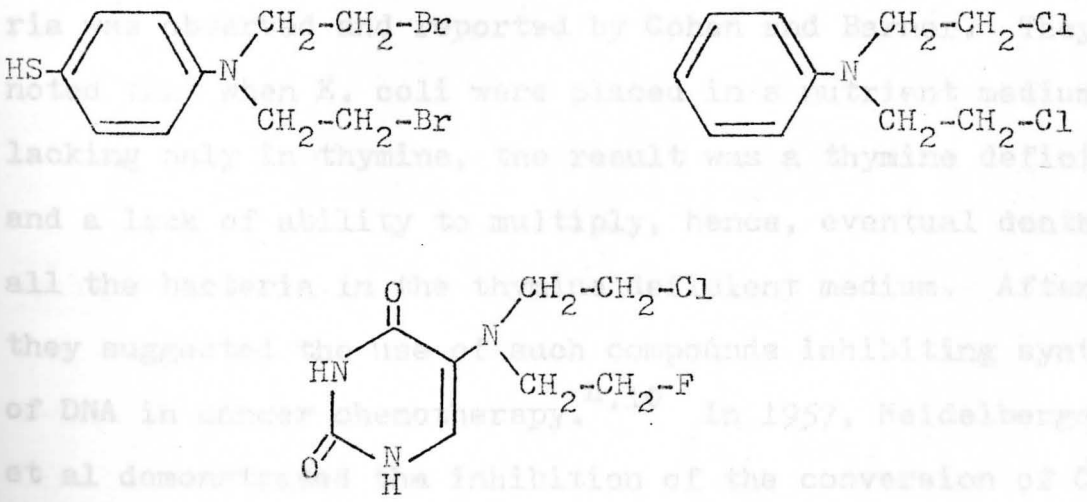


Figure 3. Examples of nitrogen mustards.

In 1947, Farber synthesized a drug known as aminopterin (fig. 4) which blocks the reduction of dihydrofolate to tetrahydrofolate by a specific reductase. This drug was used in treatment of children exhibiting acute leukemic disease after it was found that the administration of folic acid actually accelerated the disease process.[4,9]

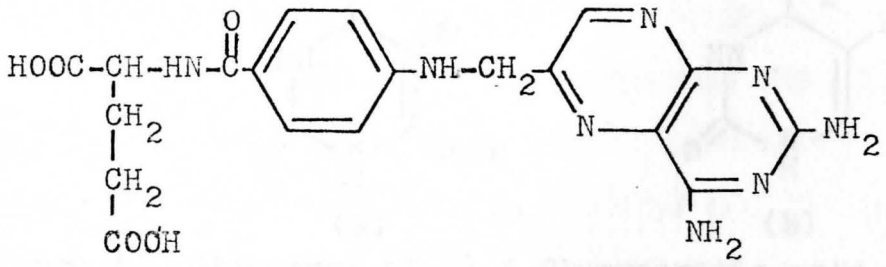
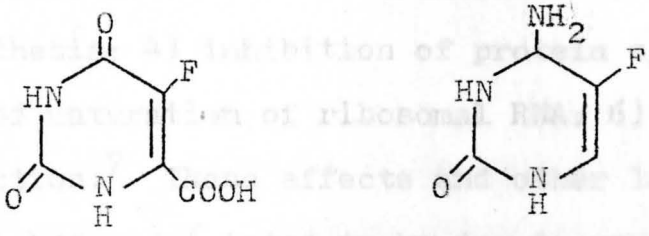


Figure 4. Structure of antifolate, aminopterin (4-aminopteroylglutamic acid).

Likewise it was observed by Rutman in 1954 that more uracil was required for nucleic acid synthesis in rat liver tumor than in normal liver tissue.[4] Following this discovery, in 1956, the phenomenon of "thymineless death" in bacteria was observed and reported by Cohen and Barner. They noted that when E. coli were placed in a nutrient medium, lacking only in thymine, the result was a thymine deficiency and a lack of ability to multiply, hence, eventual death of all the bacteria in the thymine deficient medium. Afterwards they suggested the use of such compounds inhibiting synthesis of DNA in cancer chemotherapy.[4,10] In 1957, Heidelberger et al demonstrated the inhibition of the conversion of C^{14} labled formate into the methyl group of thymine by 5-fluoro-

uracil in vitro.[4,7,11,12] In comparisons with 5-fluoroorotic acid (fig. 5), 5-fluorocytosine (fig. 5) and 5-bromouracil (fig. 2) it was found that the activity of 5-fluorouracil was 25 times, 5 times and 500 times the activities of those compounds respectively.[12]



(a) (b)

Figure 5. Structure of a) 5-fluoroorotic acid and b) 5-fluorocytosine

Fluorine was chosen because of its close similarity to hydrogen in molecular weight, atomic radii, etc. as opposed to bromine or chlorine as can be seen when some of the physical characteristics of the naturally occurring pyrimidines, uracil and thymine are compared to their fluoroanalogues in table 1.[4,7,11]

TABLE 1

Physical Characteristics of the Naturally Occurring Pyrimidines and Their Fluoro Analogues

Pyrimidine	Mol. wt.	Size Å	pKa	λH^+(nm)
Uracil	112	H=1.20	9.45	259
5-fluorouracil	130	F=1.35	8.15	265
Thymine	126	CH_3=2.00	9.82	264
Trifluorothymine	180	CF_3=2.44	7.35	257

The metabolism of 5-fluorouracil was studied in suspensions of Erlich ascites tumor cells and was found to be incorporated into ribosomal and transfer RNA's at non-terminal positions.[4,7,11,13] Some of the biological effects of this incorporation are: 1) mutagenisis in RNA viruses; 2) changes in acceptor activities of transfer RNA; 3) miscoding of protein synthesis; 4) inhibition of protein synthesis; 5) inhibition of maturation of ribosomal RNA; 6) inhibition of enzyme induction.[7] These effects and other less documented effects have been postulated to be due to errors in transcription resulting from fluorouracil base-pairing, however, efforts to demonstrate this phenomenon have failed.[7,14]

Since it was known that thymine, an essential building block of DNA, is made by the attachment of a methyl group to the 5-carbon of uracil, it was postulated that a fluorine atom at this position would inhibit that reaction. This type of inhibition had been suggested by Heidelberger et al in 1957 when he found that only a very small quantity of thymine or thymidine is required to reverse the inhibition of 5-fluorouracil indicating a non-competitive relationship.[12] The fact that fluorine does indeed inhibit methylation was shown by Bosch et al in 1958.[7] It was found however, that although fluorouracil is effective in inhibiting the methylation reaction, its' nucleoside derivative, 5-fluoro-2'deoxyuridine (FUDR) (fig. 6) was the most active in this respect.[7]

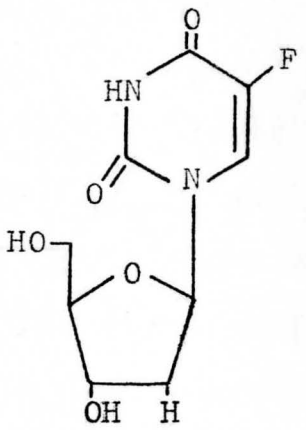


Figure 6. Structure of 5-fluoro-2'-deoxyuridine (FUDR)

The substrate for the methylation reaction is deoxyuridylate, the coenzyme is methylene tetrahydrofolate, the product is thymidylate and the enzyme that catalyzes the conversion is thymidylate synthetase.[4,7,11] Since all of the above mentioned compounds are phosphorylated it was found that it is not actually FUDR which inhibits thymidylate synthetase but rather its 5'-monophosphate (fig. 7).[7,15] Considerable evidence has been demonstrated in works by Heidelberger et al in 1960 and Kessel and Hall in 1969 that the inhibition of the enzyme, thymidylate synthetase, carries the responsibility for the major tumor-inhibitory effect of 5-fluorouracil and trifluorothymine keeping in mind that the incorporation into RNA mentioned earlier also exhibits some tumor-inhibitory effect.[4,7,11,16,17] Figure 8 demonstrates the metabolic pathway of 5-fluorouracil,[4,5,9,18]

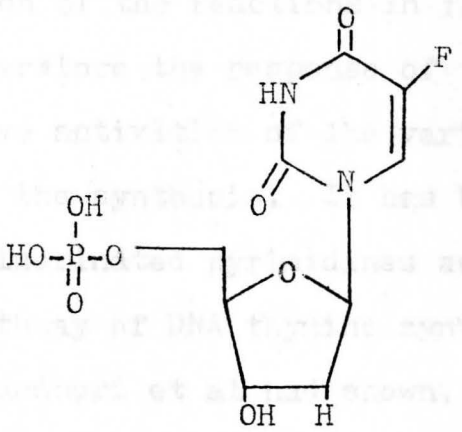


Figure 7. Structure of 5-fluoro-2'-deoxyuridine-5'-monophosphate

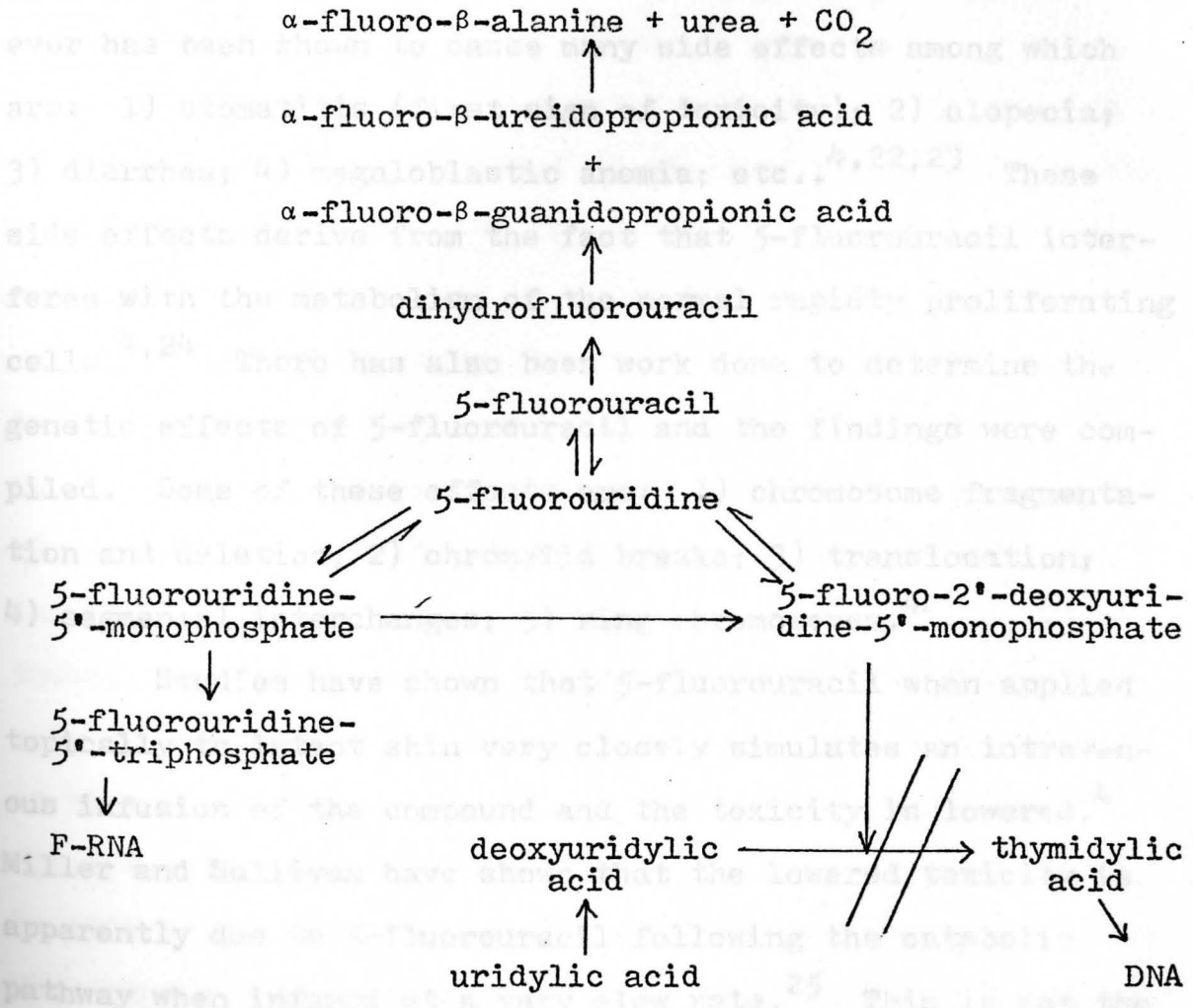


Figure 8. Metabolic pathway of 5-fluorouracil.

Each of the reactions in figure 8 requires a specific enzyme, therefore the response of tumors is dependent upon the relative activities of the various enzymes required to accomplish the synthesis. It has been clearly shown however, that the fluorinated pyrimidines act by the inhibition of the de novo pathway of DNA thymine synthesis.[4,7,11]

Chaudhuri et al had shown, in 1958, that the liver is the principal site of the catabolism of 5-fluorouracil and it was further shown that the degradative products of 5-fluorouracil are ineffective against malignant tumors and are nontoxic to normal tissues.[19,20,21] 5-Fluorouracil itself however has been shown to cause many side effects among which are: 1) stomatitis (first sign of toxicity); 2) alopecia; 3) diarrhea; 4) megaloblastic anemia; etc..[4,22,23] These side effects derive from the fact that 5-fluorouracil interferes with the metabolism of the normal rapidly proliferating cells.[4,24] There has also been work done to determine the genetic effects of 5-fluorouracil and the findings were compiled. Some of these effects are: 1) chromosome fragmentation and deletion; 2) chromatid breaks; 3) translocation; 4) segmental interchanges; 5) ring chromosomes.[4]

Studies have shown that 5-fluorouracil when applied topically to intact skin very closely simulates an intravenous infusion of the compound and the toxicity is lowered.[4] Miller and Sullivan have shown that the lowered toxicity is apparently due to 5-fluorouracil following the catabolic pathway when infused at a very slow rate.[25] This is not the

case however when 5-fluorouracil is applied topically to excised skin in which a high penetration was shown by two different analytical methods of determination, thereby eliciting toxic effects.[26]

Avoidance of toxic side effects is a main concern of the medical profession and much work has been done in this field. Although topical applications to intact skin seems promising, there are cases in which this means of drug administration is not practical since, like intravenous infusion, it can be readily removed. This method would also require restriction of the patient, in order to administer the drug adequately.

It has long been desired by the medical profession to devise an automatic method of administering a therapeutic drug over a period of days or weeks without restricting the patient. One of the ways in which this has been attempted is a biodegradeable, drug impregnated polymer which would be implanted under the skin thereby allowing the drug to diffuse out over a period of time. Problems have been encountered with this method however, in the rate of release of the drug. This rate of release, by the classical diffusion theory, will decrease with time making this method useful only in cases where a decrease in drug dosage over a period of time is desireable. A second way in which this has been attempted is the use of non-biodegradeable polymeric drugs. In 1974 Croswell and Becker had found that polystyrene beads when expanded and allowed to absorb the analgesic acetamin-

ophen demonstrated time release properties.[27] In 1973 Kornblum and Stoopak had determined that polyvinylpyrrolidone (normally a plasma substitute) (fig. 9), when crosslinked, possesses very acceptable properties as a tablet disintegrating agent as compared with starch.[28] Also in 1973 Stupak and Bates had found that polyvinylpyrrolidone, when coprecipitated with digitoxin, enhances the rate of absorption of digitoxin by eleven times.[29] There are several other uses of non-biodegradeable polymeric drugs which have been cited in the literature.[30,31,32,33,34,35] The major concern with this type of polymeric drug is the still unresolved problem of excretion. Since these polymers tend to accumulate in tissues throughout the body, they appear to be useful only in short term applications or extremely bad diseases.[36]

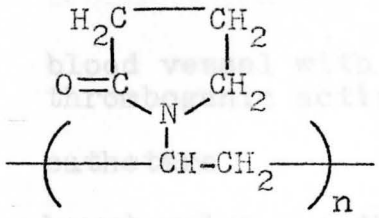


Figure 9. Structure of polyvinylpyrrolidone

Although the use of polymers as drugs is relatively new to the medical field, polymers are by no means a recent addition to medicine in general. Some of the uses to which polymers have been applied in the medical field throughout the years are shown in table 2. It is beyond the scope of this thesis to delve deeply into the subject of biomedical polymers in general, however, for an excellent review of bio-

medical polymers of the past and present the reader is referred to reference 37. There are also many more uses of pharmacologically active polymers which have been noted in the literature.[54,55,56,57,58,59]

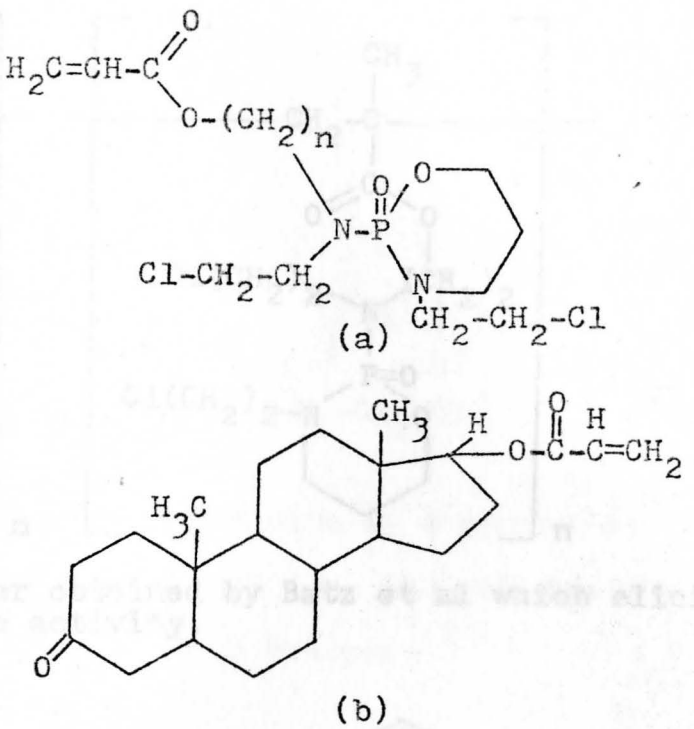
TABLE 2

Biomedical Polymers and Uses

Polymer	Use	Ref.
Polyethylene	bandage backing	37, 38
	bile duct prosthesis	37, 39
Polymethylmethacrylate	arterial prosthesis	37, 40
	blood filters	37, 41
4,4'-Diaminodiphenylsulphone dimethylolurea copolymer	antimalarial drug	42
Poly(vinylpyridine-N-oxide)s	active against silicosis	43
IOPLEX 101	blood vessel with antithrombogenic activity	44, 45
Polypropylene	catheters	37, 46
	heart valve prosthesis	37, 47
Polystyrene	dialysis membrane	37, 48
Polyvinylpyrrolidone	plasma substitute	37, 50
	drug use	28, 29
Silicone rubber	heart valve prosthesis	37, 51, 53
	middle ear implants	37, 52

It was inevitable that polymers would soon find their way into cancer chemotherapy. In 1974 Batz et al had prepared

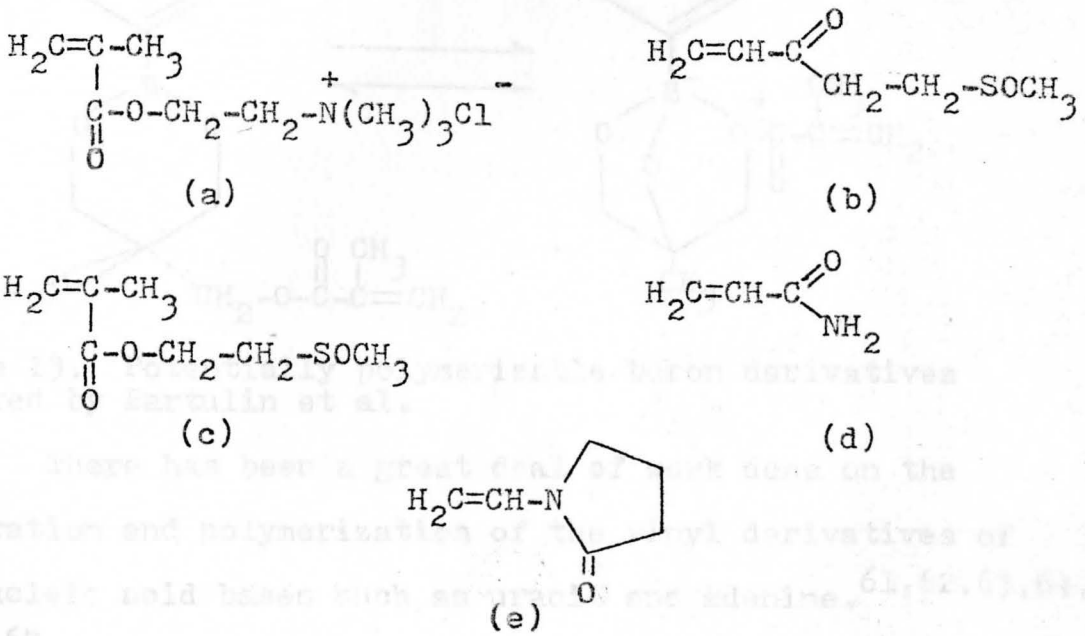
cyclophosphamide and hormone containing monomers. (fig. 10) These monomers were then copolymerized with the following comonomers: 1) 2-methacryloyloxyethyltrimethylammonium chloride; 2) 2-methylsulfinylethyl acrylate; 3) 2-methylsulfinylethyl methacrylate; 4) 2-methylsulfinylethyl acrylamide; 5) N-vinyl-2-pyrrolidone. Water soluble polymers were obtained in all cases. The structures of the comonomers are shown in figure 11. This work was done with the belief that the copolymers would demonstrate carcinostatic properties, however, only one copolymer (fig. 12) had been tested prior to the publication of that work and it had demonstrated slight activity against Yoshida ascites tumor in mice.[60] Also in 1974 Bartulin et al did a study on the preparation of potentially polymerizable boron derivatives (fig. 13) which they felt, based on studies by Kruger in 1940 and Soloway et al in 1964, would become localized in the cancerous tissue.[56]



(a)

(b)

Figure 10. a) Cyclophosphamide monomer and b) 3-oxo-androst-4-en-17 -yl acrylate (hormone containing monomer).



(a)

(b)

(c)

(d)

(e)

Figure 11. Structures of comonomers; a) 2-methacryloyloxy-ethyltrimethyl ammonium chloride; b) 2-methylsulfinylethyl acrylate; c) 2-methylsulfinylethyl methacrylate; d) 2-methyl-sulfinylethyl acrylamide; e) N-vinyl-2-pyrrolidone.

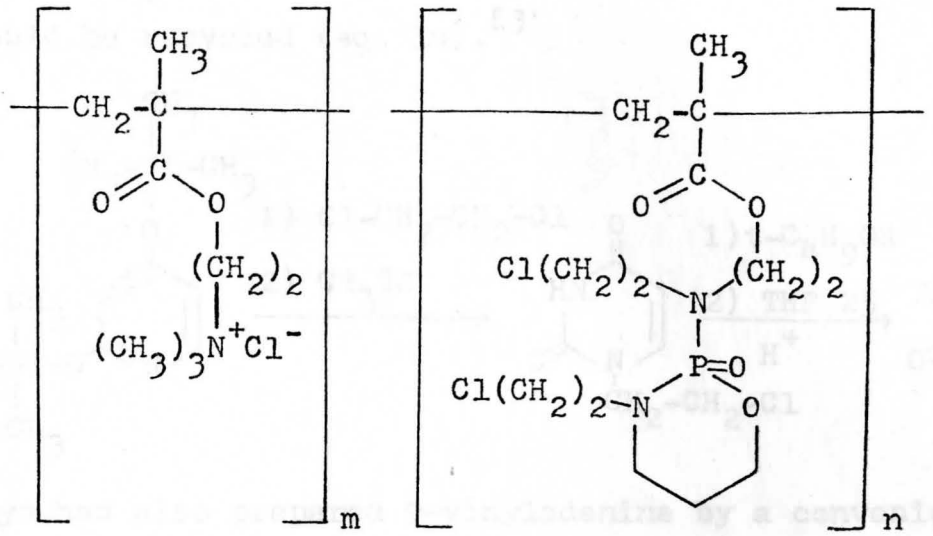


Figure 12. Copolymer obtained by Batz et al which elicited slight carcinostatic activity.

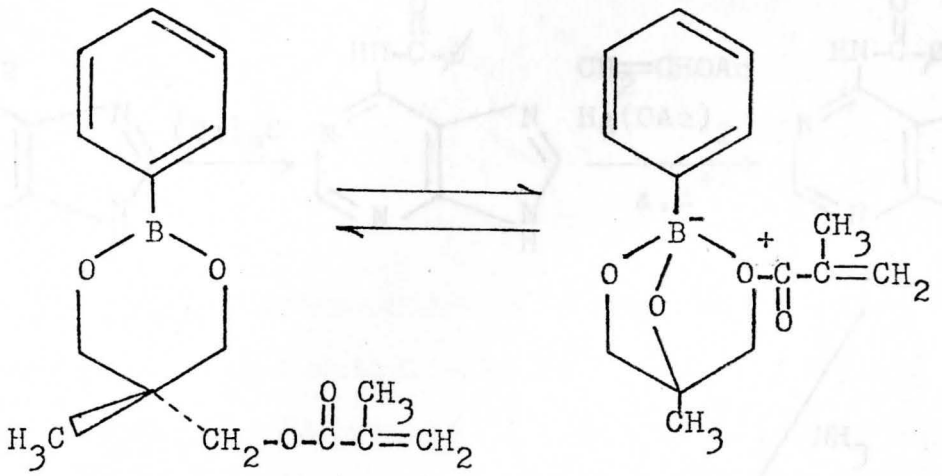
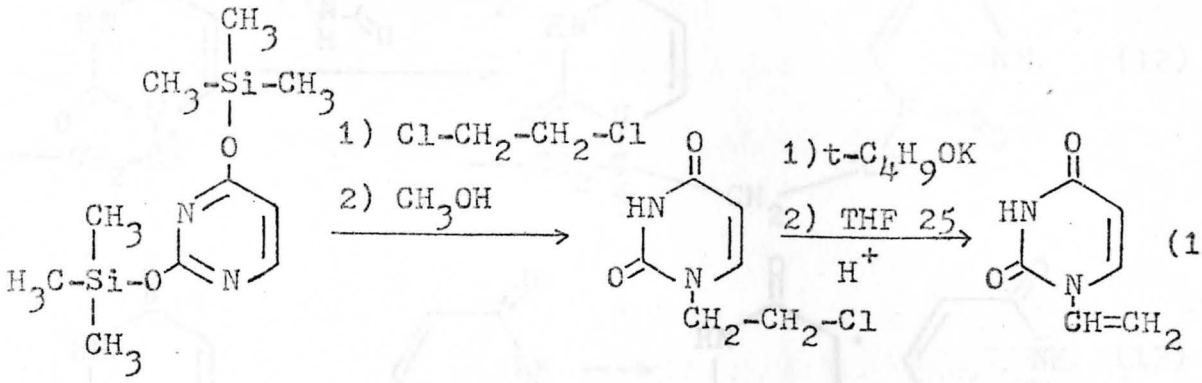


Figure 13. Potentially polymerizable boron derivatives prepared by Bartulin et al.

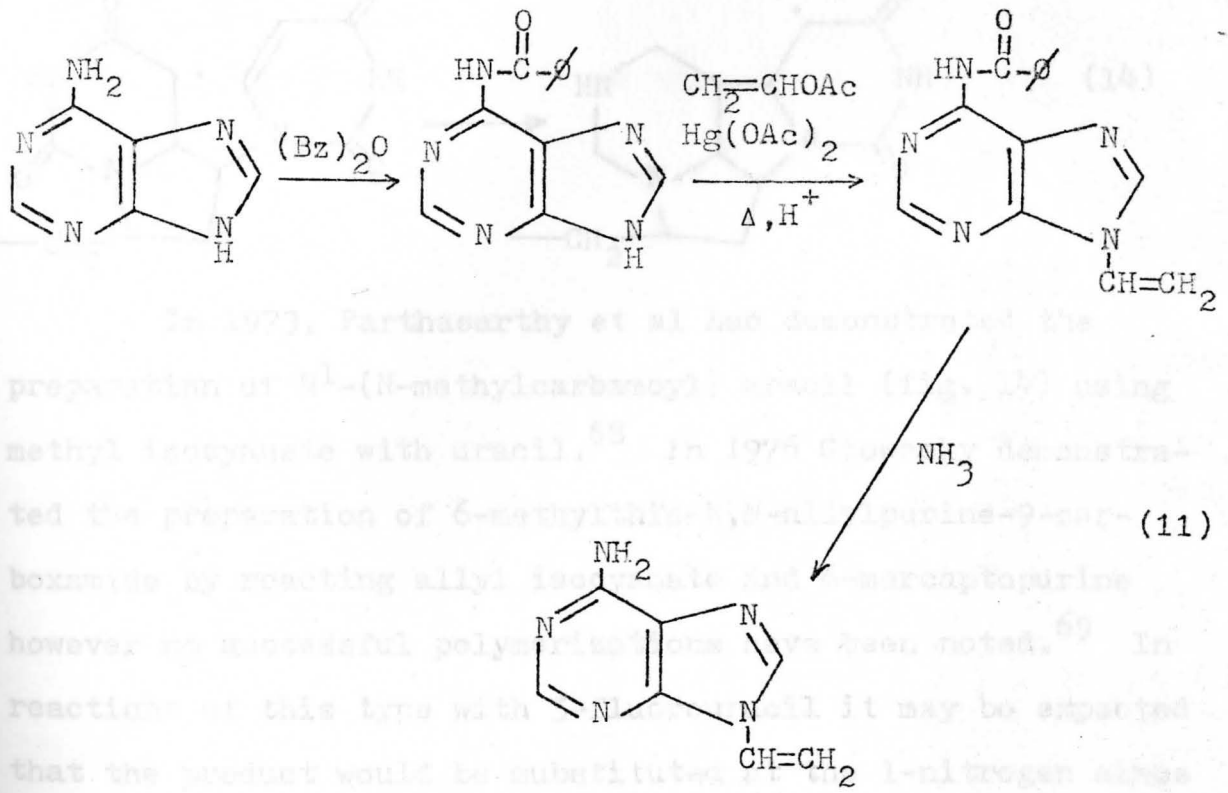
There has been a great deal of work done on the preparation and polymerization of the vinyl derivatives of the nucleic acid bases such as uracil and adenine.[61,62,63,64,65,66,67] The monomers, 1-vinyluracil and 9-vinyladenine (fig. 14) were first prepared by Pitha and Ts'o in 1967 and then again by Ueda et al in 1968.[61,67] However, in 1969, Kaye had achieved a more practical synthesis of 1-vinyluracil in which the yield was not high but recovered uracil

could be recycled (eq. 10).[63]



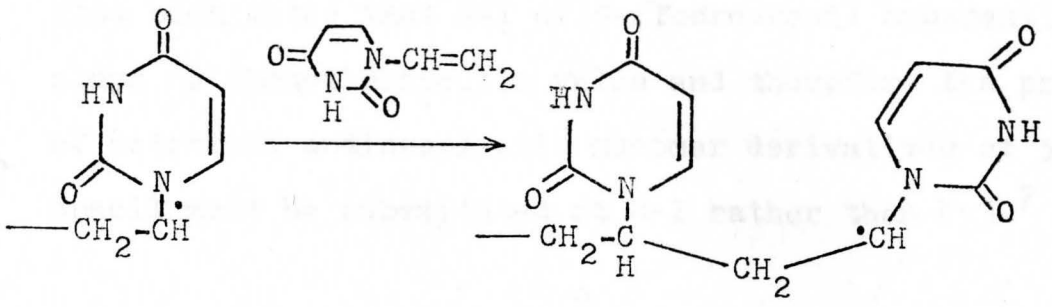
(10)

Kaye had also prepared 9-vinyladenine by a convenient method which afforded good yields (eq. 11) and demonstrated the first polymerization of both monomers.[63]



(11)

In 1971 Kaye had demonstrated, with supporting NMR, IR and UV data, that the free radical initiation of 1-vinyluracil caused a back-biting cyclopolymerization reaction to occur via the proposed mechanism shown in equations 12-14.[65]



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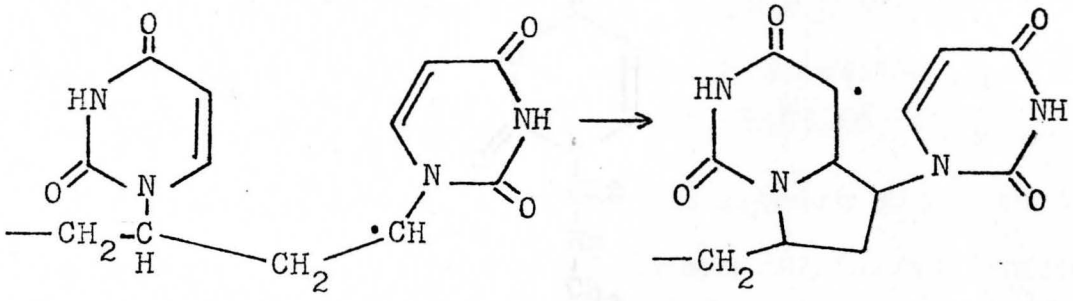
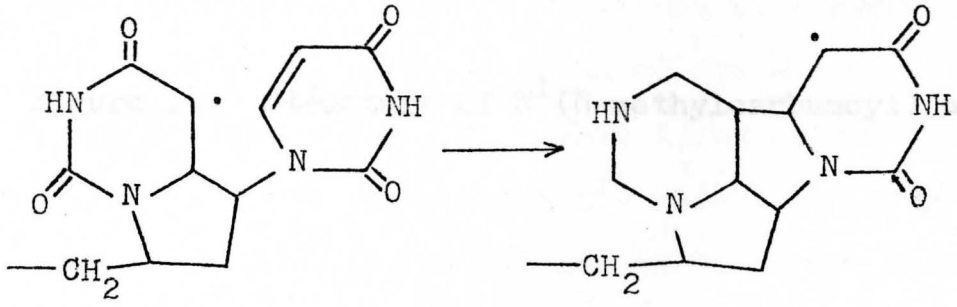


(13)



(14)

In 1973, Parthasarthy et al had demonstrated the preparation of N^1-(N-methylcarbamoyl) uracil (fig. 14) using methyl isocyanate with uracil.[68] In 1976 Glowacky demonstrated the preparation of 6-methylthio-N,N-allylpurine-9-carboxamide by reacting allyl isocyanate and 6-mercaptopurine however no successful polymerizations have been noted.[69] In reactions of this type with 5-fluorouracil it may be expected that the product would be substituted at the 1-nitrogen since it has been noted that unsaturated compounds react at N-1 and saturated compounds react at N-3.[11] In order to retain carcinostatic properties it has been noted that N-3 must remain unsubstituted and with a proton of the correct pKa. It has

also been noted that N-1 of 5-fluorouracil apparently displays no chemotherapeutic value and therefore the preparation of potential antineoplastic monomer derivatives of 5-fluorouracil must be substituted at N-1 rather than N-3.[7]

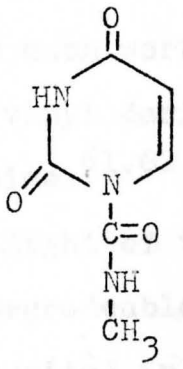


Figure 14. Structure of N^1(N-methylcarbamoyl) uracil.

CHAPTER II

STATEMENT OF THE PROBLEM

There has been much work in the preparation and polymerization of the vinyl derivatives of the nucleic acid bases, uracil and adenine.[61,62,63,64,65,66,67] However, it is surprising that in light of the current interest in polymeric drugs, both biodegradeable and non-biodegradeable, there has been no work cited in the literature concerning the preparation and polymerization of the antineoplastic derivatives of these compounds. This is especially surprising since the currently known toxic side effects of these derivatives (eg. 5-fluorouracil) are quite numerous and it has been shown that slow introduction of these compounds reduces, quite considerably, these effects.[4,22,23,25] There has been a recent study in which allyl isocyanate was reacted with 6-mercaptopurine yielding the product 6-methylthio-N,N-allyl-purine-9-carboxamide, however, polymerization attempts with this product had failed.[69]

Recently the compound N^1-(N-methylcarbamoyl) uracil (fig. 13) had been prepared by reacting methyl isocyanate with uracil using dimethylsulfoxide (DMSO) as the solvent.[68] After a careful search of the literature, no other carbamoyl derivatives of uracil or uracil derivatives could be found therefore it was assumed that these reactions are currently unknown.

This study will be concerned with the preparation of four different carbamoyl derivatives of both uracil and 5-fluorouracil, three of which will be potentially polymerizable. Benzene will be used as the solvent for purposes of minimizing temperature requirements upon evaporation. Minimum temperatures are desireable in order to prevent polymerization reactions from occurring uncontrollably. The isocyanates used in the reactions will be: 1) ethyl isocyanate; 2) allyl isocyanate; 3) isopropylidene isocyanate; 4) vinyl isocyanate the structures of which are shown in figure 15. Triethylamine will be used as the catalyst to facilitate the raaction.

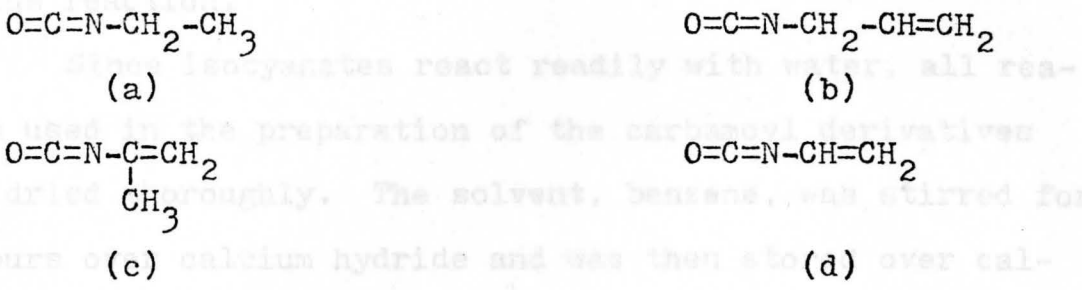


Figure 15. Structure of a) ethyl isocyanate; b) allyl isocyanate; c) isopropylidene isocyanate; d) vinyl isocyanate

The preparation of these potentially polymerizable, carbamoyl derivatives of uracil and 5-fluorouracil may lead to further investigations concerning the possible antineoplastic properties of the polymeric compounds.

CHAPTER III

EXPERIMENTAL

Reagents

All of the chemicals used in this study were of practical grade or better and were used without further purification. Table 4 gives the chemicals used, the grade of the reagent and the manufacturer. Isopropylidene and vinyl isocyanates were prepared immediately prior to use via the Curtius reaction.

Since isocyanates react readily with water, all reagents used in the preparation of the carbamoyl derivatives were dried thoroughly. The solvent, benzene, was stirred for 24 hours over calcium hydride and was then stored over calcium hydride. Toluene, used in the preparation of isopropylidene isocyanate was stirred for 24 hours over calcium hydride and was then stored over calcium hydride. Uracil and 5-fluorouracil were stored in a vacuum oven at 97°C and 14 torr pressure.

Equipment

Unless otherwise stated, all of the apparatus used in this study was made from glass with standard taper joints. Since anhydrous conditions are necessary, all glassware was washed with soap, rinsed thoroughly with distilled water and

dried overnight in an oven at 110°C.

A Buchler flash evaporator was used in evaporating the benzene and a Mettler P 1000 balance was used in determining weights of reactants and products. The Perkin-Elmer Infra-cord spectrometer was used to obtain infra-red spectral data.

TABLE 3

Reagents Used

Material	Formula	Grade of Reagent	Manufacturer
Allyl isocyanate	$H_2C{:}CHCH_2NCO$	Analytical	Aldrich
Methacrylyl chloride	$H_2C{:}C(CH_3)COCl$	"	Polyscience
Acryloyl chloride	$H_2C{:}CHCOCl$	"	"
Triethylamine	$N(C_2H_5)_3$	"	Matheson, Coleman and Bell
Hydroquinone	$C_6H_6O_2$	Purified	Fisher
Sodium azide	NaN_3	Practical	Matheson, Coleman and Bell
Uracil	$C_4H_4N_2O_2$	Practical	Aldrich
Calcium chloride	$CaCl_2$	A.C.S.	Baker
Benzene	C_6H_6	A.C.S.	Baker
Calcium sulfate	$CaSO_4$	Practical	Hammond
Chloroform	$CHCl_3$	A.C.S.	Baker
Ethyl isocyanate	CH_3CH_2NCO	Analytical	Ott
Toluene	C_7H_8	A.C.S.	Baker
5-Fluorouracil	$C_4H_3N_2O_2F$	Practical	P.C.R.
Dimethylsulfoxide	$(CH_3)_2SO$	Analytical	Mallinckrodt

Procedures

Preparation of Vinyl Isocyanate

The general procedure for this reaction was the method of Butler and Monroe.[70]

Into a 500-ml, three-neck flask, equipped with a water jacket condenser fitted with a calcium sulfate drying tube, trubore stirrer and addition funnel were placed 35.3 g (0.50 moles) of sodium azide, 100 ml of water and 0.3 g of hydroquinone. The reaction vessel was then immersed in an ice-water bath and cooled at 10-15°C. A mixture of 33 g (0.4 moles) acryloyl chloride and 100 ml of benzene was then added at such a rate that the reaction temperature remained at 10-15°C. After completion of this addition the mixture was cooled to 0°C and stirred for 6 hours. The organic or azide layer was then removed and dried over calcium chloride for 24 hours. The anhydrous azide solution, 0.3 g of hydroquinone and 300 ml of anhydrous benzene were placed in a one-liter, three-neck flask equipped with a magnetic stirring bar, thermometer and dry ice/acetone reflux condenser guarded by a calcium sulfate drying tube. The reaction vessel was then immersed in a water bath and heated, with stirring, at 70-80°C until the evolution of nitrogen ceased. The mixture was then transferred to a one-liter, single-neck, round-bottom flask equipped with a 40.6 cm Vigereux column. The Vigereux column was fitted with a 40.6 cm cold water condenser backed by a dry ice/acetone trap, the latter being guarded

by a calcium sulfate drying tube. The reaction vessel was then immersed in a hot water bath and distilled into a 150-ml receiving flask which had been immersed in a dry ice/acetone bath until a vapor temperature of 80°C was reached. The distillates in the receiving flask and the dry ice/acetone trap were then combined and 0.3 g of hydroquinone was added to the mixture. The mixture was then redistilled through a 12 inch, helix packed column into a 150-ml receiving flask which had been immersed in a dry ice/acetone bath. The product was 17 g of vinyl isocyanate the boiling point of which was found to be 39°C. The IR spectrum of the product was compared with that of the literature and was found to be in agreement as shown in table 4.

TABLE 4

Literature IR Spectrum of Vinyl Isocyanate vs Product IR Spectrum

Group	Literature frequency(cm^{-1})	Product frequency(cm^{-1})
C-H	3100	3100
NCO	2270	2270
C=C	1630	1630
C-H deformations	1460	1465
	1380	1380
	1310	1310
	835	835
=CH-	957	957
CH_2	895	895

The product is a severe lachrymator therefore the reaction should be performed in an exhaust hood and with proper ventilation. Also since a great deal is not known concerning the biological effects of vinyl isocyanate, proper care should be exercised in avoiding skin contact while handling.

Preparation of Isopropylidene Isocyanate

No report of the previous preparation of isopropylidene isocyanate could be found in the literature. The technique used initially in this preparation was the same as that used in the preparation of vinyl isocyanate using methacrylyl chloride in place of acryloyl chloride. This technique however, proved impractical since it was found that the product had a boiling point close to that of benzene (80° C) thereby limiting separation to a very narrow temperature range. The procedure was then modified by substituting toluene in place of benzene. The distillation was then performed until a vapor temperature of 110 C was reached. The product was then redistilled in the same manner as was the vinyl product. The product was 12.6 g of isopropylidene isocyanate the boiling point of which was found to be 66°C. The IR data is shown in table 5. This isocyanate, like vinyl isocyanate, is a severe lachrymator and therefore the same safety precautions should be followed on handling.

TABLE 5

IR Data of Isopropylidene Isocyanate

Group	Frequency(cm^{-1})
NCO	2260
CH_2	890
$-C(CH_3)$	922
CH_3	2962
	2872

Preparation of 5-Fluoro-N^1(N-Ethylcarbamoyl) Uracil

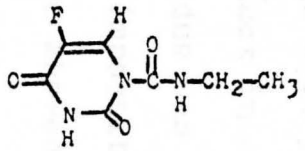
To a 125-ml Ehrlenmeyer flask equipped with a magnetic stirring bar was added 2 g (0.015 moles) of 5-fluorouracil, 20 ml of anhydrous benzene, 6 ml (0.03 moles) of ethyl isocyanate and 2 drops of triethylamine. The flask was tightly stoppered and the top of the flask was wrapped tightly with parafilm. The mixture was then allowed to stir at room temperature for 24 hours. At the end of the reaction period the benzene was filtered into a 150-ml round bottom flask and evaporated in vacuo using a Buchler flash evaporator. A slight residue was observed upon completion of evaporation and upon inspection of the IR spectrum it was noted that peaks were present which may indicate the presence of desired product in contaminated form. Since the quantity of the residue was negligible, an elemental analysis of the product was impossible. The dry filtrate was then placed in

a 130-ml beaker and was extracted 5 times with 50-ml portions of boiling chloroform filtering the chloroform through a Buchner funnel into a 500-ml filter flask between each extraction. At the completion of the extractions the chloroform extract was concentrated to 25 ml and cooled. The product was then collected in a Buchner funnel and was recrystallized from boiling chloroform. The product was white needles with a melting point of 280-285°C. The yield was 1.200 g (39.8% of the theoretical). The elemental analysis of the product is shown in table 6 and the IR spectrum is shown in figure 16. New peaks were observed in the IR at 3445, 3200, 1580 and 1300 cm^{-1} which all seem to indicate the formation of a secondary amide. The undissolved portion of the filtrate was found, upon examination of the IR spectrum, to be unreacted 5-fluorouracil (m.p. 284-286°C_{dec}).

TABLE 6

Elemental Analysis of 5-Fluoro-N^1(N-Ethylcarbamoyl) Uracil vs Elemental Analysis Calculated for $C_7H_8N_3O_3F$

Element	Calculated(%)	Found(%)
C	41.79	41.98
H	3.98	4.01
N	20.89	21.05
F	9.45	9.73
O	23.88	23.23



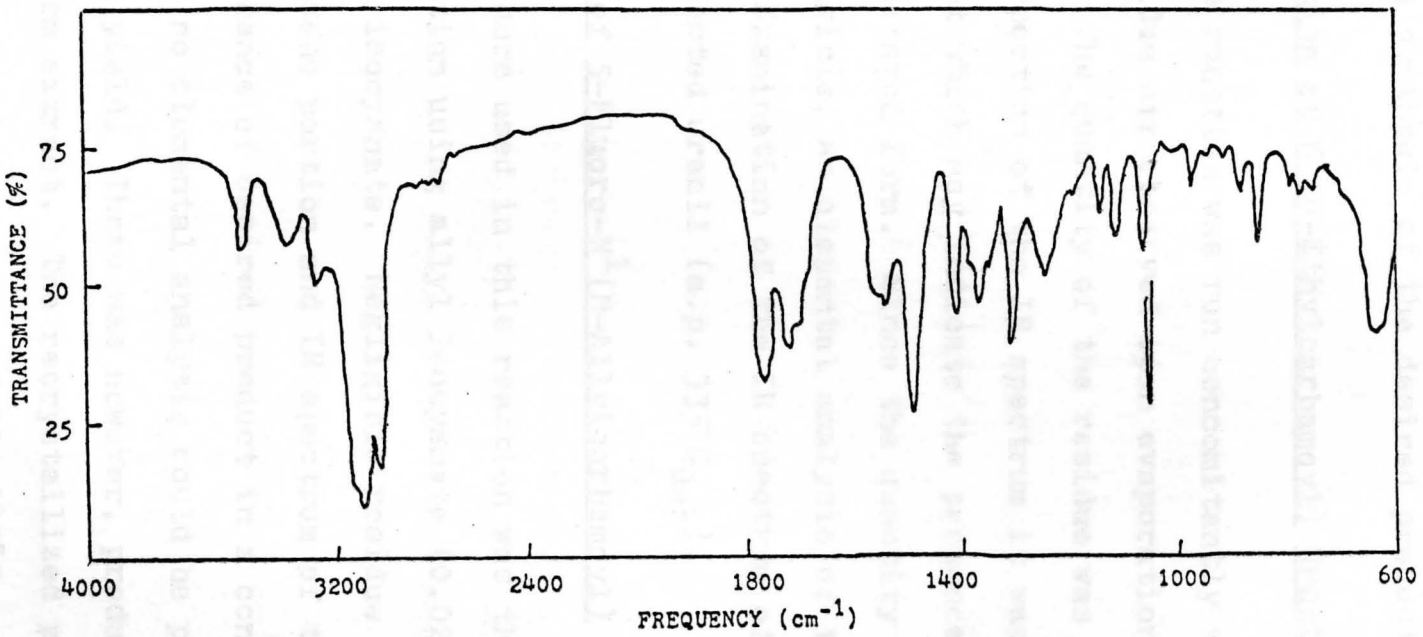


Figure 16. Infra-red spectrum of 5-fluoro-N^1(N-ethylcarbamoyl) uracil.

As can be seen in table 6, the observed results of the elemental analysis corresponded well with the theoretical values and, in conjunction with the IR spectral data, further substantiated the synthesis of the desired product.

Preparation of N^1(N-Ethylcarbamoyl) Uracil

The above reaction was run concomitantly with uracil and a slight residue was observed upon evaporation of the benzene portion. The quantity of the residue was negligible. However, upon inspection of the IR spectrum it was noted that peaks were present which may indicate the presence of desired product in contaminated form. Since the quantity of the residue was negligible, an elemental analysis of the product was impossible. Examination of the IR spectrum of the filtrate showed unreacted uracil (m.p. 335°C$_{dec}$).

Preparation of 5-Fluoro-N^1(N-Allylcarbamoyl) Uracil

The procedure used in this reaction was the same as the previous reaction using allyl isocyanate (0.026 moles) rather than ethyl isocyanate. Negligible residue was observed in the benzene portion and IR spectrum of the residue indicated the presence of desired product in a contaminated form. Once again no elemental analysis could be performed due to negligible yield. There was however, product obtained from the chloroform extract. The recrystallized product was white needles with a melting point of 110-115°C. The yield was 0.850 g (26.5% of the theoretical). The elemental analysis of the product is shown in table 7 and the IR spectrum

is shown in figure 17. New peaks were observed in the IR at 3400, 3260, 1560, 1300, 945 and 895 cm^{-1} which all seem to indicate the formation of a secondary amide and the presence of a vinylic double bond.

TABLE 7

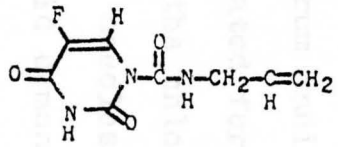
Elemental Analysis of 5-Fluoro-N^1(N-Allylcarbamoyl) Uracil vs Elemental Analysis Calculated for $C_8H_8N_3O_3F$

Element	Calculated(%)	Found(%)
C	45.08	44.87
H	3.78	4.17
N	19.71	19.63
F	8.91	9.00
O	22.52	22.33

As can be seen in table 7, the observed results of the elemental analysis corresponded well with the theoretical values and, in conjunction with the IR spectral data, further substantiated the synthesis of the desired product.

Preparation of N^1(N-Allylcarbamoyl) Uracil

As in the reaction with ethyl isocyanate, very little residue was left upon evaporation of the benzene portion of the reaction between uracil and allyl isocyanate. IR spectrum of the residue indicated peaks which may be due to the presence of desired product in contaminated form, however,



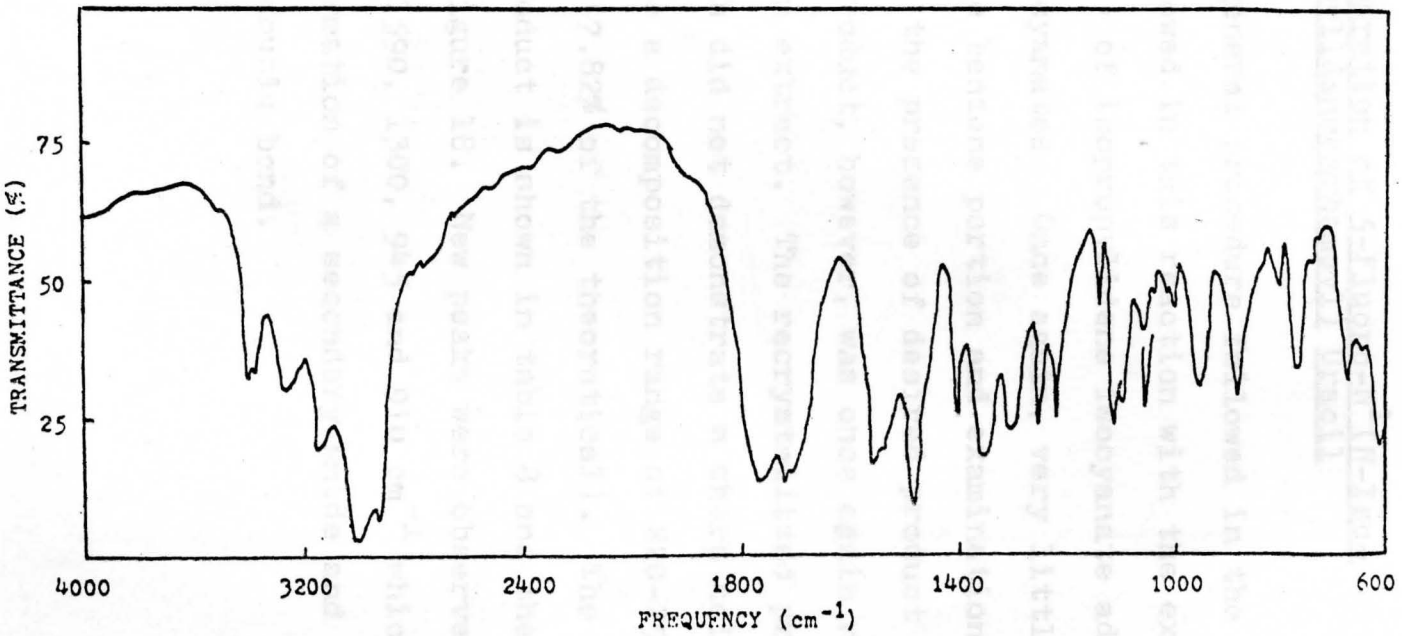


Figure 17. Infra-red spectrum of 5-fluoro-N^1(N-allylcarbamoyl) uracil.

the yield made an elemental analysis impossible. No product was obtained from the chloroform extract and inspection of IR spectrum of the filtrate indicated unreacted uracil.

Preparation of 5-Fluoro-N^1(N-Isopropylidenecarbamoyl) Uracil

The same general procedure followed in the previous reactions was followed in this reaction with the exception of 4.5 ml (0.08 moles) of isopropylidene isocyanate added in place of other isocyanates. Once again, very little residue was observed in the benzene portion and examination of the IR spectrum indicated the presence of desired product in a contaminated form. Product, however, was once again recovered from the chloroform extract. The recrystallized product was white needles which did not demonstrate a sharp melting point but did demonstrate a decomposition range of 220-250°C. The yield was 0.250 g (7.82% of the theoretical). The elemental analysis of the product is shown in table 8 and the IR spectrum is shown in figure 18. New peaks were observed in the IR at 3255, 3150, 1590, 1300, 945 and 910 cm^{-1} which all seem to indicate the formation of a secondary amide and the presence of a vinylic double bond.

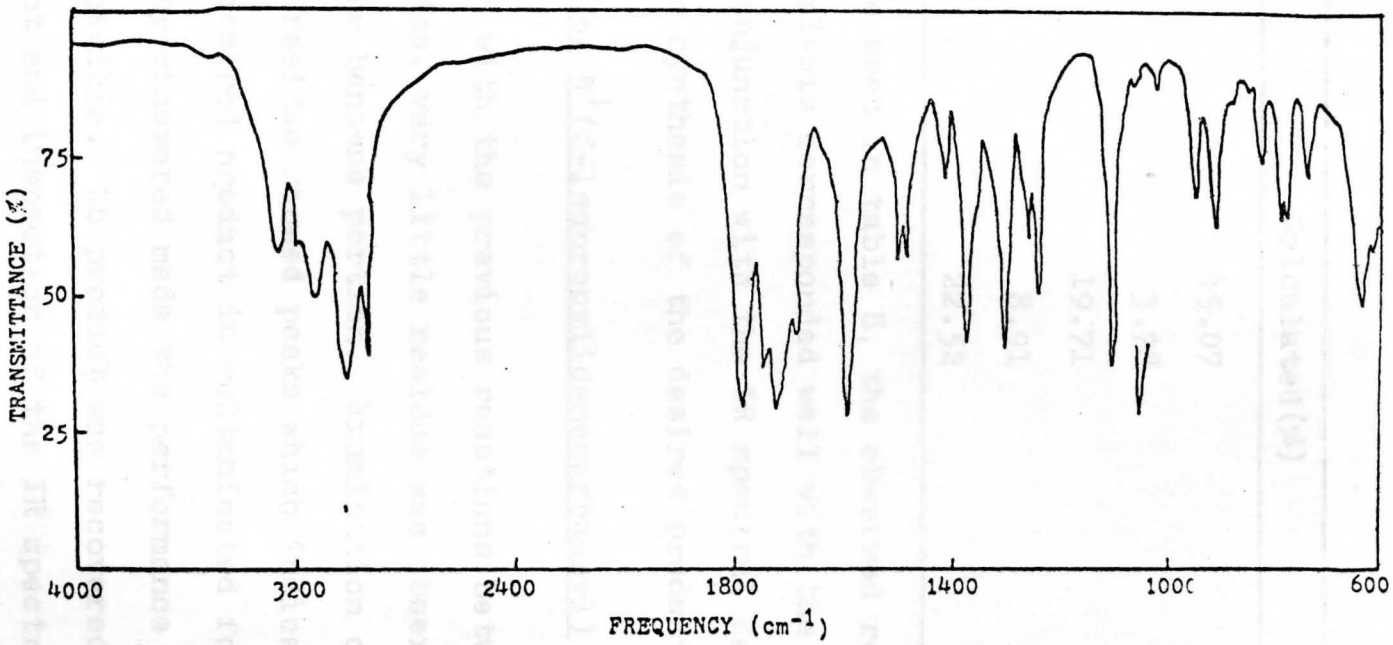


Figure 18. Infra-red spectrum of 5-fluoro-N^1(N-isopropylidenecarbamoyl) uracil.

TABLE 8

Elemental Analysis of 5-Fluoro-N^1(N-Isopropylidenecarbamoyl) Uracil vs Elemental Analysis Calculated for $C_8H_8N_3O_3F$

Element	Calculated(%)	Found(%)
C	45.07	44.81
H	3.78	3.68
N	19.71	19.63
F	8.91	8.76
O	22.52	23.12

As can be seen in table 8, the observed results of the elemental analysis corresponded well with the theoretical values and, in conjunction with the IR spectral data, further substantiated the synthesis of the desired product.

Preparation of N^1(N-Isopropylidenecarbamoyl) Uracil

Again, as with the previous reactions between uracil and the isocyanates, very little residue was observed upon evaporation of the benzene portion. Examination of the IR spectrum of this residue showed peaks which indicated the presence of the desired product in contaminated form, however, the quantity recovered made the performance of elemental analysis impossible. No product was recovered from the chloroform extract and inspection of the IR spectrum of the filtrate indicated unreacted uracil.

Preparation of 5-Fluoro-N^1(N-Vinylcarbamoyl) Uracil

The same procedure followed in the previous reactions was again followed for this reaction with the exception of the addition of 6.5 ml (0.12 moles) of vinyl isocyanate in place of other isocyanates. Negligible residue was observed upon evaporation of the benzene portion and upon examination of the IR spectrum of the residue peaks were observed which may possibly have indicated the presence of desired product in contaminated form. Due to the very small quantity of residue recovered, no elemental analysis was performed. Product was recovered from the chloroform extract and upon recrystallization was found to be white needles with a decomposition range of 230-270°C. The yield was 0.290 (9.24% of the theoretical). The elemental analysis of the product is shown in table 9 and the IR spectrum is shown in figure 19. New peaks were observed in the IR spectrum at 3300, 3150, 1540, 1300, and 910 cm^{-1} which all seem to indicate the formation of a secondary amide and the presence of a vinylic double bond.

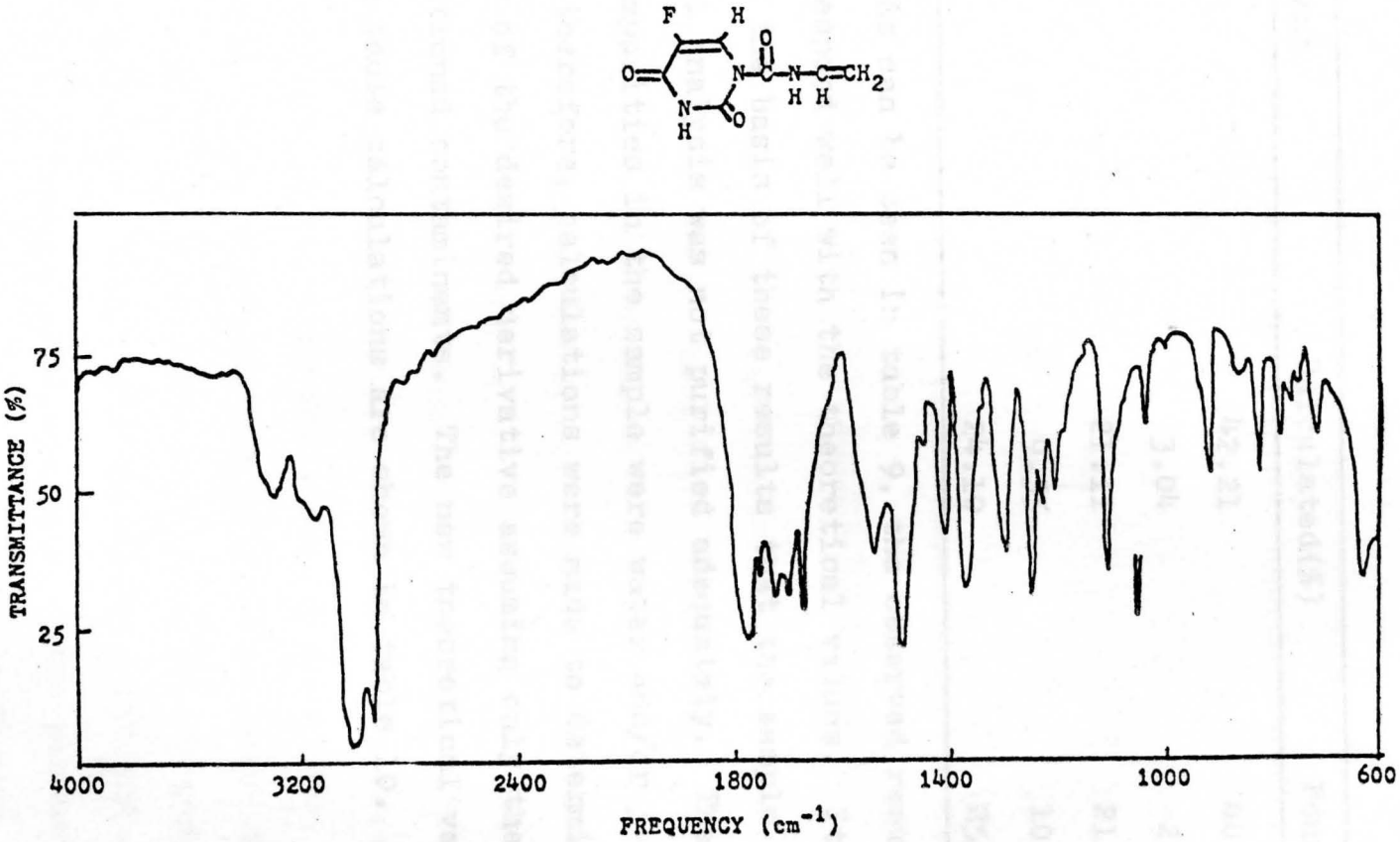


Figure 19. Infra-red spectrum of 5-fluoro-N^1(N-vinylcarbamoyl) uracil.

TABLE 9

Elemental Analysis of 5-Fluoro-N^1(N-Vinylcarbamoyl) Uracil vs Elemental Analysis Calculated for $C_7H_6N_3O_3F$

Element	Calculated(%)	Found(%)
C	42.21	40.66
H	3.04	2.94
N	21.11	21.02
F	9.55	10.15
O	24.10	25.23

As can be seen in table 9, the observed results did not correspond well with the theoretical values. It was assumed on the basis of these results that the sample used for elemental analysis was not purified adequately. The most likely impurities in the sample were water and/or 5-fluorouracil, therefore, calculations were made to determine the % purity of the desired derivative assuming only the two aforementioned contaminants. The new theoretical values based on those calculations are shown in table 10.

TABLE 10

Observed Elemental Analysis of Product vs Elemental Analysis Calculated for 85.0% 5-Fluoro-N^1(N-Vinylcarbamoyl) Uracil, 13.5% Fluorouracil and 1.5% H_2O

Element	Calculated(%)	Found(%)
C	40.87	40.66
H	3.07	2.94
N	20.84	21.02
F	10.08	10.15
O	25.14	25.23

Preparation of N^1(N-Vinylcarbamoyl) Uracil

This reaction was run concomitantly with the 5-fluorouracil and vinyl isocyanate reaction and 1.7 g (0.015 moles) of uracil was used. Negligible residue was recovered upon evaporation of the benzene portion and examination of the IR spectrum of the residue indicated peaks which could possibly have been due to desired product in contaminated form. No elemental analysis was performed on the residue due to the very small amount recovered. Product was obtained from the chloroform extract and upon recrystallization was found to be white needles with a decomposition range of 260-295°C. The yield was 0.395 g (14.52% of the theoretical). The elemental analysis of the product is shown in table 11 and the IR spectrum is shown in figure 20. New peaks were observed in the IR spectrum at 3395, 3200, 1560,

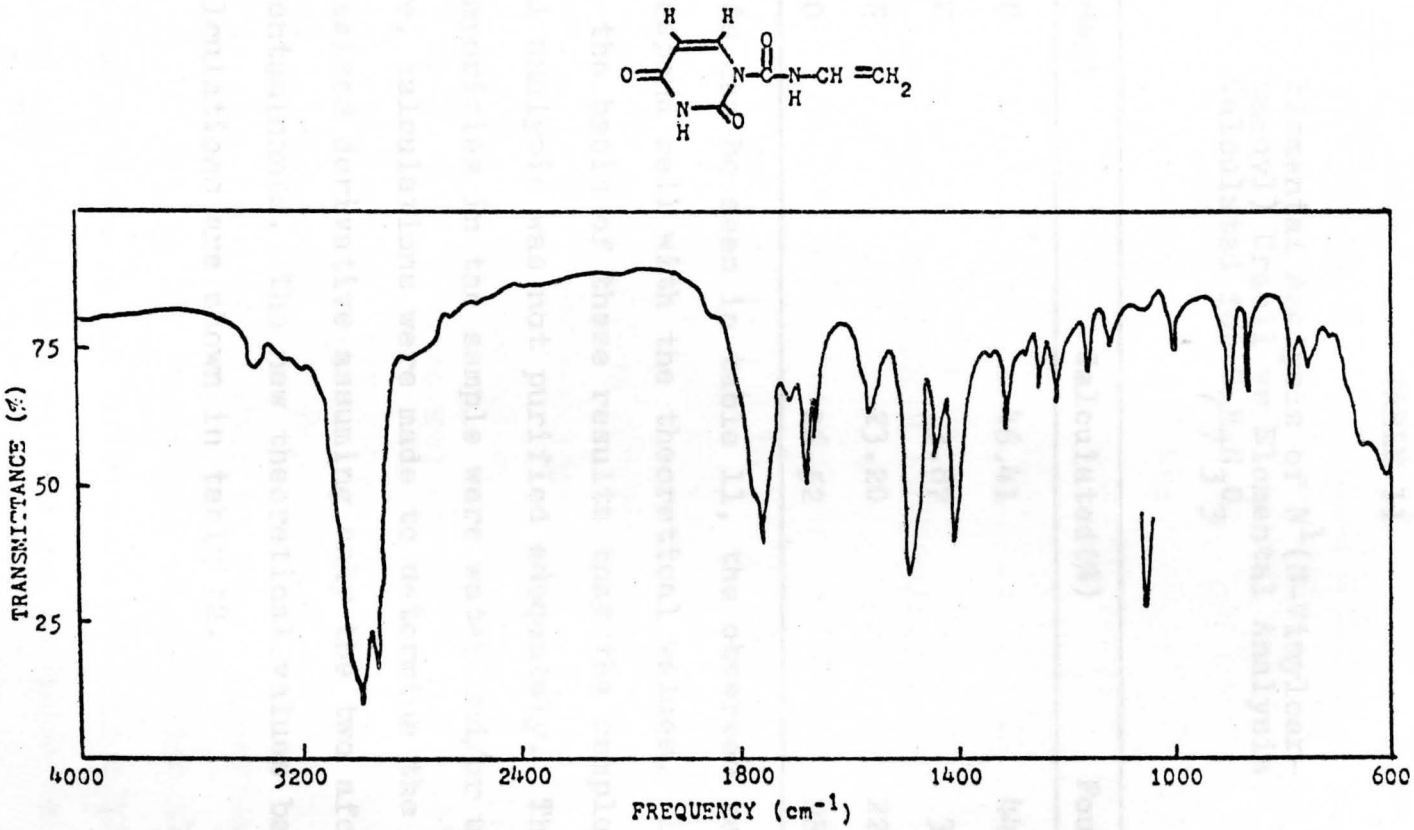


Figure 20. Infra-red spectrum of N^1(N-vinylcarbamoyl) uracil.

1300, 900, and 865 cm^{-1} which all seem to indicate the formation of a secondary amide and the presence of a vinylic double bond.

TABLE 11

Elemental Analysis of N^1(N-Vinylcarbamoyl) Uracil vs Elemental Analysis Calculated for $C_7H_7N_3O_3$

Element	Calculated(%)	Found(%)
C	46.41	44.42
H	3.87	3.71
N	23.20	22.88
O	26.52	28.99

As can be seen in table 11, the observed results did not correspond well with the theoretical values. It was assumed on the basis of these results that the sample used for elemental analysis was not purified adequately. The most likely impurities in the sample were water and/or uracil, therefore, calculations were made to determine the % purity of the desired derivative assuming only the two aforementioned contaminants. The new theoretical values based on those calculations are shown in table 12.

TABLE 12

Observed Elemental Analysis of Product vs Elemental Analysis Calculated for 80.6% N^1(N-Vinylcarbamoyl) Uracil, 16.6% Uracil and 2.8% H_2O

Element	Calculated(%)	Found(%)
C	44.56	44.42
H	4.01	3.71
N	22.89	22.88
O	28.52	28.99

Preparation of 5-Fluoro-N^1(N-Ethylcarbamoyl) Uracil

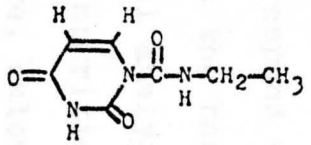
In order to determine solvent effects uracil and 5-fluorouracil were reacted with ethyl isocyanate using dimethylsulfoxide (DMSO) as the solvent and triethylamine as the catalyst. The following procedures were followed.

To a 125-ml flask equipped with a magnetic stirring bar was added 2 g (.015 moles) of 5-fluorouracil, 20 ml of anhydrous DMSO, 6 ml (.03 moles) of ethyl isocyanate and 2 drops of triethylamine. The flask was tightly stoppered and the top of the flask was wrapped tightly with parafilm. The mixture was then allowed to stir at room temperature for 24 hours. At the end of the reaction period, since all traces of solid had dissolved, the DMSO was placed in a 125-ml round bottom flask and evaporated to dryness in vacuo using a Buchler flash evaporator. The off white filtrate was then washed with 50 ml of cold chloroform five times to remove any excess DMSO. The filtrate was then extracted five times with 50-ml

portions of boiling chloroform, filtering the chloroform through a buchner funnel into a 500 ml filter flask between each extraction. At the completion of the extractions the chloroform extract was concentrated to 25 ml and cooled. The product was then collected in a buchner funnel and was recrystallized two times from boiling chloroform. The product was white needles with a melting point of 281-285°C. The yield was 1.17 g (38.7% of the theoretical). Since the IR spectrum and melting point of the product were identical to that given by the product in benzene, no elemental analysis was performed.

Preparation of N^1(N-Ethylcarbamoyl) Uracil

The same procedure had been followed for this reaction as with the previous reaction of 5-fluorouracil and ethyl isocyanate in DMSO with the exception of the addition of 1.7 g (0.015 moles) of uracil. The recrystallized product was found to be white needles with a melting point of 335-339°C. The yield was 1.475 g (53.6% of the theoretical). The elemental analysis of the product is shown in table 12 and the IR spectrum is shown in figure 21. New peaks were observed in the IR spectrum at 3395, 3200, 1590, and 1300 cm^{-1} which all seem to indicate the formation of a secondary amide.



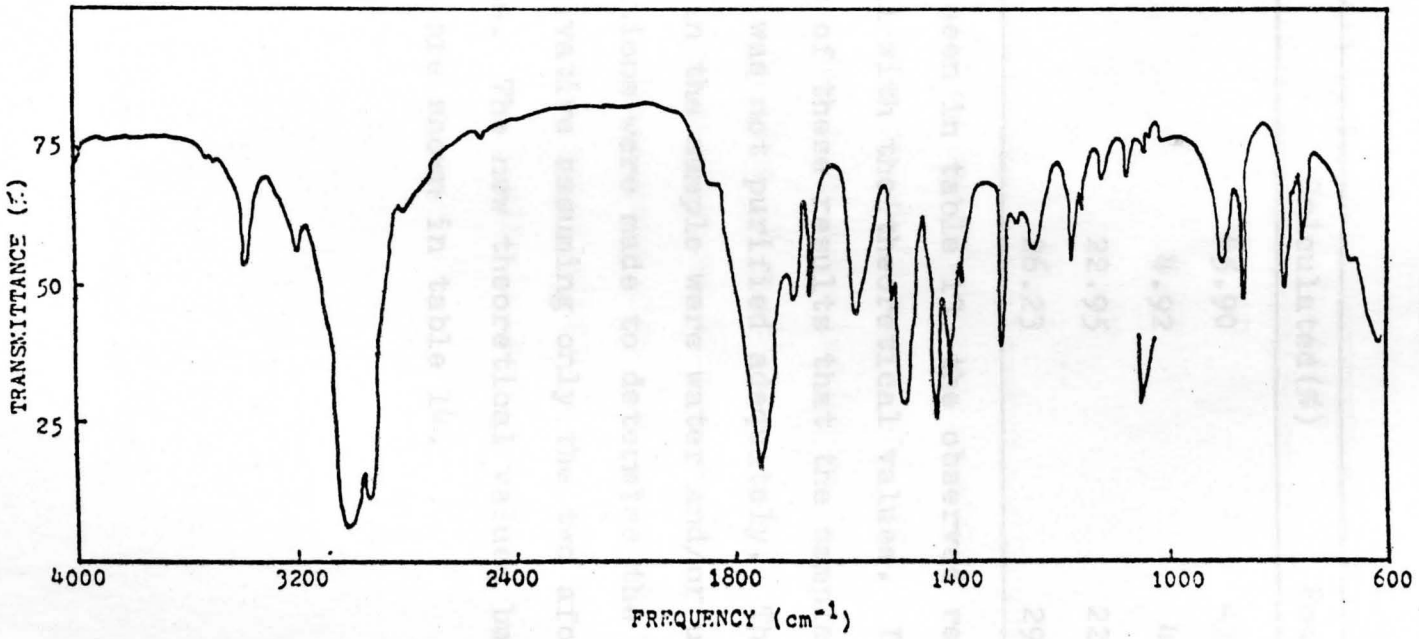


Figure 21. Infra-red spectrum of N^1(N-ethylcarbamoyl) uracil.

TABLE 13

Elemental Analysis of N^1(N-Ethylcarbamoyl) Uracil vs Elemental Analysis Calculated for $C_7H_9N_3O_3$

Element	Calculated(%)	Found(%)
C	45.90	43.42
H	4.92	4.74
N	22.95	22.47
O	26.23	29.37

As can be seen in table 13, the observed results did not correspond well with the theoretical values. It was assumed on the basis of these results that the sample used for elemental analysis was not purified adequately. The most likely impurities in the sample were water and/or uracil, therefore, calculations were made to determine the % purity of the desired derivative assuming only the two aforementioned contaminants. The new theoretical values based on those calculations are shown in table 14.

TABLE 14

Observed Elemental Analysis of Product vs Elemental Analysis Calculated for 79.8% N^1(N-Ethylcarbamoyl) Uracil, 16.3% Uracil and 3.9% H_2O

Element	Calculated(%)	Found(%)
C	43.59	43.42
H	4.94	4.74
N	22.37	22.47
O	29.07	29.37

All of the above reactions were performed two times to insure reproducability and it was found upon inspection of IR data that the reaction does indeed repeat itself. For purposes of comparison, the IR spectra of uracil and 5-fluorouracil are submitted as figures 22 and 23 respectively. All of the above reactions were also run one time in the absence of the catalyst, triethylamine, and no reaction was observed with either the 5-fluorouracil or uracil in 24 hours.

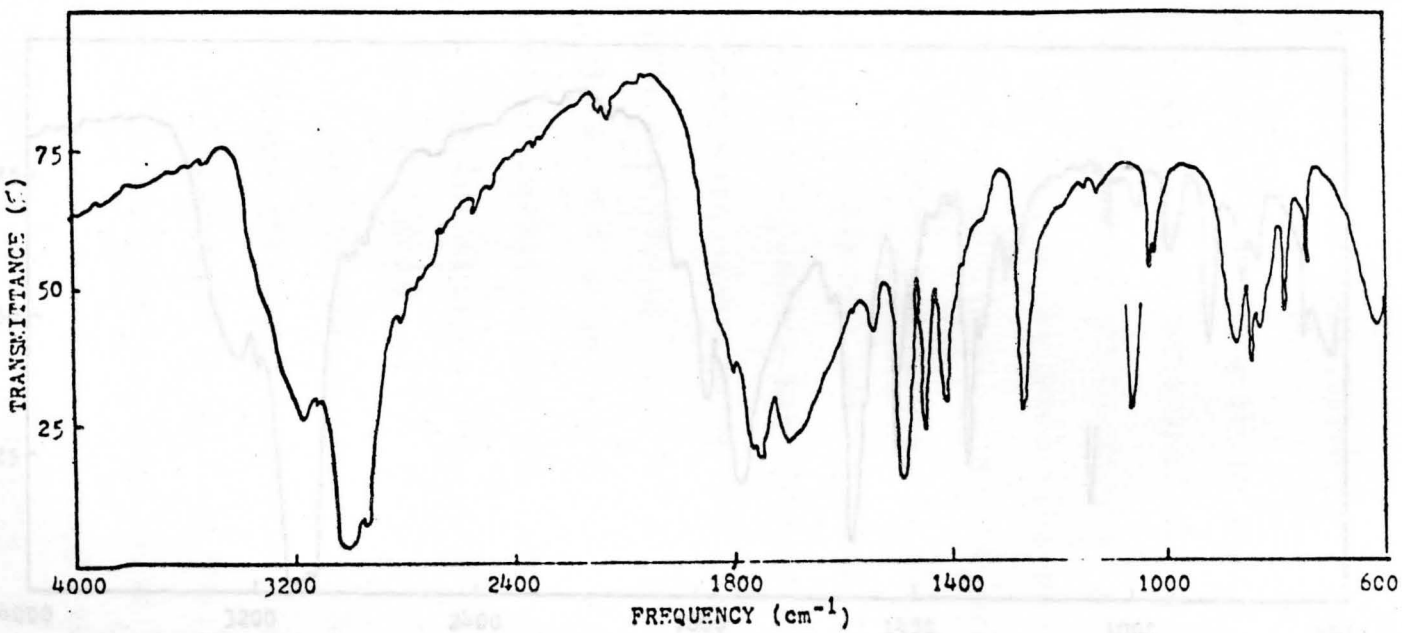


Figure 22. Infra-red spectrum of uracil.

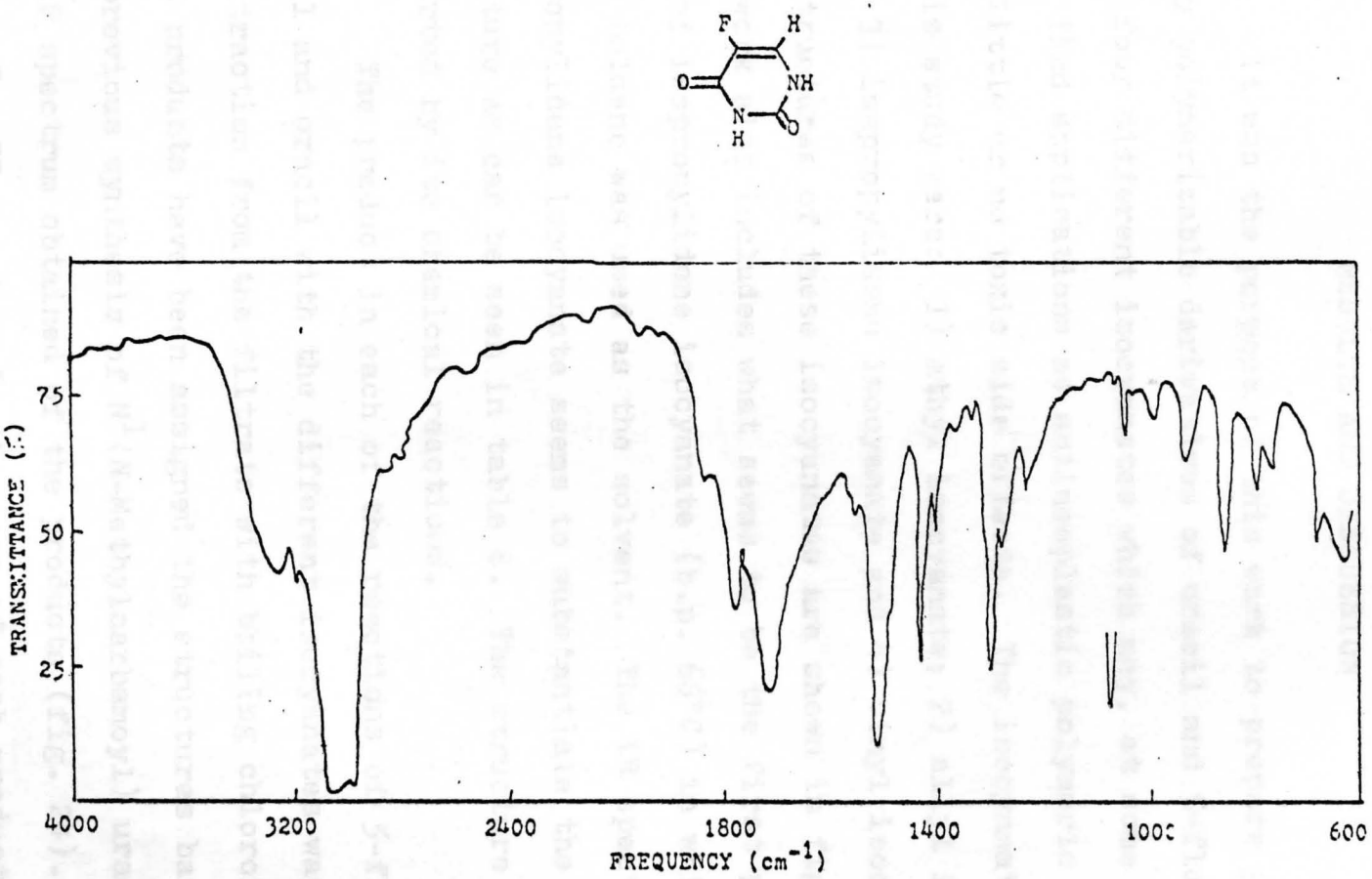


Figure 23. Infra-red spectrum of 5-fluorouracil.

CHAPTER IV

RESULTS AND DISCUSSION

It was the purpose of this work to prepare potentially polymerizable derivatives of uracil and 5-fluorouracil using four different isocyanates which may, at some later date, find applications as antineoplastic polymeric drugs with little or no toxic side effects. The isocyanates used in this study were: 1) ethyl isocyanate; 2) allyl isocyanate; 3) isopropylidene isocyanate and 4) vinyl isocyanate. The structures of these isocyanates are shown in figure 15. This work also includes what seems to be the first preparation of isopropylidene isocyanate (b.p. 66°C) in which anhydrous toluene was used as the solvent. The IR spectrum of isopropylidene isocyanate seems to substantiate the proposed structure as can be seen in table 6. The structure is also supported by its chemical reactions.

The product in each of the reactions of 5-fluorouracil and uracil with the different isocyanates was isolated by extraction from the filtrate with boiling chloroform and these products have been assigned the structures based upon the previous synthesis of N^1(N-Methylcarbamoyl) uracil[68] and the IR spectrum obtained of the products (fig. 24).

The IR spectrum in the case of each product showed strong absorption peaks which seem to indicate that the de-

sired products have been obtained. These peaks along with the possible assignments are shown in table 15 for each of the aforementioned products and the IR spectrum are shown in figures 16-21. The polymerizable derivatives of 5-fluorouracil appear to be the first examples of monomers based on this antineoplastic compound. The uracil derivatives were also prepared for the first time but some polymerizable uracil derivatives had been previously prepared.[61-65]

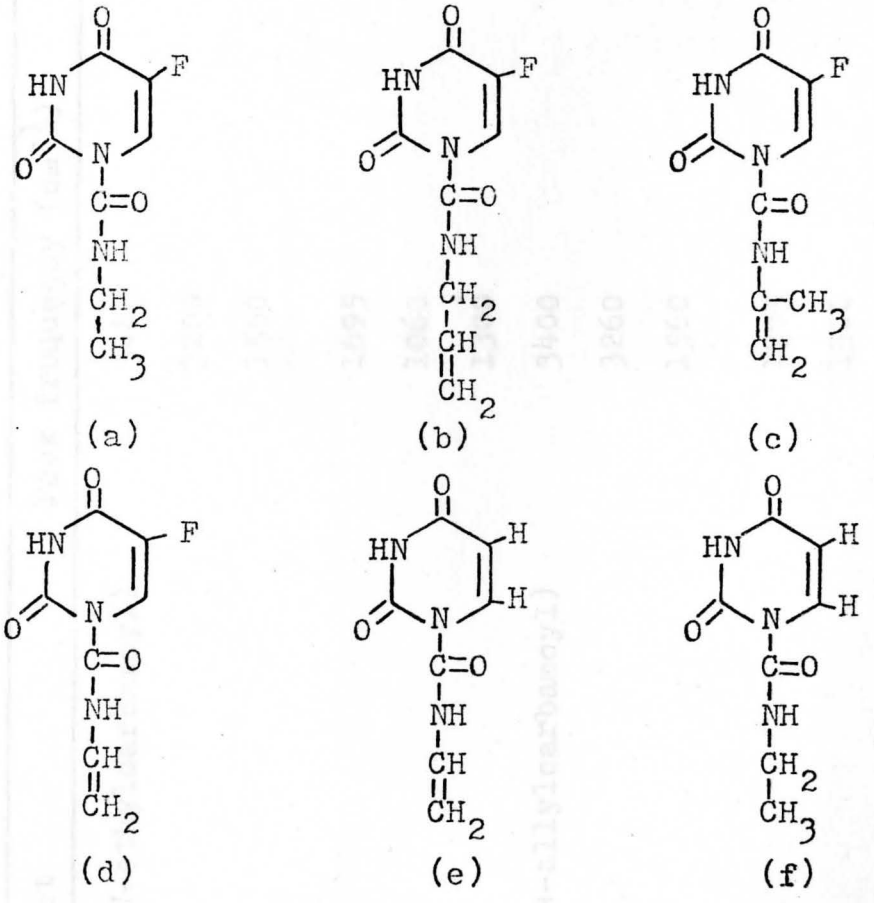


Figure 24. Structures assigned to products: a) 5-fluoro-N^1(N-ethylcarbamoyl) uracil; b) 5-fluoro-N^1(N-allylcarbamoyl) uracil; c) 5-fluoro-N^1(N-isopropylidenecarbamoyl) uracil; d) 5-fluoro-N^1(N-vinylcarbamoyl) uracil; e) N^1(N-vinylcarbamoyl) uracil; f) N^1(N-ethylcarbamoyl) uracil.

TABLE 15

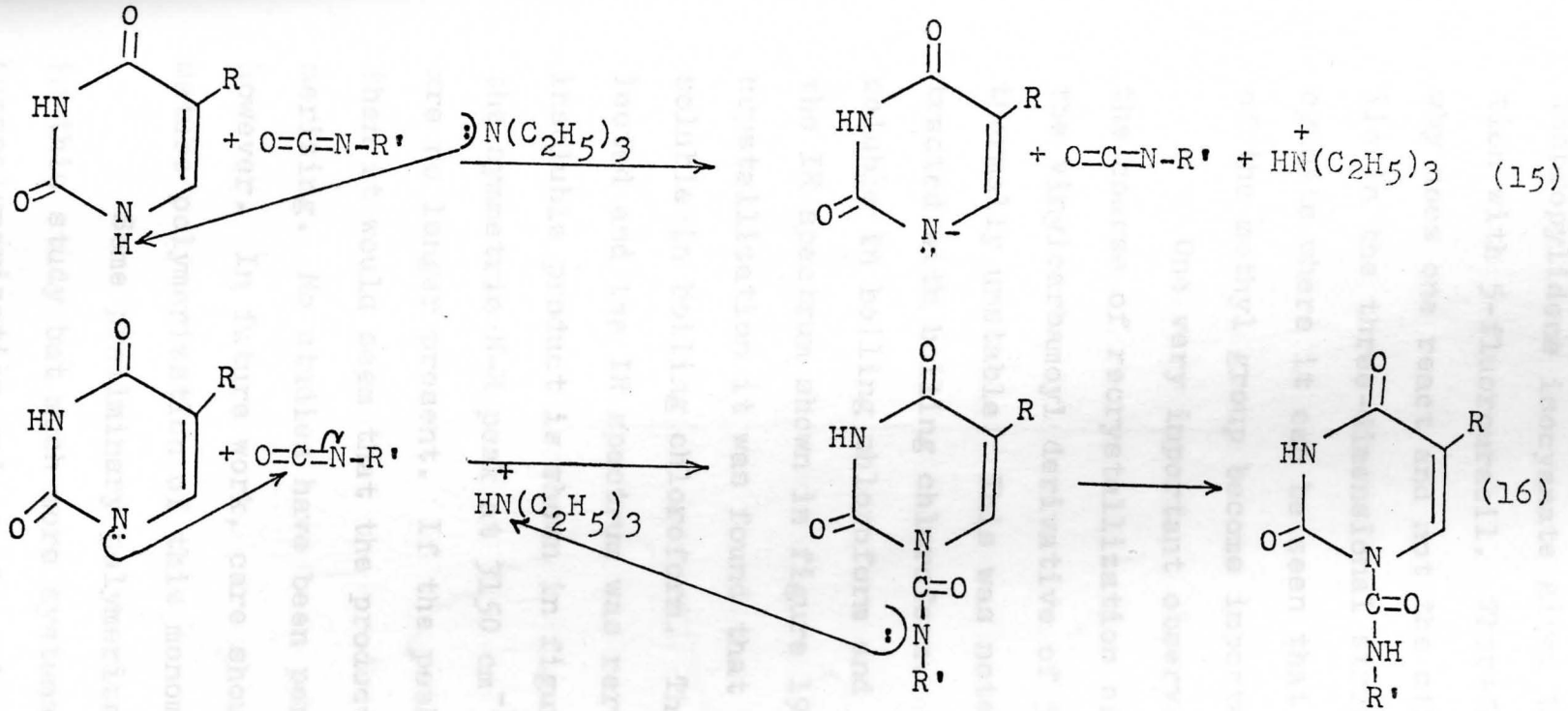
IR Peaks Indicating the Desired Products

Product	Peak frequency (cm^{-1})	Assignment
5-Fluoro-N^1(N-ethylcarbamoyl) uracil	3445	asymmetric N-H
	3200	symmetric N-H
	1580	C=C ring stretch or -C=O
	1695	amide I
	1060	C-F stretch
	1300	amide III
5-Fluoro-N^1(N-allylcarbamoyl) uracil	3400	asymmetric N-H
	3260	symmetric N-H
	1560	C=C conjugated, C=C ring stretch or -C=O
	1705	amide I
	1300	amide III
	1105	=C-F stretch
	895 and 945	=C-H out of plane bend

Product	Peak frequency (cm^{-1})	Assignment
5-Fluoro-N^1(N-isopropylidene-carbamoyl) uracil	3255	asymmetric N-H
	3150	symmetric N-H
	1590	C=C ring stretch, C=C conjugated or -C=O
	1300	amide III
	1100	=C-F stretch
	910 and 945	=C-H out of plane bend
5-Fluoro-N^1(N-vinylcarbamoyl) uracil	3300	asymmetric N-H
	3150	symmetric N-H
	1540	C=C ring stretch, C=C conjugated or -C=O
	1300	amide III
	1100	=C-F stretch
	910	=C-H out of plane bend
N^1(N-ethylcarbamoyl) uracil	3395	asymmetric N-H
	3200	symmetric N-H
	1590	C=C ring stretch or -C=O
	1300	amide III

Product	Peak frequency (cm^{-1})	Assignment
N^1(N-vinylcarbamoyl) uracil	3350	asymmetric N-H
	3200	symmetric N-H
	1560	C=C ring stretch, C=C conjugation or -C=O
	1680	amide I
	1300	amide III
	900 and 865	=C-H out of plane bend

It has been found in this study that 5-fluorouracil reacts readily with each of the isocyanates whereas uracil reacts well with only vinyl isocyanate. It has also been found that neither 5-fluorouracil nor uracil react with any of the isocyanates in the absence of the catalyst, triethylamine. This seems to indicate that the reaction proceeds via the formation of a quaternary ammonium ion formed by the extraction of a hydrogen from the N-1 position of uracil or 5-fluorouracil. This process is shown in equations 15 and 16. This reasoning however is complicated by the fact that uracil does not react readily with any of the isocyanates used except for vinyl isocyanate. This seems to suggest that more factors are involved than the formation of a quaternary ammonium ion. One factor which seems to take a leading role is the solvent polarity. 5-Fluorouracil has a lower pKa value, hence a more acidic nature, and would more readily lose its proton to form the quaternary ammonium ion. When uracil was reacted with ethyl isocyanate using the more polar solvent, dimethylsulfoxide, as the reaction medium, it was found that uracil did react more readily in DMSO than in benzene and this observation supports the hypothesis that solvent polarity does have an important bearing on the rate of reaction. The fact that vinyl isocyanate reacts readily with uracil, in benzene, suggests that conjugation effects may also play a role in ease of reaction since the non-conjugated isocyanates did not react. However, isopropylidene isocyanate, which is also conjugated, does not react readily with uracil. In fact,



(15)

(16)

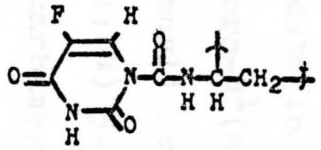
R = H, F

R' = C_2H_5, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH_2$

isopropylidene isocyanate gives the lowest yield in the reaction with 5-fluorouracil. Therefore, the question arises, why does one react and not the other? The answer appears to lie in the three-dimensional structure of isopropylidene isocyanate where it can be seen that steric effects and the size of the methyl group become important.

One very important observation which had been made in the course of recrystallization of products is the fact that the vinylcarbamoyl derivative of 5-fluorouracil appears to be thermally unstable. This was noted when the filtrate was extracted with boiling chloroform. The product was initially soluble in boiling chloroform and the product collected had the IR spectrum shown in figure 19. However upon second recrystallization it was found that the product was no longer soluble in boiling chloroform. The product was then recollected and the IR spectrum was rerun. The IR spectrum of the insoluble product is shown in figure 25. It can be seen that the symmetric N-H peak at 3150 cm^{-1} and the peak at 1540 cm^{-1} are no longer present. If the peak at 1540 cm^{-1} is a -C=C- then it would seem that the product is spontaneously polymerizing. No studies have been performed on this polymer, however. In future work, care should be taken to avoid premature polymerization of this monomer.

Some preliminary polymerization experiments were made in this study but much more systematic work is needed on the homopolymerization and copolymerization of these new monomers.



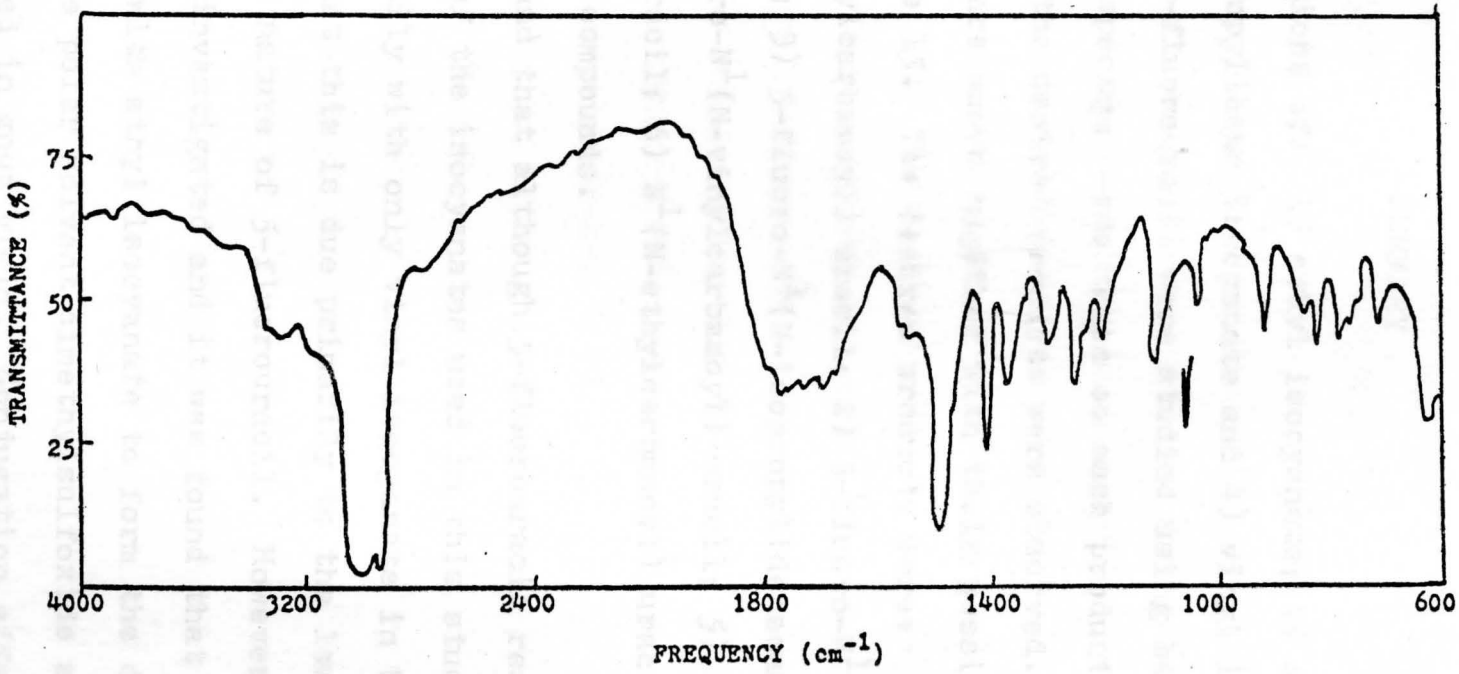


Figure 25. Infra-red spectrum of poly-5-fluoro-N^1(N-vinylcarbamoyl) uracil.

CHAPTER V

SUMMARY

The reactions of: 1) ethyl isocyanate; 2) allyl isocyanate; 3) isopropylidene isocyanate and 4) vinyl isocyanate with uracil and 5-fluorouracil were studied using benzene as the solvent. IR spectra were taken on each product and new peaks indicating the desired products were observed. The peak frequencies are shown together with their possible assignments in table 15. The desired products were: 1) 5-fluoro-N^1(N-ethylcarbamoyl) uracil; 2) 5-fluoro-N^1(N-allylcarbamoyl) uracil; 3) 5-fluoro-N^1(N-isopropylidenecarbamoyl) uracil; 4) 5-fluoro-N^1(N-vinylcarbamoyl) uracil; 5) N^1(N-vinylcarbamoyl) uracil; 6) N^1(N-ethylcarbamoyl) uracil. These are all new compounds.

It was found that although 5-fluorouracil reacts readily with all of the isocyanates used in this study, uracil reacts readily with only vinyl isocyanate in benzene. It is suggested that this is due primarily to the lower pKa, hence, more acidic nature of 5-fluorouracil. However, solvent effects were investigated and it was found that uracil did react readily with ethyl isocyanate to form the desired product in the more polar solvent dimethylsulfoxide and the product was obtained in good yield. Conjugation effects and steric effects were also shown to increase or decrease reac-

tion yields respectively when vinyl isocyanate was compared with isopropylidene isocyanate.

The vinylcarbamoyl derivative of 5-fluorouracil was also shown to be thermally unstable and appears to polymerize when recrystallized from boiling chloroform.

All of the products prepared were initially soluble in boiling chloroform and with the exception of the ethyl carbamoyl derivatives of 5-fluorouracil and uracil, all were potentially polymerizable. All these derivatives are new compounds and the derivatives of 5-fluorouracil are the first polymerizable derivatives for this antineoplastic compound.

This study also demonstrated what appears to be the first preparation of isopropylidene isocyanate (b.p. 66° C) having the structure shown in figure 15. The IR spectrum was taken and the major peaks were recorded in table 5. This spectrum and the resulting chemical reactions appear to substantiate the structure ascribed to this product.

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