Phase-transfer catalysis and ultrasonic acceleration of the reaction are widely used at the institute for the synthesis of new heterocyclic compounds. The obtained compounds are studied by multinuclear magnetic resonance, including ^{15}N, ^{17}O, ^{29}Si, and ^{73}Ge NMR spectroscopy and mass spectrometry. The stereochemical structure of the molecules of the nitrogen-containing heterocycles and the nucleoside derivatives in the crystals is determined by x-ray crystallographic analysis. A list of the publications of workers at the Institute of Organic Synthesis of the Latvian Academy of Sciences on the chemistry of heterocyclic compounds is included in the annual bibliography of the Institute's work [1,2]. Some of the new results are published in articles in the present issue of the journal.

LITERATURE CITED

1. Latvijas Zinatņu Akademijas Organiskas Sintezes Instituts, Bibliografija, 1990, Riga (1991).
2. Latvijas Zinatnu Akademijas Organiskas Sintezes Instituts, Monografijas, Rakstu Krajumi, Autoreferati, 1987-1990, Riga (1991).

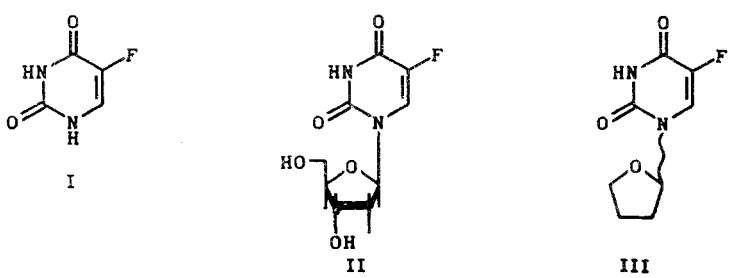
SYNTHESIS OF FTORAFUR (REVIEW)

É. Lukevits and A. Zablotskaya

UDC 547.854.4'722+615.012.1.(048.8)

Published data on methods for the synthesis of the antitumor compound "Ftorafur" by the tetrahydrofurylation of 5-fluorouracil and its derivatives and also by fluorination, cyclization, solvolysis, oxidation, and other reactions are reviewed.

One method of fighting tumor diseases involves the use of antimetabolites. The therapeutic effect of antimetabolites (analogs of nucleic acid components [1]) both of bases (e.g., 5-fluorouracil [2-4]) and of nucleosides (e.g., 2′-deoxy-5-fluorouridine) is due to the possibility of their inclusion in the nucleic acids. This takes place when the products are substrates for DNA or RNA polymerases, which use them in the form of the triphosphates of the respective deoxyribosides or ribosides. The analogous nucleic bases or nucleosides are converted by the cell enzymes into modified nucleotides. In the tumor cell the action of the individual enzymes is changed, the synthesis of isoenzymes is often observed, and the inclusion of the analogs in the nucleic acids may therefore be much stronger than in normal cells. The so-called lethal synthesis, which disrupts replication and transcription when the modified deoxynucleoside is included in the DNA or disrupts the translation and protein synthesis processes when the modified riboside is included in the RNA, is observed more frequently in tumor cells than in normal cells. Modification of the base can be achieved by substitution of a hydrogen atom in the ring by a fluorine atom [as in 5-fluorouracil (I) and 2′-deoxy-5-fluorouridine (II)], while modification of the sugar can be achieved by substitution of the 1-β-D-pentosyl residue by a 2-tetrahydrofuryl fragment.



Institute of Organic Synthesis, Latvian Academy of Sciences, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1590-1620, December, 1991. Original article submitted June 19, 1991.

TABLE 1. Reaction of 5-Chlorouracil with 2,3-Dihydrofuran in the Absence of a Catalyst [29]*

Expt. No.	Solvent	T, °C	Reaction time, h	Yield, %	Expt. No.	Solvent	T, °C	Reaction time, h	Yield, %
1	Pyridine	150	8	88	4	Dioxane	180	5	80
2	$HCONMe_2$	170	5	88	5	MeCOEt	180	2	79
3	$MeCONMe_2$	180	5	86	6	THF	170	5	83

*The amounts of the reagents were: 5-FU 1.3 g; 2,3-DHF 1.4 g; solvent 20 ml in expts. 1-3 and 30 ml in expts. 4-6.

TABLE 2. Effect of the Catalysts on the Reaction of 5-Fluorouracil with 2,3-Dihydrofuran [32]

Expt. No.	Catalyst	Amount, g			Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %
		Cat.	5-FU	2,3-DHF					
1	$C_5H_5N \cdot HCl$	2,4	2,5	3,9	Pyridine	50	120	20	70
2	$PhNMe_2 \cdot HOAc$	1,8	1,3	1,3	$HCONMe_2$	20	140	20	75
3	Me_4NCl	0,6	1,3	1,9	$HCONMe_2$	20	150	9	69
4	H_2NCH_2COOH	0,75	1,3	2,8	$HCONMe_2$	20	145	8	56
5	Nicotinic acid	0,25	2,6	7,0	$HCONMe_2$	30	···	8	67*
6	H-Type zeolite	6,5	13,0	10,5	Pyridine	100	130	10	72
7	Amberlyst A-27	2,6	2,6	3,5	$HCONMe_2$	50	130	7	62
8	$CuNa_2$ – EDTA	0,3	0,39	0,42	α-Picoline	10	150	5	63,3

*The bisproduct.

The idea of substituting the sugar by a tetrahydrofuran residue resulted from the more general concept of creating model nucleosides by drug design [5]. This view was supported by Academician S. A. Giller [6], under whose guidance 1-(2-tetrahydrofuryl)-5-fluorouracil (III), given the trade name "Ftorafur," was synthesized at the Institute of Organic Synthesis of the Latvian Academy of Sciences.

The presence of the tetrahydrofuran group in the molecule of Ftorafur determined its physicochemical, biochemical, and pharmacological characteristics and unique pharmacokinetic characteristics. Ftorafur as the nucleosidic analog of 5-fluorouracil has unusually high lipophilicity [7], while remaining a water-soluble compound. The high lipophilicity of Ftorafur secures its rapid passage through biological membranes, its wide distribution in the organism, and its penetration through the hematoencephalic barrier.

Being an antimetabolite [8], Ftorafur can be regarded as the transporting form of 5-fluorouracil, which requires bioactivation by enzymatic systems. The activation of Ftorafur by microsomal oxidases of the liver leads to the appearance of a whole series of metabolites, the central position among which belongs to 5-fluorouracil, formed as a result of hydrolysis of the pseudoglycosidic C—N bond.

By virtue of the high antitumor activity Ftorafur (Tegafur, Futraful, FT-207) has acquired world-wide familiarity [8-15]. The presence of the asymmetric carbon atom in the tetrahydrofuran ring of Ftorafur gives rise to the existence of R and S stereoisomers [15,16] by analogy with the α and β anomers of nucleosides. However, detailed biological investigation of each of them showed that they had identical activity in test systems [17].

Ftorafur was first synthesized in 1964 under the leadership of Giller at the Institute of Organic Synthesis by Zhuk using the mercury method. This method was subsequently substituted by the silyl method, by which Ftorafur is produced to this day at the pilot plant of the Institute of Organic Synthesis.

The widespread clinical use of Ftorafur prompted the search for new methods for its production. All the methods so far described for the synthesis of 1-(2-tetrahydrofuryl)-5-fluorouracil can be categorized as follows: N-Alkylation of 5-fluorouracil by furan derivatives; reaction of the salts of 5-fluorouracil with 2-substituted tetrahydrofuran; synthesis of Ftorafur by the Hilbert—Johnson method; the silyl method for the synthesis of Ftorafur.

In addition to the above-mentioned methods for the synthesis of Ftorafur (which are the main methods), other original procedures have been described in the literature, e.g., direct fluorination of the aglycone, construction of the tetrahydrofuran ring from the $N_{(1)}$-acyclic derivatives of 5-fluorouracil, hydrolysis of $N_{(1)}$,$N_{(3)}$,-bis(2-tetrahydrofuryl)-5-fluorouracil, and various other methods.

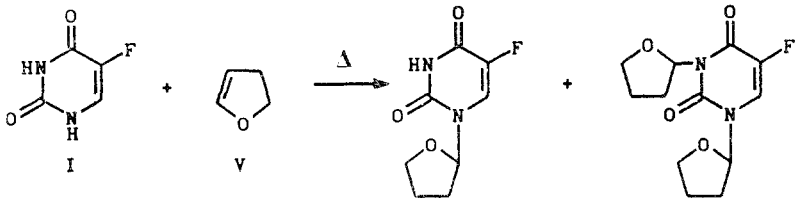
In so far as the search for antimetabolites of natural nucleosides in the series of 5-fluorouracil derivatives continues [18-21], we have reviewed the published data and the results of our own investigations on the synthesis of Ftorafur published up to 1991.

1. N-ALKYLATION OF 5-FLUOROURACIL BY FURAN DERIVATIVES

The direct 2-tetrahydrofurylation of 5-fluorouracil with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil is possible either with 2,3-dihydrofuran (V) or with a 2-substituted tetrahydrofuran.

1.1. Addition of 5-Fluorouracil to 2,3-Dihydrofuran

It was shown [22-25] that in spite of repeated unsuccessful attempts [26-28] at the addition of uracils at the C=C double bond of 2,3-dihydrofuran, it takes place smoothly at elevated pressure and temperature in an aprotic solvent without a catalyst:



I V III IV

The main reaction products are 1-(2-tetrahydrofuryl)-5-fluorouracil and 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil (IV), the content of which in the reaction mixture depends on the molar ratios of the initial reagents and on the reaction temperature [25]. Thus, if the molar concentration of 2,3-dihydrofuran is low (up to a fourfold excess in relation to the 5-fluorouracil), e.g., with a [5-FU]—2,3-[DHF] ratio of 0.04:0.137, and the reaction is conducted in a dilute pyridine solution at 180°C in a tube, the formation of the monosubstituted compound (III) is preferred (83%). 1,3-Bis(2-tetrahydrofuryl)-5-fluorouracil (7%), 3-(2-tetrahydrofuryl)-5-fluorouracil (2%), and 5-fluorouracil (8%) were also found among the reaction products [22]. Under these conditions and at high temperatures especially the formed bis-substituted compound is susceptible to decomposition with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil. If a large excess of 2,3-dihydrofuran, which can at the same time act as solvent, is used in the reaction, only 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil is obtained [22,25]. The constant small presence (<2%) of the isomeric 3-(2-tetrahydrofuryl)-5-fluorouracil in the reaction mixture should be noted. This indicates that the main path along which the acylation occurs is attack by the dihydrofuryl group at the $N_{(1)}$ atom of the pyrimidine base [22].

In addition to pyridine, the following polar solvents were tried in the reaction: Picoline, quinoline, DMFA, dimethylacetamide, DMSO, hexamethylphosphorotriamide, dioxane, acetone, methyl ethyl ketone, diisobutyl ketone, tetrahydrofuran (Table 1). A [5-FU]—[DHF] molar ratio of 1:(1-2) is preferred [29,30]. The method is simple but requires reaction at high temperature and with a considerable amount of the solvent.

In order to inhibit the conversion of the 2,3-dihydrofuran into the unreactive side products it was proposed to conduct the reaction in the presence of other furan compounds, e.g., 2-alkoxy-, 2-acyloxy-, and 2-hydroxytetrahydrofurans, 2,5-dihydrofuran, and tetrahydrofuran. It was supposed that certain types of furans would serve under the reaction conditions as a source of 2,3-dihydrofuran and would thereby lead to a smooth process [31].

1-(2-Tetrahydrofuryl)-5-fluorouracil can also be produced in the reaction of 5-fluorouracil and 2,3-dihydrofuran in a polar aprotic solvent at 80-200°C in the presence of catalysts [32]. An amine salt, a quaternary ammonium salt, a mixture of an organic base and a metal halide, amphoteric compounds (the amino acids glycine and alanine), and also ion-exchange resins, chelates, and Lewis acids have been proposed as catalysts [32] (Table 2). The reaction usually takes place in a solvent (DMFA, DMSO, pyridine, picoline) with the reagents in molar ratios of 1:(1-4).

TABLE 3. Reaction of 5-Fluorouracil with 2,3-Dihydrofuran in the Presence of Lewis Acids

Expt. No.	Catalyst	Amount, g			Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
		Cat.	5-FU	DHF						
1	$ZnCl_2$	0,1	0,78	0,8	Pyridine	5	100	17	41	[35]
2	BF_3	0,1	0,78	0,8	Pyridine	5	100	17	45	[35]
3	$AlCl_3$	0,1	0,78	0,8	Pyridine	10	100	17	25	[35]
4	$AlCl_3$	0,35	2,5	2,0	Pyridine	50	120	6	75	[32]
									50	[40]
5	$AlCl_3$	2,66	2,6	2,66	DMFA	30	130	6	60	[32]
6	$AlCl_3$	2,0	0,5	0,45	DMFA	5	65	2	70	[41, 42]
7	$AlCl_3$	0,3	0,3	0,3	DMSO	15	60	3	65	[41, 42]
8	$TiCl_4$	0,8	5,2	5,32	Pyridine	50	80	5	69	[32, 33]
									46	[40]
9*	$SnCl_4$	0,26	1,3	1,4	DMFA	20	120	6	65	[34]
10	$SbCl_3$	0,1	0,78	0,8	Pyridine	5	100	17	27	[35]
11	$FeCl_3$	0,64	2,5	2,0	Pyridine	50	120	8	69	[32, 33]

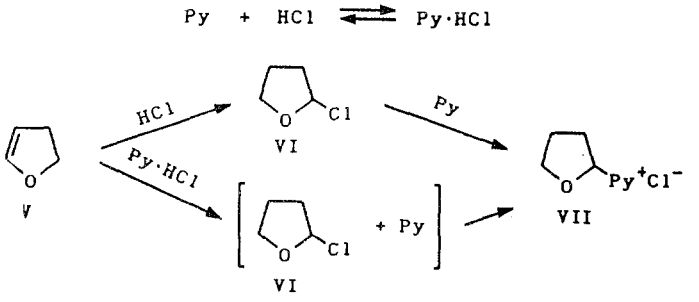
*Na_2CO_3 was used as inorganic base at the rate of 0.11 g.

Organic amines [33] or inorganic bases [34] can be used to accelerate the reaction.

It has been pointed out that the use of metal halides and nonmetals and also trisubstituted organic ammonium salts of organic and inorganic acids as catalysts makes it possible to reduce the temperature of the reaction of 5-fluorouracil with 2,3-dihydrofuran a little (to 50-150°C) [35-38]. The best results here were obtained with lithium chloride in methyl ethyl ketone and dioxane [39].

The most effective among the Lewis acids (Table 3) was aluminum chloride [32,33]. Realization of the reaction in DMFA or DMSO in the presence of aluminum chloride makes it possible to reduce the reaction temperature (to 60°C) and time (to 2 h) with retention of a high yield (70%) [41,42]. The effectiveness of aluminum oxide was mentioned in the patent [32]. A threefold or larger increase in the molar concentration of 2,3-dihydrofuran in relation to 5-fluorouracil in this reaction leads to the formation of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil [43].

Investigation of the reaction of 5-fluorouracil with 2,3-dihydrofuran at 120°C in pyridine in the presence of such Lewis acids as aluminum chloride and titanium tetrachloride showed that (2-tetrahydrofuryl)pyridinium chloride is formed as intermediate [40]. The reaction is initiated by the reaction of the 5-fluorouracil with the aluminum or titanium chloride (the structure of the reaction product was not established), as a result of which hydrogen chloride is formed. The latter partly combines with the pyridine into pyridine hydrochloride and partly reacts with the 2,3-dihydrofuran with the formation of 2-chlorotetrahydrofuran (VI) [22], capable of combining the pyridine concurrently into (2-tetrahydrofuryl)pyridinium chloride (VII). The latter is also formed from pyridine hydrochloride and 2,3-dihydrofuran [44]. Here it was shown [40] that the reaction takes place through the intermediate formation of 2-chlorotetrahydrofuran:

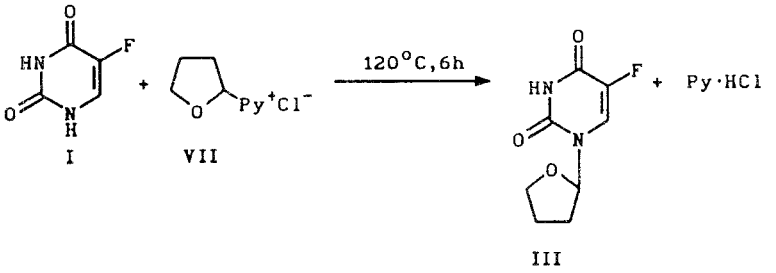


The unreacted 5-fluorouracil then enters into reaction with the (2-tetrahydrofuryl)pyridinium chloride, and this leads to the formation of Ftorafur.

TABLE 4. Reaction of 5-Fluorouracil with 2,3-Dihydrofuran in the Presence of Halogenoalkylsilanes [47]*

Expt. No.	Catalyst	Reaction time, min	Yield, %	Expt. No.	Catalyst	Reaction time, h	Yield, %†
1	Me_3SiCl	···	36	7	Ph_2SiCl_2	113	55
2	Me_2SiCl_2	30	79	8	$MeSiCl_3$	79	44
3	Me_2SiCl_2	30	69	9	$SiHCl_3$	45	35
4	$MeSiHCl_2$	60	79	10	$VynSiCl_3$	40	53
5	$MePhSiCl_2$	52	72	11	$PhSiCl_3$	60	64
6	$MeVynSiCl_2$	42	81				

*Reaction conditions: a) Amounts of reagents: 5-FU 5.0 g; 2,3-DHF 4.1 g; b) solvent acetonitrile, 40 ml; c) organic amine, triethylamine, 0.45 g (in the second experiment piperidine, 0.33 g, in the third experiment benzylamine, 0.41 g). †The yield of 1-(2-tetrahydrofuryl)-5-fluorouracil after treatment of the reaction mixture with an alkaline solution.



I VII III

Consequently, the role of the aluminum chloride (and also of the titanium tetrachloride) in this reaction amounts to the generation of hydrogen chloride, which adds at the double bond of 2,3-dihydrofuran with the formation of 2-chlorotetrahydrofuran. The latter is stabilized in the form of a pyridine complex and participates in tetrahydrofurylation in such a form.

Realization of the reaction in the presence of a nonmetal halide (e.g., $SiCl_4$) [45] in a tertiary amine medium (e.g., pyridine) at 60°C helps to shift the process toward the formation of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil, the yield of which amounts to 80% with a general nucleoside yield of 96% [46]. The method for the production of Ftorafur from 5-fluorouracil and 2,3-dihydrofuran in the presence of halogenosilanes therefore requires additional treatment of the reaction mixture with an alkaline solution [47,48] or with hot alcohol [49] in order to convert the 1,3-bisproduct completely into 1-(2-tetrahydrofuryl)-5-fluorouracil.

Among the numerous silanes tested as catalyst the most effective was dimethyldichlorosilane (Table 4) [47,50-53]. The reaction is conducted in a solvent (preferably acetonitrile) at 20-26°C in the presence of an organic amine, as a rule, triethylamine (0.05-0.20 mole/mole of 5-FU) for 2 h. The molar ratios of the employed reagents [5-FU], [2,3-DHF], [NR_3], and [Me_2SiCl_2] are 1:(1-1.5):(0.05-0.1):(2-2.5).

It is suggested that in this case the silane acts as catalyst (a Lewis acid) and the reaction takes place without the formation of a silylated intermediate [53], although this is not excluded in the presence of triethylamine.

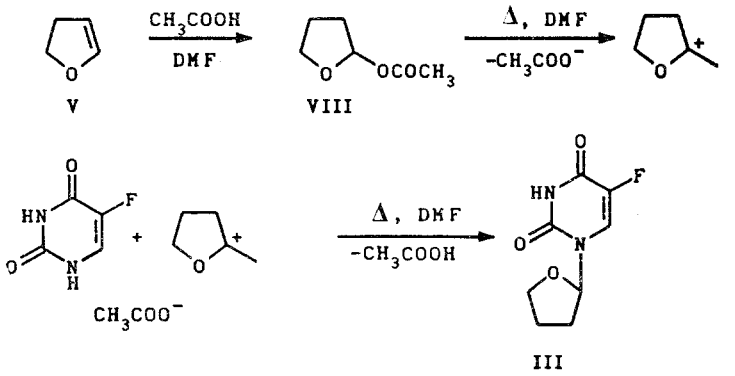
If trimethylchlorosilane is used as catalyst, it is possible to obtain a significant increase in the yield of 1-(2-tetrahydrofuryl)-5-fluorouracil when the reaction is conducted in the presence of 2,6-lutidine in boiling 1,2-dichloroethane for 2 h. The 3-(2-tetrahydrofuryl) group is removed as a result of treatment of the compound with ethanol [49].

Attention is drawn to the method of tetrahydrofurylation in the presence of phosphorus(III) [54,55] and phosphorus(V) [56] compounds, by means of which it is possible to reduce the reaction temperature to room temperature and to achieve $N_{(1)}$-regiospecificity (Table 5). The use of phosphorus(III), i.e., organic compounds (halogenophosphites) [54] and phosphorus trichloride [55], requires the presence of a tertiary amine (e.g., trimethylamine, triethylamine, N-methylmorpholine, pyridine, dimethylaniline, N-methylpiperidine) and an aprotic solvent (dichloromethane, chloroform, dichloroethane, acetonitrile, benzene).

TABLE 5. Reaction of 5-Fluorouracil with 2,3-Dihydrofuran in the Presence of Phosphorus Compounds

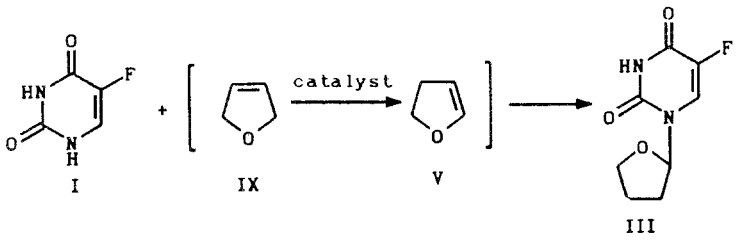
Expt. No.	Catalyst	Amount, g			Amine	Amount of amine, g	Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
		Cat.	5-FU	2,3-DHF								
1	CDP*	5,4	1,3	1,05	C_5H_5N	0,87	—	—	20	24	81	[54]
2	CDP	3,0	1,3	1,05	Et_3N	1,11	$HCONMe_2$	10	20	24	86	[54]
3	CDP	3,0	1,3	1,05	Et_3N	1,11	$(CH_2Cl)_2$	20	Heating	6	70	[54]
4	PCl_3	1,37	1,3	0,84	Et_3N	1,0	CH_2Cl_2	15	20	18	65	[55]
5	PCl_5	3,2	2,0	1,6	—	—	Tetramethylurea	10	15 . . . 20	0,5	64	[41, 42, 57]
6	PCl_5	2,25	5,0	4,0	—	—	$MeCONMe_2/CCl_4$	10/12,5	60	1	63	[42]
7	PCl_5	2,25	5,0	4,0	—	—	$MeCONMe_2/CCl_4$	10/12,5	15 . . . 20	1	63	[41, 57]
8	PCl_5	4,0	5,0	3,5	—	—	$MeCONMe_2/CH_3NO_2$	5/20	15 . . . 20	1	65	[41]
9	PCl_5	4,0	5,0	3,5	—	—	$MeCONMe_2$	5	15 . . . 20	1	65	[57]
10	PCl_5	1,6	2,0	1,4	—	—	$(Me_2N)_3PO$	4	20	1	75	[41, 42, 57]
11	PCl_5	1,6	2,0	1,4	—	—	$(Me_2N_3)_3PO$	4	20	0,5	88	[56]

*CDP = 2-chloro-1,3-dioxaphosphorane.



Direct and selective $N_{(1)}$-tetrahydrofurylation of 5-fluorouracil by 2,3-dihydrofuran is observed in the presence of phosphorus pentachloride in hexamethylphosphorotriamide (HMPTA) [56] with the reagents [5-FU], [2,3-DHF], and [PCl_5] in molar ratios of 1:1.3:0.5. The reaction takes place under mild conditions (stirring at room temperature for 30 min) and gives a high yield of 1-(2-tetrahydrofuryl)-5-fluorouracil (88%). In the case of the analogous reaction in DMFA or dimethylacetamide the yield of the final product is reduced [41,42,57], while the use of phosphorus trichloride instead of phosphorus pentachloride in this reaction does not guarantee its regioselectivity [56].

5-Fluorouracil is also capable of adding to 2,3-dihydrofuran in the presence of Brönsted acids in a solvent of amine or amide type [40,58-60]. It was found that Ftorafur is formed when 5-fluorouracil is heated with 2,3-dihydrofuran in DMFA solution at 140°C in the presence of acetic acid [40]. Here, if the ratio of the reagents is close to equimolar, the yield of Ftorafur is 35%. Increase in the amount of 2,3-dihydrofuran (1:2:1) raises the yield of Ftorafur to 47%. The same yield can be obtained with a 10-fold reduction in the amount of acetic acid. The acetic acid evidently adds initially at the double bond of the 2,3-dihydrofuran with the formation of 2-acetoxytetrahydrofuran (VIII) as intermediate [22], which decomposes at the high temperature (higher than 120°C) with the elimination of the acetate anion and the formation of the tetrahydrofuryl cation as counterion [61]. The latter attacks the nitrogen atom of the 5-fluorouracil with release of a proton, which can recombine with the acetate anion and continue the reaction. It is also impossible to reject the alternative path involving an S_N1 or S_N2 reaction between 5-fluorouracil and the obtained 2-acetoxy intermediate.



The possibility of using 2,5-dihydrofuran (IX) in 1-(2-tetrahydrofurylation) in the presence of transition-metal complexes has been reported [62]. Under these conditions the 2,5-dihydrofuran isomerizes to 2,3-dihydrofuran, which secures the alkylation reaction.

The reaction takes place in the presence of a crown ether in a solvent at 60-120°C for 2-16 h. A 2-4-fold molar excess of 2,5-dihydrofuran and a 1-10% molar excess of the catalyst in relation to the 5-fluorouracil are used.

Under these conditions isomerization and alkylation are conducted in succession in a single technological stage without isolation of the intermediates.

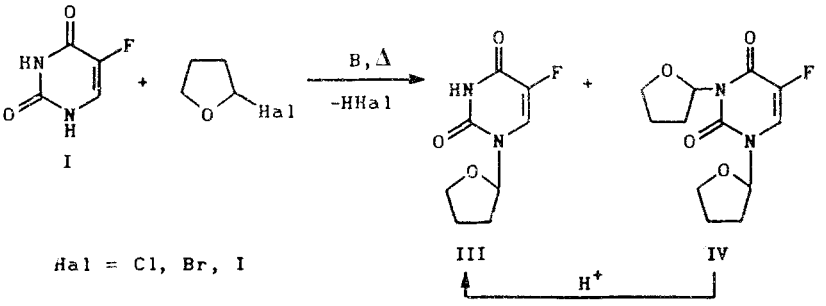
1.2. Reaction of 5-Fluorouracil with 2-Halogenotetrahydrofurans

Successful reaction of 5-fluorouracil with 2-halogen-substituted tetrahydrofurans requires the presence of an acid-combining reagent, which may be an organic or an inorganic base (Table 6).

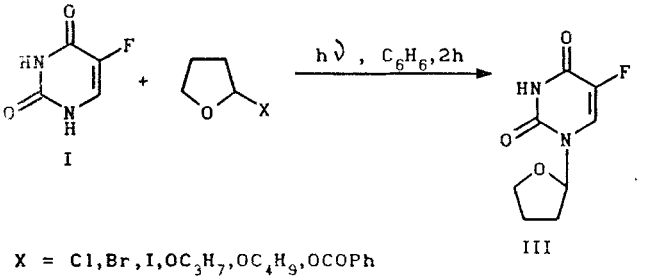
TABLE 6. Reaction of 5-Fluorouracil with 2-Chlorotetrahydrofuran

Expt. No.	Amount of 5-FU, g	Amount of 2-chloro-tetrahydro-furan, g	Base	Amount of base, g	Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
1	1,3	1,1	Et_3N	1,1	$HCONMe_2$	15	35	5	75	[63]
2	2,6	2,4	Et_3N	2,4	$HCONMe_2$	30	−10 ... +5	15	82	[64]
3	1,3	1,4	Et_3N	1,4	C_6H_6	20	40	4	80	[64]
4	1,3	1,6	Et_3N	1,6	C_6H_6	20	35	5	35	[63]
5	1,3	1,2	NaH	2,7	$HCONMe_2$	20	100	1	69	[65]
6	1,3	1,2	KH	4,5	$HCONMe_2$	20	100	1	74	[65]
7	1,3	1,2	NaOH	4,5	$HCONMe_2$	20	100	1	82	[65]
8	1,3	1,2	KOH	6,2	$HCONMe_2$	20	100	1	84	[65]
9	1,3	1,2	CH_3ONa	6,3	$HCONMe_2$	20	100	1	80	[65]
10	1,3	1,2	K_2CO_3	2,0	Me_2SO	20	100	1	90	[65]
11	1,0	0,9	$MgSiO_3$	2,0	—	—	40	1	95	[66]
12	1,0	0,9	$Ba(CH_3COO)_2$	1,0	C_6H_6	...	...	...	95	[66]
13	1,0	0,9	BaO	1,2	C_6H_6	...	80	0,8	95	[66]

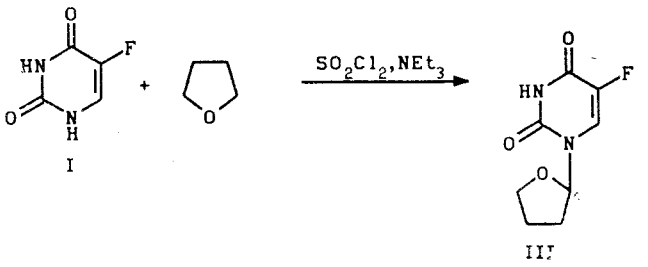
A nitrogen-containing aprotic solvent (e.g., trialkylamine [63,64,67-70], diethylamine [69], pyridine [63,64,69], diazo compounds [68], dimethylaniline [63,64]) is used as organic base and is in some cases at the same time the solvent [68,69]. Alkali-metal hydroxides [65,68], carbonates [65,68], hydrides [65,68], alcoholates [65], oxides [66], and acetates [66] and also basic ion-exchange resins [66], basic silica gel [66], or fluorosil [66] can be used as inorganic base. The basic additions are used in amounts larger than equimolar in relation to the 2-halogenotetrahydrofuran. In the case, therefore, where alkali-metal alcoholates, hydrides, and hydroxides are used as catalysts the Ftorafur can be synthesized through the formation of a salt of the alkali metal with the 5-fluorouracil. As a rule the reaction is short and takes place in a solvent (e.g., DMFA) at temperatures up to 100°C. As a result 1-(2-tetrahydrofuryl)- and 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil are formed. Subsequent acid treatment of the reaction mixture with an inorganic or organic acid secures quantitative bissubstituted product → monosubstituted product conversion and significantly increases the yield of the target product [64,71].



The production of 1-(2-tetrahydrofuryl)-5-fluorouracil from 5-fluorouracil and 2-substituted tetrahydrofuran under the influence of UV irradiation has been described [72]:



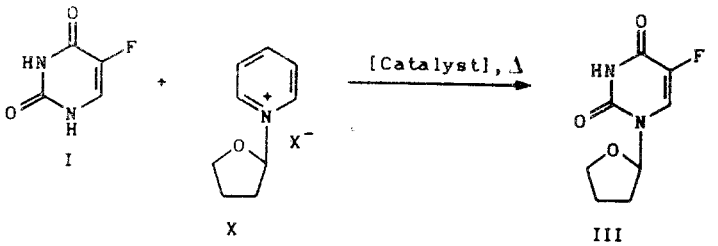
Tetrahydrofurylation takes place in single stage and gives a high yield (93-95%). The fundamental possibility of the reaction of 5-fluorouracil with tetrahydrofuran in the presence of sulfuryl chloride [73] and of a liquid amine (preferably triethylamine) [74] has been demonstrated experimentally.



I III

This simple procedure involves two consecutive processes (chlorination of the tetrahydrofuran at position 2 and subsequent N-alkylation of the 5-fluorouracil) without isolation of the intermediates.

The previously obtained 2-tetrahydrofurylpyridinium salt (X) can be used as alkylating agent [75].



I X III

$X^- = Cl^-$, AcO^-, $CH_3SO_3^-$, $p\text{-}CH_3C_6H_4SO_3^-$, HSO_4^-, NO_3^-, $H_2PO_4^-$, picrate

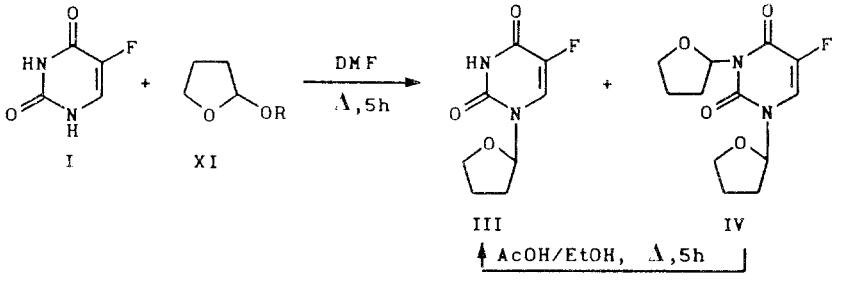
Here the reaction takes place in a solvent at 90-150°C, depending on the counterion, in the possible presence of a catalyst. Alkali-metal halides (sodium iodide, potassium iodide, lithium iodide) or Lewis acids (aluminum chloride, titanium tetrachloride) are used as catalysts. Under such general conditions in some cases alkylation takes place at both nitrogen atoms with the preferential formation of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil, the yield of which amounts to more than 64%.

1.3. Reaction of 5-Fluorouracil with 2-Alkoxytetrahydrofurans

The formation of 1-(2-tetrahydrofuryl)-5-fluorouracil in the reaction of 5-fluorouracil and tetrahydrofuran derivatives with an oxygen-containing function at position 2 of the ring has been studied widely. Such compounds are 2-alkoxytetrahydrofuran (XI), 2-acyloxytetrahydrofuran (XII), and silyloxytetrahydrofuran.

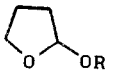
2-Alkoxytetrahydrofurans are obtained by the addition of alcohols to 2,3-dihydrofuran [76,77], which is produced by the isomerization of the readily obtainable 2,5-dihydrofuran [62]. Use of various 2-alkoxytetrahydrofurans under reaction conditions of the same type makes it possible to compare their reactivity in relation to the structure and the nature of the substituent at position 2 [78-81] (Table 7).

The reaction of 5-fluorouracil with 2-methoxytetrahydrofuran (R = CH_3) in DMFA at 150-155°C takes place slowly, and the yield of Ftorafur after heating (5 h) does not exceed 3%. The maximum yield was obtained in the case of 2-tert-butoxytetrahydrofuran [78,79,82] as a result, probably, of the greater susceptibility of the tert-butoxy group to elimination compared with the other alkoxy substituents.



I XI III IV

R = CH_3, C_2H_5, C_3H_7, i-C_3H_7, C_4H_9, i-C_4H_9, sec-C_4H_9, t-C_4H_9, C_5H_{11}, C_6H_{13}, $CH_2C_6H_5$

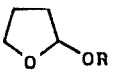
TABLE 7. Reaction of 5-Fluorouracil with 2-Alkoxytetrahydrofuran  [78, 79]*

XI

R	T, °C	Reaction time	Yield, %	R	T, °C	Reaction time	Yield, %
CH_3	150...155	5	3	*sec*-C_4H_9	160...165	5	16
C_2H_5	150...155	5	12	*t*-C_4H_9	160...165	5	67
C_3H_7	153...157	4,5	13	C_5H_{11}	160...165	5	8
i-C_3H_7	155...160	5	15	C_6H_{13}	160...165	6	5
C_4H_9	155...160	5	9	$CH_2C_6H_5$	160...165	6	2
i-C_4H_9	160...165	4	8				

*Amounts of reagents: 2-Alkoxytetrahydrofuran 11.6 mmole, 5-FU 7.7 mmole.

TABLE 8. Reaction of 5-Fluorouracil with 2-Alkoxytetrahydrofuran in the Presence of a Catalyst and Base [83]

Expt. No.	 R	Amt., g	Amount of 5-FU, g	Catalyst	Amount of catalyst, g	Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %
1	C_2H_5	0,697	0,52	$ZnCl_2$	0,55	$HCONMe_2$	10	130	8	81
2	*i*-C_3H_7	2,34	1,56	BF_3	0,36	Picoline	25	160	8	82
3	*i*-C_3H_7	0,781	0,52	$AlCl_3$	0,53	C_5H_5N	10	130	8	82
4	*t*-C_4H_9	0,649	0,39	$ZnCl_2$	0,4	C_5H_5N	10	130	5	86
5	*t*-C_4H_9	0,649	0,39	$AlCl_3$	0,4	C_5H_5N	10	130	5	91
6	*t*-C_4H_9	0,65	0,39	$AlCl_3$	0,04	$HCONMe_2$	5	120	5	75
7	*t*-C_4H_9	21,6	0,39	$AlCl_3$	0,4	$HCONMe_2$ Et_3N	6 1,52g	150	7	40
8	*t*-C_4H_9	1,95	1,17	$AlCl_3$	0,4	$MeCONMe_2$	20	150	5	90
9	*t*-C_4H_9	0,649	0,39	$AlCl_3$	0,4	β-Picoline	10	160	4	92
10	*t*-C_4H_9	0,649	0,39	$TiCl_4$	0,5	C_5H_5N	10	130	5	...
11	*t*-C_4H_9	0,649	0,39	$TiCl_4$	0,57	$HCONMe_2$ Et_3N	10 1,52g	130	5	85

The use of aluminum chloride as catalyst in the reaction does not give an increase in the yield. However, it can be increased slightly by increasing the length of the reaction or by using an excess of the alkylating agent.

In addition to the main reaction product 1-(2-tetrahydrofuryl)-5-fluorouracil, the presence of small amounts of the accompanying 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil in the reaction mixture was established. Its acid hydrolysis provides an additional source for increase in the yield of Ftorafur [71,78,79].

A considerable expansion in the possibilities of this reaction with catalysts of the Lewis acid type (Table 8) in conjunction with an organic (amines of various types) or inorganic base (calcium hydroxide, aluminum hydroxide, sodium carbonate, etc.) is indicated in the Japanese patent [83]. The organic base can at the same time act as solvent. In addition [83,84], another $N_{(1,3)} \rightarrow N_{(1)}$ conversion path apart from acid hydrolysis has been mentioned in the form of alkali hydrolysis, as a result of which a Ftorafur yield close to quantitative is achieved in some cases.

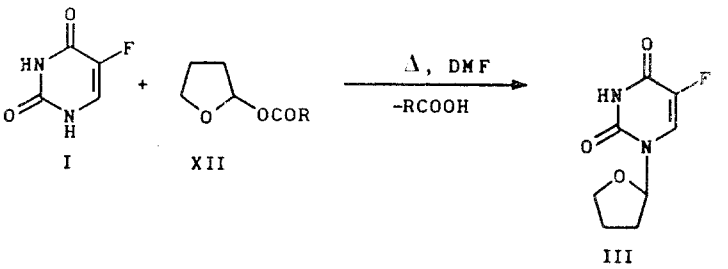
Metal oxides (aluminum oxide, zinc oxide, titanium dioxide, cerium dioxide, silica, magnesium oxide, etc.), molecular sieves, acidic clays, sulfides (zinc sulfide, calcium sulfide, etc.), and sulfates (zinc sulfate, aluminum sulfate, magnesium sulfate, barium sulfate, etc.) of metals have also been proposed as accelerators of $N_{(1)}$-alkylation [84].

Ftorafur can be synthesized in a short time (30 min) and with a high yield without the formation of side products if the reaction between the 5-fluorouracil and 2-alkoxytetrahydrofuran is conducted in a dry organic solvent (e.g., acetonitrile) in the presence of dimethyldichlorosilane as catalyst in a tertiary amine medium (e.g., triethylamine) [85,86]. A significant advantage of this method is the fact that the reaction takes place at room temperature.

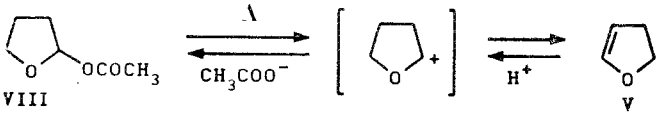
The use of 2-trimethylsilyloxytetrahydrofuran [87] and 2-tetrahydrofuranol [88] has been described in the patent literature. However, this and the other method are not very promising, since the use of 2-trimethylsilyloxytetrahydrofuran requires harsh reaction conditions (150-170°C, 20 h, DMFA) with absolutely dry reagents. In the case of 2-tetrahydrofuranol the reaction is promoted by Lewis acids ($AlCl_3$, $ZnCl_2$, Me_3SiCl), and the water formed in the reaction is removed from the reaction system by azeotropic distillation with toluene or by other water-removing agents (molecular sieves, trimethylchlorosilane, hexamethyldisilazane, dicyclohexylcarbodiimide). The reaction takes place in an inert solvent (DMFA, dimethylacetamide, DMSO, pyridine, picoline, quinoline) at high temperature (144-154°C), and the yield of Ftorafur amounts to 45-67%.

1.4. Reaction of 5-Fluorouracil with 2-Acyloxytetrahydrofurans

It was shown [89] that 5-fluorouracil reacts smoothly with 2-acyloxytetrahydrofuran in DMFA at 120°C without a catalyst and gives 1-(2-tetrahydrofuryl)-5-fluorouracil with a 53% yield.



As a result of investigation of the mechanism of the reaction with 2-acetoxytetrahydrofuran as alkylating agent it was established that it is in some respects similar to the mechanism of the reaction of 5-fluorouracil with 2,3-dihydrofuran in the presence of acetic acid and can take place both by direct S_N1 or S_N2 substitution of the 2-acetoxy group by 5-fluorouracil and through the formation (initial generation) of 2-tetrahydrofurylcarbonium ion [61,90]. With increase in the reaction temperature (from 120 to 170°C) the last process predominates [61] as a result, probably, of the facilitated elimination of the 2-acetoxy group, after which the following equilibrium is established:



Concurrent alkylation by the carbocation becomes preferred.

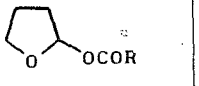
It should be noted that 2-acetoxytetrahydrofuran is a more reactive reagent than 2,3-dihydrofuran under the given conditions. This is indicated by the fact that 2-tetrahydrofurylation with 2-acetoxytetrahydrofuran takes place under milder conditions than in the case of 2,3-dihydrofuran (170°C) [22]. Data from the patent literature [67,71,83,84,86,89,91] indicate that the use of catalysts in the direct alkylation of 5-fluorouracil by 2-acyloxytetrahydrofuran helps to increase the product yield substantially (Table 9). The presence of alkali-metal halides (sodium iodide, potassium iodide) in the reaction mixture makes it possible to realize the process under milder conditions [71].

Ftorafur can be obtained in a short time (30-40 min) at room temperature without the formation of side products and with a high yield (more than 70%) if the reaction is conducted in the presence of dimethyldichlorosilane and a tertiary amine in a dry organic solvent (acetonitrile, DMFA, dimethylacetamide, or dioxane) [86].

The synthesis of Ftorafur by the reaction of a compound obtained as a result of previous treatment of 5-fluorouracil with a Lewis acid (e.g., dimethyldichlorosilane) [85] in the presence of triethylamine or halogenophosphite [92], with 2-acetoxytetrahydrofuran in acetonitrile in the presence of sodium iodide for 4 h at 55-60°C has also been described in the patent literature. The yield amounted to ~68%.

There are examples of the alkylation of 5-fluorouracil by derivatives of carbonic ester (2-ethoxycarbonyloxy- or 2-phenoxycarbonyloxytetrahydrofuran) with heat (130-135°C) in an inert solvent (DMFA, dimethylacetamide, DMSO) for 8 h with the reagents [5-FU] and [2-R-THF] in molar ratios of 1:(1-2). The yield here amounts to about 70% [93].

TABLE 9. Reaction of 5-Chlorouracil with 2-Acyloxytetrahydrofuran in the Presence of a Catalyst

Expt. No.	Amount of 5-FU, g	 R	amount, g	Catalyst	Amount of catalyst, g	Base	Amount of base, g	Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
1	13,0	CH_3	19,5	KI	24,9	—	—	$HCONMe_2$	150	80 ... 90	8	75	[91]
2	6,5	CH_3	9,8	NaI	4,0	K_2CO_3	3,8	$HCONMe_2$	80	90	3	93*	[71]
3	6,5	CH_3	13,0	—	—	K_2CO_3	6,9	$HCONMe_2$	90	100 ... 120	5	88*	[71]
4	1,3	CH_3	1,95	$AlCl_3$	1,36	—	—	C_5H_5N	15	130	5	90*	[83]
5	1,12	CH_3	2,6	$SnCl_4$	2,0	—	—	$HCONMe_2$	20	120	5	72	[67]
6	2,6	CH_3	3,9	Me_2SiCl_2	5,2	Et_3N	...	MeCN	26	20	0,5	70	[86]
7	13,0	C_4H_9	23,7	KI	9,0	—	—	$HCONMe_2$	150	100	15	89	[91]
8	13,0	C_6H_5	28,8	NaCl	30,0	—	—	$HCONMe_2$	200	100	15	77	[91]
9	13,0	C_6H_5	28,8	KI	30,0	—	—	$HCONMe_2$	200	100	15	77	[89]

*The reaction products were submitted to acid or base hydrolysis.

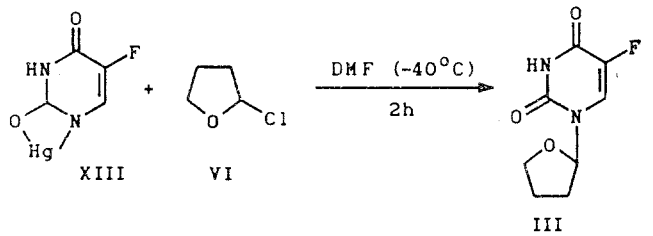
TABLE 10. Reaction of the Alkali-Metal Salts of 5-Fluorouracil with 2-Substituted Tetrahydrofuran

Expt. No.	Amount of 5-FU, g	MH				Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
		M	Amt., g	Y	Amt., g						
1	1,3	Na	0,53	Cl	1,17	$HCONMe_2$	20	80	5	62	[102]
2	1,3	Na	0,53	Cl	1,17	$HCONMe_2$	10	5	0,66	60	[102]
3	1,3	Na	0,53	Cl	1,17	Me_2SO	20	40	1	64	[102]
4	1,3	Li	0,09	CH_3COO	1,95	$(Me_2N)_3PO$	20	150	1	70	[103]
5	1,3	Na	0,53	CH_3COO	1,95	$HCONMe_2$	50	150	1	68	[103]
6	1,3	Na	0,53	CH_3COO	1,95	Me_2SO	20	130	5	62	[103]
7	1,3	Na	0,53	C_4H_9COO	1,9	$HCONMe_2$	50	150	5	68	[103]

In the direct tetrahydrofurylation of 5-fluorouracil 2-p-toluenesulfonyloxytetrahydrofuran can also be used as alkylating component [94,95]. The reaction is conducted in a solvent in the presence of a base (an alkaline-metal carbonate) preferably with a catalyst (a Lewis acid). The reaction takes 12 h at 100-120°C and gives a good yield (more than 80%) [95].

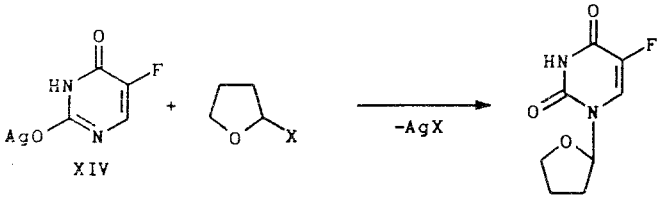
2. REACTION OF 5-FLUOROURACIL SALTS WITH 2-SUBSTITUTED TETRAHYDROFURAN

Four types of salts have been used in the synthesis of Ftorafur. Historically the first method for the synthesis of Ftorafur was its production from the mercury salt of 5-fluorouracil (XIII) [5,28,96-98].



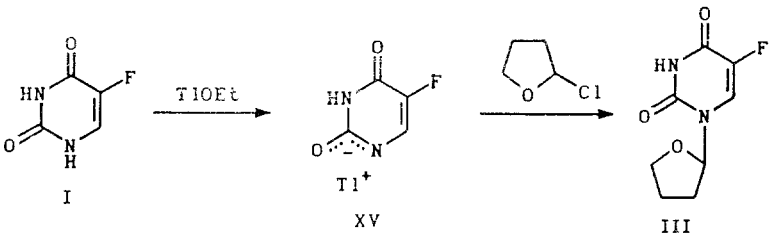
The reaction takes place comparatively easily in DMFA at extremely low temperatures (−40 to −20°C), and this is important in view of the low stability of 2-chlorofuranidine even at room temperature. The process requires absolutely dry conditions. It is recommended to avoid too large an excess of 2-chlorotetrahydrofuran in the reaction mixture. The optimum molar ratio of the reagents mercurated base and 2-chlorotetrahydrofuran is 1:1.8. The yield of Ftorafur amounts to 70% (calculated on the monomercury derivative) [28].

The main shortcoming of the method is the use and formation of toxic mercury salts, which is extremely undesirable in the production of a product for medical purposes. It can be avoided by using the silver salt method:

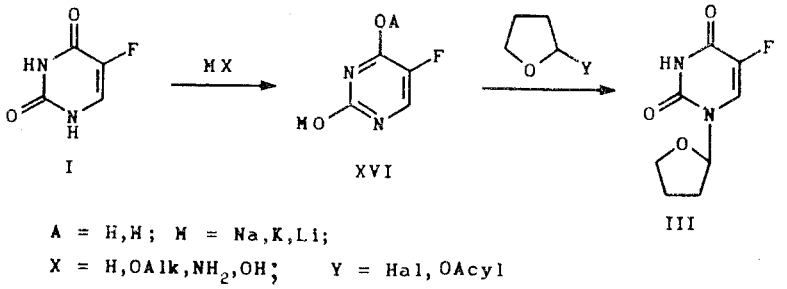


X = Cl, OCOR

The silver salt (XIV), prepared by treatment of the alkali-metal salt of 5-fluorouracil with silver nitrate or acetate, reacts with 2-substituted tetrahydrofuran in DMFA (or DMSO). Here, in the case of the unstable 2-chlorotetrahydrofuran [99] the reaction is conducted at low temperatures (−40 to −30°C), whereas during alkylation with 2-acyloxytetrahydrofuran [100] it is preferable to conduct the reaction at the boiling point of the solvent. The method gives good yields [99,100] (not indicated in the primary source) but is not hopeful on account of the use of the expensive reagents.



Another type of heavy-metal salt of 5-fluorouracil, i.e., thallium salts, has been proposed for the synthesis of Ftorafur [101]. It was found that 5-fluorouracil reacts readily with thallium ethoxide with the formation of the thallium salt of 5-fluorouracil (XV). Subsequent reaction of the latter with 2-chlorotetrahydrofuran in an anhydrous organic solvent (dioxane, methylene chloride, acetonitrile, DMFA, toluene) (~20°C, 36 h) leads to the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil. The best yield (48%) was obtained with dioxane as solvent. At higher temperatures (30-150°C) a mixture of products is obtained, and the yield of Ftorafur is reduced. At lower temperatures (10 to −40°C) the reaction rate is greatly reduced, and the yield of the target product does not exceed 36%. The use of an excess of 2-chlorotetrahydrofuran does not substantially alter the yield of Ftorafur but leads to the additional formation of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil. With the use of the thallium salt of 5-fluorouracil in the synthesis of Ftorafur it is only possible to speak of the fundamental possibility of its production by this method, since the yield is substantially lower than with the other proposed methods.



Apart from the heavy-metal salts of 5-fluorouracil it is possible to use alkali-metal salts (XVI), which are prepared by the reaction of 5-fluorouracil with the alkali-metal hydride, alcoholate, amide, or hydroxide [102-104], in the synthesis of Ftorafur. The obtained compound then reacts with 2-halogenotetrahydrofuran [102] or 2-acyloxytetrahydrofuran [103,104] with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil with a yield of 60-70% (Table 10).

The reaction with 2-halogenotetrahydrofuran takes place under milder conditions (1 h at 5-80°C) than the reaction with the 2-acyloxy derivative, when the successful process requires more prolonged boiling (1-5 h) of the reaction mixture (130-170°C). As a result of the $N_{(1)}$-directing effect of the 2-MO group the $N_{(1)}$-alkylation product is formed preferentially.

3. SYNTHESIS OF FTORAFUR BY THE HILBERT—JOHNSON METHOD

The Hilbert—Johnson method is a method for the creation of a C—N glycosidic bond through the reaction of a 2,4-dialkoxypyrimidine base with 1-halogenoses and is widely used in the chemistry of nucleosides. It was, therefore, quite natural to test it in the synthesis of Ftorafur with 2-halogen-substituted tetrahydrofuran instead of 1-halogenose as alkylating agent (Table 11).

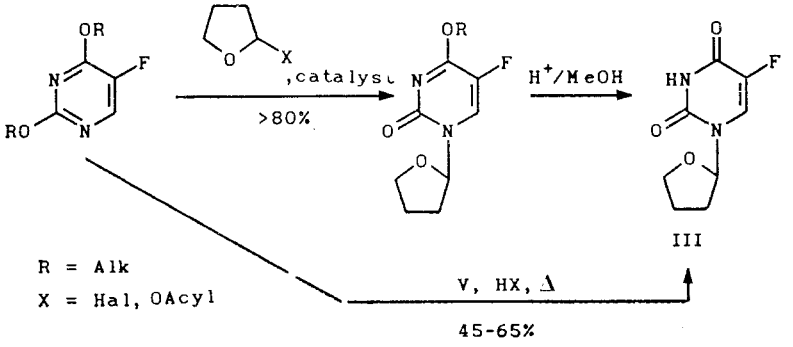


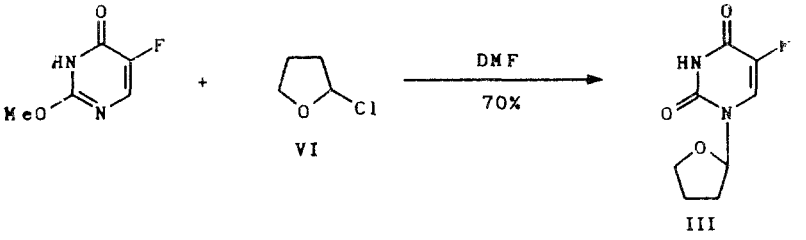
TABLE 11. Reaction of 2,4-Dialkyl-5-fluorouracil with 2-Substituted Tetrahydrofuran

Expt. No.	R	Amt., g	X	Amt., g	Catalyst	Amount of catalyst, g	Solvent	Amount of solvent ml	T, °C	Reaction time, h	Yield, %	Reference
1	CH_3	13,43	Cl	10,6	$SnCl_4$	26,0	MeCN	130	40	8	84	[105]
2	i-C_3H_7	2,14	Cl	1,27	$SnCl_4$	2,6	$(CH_2Cl)_2$	50	40	10	87	[105, 106]
3	C_4H_9	2,42	OMe	1,55	$TiCl_4$	2,0	CH_2Cl_2	50	40	12	90	[105]
4	i-C_3H_7	2,14	CH_3COO	1,55	$SnCl_4$	26,0	$(CH_2Cl)_2$	50	40	8	81	[105]

The reaction of 2,4-dialkyl-5-fluorouracil with 2-halogenotetrahydrofuran in the presence of a Lewis acid gives a 1,4-substituted intermediate, which is converted into 1-(2-tetrahydrofuryl)-5-fluorouracil by treatment with acid in an organic solvent (e.g., HCl in methanol) [105,106]. Treatment with acid is not a innocuous procedure on account of the lability of the glycosidic bond in an acidic medium, but the yields in this case amount to 81-90%.

Also possible is reaction of 2,4-dialkyl-5-fluorouracil with 2,3-dihydrofuran in the presence of Brönsted or Lewis acids [107]. The former promote the formation of a carbocation from the 2,3-dihydrofuran, and the latter are themselves alkylation catalysts. The process takes place at elevated temperature and gives yields of 45-65%.

If a semisubstituted 5-fluorouracil, e.g., 2-methyl-5-fluorouracil, is used in the alkylation with 2-chlorotetrahydrofuran, it is possible to avoid the undesirable procedure involved in the removal of the protecting 4-alkyl group [108].



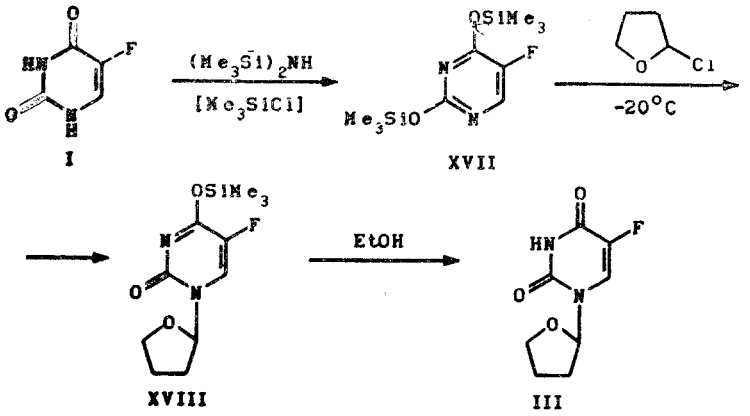
Here, however, it is necessary to bear in mind the difficulty in the production of the 2-alkyl-5-fluorouracil by selective alkylation of fluorouracil. With 2-alkoxytetrahydrofuran [109] and 2-acyloxytetrahydrofuran [110] the reaction is realized in the presence of a Lewis acid in the first case and in the presence of an organic base in the second.

4. SILYL METHOD FOR THE SYNTHESIS OF FTORAFUR

The silyl method for the synthesis of nucleosides involves reaction of the trialkylsilyloxy derivatives of bases and the $C_{(1)}$ derivatives of carbohydrates. In the case of Ftorafur the role of the carbohydrate component is played by the tetrahydrofuryl residue. The alkylsilyl derivatives of 5-fluorouracil (as a rule, trimethylsilyl) are prepared by direct silylation with trialkylchlorosilanes, hexamethyldisilazane, or other silylating agents [111-113]. Attention should be paid to the fact that these compounds have the structure of O-trialkylsilyl derivatives, and this is due to the higher strength of the Si—O bond compared with the Si—N bond. The trialkylsilyl esters of 5-fluorouracil obtained in this way can then react with the 2-substituted tetrahydrofuran with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil [114,115].

4.1. Reaction with 2-Chlorotetrahydrofuran

The condensation of 2,4-bis(trimethylsilyl)-5-fluorouracil (XVII) with 2-chlorotetrahydrofuran is one of the preparative methods for the production of Ftorafur [97,116-118]. It gives the final product with a high degree of purity and with a yield of up to 70% [118]. The bistrimethylsilyl derivative of 5-fluorouracil is obtained with a high yield (about 90%) by the reaction of the base with hexamethyldisilazane in the presence of catalytic amounts of TMCS and can be used for the condensation with 2-chlorotetrahydrofuran without previous purification.



It is necessary to point out the advantage of using alkylsilyl groups compared with alkyl groups. They fulfil a dual role: First, they are protecting groups, preventing O-alkylation, and second they increase the nucleophilicity of the nitrogen atom of the pyrimidine base. However, unlike alkoxy groups their removal does not require H^+ hydrolysis and can be easily realized by treatment of the reaction product (XVIII) with water or alcohol.

The yield of Ftorafur is increased by the addition of molecular sieves (3-4 Å) to the reaction mixture as acceptors of hydrogen chloride (a possible side product) and water (the moisture of the reagents) [119,120]. The yield is also increased to 80% by changing the order in which the reagents are mixed, i.e., the previously obtained 2,4-bis(trimethylsilyl)-5-fluorouracil is added to 2-chlorotetrahydrofuran, formed from 2,3-dihydrofuran and dry hydrogen chloride [121,122]. A method has also been developed for the simultaneous addition of hydrogen chloride and the disilylated 5-chlorouracil to the 2,3-dihydrofuran [121]. In the Japanese patent [73] a method is proposed for the synthesis of Ftorafur from 2,4-bis(trimethylsilyl)-5-fluorouracil and 2-chlorotetrahydrofuran, produced at the moment of the reaction from sulfuryl chloride and tetrahydrofuran, serving at the same time as solvent.

2,3-Dihydrofuran is used similarly in the presence of Lewis and Brönsted acids. The action of the catalyst is largely directed to the formation of the alkylating carbocation, which then reacts with the 2,4-bis(trimethylsilyl)-5-fluorouracil (true alkylation) with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil. 1,3-Bis(2-tetrahydrofuryl)-5-fluorouracil can be formed, depending on the reaction conditions and on the amount of 2,3-dihydrofuran used [123-135].

In the presence of the salts of tertiary amines with hydrochloric or organic acids (acetic, p-toluenesulfonic) [75,136] the reaction takes place in an aprotic solvent (dioxane, chloroform, dichloromethane, dichloroethane, benzene, toluene, DMFA) at 50-70°C. A catalyst (alkali-metal halide or Lewis acid) can be used [75].

Study of the mechanism of this reaction [44] in the case of the reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with 2,3-dihydrofuran in the presence of pyridine hydrochloride and p-toluenesulfonate showed that, as in the case of 5-fluorouracil [40] (see Section 1), the actual initial product is evidently a 2-substituted intermediate (VII) (X = Cl) or (XIX) (X = p-$CH_3C_6H_4SO_3$), which is formed from the reagents present in the reaction mixture and reacts with 2,4-bis(trimethylsilyl)-5-fluorouracil with the formation of Ftorafur.

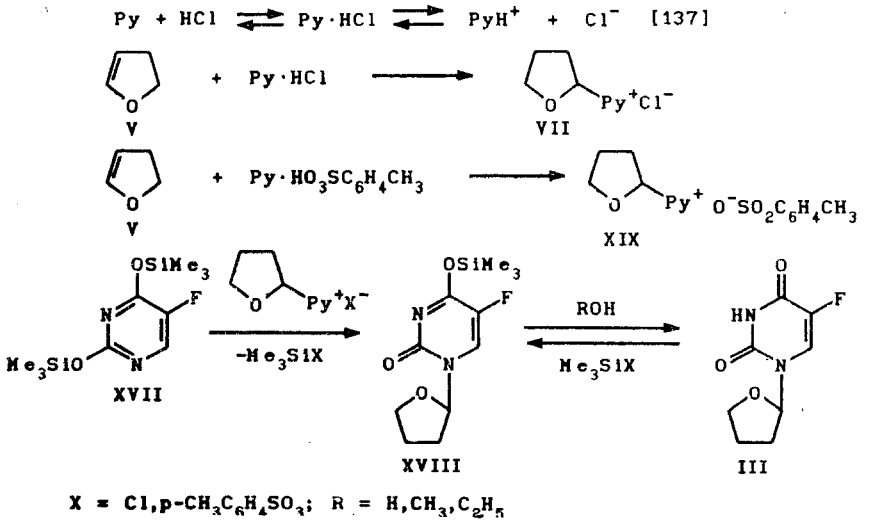
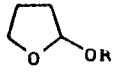
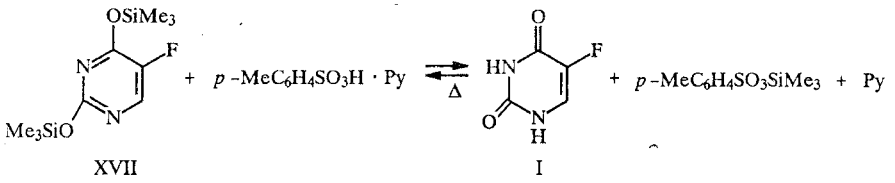


TABLE 12. Reaction of 2,4-Bis(trimethylsilyl)-5-fluorouracil with 2-Alkoxytetrahydrofuran in the Presence of Catalysts

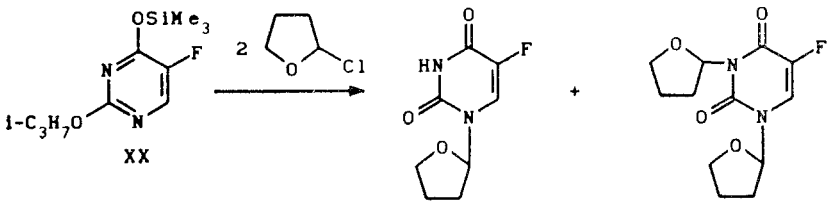
Expt. No.	Amount of 5-FU, g	Hexamethyldisilazane, g	 R	amount, g	Catalyst	Amount of catalyst, g	Solvent	Amount of solvent, ml	T, °C	Reaction time, h	Yield, %	Reference
1	65,0	96,59	CH_3	75,0	NaI	5,6	$HCONMe_2$	130	180	3	58	[139]
2	65,0	96,59	CH_3	75,0	NaI	5,6	MeCN	700	160	2,5	77	[139]
3	13,0	19,3	CH_3	12,2	NaI	23,3	MeCN	100	150 . . . 160, 60 . . . 80	4 5	84	[140]
4	65,0	96,59	CH_3	75,0	KI	12	MeCH	1000	170	3	66	[139]
5	13,0	19,3	CH_3	12,2	$SnCl_4$	21,8	CH_2Cl_2	120	100	3	88	[141]
6	13,0	20,0	CH_3	13,0	p-$CH_3C_6H_4SO_3H$	0,4	MeCN	200	130	1	70	[142]
7	13,0	19,3	C_6H_5	24,6	KI	24,8	MeCN	120	60 . . . 80	7	80	[140]
8	13,0	19,3	C_6H_5	24,6	$BF_3 \cdot Et_2O$	10,6	CH_2Cl_2	120	20	5	81	[141]

In the case of p-toluenesulfonic acid it was established that a concurrent side reaction occurs between the 2,4-bis(trimethylsilyl)-5-fluorouracil and pyridine p-toluenesulfonate, resulting in desilylation of the base, decomposition of the pyridine complex, and silylation of the sulfonic acid [40]. The concurrent reaction is suppressed with increase in temperature.



XVII I

The fundamental possibility of using 2-alkyl-4-trimethylsilyl-5-fluorouracil, i.e., a mixed-substituted pyrimidine base, in the alkylation reaction has been described in the patent literature. This must also be regarded as a special case of the silyl method of synthesis of Ftorafur.



XX III IV

The reaction between 2-isopropyl-4-trimethylsilyl-5-fluorouracil (XX) and freshly prepared 2-chlorotetrahydrofuran (molar ratio 1:2), which takes place in dichloromethane at room temperature for 2 days, also makes it possible to obtain a mixture of monosubstituted ($N_{(1)}$) and disubstituted ($N_{(1)}$, $N_{(3)}$) 5-fluorouracil. In this case, however, the yield of Ftorafur, which amounts to 76%, significantly exceeds the yield of the bisalkylation product (7%) [138].

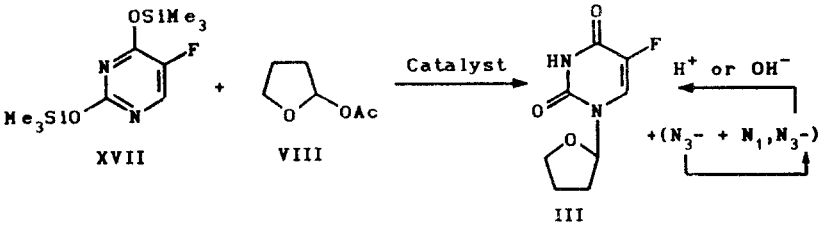
4.2. Reaction with 2-Alkoxytetrahydrofuran

The reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with 2-alkoxytetrahydrofuran is as a rule realized at elevated temperatures (80-180°C) in an aprotic solvent in the presence of catalysts (Table 12). Alkali-metal halides [139,140,143], Lewis acids [141,144], halogens [145], and H^+ acids [142] have been used as catalysts. The highest yield of Ftorafur (88%) was obtained in the reaction of 2-methoxytetrahydrofuran in boiling dichloroethane in the presence of stannic chloride [141].

The alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil by 2-hydroxytetrahydrofuran [146] with sodium iodide, H^+ acid, Lewis acid (aluminum chloride, stannic chloride, boron trifluoride), or Lewis proacid (I_2) [147] as catalysts and also with bis(2-tetrahydrofuryl) ether [148] has also been described.

4.3. Reaction with 2-Acyloxytetrahydrofurans

The method for the production of Ftorafur from 2,4-bis(trimethylsilyl)-5-fluorouracil and 2-acetoxytetrahydrofuran in the presence of a Lewis acid (stannic chloride) as catalyst [149,150] has a whole series of advantages: The use of nontoxic reagents; preparation of the chemically pure substance with a high yield (more than 80%); realization of the reaction at room temperature (whereas alkylation with 2-chlorotetrahydrofuran is realized at temperatures between −20 and −5°C); the use of the significantly more thermally stable alkylating reagent 2-acetoxytetrahydrofuran, which reduces the probability of side polymerization processes resulting from decomposition of the alkylating agent.



XVII VIII III

TABLE 13. Reaction of 2,4-Bis(trimethylsilyl)-5-fluorouracil with 2-Acetoxytetrahydrofuran at Room Temperature in the Presence of a Catalyst

Expt. No.	Catalyst	Amount of catalyst, g	Molar ratios of 2,4-bis-TMS-5-FU and 2-OAC-THF	Solvent	Reaction time, h	Yield, %
1	$BF_3 \cdot Et_2O$	1,0	1,0:1,5	CH_2Cl_2	1,0	70
2	$TiCl_4$	1,0	1,0:1,5	CH_2Cl_2	0,5	60
3	$SbCl_5$	1,0	1,0:1,5	CH_2Cl_2	0,1	8
4	$SnCl_4$	0,1	1,0:1,5	CH_2Cl_2	1,5	81
5	$SnCl_4$	0,01	1,0:1,0	CH_2Cl_2	8	61
6	$SnCl_4$	0,01	1,0:2,0	CH_2Cl_2	3	93
7	NaI	1,0	1,0:1,0	CH_3CN	23	68
8	NaI	1,0	1,0:2,0	CH_3CN	9	91
9	$SnCl_4$	0,01	1,0:2,0	CH_2Cl_2	3	96*
10	NaI	1,0	1,0:2,5	CH_3CN	8	92*
11	$BF_3 \cdot Et_2O$	0,02	1,0:2,5	CH_2Cl_2	3	79*
12	CsCl	0,1	1,0:1,2	CH_3CN	3	87**

*The yield of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil. In expts. 1-8 treatment of the reaction mixture with aqueous sodium hydroxide, in expts. 9-11 with Et_3N—EtOH. **According to published data [156].

It was shown by special investigations [151,152] that the absence of the catalyst requires more drastic conditions for the reaction, i.e., increase in temperature and increase in the reaction time, and this did not make it possible to increase the yield.

The most effective catalysts are $BF_3 \cdot Et_2O$ and $SnCl_4$ [152-155] (Table 13). However, the production of a high yield requires the use of an excess of the alkylating 2-acetoxytetrahydrofuran. The highest yield of Ftorafur (91-93%) is observed with base—furan—stannic chloride ratios of 1.0:2.0:(0.01-0.1). If the amount of stannic chloride is reduced (below 0.005 eq), the yield is reduced.

As a result of study of the kinetics of this reaction in acetonitrile [17,152,157] it was found that the reagents react at the highest rate in the early stage of the reaction with the formation of 1-(2-tetrahydrofuryl)-5-fluorouracil, which is then alkylated slowly but progressively with the formation of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil. At the early stage a small amount of 3-(2-tetrahydrofuryl)-5-fluorouracil is formed, and this is also transformed with time into 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil. The latter is easily $N_{(3)}$-dealkylated by treatment of the reaction mixture with a solution of acid or alkali [152].

Recently [156] a new reagent of the Lewis acid type (CsCl) was proposed as catalyst. It secures high regioselectivity of alkylation in acetonitrile under mild conditions. The reaction is conducted at room temperature in the presence of 0.1 eq of CsCl in relation to the 2,4-bis(trimethylsilyl)-5-fluorouracil. The best result is obtained with a small excess of 2-acetoxytetrahydrofuran in relation to the silylated base (1.2-1.5 eq). In this case 100% $N_{(1)}$-alkylation is secured, and the yield of 1-(2-tetrahydrofuryl)-5-fluorouracil amounts to 87%. Increase in the amount of alkylating agent to 2 eq in relation to the 2,4-bis(trimethylsilyl)-5-fluorouracil leads to the formation of a mixture of $N_{(1)}$- and $N_{(1)},N_{(3)}$-substituted compounds in a ratio of 50:43 respectively with an overall yield of 93%.

In the reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with 2-acetoxytetrahydrofuran halogens and organic sulfonic acids were tried as catalyst [158,159]. The reaction conditions in this case are more drastic (temperature 90-130°C) and give the same average yields of the reaction product (73-86%).

It was also proposed [160] to alkylate 2,4-bis(trimethylsilyl)-5-fluorouracil with 2-halogenoacetoxytetrahydrofurans in a solvent (acetonitrile, DMFA) at increased temperature with the possible presence of a catalyst (sodium iodide, iodine). The yield amounted to 60-79%.

The analogous alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil with the ester of 2-hydroxytetrahydrofuran and boric acid [161, 162] or with 2-p-toluenesulfonyloxytetrahydrofuran [94,95] takes place at increased temperature. In the case of 2-p-toluenesulfonyloxytetrahydrofuran it is expedient to use catalysts, for which stannic chloride, boron trifluoride, or aluminum chloride are used. The yield of 1-(2-tetrahydrofuryl)-5-fluorouracil here amounts to more than 90%.

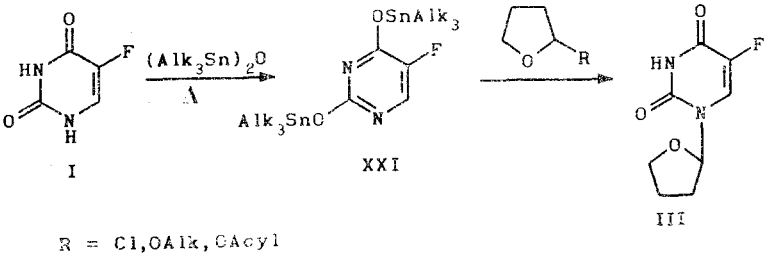
The reaction of 2-methyl-4-trimethylsilyl-5-fluorouracil with 2-benzoyloxytetrahydrofuran in pyridine in the presence of stannic chloride at 80-90°C for 17 h with the base, furan, and stannic chloride in molar ratios of 2:4:0.19 gives a mixture

of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil with yields of 38 and 33% respectively [163].

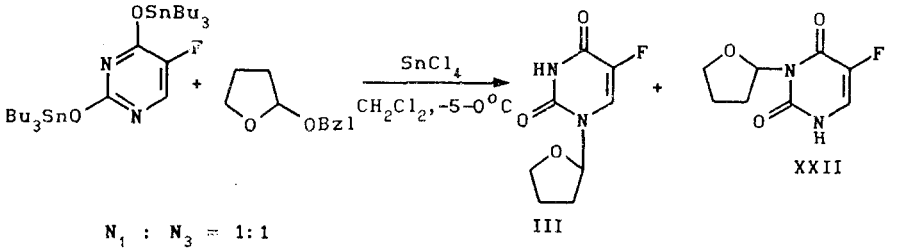
4.4. Stannyl Modification of the Silyl Method

A special case of the silyl method for the synthesis of Ftorafur is alkylation of a heteroorganic derivative of 5-fluorouracil, when the 2,4-bis(trialkylstannyl) analog is used instead of 2,4-bis(trialkylsilyl)-5-fluorouracil. In other respects all the previously discovered relationships of alkylation can be also attributed to the reaction of 2,4-bis(trialkylstannyl)-5-fluorouracil (XXI) with furan derivatives.

2,4-Bis(trialkylstannyl)-5-fluorouracil is obtained by the reaction of 5-fluorouracil with bis(trialkylstannyl) oxide in an aprotic solvent (e.g., toluene) at its boiling point [164].



2,3-Dihydrofuran [165,166], 2-chlorotetrahydrofuran [164,167], a mixture of tetrahydrofuran and sulfuryl chloride [168], and 2-hydroxy-substituted tetrahydrofurans have been used as alkylating agent. The tetrahydrofurylation of 2,4-bis(trialkylstannyl)-5-fluorouracil with 2-hydroxytetrahydrofuran [169], 2-alkoxytetrahydrofuran [164,170], 2-aryloxytetrahydrofuran [164,170], and 2-acyloxytetrahydrofuran [164,170,171] with the formation of Ftorafur is realized in an aprotic solvent in the presence of a catalyst. Lewis acids (stannic chloride, boron trifluoride etherate, aluminum chloride, phosphorus trichloride, zinc chloride) [164,170,171], halogens (chlorine, bromine, iodine) [170], alkali-metal iodides [170], and organic (sulfonic) acids (acetic, propionic, methanesulfonic, p-toluenesulfonic) [170] have been used as catalysts. The reaction takes place with the reacting components, i.e., the base and 2-R-THF, in a molar ratio of 1: ≥2. When necessary the reaction product is hydrolyzed without isolation by acid with the formation of a high yield of Ftorafur [164,171]. It was established that the alkylation of 2,4-bis(tri-n-butylstannyl)-5-fluorouracil with 2-benzyloxytetrahydrofuran in dichloromethane at −5 to 0°C for 7 h in the presence of stannic chloride gives an equimolar mixture of $N_{(1)}$- and $N_{(3)}$-(2-tetrahydrofuryl)-5-fluorouracil (XXII) [172]:

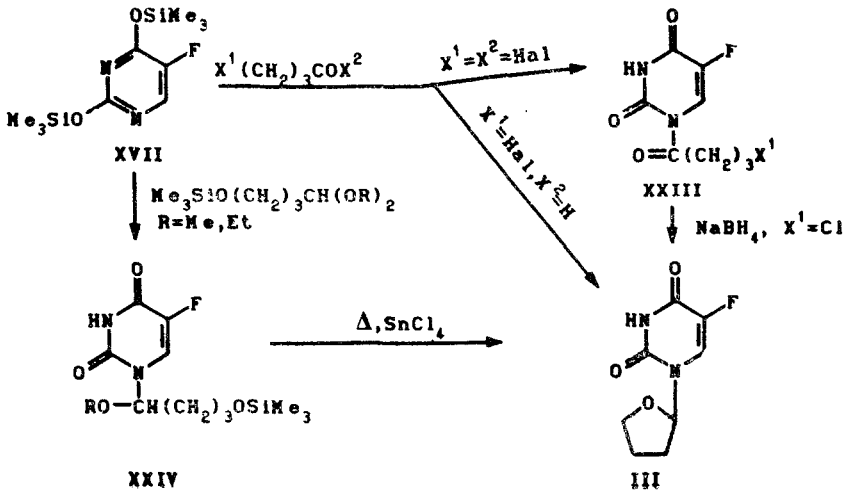


5. OTHER METHODS FOR THE SYNTHESIS OF FTORAFUR

Other methods are possible in addition to the methods for the coupling of 5-fluorouracil with tetrahydrofuryl residue examined in sections 1-4. These include cyclization of acyclic intermediates, transformations in the hydrofuryl fragment, and transformations in the uracil fragment (fluorination, oxidation of the thio derivatives, solvolysis of the 1,3-disubstituted uracil).

5.1. Cyclization of Functionally 1-Substituted 5-Fluorouracils

An original approach to the synthesis of Ftorafur involves the reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with an acyclic alkylating agent in the form of pro-tetrahydrofuran. γ-Halogenobutyryl halides [173], γ-halogenobutyraldehyde [174], or γ-trimethoxysilyloxybutyraldehyde dialkyl acetal [175-178] can be used as such acyclic compounds:



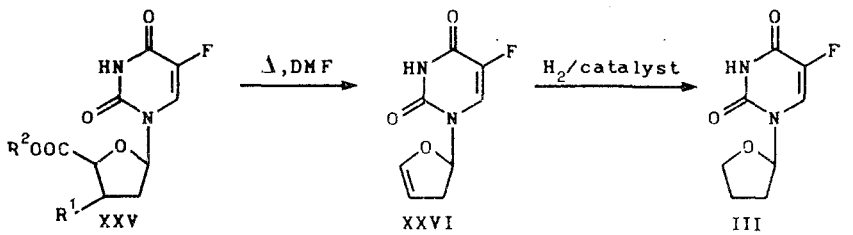
In the case of γ-halogenobutyryl halides the reaction takes place in an aprotic solvent at room temperature and results in the production of 1-(γ-halogenobutyryl)-5-fluorouracil (XXIII) [173]. Closure of the ring takes place during reduction of the intermediate in a solvent (alcohol, pyridine, benzene) with sodium borohydride or lithium aluminum hydride. 1-(2-Tetrahydrofuryl)-5-fluorouracil is formed with a yield of 72% [179].

The reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with γ-halogenobutyraldehyde takes place in boiling acetonitrile in the presence of a tertiary amine. As a result a cyclic adduct is immediately formed with a yield of 68% [174]. An interesting method is the method based on the condensation of trimethylsilyloxybutyraldehyde and 2,4-bis(trimethylsilyl)-5-fluorouracil, catalyzed by Lewis acids, in a solvent (e.g., acetonitrile or dichloroethane) at room temperature in the presence of stannic chloride with the reagents 5-FU, acetal, and stannic chloride in molar ratios of 1:1.1:0.5 [175-178]. The yield of Ftorafur in such a method amounts to 84%. Investigation of the effect of the nature of the catalyst and the solvent on this reaction showed that the best combination is provided by the use of stannic chloride or trimethylsilyl triflate as catalyst in acetonitrile. The optimum temperature depends on the amount of the employed Lewis acid; if it is about 1.5 mole equivalents with respect to the 5-fluorouracil, it is recommended that the temperature should be kept not higher than −30°C. It should be noted that whereas the trimethylsilyl acetal reacts with 2,4-bis(trimethylsilyl)-5-fluorouracil in acetonitrile at −5°C for 3 h with 0.25 mole equivalent of stannic chloride, the acyclic compound (XXIV) is formed as a result with a yield of 81%. If, however, the reaction mixture is kept additionally at 5°C for 3 h, the exclusive formation of the cyclization product is observed [178,180].

It was established [178] that the rate constant of nucleophilic substitution, leading to the formation of the acyclic intermediate, is larger than that for intramolecular cyclization with the formation of 2-methoxytetrahydrofuran. Consequently, alkylation predominates.

5.2. Transformations of the Tetrahydrofuryl Substituent

Ftorafur can be synthesized by decarboxylation of the 5′-carboxy-substituted precursor (XXV) with the formation of 1-(2,3-dihydro-2-furyl)-5-fluorouracil (XXVI), which is subsequently converted into Ftorafur by hydrogenation in the presence of Raney nickel or 5% Pd/C [181]:



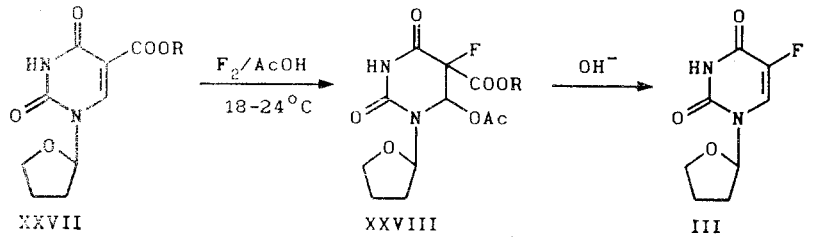
XXV XXVI III

R^1=OH, OAcyl; R^2=H, Alkyl, Aryl

5.3. Transformations of the Pyrimidine Substituent

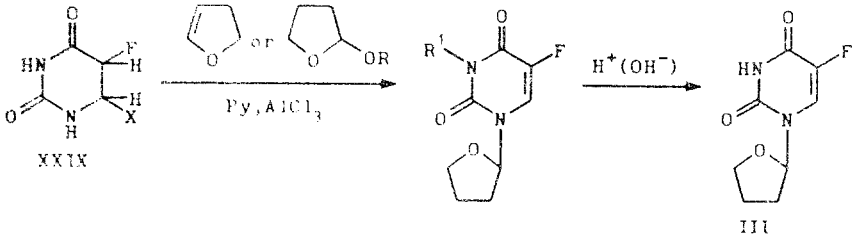
The direct fluorination of 1-(2-tetrahydrofuryl)uracil is realized with trifluoromethyl hypofluorite in methylene chloride at −78°C [182-184]. The hypofluorite is used in a small molar excess in relation to the base (1.1:1.0), and the yield here amounts to only 60%.

Ftorafur can also be produced by the mediated fluorination of 1-(2-tetrahydrofuryl)-5-carboxy derivatives of uracil (XXVII) [185,186]. Fluorination takes place initially at the C=C bond of the uracil in the presence of acetic acid, and decarboxylation and deacetylation of the intermediate (XXVIII) by the alkali then occur:



XXVII XXVIII III

Another sequence of reactions is possible: Initial fluorination of the pyrimidine base [20,185,187], reaction of the obtained 5-fluoro-6-substituted 5,6-dihydrouracil (XXIX) with 2,3-dihydro- or 2-alkoxytetrahydrofuran in pyridine in the presence of aluminum chloride, and subsequent H^+ or OH^- hydrolysis with the formation of a high yield of Ftorafur [188]:



XXIX III

X=OAcyl, OH; R=Et, *i*-Pr, *t*-Bu; R^1=H, 2-THF

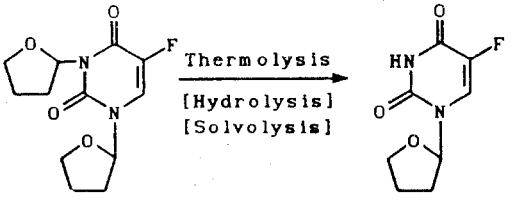
Another possible method is the production of Ftorafur from 2-thiouracil by its reaction with 2,3-dihydrofuran by the silyl method and subsequent treatment of the obtained reaction product with hydrogen peroxide under alkaline conditions. The yield of 1-(2-tetrahydrofuryl)-5-fluorouracil amounts to 70% [189,190].

5.4. Solvolysis of 1,3-Bis(tetrahydrofuryl)-5-fluorouracil

The formation of an $N_{(1)}$-monosubstituted compound from $N_{(1)}$,$N_{(3)}$-bis(2-tetrahydrofuryl)-5-fluorouracil represents yet another possibility for the production of Ftorafur or an additional quantity of the compound.

The reaction, realized by any of the proposed methods (except for the method involving the use of 5-fluorouracil salts) leads as a rule to the formation of a mixture, in which 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil inevitably predominates if the reaction is subject to thermodynamic control [75,191,192] or is conducted in the absence of an acid catalyst [23,37,46,71,110] or with a large excess of an alkylating agent [41,53,69,193,194]. In some cases a directed synthesis of the bisalkylation product has been undertaken [25,59,192,195,196], and this is then used independently, since it also exhibits antitumor activity [197-200], or acts as an intermediate in the synthesis of Ftorafur [68,70,134,199,201,202].

1-(2-Tetrahydrofuryl)-5-fluorouracil is produced from 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil by selective elimination of the 2-tetrahydrofuryl group from position 3 of the pyrimidine base. This is only possible as a result of thermolysis (see section 1) [22,203], hydrolysis [71,204], or solvolysis [25,196].



Thermolysis is realized at 120-170°C at slightly reduced pressure (melt) or at 120-200°C after dissolution in an aprotic organic solvent such as picoline [203].

Hydrolysis is possible both under acidic conditions in an inert solvent [24,35,46,188,190] and under alkaline conditions [152,188,204] (1N sodium hydroxide, 20°C, 2-2.5 h, yield 91%). The last alternative is probably preferred on account of the lability of the glycosidic bond in the acidic medium.

Solvolysis is a more suitable procedure [152,196]. It is conducted in alcohol (methanol, ethanol), pyridine, dioxane, tetrahydrofuran, acetone, or their aqueous solutions at 40-80°C. Thus, treatment of 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil with 50% aqueous ethanol at 60-80°C for 1.5-2 h gives Ftorafur with a yield of 94% [152].

The authors thank T. Shidlovskaya for assistance in the compilation of the tables.

LITERATURE CITED

1. A. V. Stetsenko, Vest. Kievskogo Un-ta, **24**, 42 (1983).
2. Daikin Industries Co., Japanese Patent No. 59681. Derwent CPI, 48676A/27.
3. Daikin Industries Co., Japanese Patent No. 36281. Derwent CPI, 32507B/17.
4. R. Duschinsky, E. Pleven, and C. Heidelberg, J. Am. Chem. Soc., **79**, 4559 (1957).
5. R. A. Zhuk, History of the Creation of Ftorafur [in Russian]; S. A. Giller, Life and Scientific Activity [in Russian] (editor Ya. P. Stradyn'), Zinatne, Riga (1982), p. 103.
6. Ya. P. Stradyn', Experimental and Clinical Pharmacotherapy [in Russian], Zinatne, Riga, No. 12, 5 (1983).
7. R. A. Zhuk, L. Kaulina, A. Ludzisa, E. Liepins, and M. Lidaks, Nucleic Acids Symp. Ser., **9**, 123 (1981).
8. Ftorafur. An Antitumor Drug (Pamphlet), Zinatne, Riga (1979).
9. Ftorafur. A New Soviet Antitumor Preparation [in Russian], Institut Organicheskogo Sinteza, Riga (1972).
10. S. A. Giller, R. A. Zhuk, and M. Yu. Lidak, Éksp. i Klin. Farmakoter., No. 7, 9 (1977).
11. R. A. Zhuk (ed.), Ftorafur. Proceedings of the International Symposium on Ftorafur, Riga, 1979, Zinatne, Riga (1985).
12. A. A. Zidermane, Fluoropyrimidines in the Chemotherapy of Tumors [in Russian], Zinatne, Riga (1982).
13. N. G. Blokhina, B. T. Garibdzhanyan, M. Yu. Lidak, and A. B. Syrkin, The Antitumor Product Ftorafur [in Russian] (1981) (cited in [12]).
14. A. Eisenstadt, R. R. G. Haber, and U. Michael, Israeli Patent No. 52565. Chem. Abs., **93**, 168296 (1980).
15. S. Hashimoto and T. Suzue, J. Synth. Org. Chem. Japan, **38**, 528 (1980).
16. J. Žemlička, R. Gassner, J. V. Fleisler, and J. P. Horwitz, J. Am. Chem. Soc., **94**, 3213 (1972).
17. M. Yasumoto, A. Moriyama, N. Unemi, S. Hashimoto, and T. Suzue, J. Med. Chem., **20**, 1592 (1977).
18. J. Yamashita, I. Yamawaki, S. Ueda, M. Yasumoto, N. Unemi, and S. Hashimoto, Chem. Pharm. Bull., **30**, 4258 (1982).
19. H. Fujita, S. Hiller Memorial Lectures, Riga (1990).
20. O. Miyashita, K. Matsumura, T. Kasahara, H. Shimadzu, and N. Hashimoto, Chem. Pharm. Bull., **30**, 887 (1982).
21. S. Osaki, Y. Watanabe, T. Hoshiko, T. Nagasi, T. Ogasawara, H. Furukawa, A. Uemura, K. Ishikawa, H. Mori, A. Hoshi, M. Iigo, and R. Tokuzen, Chem. Pharm. Bull., **34**, 150 (1986).
22. H. Nomura, Y. Yoshioka, and I. Minami, Chem. Pharm. Bull., **27**, 899 (1979).
23. Netherlands Patent No. 7702516 (1977). Derwent CPI, 2436A/02. Y. Hoshide, Y. Hashimoto, H. Ogawa, and S. Tasaka, German Patent No. 2709839; Chem. Abs., **88**, 121667 (1978).
24. Y. Hoshide, Y. Hashimoto, H. Ogawa, and S. Tasaka, Japanese Patent No. 119880; Chem. Abs., **90**, 204125 (1979).
25. I. Minami, Y. Yoshioka, and H. Nomura, Belgian Patent No. 848662 (1977); German Patent No. 2653398 (1977); Chem. Abs., **87**, 135384 (1977); Japanese Patent No. 89679 (1977); Japanese Patent No. 9778 (1978); Japanese Patent No. 16484 (1979); Derwent CPI, 36283 Y/21.
26. A. Takamizawa and K. Hirai, Chem. Pharm. Bull., **13**, 681 (1965).
27. N. Nagasawa, J. Kumashiro, and T. Takenishi, J. Org. Chem., **31**, 2685 (1966).
28. S. Giller, R. A. Zhuk, and M. Yu. Lidak, Dokl. Akad. Nauk SSSR, 332 (1967).
29. Y. Kojima, A. Okabe, A. Okubo, H. Izuka, and Y. Jinno, Japanese Patent No. 118477 (1977); Chem. Abs., **88**, 105718 (1978).

30. Y. Kojima, A. Okabe, A. Okubo, H. Izuka, and Y. Jinno, Japanese Patent No. 105483 (1978); Chem. Abs., **90**, 23106 (1979).
31. Mitsui Toatsu Chem. Ind., Japanese Patent No. 15285 (1981); Chem. Abs., **95**, 7322 (1981).
32. A. Kojima, Y. Kono, Y. Ike, T. Yokoyama, and M. Odate, Netherlands Patent No. 7614220; Japanese Patent No. 89678 (1977); Japanese Patent No. 89680 (1977); Japanese Patent No. 85180 (1977); Chem. Abs., **87**, 202041 (1977); Japanese Patent No. 142079 (1977); Japanese Patent No. 125177 (1977); German Patent No. 2656604 (1977); Chem. Abs., **87**, 135397 (1977); Derwent CPI, 49783Y/28.
33. A. Kojima, Y. Jinno, S. Ike, T. Yokoyama, and M. Odate, Japanese Patent No. 2478 (1978); Chem. Abs., **89**, 24347 (1978).
34. A. Kojima, T. Yokoyama, M. Odate, Y. Ike, and Y. Kamino, Japanese Patent No. 108987 (1978); Chem. Abs., **90**, 137855 (1979).
35. T. Nakamura, Y. Hoshimoto, Y. Hoshide, K. Suzuki, and Y. Yoshida, Netherlands Patent No. 7702515 (1977); German Patent No. 2709838 (1978); Chem. Abs., **88**, 152656 (1978). Japanese Patent No. 2479 (1978); Japanese Patent No. 31673 (1978); Japanese Patent No. 121771 (1978); Derwent CPI, 4538A/03.
36. O. Maruyama, T. Sato, T. Kawashima, H. Suehiro, S. Ishida, Y. Yanase, and A. Aoki, Japanese Patent No. 21178 (1978); Chem. Abs., **89**, 24350 (1978).
37. T. Nakamura, Y. Hoshide, Y. Hashimoto, K. Suzuki, and Y. Yoshida, Japanese Patent No. 70287 (1979); Chem. Abs., **91**, 193334 (1979).
38. Y. Otsuka, Y. Fujimori, and H. Kondo, Japanese Patent No. 27584 (1979); Chem. Abs., **91**, 5246 (1979).
39. ABIC, Japanese Patent No. 98979 (1978); Chem. Abs., **90**, 72224 (1979).
40. É. Ya. Lukevits, M. A. Trushule, V. É. Udre, and É. É. Liepin'sh, Izv. Akad. Nauk Latv. SSR. Ser. Khim., No. 3, 317 (1982).
41. K. Sakurai, Japanese Patent No. 2484 (1978); Chem. Abs., **89**, 129530 (1978).
42. K. Sakurai, Japanese Patent No. 5986 (1979); Chem. Abs., **90**, 204136 (1979).
43. Mitsui Toatsu Chem. Inc., Japanese Patent No. 139079 (1977); Derwent CPI, 2747A/02.
44. É. Ya. Lukevits, M. A. Trushule, D. É, Zarinya, L. M. Ignatovich, and É. É. Liepin'sh, Zh. Obshch. Khim., **51**, 827 (1981).
45. H. Fukatsu, T. Miyano, I. Iwatsuki, and I. Matsumoto, Japanese Patent No. 98785 (1979); Chem. Abs., **92**, 146795 (1980).
46. T. Nakamura, Y. Hoshide, Y. Hashimoto, and K. Suzuki, Japanese Patent No. 55581 (1979); Chem. Abs., **91**, 175384 (1979).
47. K. Ishibashi, S. Ishiguro, and R. Komaki, German Patent No. 2834698 (1979); Chem. Abs., **91**, 20334 (1979). Japanese Patent No. 46788 (1979); US Patent No. 4159378 (1979); Japanese Patent No. 84582 (1979); Derwent CPI, 24163B/13.
48. I. Minami, Y. Yoshioka, and H. Nomura, Belgian Patent No. 849651 (1977); Netherlands Patent No. 7614420 (1977); German Patent No. 2657709 (1977); Chem. Abs., **87**, 135396 (1977); Japanese Patent No. 78887 (1977); Derwent CPI, 43509Y/25.
49. K. Sakai, Y. Inamoto, and H. Matsuzawa, Japanese Patent No. 46985 (1978); Chem. Abs., **89**, 109567 (1978); Japanese Patent No. 20506 (1979); Derwent CPI, 41273A/23.
50. H. Fukatsu, T. Miyano, I. Iwatsuki, and I. Matsumoto, Japanese Patent No. 41882 (1979); Chem. Abs., **91**, 123750 (1979).
51. H. Fukatsu, T. Miyano, I. Iwatsuki, and I. Matsumoto, Japanese Patent No. 103880 (1979); Chem. Abs., **92**, 128954 (1980).
52. K. Ishibashi, S. Ishiguro, and R. Komaki, Japanese Patent No. 98784 (1979); Chem. Abs., **92**, 146796 (1980).
53. Banya Pharm. Co., Japanese Patent No. 79290 (1979); Derwent CPI, 58592B/32.
54. H. Fukatsu and T. Miyano, Japanese Patent No. 30187 (1979); Chem. Abs., **91**, 39525 (1979).
55. H. Fukatsu and T. Miyano, Japanese Patent No. 52085 (1979); Chem. Abs., **91**, 157760 (1979).
56. K. Sakurai, S. Aoyagi, H. Toyofuku, M. Ohki, T. Yoshizawa, and T. Kuroda, Chem. Pharm. Bull., **26**, 3665 (1978).
57. K. Sakurai, Japanese Patent No. 27583 (1979); Chem. Abs., **91**, 5245 (1979).
58. Y. Otsuka, Y. Fujimori, and H. Kondo, Japanese Patent No. 27585 (1979); Chem. Abs., **91**, 5247 (1979).

59. T. Nakamura, Y. Hoshide, Y. Hashimoto, K. Suzuki, and H. Yoshida, Japanese Patent No. 52086 (1979); Chem. Abs., **91**, 175381 (1979).
60. T. Umemoto, E. Ogura, T. Mukono, Japanese Patent No. 112073 (1986); Chem. Abs., **106**, 18602 (1987).
61. J. Yamashita, M. Yasumoto, and S. Hashimoto, Chem. Pharm. Bull., **31**, 3872 (1983).
62. T. Sato, T. Kawashima, H. Suehiro, O. Maruyama, and M. Yokoyama, Japanese Patent No. 27579 (1979); Chem. Abs., **91**, 20539 (1979).
63. T. Narimoto and Y. Ichikawa, Japanese Patent No. 131587 (1977); Chem. Abs., **88**, 105399 (1978).
64. T. Narimoto and Y. Ichikawa, Japanese Patent No. 131586 (1977); Chem. Abs., **88**, 121230 (1978).
65. T. Ishida and K. Akashi, Japanese Patent No. 127981 (1974); Chem. Abs., **83**, 10132 (1975).
66. N. Kamano, Japanese Patent No. 98976 (1978); Chem. Abs., **90**, 54967 (1979).
67. S. Ozaki and K. Ishikawa, Japanese Patent No. 52182 (1976); Chem. Abs., **85**, 192753 (1976).
68. Mitsui Toatsu Chem. Inc. Japanese Patent No. 33682 (1977); Derwent CPI 29784Y/17.
69. K. Sakurai, M. Amino, and H. Toyofuku, Japanese Patent No. 77071 (1978); Chem. Abs., **89**, 197590 (1978).
70. Institute of Organic Synthesis Academy of Sciences of the Latvian SSR, Russian Patent No. 791753 (1981); Derwent CPI 71150D/39.
71. M. Yasumoto, J. Yamashita, I. Yamawaki, S. Ueda, S. Hashimoto, and T. Suzue, Japanese Patent No. 89481 (1978); Chem. Abs., **90**, 54965 (1978).
72. N. Kamano, Japanese Patent No. 95980 (1978), Chem. Abs., **90**, 23102 (1979); Japanese Patent No. 20508 (1979), Derwent CPI 69523A/39.
73. T. Hayasaka, K. Saito, and T. Goto, Japanese Patent No. 119881 (1978); Chem. Abs., **90**, 204126 (1979).
74. O. Futsukaichi, S. Kumata, and H. Hayashiichi, Japanese Patent No. 137972 (1978); Chem. Abs., **90**, 121647 (1979).
75. M. Yasumoto, S. Hashimoto, and T. Suzue, Japanese Patent No. 30188 (1979); Chem. Abs., **91**, 39524 (1979).
76. M. H. Normant and M. M. Delepine, Compt. Rend., **228**, 102 (1949).
77. E. L. Bliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, J. Org. Chem., **30**, 2441 (1956).
78. T. Kametani, Heterocycles, **6**, 529 (1977).
79. T. Kametani, J. Heterocycl. Chem., **14**, 473 (1977).
80. K. Kigasawa, M. Kukiki, K. Wakisaka, O. Kusama, H. Sugi, and K. Kawasaki, Japanese Patent No. 93778 (1977); Chem. Abs., **88**, 121226 (1978).
81. Y. Kamano, Japanese Patent No. 84581 (1979); Chem. Abs., **91**, 157764 (1979).
82. K. Kigasawa, M. Hiragi, K. Wakisaka, O. Kasuma, H. Sugi, and K. Kawasaki, Japanese Patent No. 118479 (1977); Chem. Abs., **88**, 89707 (1978).
83. K. Mikami, A. Matsubara, Y. Ike, T. Nakano, and S. Ozaki, Japanese Patent No. 139076 (1977); Chem. Abs., **88**, 105404 (1978).
84. A. Matsubara, K. Mikami, Y. Ike, T. Nakano, and S. Ozaki, Japanese Patent No. 139077 (1977); Chem. Abs., **88**, 121231 (1978).
85. H. Fukatsu, T. Miyano, and I. Matsumoto, Japanese Patent No. 2480 (1978); Chem. Abs., **89**, 59896 (1978).
86. K. Ishibashi, S. Ishiguro, and R. Komaki, Japanese Patent No. 46789 (1979); Chem. Abs., **91**, 140863 (1979).
87. K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusama, H. Sugi, K. Kawasaki, and T. Iwama, Japanese Patent No. 125178 (1978); Chem. Abs., **88**, 170183 (1978).
88. Y. Minami, Y. Hirose, and N. Ida, Japanese Patent No. 118478 (1977); Chem. Abs., **88**, 89706 (1978).
89. M. Yasumoto, T. Marunaka, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 64281 (1975); Chem. Abs., 131631 (1975).
90. J. Yamashita and M. Yasumoto, Nucleic Acids Symp. Ser., **10**, 7 (1981).
91. M. Yasumoto, T. Marunaka, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 285 (1977); Chem. Abs., **87**, 68407 (1977).
92. H. Fukatsu, Japanese Patent No. 12875 (1978); Derwent CPI 20785A/11.
93. K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusuma, H. Sugi, and K. Kawasaki, Japanese Patent No. 7688 (1978); Chem. Abs., **88**, 170185 (1978).
94. ABIC, Japanese Patent No. 34778 (1978); Chem. Abs., **89**, 129531 (1978).
95. O. Asano, S. Makino, and B. Kato, Japanese Patent No. 59288 (1979); Chem. Abs., **91**, 175386 (1979).
96. S. A. Giller, R. A. Zhuk, and M. Yu. Lidak, Russian Patent No. 272307 (1965); Byul. Izobr., No. 19, 28 (1970).

97. S. A. Hiller, R. A. Zhuk, M. J. Lidaks, and A. A. Zidermane, British Patent No. 1168391 (1969); Chem. Abs., **72**, 43715 (1970); French Patent No. 1574684 (1969); Chem. Abs., **73**, 77281 (1970); US Patent No. 3635946 (1972); Chem. Abs., **76**, 140864 (1972); Japanese Patent No. 4554 (1977); Chem. Abs., **88**, 89985 (1978); Derwent CPI 32845F/00.
98. Ferrer International S. A., Spanish Patent No. 458679 (1978), Chem. Abs., **91**, 20990 (1979).
99. K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusuma, H. Sugi, K. Kawasaki, and S. Kimura, Japanese Patent No. 108987 (1977); Chem. Abs., **88**, 190878 (1978).
100. K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusuma, H. Sugi, K. Kawasaki, and S. Kimura, Japanese Patent No. 108988 (1977); Chem. Abs., **88**, 136649 (1978).
101. É. Ya. Lukevits and L. M. Ignatovich, Izv. Akad. Nauk Latv. SSR. Ser. Khim., No. 4, 492 (1981).
102. T. Sowa, N. Suzuki, Y. Ono, T. Ishida, and K. Akashi, Japanese Patent No. 8282 (1976); Chem. Abs., **84**, 180278 (1976).
103. N. Suzuki, S. Tagaki, K. Iizuka, M. Kobayashi, Y. Kobayashi, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 83476 (1977); Chem. Abs., **87**, 202040 (1977).
104. K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusuma, H. Sugi, and K. Kawasaki, Japanese Patent No. 142080 (1977); Chem. Abs., **88**, 136661 (1978).
105. S. Ozaki, Japanese Patent No. 75079 (1976); Chem. Abs., **86**, 106631 (1977).
106. S. Ozaki, Japanese Patent No. 111084 (1978); Derwent CPI 79176A/44.
107. Y. Kojima, M. Odate, T. Yokoyama, Y. Ike, and Y. Jinno, Japanese Patent No. 68790 (1978); Chem. Abs., **89**, 197591 (1978).
108. I. Nakajima, Y. Kanei, and T. Shinuchi, Japanese Patent No. 83385 (1977); Chem. Abs., **87**, 184907 (1977).
109. I. Nakajima, Y. Kanei, and T. Shinuchi, Japanese Patent No. 83386 (1977); Chem. Abs., **87**, 184908 (1977).
110. Y. Hoshide, Y. Hashimoto, H. Ogawa, and S. Tasaka, Japanese Patent No. 14981 (1979); Chem. Abs., **91**, 57051 (1979).
111. S. Ozaki and T. Takahashi, Japanese Patent No. 5387 (1975); Chem. Abs., **82**, 140297 (1975).
112. PCR Corp., US Patent No. 4024143 (1977); Japanese Patent No. 8836 (1981); Derwent CPI 37967Y/21.
113. Mitsui Toatsu Chem. Inc., Japanese Patent No. 135988 (1978); Derwent CPI 2899B/02.
114. S. A. Giller, M. Yu. Lidak, R. A. Zhuk, K. Ya. Pets, I. N. Getsova, and A. É. Berzinya, First All-Union Conference on the Chemotherapy of Malignant Tumors [in Russian], Riga (1968).
115. R. A. Zhuk, Advances in the Chemistry of Furan [in Russian] É. Ya. Lukevits,(ed.), Zinatne, Riga (1978), p. 184.
116. S. A. Giller, M. Yu. Lidak, R. A. Zhuk, A. E. Berzinya, K. Ya. Pets, I. N. Getsova, and É I. Bruk, Khim. Geterotsikl. Soedin., No. 2, 375 (1969).
117. S. A. Giller, R. A. Zhuk, M. Yu. Lidak, A. E. Berzin', A. É. Getsova, K. Ya. Pets, and É. I. Bruk, Russian Patent No. 287952; Byul. Izobr., No. 47, 32 (1970).
118. S. A. Giller, M. Yu. Lidak, R. A. Zhuk, K. Ya. Pets, I. N. Getsova, and A. E. Berzinya, Methods for Synthesis and Investigation of Antitumor Compounds [in Russian], No. Riga, 3, 109 (1970).
119. Univ. of Utah, Belgian Patent No. 832067 (1975); Chem. Abs., **85**, 160145 (1976).
120. L. B. Townsend, R. A. Earl, and S. J. Manning, German Patent No. 2519201 (1975); Chem. Abs., **84**, 59575 (1976); US Patent No. 3960864; Canadian Patent No. 1024145 (1978); Chem. Abs., **88**, 190889 (1978); Derwent CPI 78072W/47.
121. S. A. Hiller, A. A. Lazdinš, A. K. Vainberg, and A. B. Sidorov, Belgian Patent No. 830215; Chem. Abs., **85**, 192757 (1976); German Patent No. 25190709 (1976); Japanese Patent No. 127087 (1976); Netherlands Patent No. 7504691 (1976); Chem. Abs., **86**, 155685 (1977). British Patent No. 1462733 (1977); Chem. Abs., **87**, 53361 (1977); US Patent No. 4039546 (1977); Chem. Abs., **87**, 168342 (1977); French Patent No. 2313933 (1978); Swedish Patent No. 7504332 (1978); Swiss Patent No. 608013 (1978); Japanese Patent No. 12467 (1979); Derwent CPI 55X/01.
122. A. A. Lazdynysh, A. K. Veinberg, A. B. Sidorov, and S. A. Giller, Russian Patent No. 721439, Byul. Izobr., No. 10, 100 (1980).
123. Y. Kobayashi, N. Suzuki, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 42887 (1977); Chem. Abs., **87**, 135385 (1977).
124. Y. Kobayashi, K. Sako, Y. Hiyoshi, N. Suzuki, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 48676 (1977); Chem. Abs., **87**, 201570 (1977).

125. Y. Kobayashi, S. Takagi, K. Nishimura, N. Suzuki, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 48677 (1977); Chem. Abs., **87**, 201569 (1977).
126. Asahi Chem. Ind. Co., German Patent No. 2650918 (1977); Japanese Patent No. 59173 (1977); Japanese Patent No. 59174 (1977); Japanese Patent No. 59175 (1977); Derwent CPI 38416Y/22.
127. T. Tomiyama, Japanese Patent No. 71480 (1977); Chem. Abs., **87**, 184905 (1977).
128. H. Nakayama and M. Ishikura, Japanese Patent No. 108989 (1977); Chem. Abs., **88**, 190877 (1978).
129. Y. Kojima, M. Odate, T. Yokoyama, Y. Ike, Y. Jinno, Japanese Patent No. 68791 (1978); Chem. Abs., **89**, 180036 (1978).
130. Y. Fujimora and Y. Otsuka, Japanese Patent No. 127485 (1978); Chem. Abs., **90**, 137853 (1979).
131. Y. Fujimori and Y. Otsuka, Japanese Patent No. 130677 (1978); Chem. Abs., **90**, 152228 (1979).
132. Y. Fujimori and Y. Otsuka, Japanese Patent No. 130678 (1978); Chem. Abs., **90**, 152227 (1979).
133. Y. Fujimori and Y. Otsuka, Japanese Patent No. 132580 (1978); Chem. Abs., **90**, 121640 (1979).
134. Y. Kobayashi, S. Takagi, T. Sone, M. Wakabayashi, and R. Kodaira, Japanese Patent No. 135989 (1978); Chem. Abs., **90**, 121642 (1979).
135. Mitsui Toatsu Chem. Ind., Japanese Patent No. 15284 (1981); Chem. Abs., **95**, 7323 (1981).
136. K. Sakai and Y. Inamoto, Japanese Patent No. 31079 (1977); Chem. Abs., **87**, 53375 (1977).
137. J. W. Shuppert and C. A. Angell, J. Chem. Phys., **67**, 3050 (1977).
138. Y. Hoshide, Y. Hashimoto, H. Ogawa, S. Tasaka, and Y. Yoshide, Japanese Patent No. 48774 (1979); Chem. Abs., **91**, 175680 (1979).
139. K. Kobayashi, T. Sone, N. Suzuki, M. Wakabayashi, and T. Sowa, Japanese Patent No. 36673 (1977); Chem. Abs., **87**, 135387 (1977).
140. T. Merunaka, M. Yasumoto, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 105673 (1975); Chem. Abs., **84**, 59543 (1976).
141. T. Marunaka, M. Yasumoto, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 105674 (1975); Chem. Abs., **84**, 59542 (1976).
142. Y. Kobayashi, N. Suzuki, S. Takagi, K. Nishimura, Y. Hiyoshi, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 59172 (1977); Chem. Abs., **87**, 168080 (1977).
143. Y. Fujimori, Japanese Patent No. 32488 (1979); Chem. Abs., **91**, 107995 (1979).
144. T. Tomiyama, Japanese Patent No. 71479 (1977); Chem. Abs., **87**, 202039 (1977).
145. N. Suzuki, T. Sone, K. Nishimura, E. Muramatsu, Y. Kobayashi, M. Wakabayashi, and T. Sowa, Japanese Patent No. 59171 (1977); Chem. Abs., **87**, 135392 (1977); Japanese Patent No. 20505 (1979); Derwent CPI 45759Y/26.
146. Tanabe Pharm. Co., Japanese Patent No. 77054 (1978); Derwent CPI 57880A/32.
147. N. Suzuki, K. Nazama, K. Iizuka, I. Himeno, Y. Kobayashi, T. Sone, M. Wakabayashi, and T. Sowa, Japanese Patent No. 83475 (1977); Chem. Abs., **87**, 202038 (1977).
148. Michael Uri, Z. Sasson, and E. Schoenberger, Belgian Patent No. 859529 (1978); German Patent No. 2744956 (1978); Chem. Abs., **89**, 24357 (1978); Japanese Patent No. 46987 (1978); German Patent No. 7903687 (1980); Derwent CPI 26970A/15.
149. S. A. Hiller, R. A. Zhuk, A. E. Berzina, L. A. Sherin, and A. A. Lazdinš, Belgian Patent No. 807556 (1974); German Patent No. 2357847 (1974); Chem. Abs., **81**, 120680 (1974); French Patent No. 2207138 (1974); Chem. Abs., **82**, 171019 (1975); Netherlands Patent No. 7315712 (1974); Chem. Abs., **83**, 10138 (1975); US Patent No. 3912734 (1975); Chem. Abs., **84**, 59538 (1976); British Patent No. 1438987 (1976); Chem. Abs., **86**, 16696 (1977); Canadian Patent No. 999863 (1976); Swiss Patent No. 586696 (1977); Swedish Patent No. 7315630 (1980); Japanese Patent No. 39545 (1980); Chem. Abs., **94**, 175151 (1981); Derwent CPI 41634V/23.
150. R. A. Zhuk, A. É. Berzinya, L. A. Sherin, L. T. Kaulinya, and S. A. Giller, Khim. Geterotsikl. Soedin., No. 9, 1258 (1977).
151. M. Yasumoto, T. Marunaka, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 50383 (1975); Chem. Abs., **83**, 206316 (1975).
152. M. Yasumoto, I. Yamayaki, T. Marunaka, and S. Hashimoto, J. Med. Chem., **21**, 738 (1978).
153. M. Yasumoto, T. Marunaka, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 50384 (1975); Chem. Abs., **83**, 193366 (1975).
154. Ferrer International S. A., Spanish Patent No. 458887 (1978); Chem. Abs., **89**, 197610 (1978).

155. T. Kanai and M. Ishino, Japanese Patent No. 65774 (1976); Chem. Abs., **86**, 29862 (1977).
156. C. H. Lee, J. Y. Kim, W. J. Kim, and Y. H. Kim, Heterocycles, **31**, 211 (1990).
157. M. Yasumoto, T. Marunaka, S. Hashimoto, K. Harima, and T. Suzue, Japanese Patent No. 146482 (1976); Chem. Abs., **87**, 53355 (1977).
158. Y. Kobayashi, T. Sone, N. Suzuki, S. Furukawa, M. Wakabayashi, and R. Kodaira, Japanese Patent No. 144581 (1978); Chem. Abs., **90**, 204127 (1979).
159. Y. Kobayashi, T. Sone, M. Wakabayashi, and R. Kodaira, Japanese Patent No. 149985 (1978); Chem. Abs., **91**, 20991 (1979).
160. Y. Kobayashi, T. Sone, K. Sako, E. Muramatsu, I. Himeno, N. Suzuki, M. Wakabayashi, and T. Sowa, Japanese Patent No. 59179 (1977); Chem. Abs., **87**, 184542 (1977).
161. T. Miyoshi, Japanese Patent No. 112884 (1978); Chem. Abs., **90**, 87504 (1979).
162. H. Morizawa, T. Miyoshi, G. Yamazaki, K. Ajisaka, and M. Kaisho, Japanese Patent No. 39084 (1979); Chem. Abs., **91**, 91660 (1979).
163. Y. Hoshide, Y. Hashimoto, H. Ogawa, K. Suzuki, and S. Tasaka, Japanese Patent No. 59289 (1979); Chem. Abs., **91**, 175387 (1979).
164. M. Matsui and T. Ogawa, German Patent No. 2648239 (1977); Chem. Abs., **87**, 102600 (1977); Japanese Patent No. 51373 (1977); Japanese Patent No. 51375 (1977); Japanese Patent No. 68189 (1977); Japanese Patent No. 68190 (1977); Japanese Patent No. 116483 (1977); Japanese Patent No. 37873 (1978); Japanese Patent No. 37874 (1978); Japanese Patent No. 12030 (1980); Chem. Abs., **93**, 204684 (1980); Derwent CPI 31342Y/17.
165. T. Sone and N. Suzuki, Japanese Patent No. 108986 (1977); Chem. Abs., **88**, 136647 (1978).
166. Y. Fujimori and Y. Otsuka, Japanese Patent No. 141283 (1978); Chem. Abs., **90**, 121649 (1979).
167. N. Suzuki, G. Kimura, M. Tomari, and M. Yajima, Japanese Patent No. 83474 (1977); Chem. Abs., **87**, 184906 (1977).
168. K. Ishibashi and R. Komaki, Japanese Patent No. 36280 (1979); Chem. Abs., **91**, 107994 (1979).
169. Y. Kobayashi, S. Kiyohide, and M. Wakabayashi, Japanese Patent No. 5983 (1979); Chem. Abs., **91**, 5244 (1976).
170. T. Sone and Y. Kobayashi, Japanese Patent No. 108985 (1977); Chem. Abs., **88**, 170182 (1977).
171. K. Ishibashi, R. Komura, R. Komaki, and H. Yamai, Japanese Patent No. 137973 (1978); Chem. Abs., **90**, 121646 (1979).
172. Institute of Physical Chemistry, Japanese Patent No. 59682 (1978); Japanese Patent No. 20510 (1979); Derwent CPI 48677A/27.
173. Asahi Chem. Ind. Co., Japanese Patent No. 59169 (1977); Derwent CPI 45757Y/26.
174. Y. Kobayashi, T. Sone, S. Takagi, K. Sako, and I. Himeno, Japanese Patent No. 108984 (1977); Chem. Abs., **88**, 136648 (1978).
175. M. Miyoshi, K. Inoue, K. Matsumoto, T. Iwasaka, and H. Horikawa, Japanese Patent No. 5984 (1979); Chem. Abs., **90**, 204135 (1979).
176. M. Miyoshi, Japanese Patent No. 79287 (1979); Derwent CPI 58589B/32.
177. Tanabe Pharm. Co., Japanese Patent No. 79289 (1979); Derwent CPI 58591B/32.
178. T. Iwasaki, T. Nishitani, H. Horikawa, and I. Inoue, Tetrahedron Lett., **22**, 1029 (1981).
179. N. Suzuki, T. Sone, S. Takage, E. Muramatsu, Y. Kobayashi, M. Wakabayashi, and T. Sowa, Japanese Patent No. 59168 (1977); Chem. Abs., **87**, 168079 (1977).
180 M. Miyoshi, K. Inoue, K. Matsumoto, and T. Iwasaki, Japanese Patent No. 79288 (1979); Chem. Abs., **92**, 6551 (1980).
181. Hoffmann—La-Roche AG, Japanese Patent No. 144678 (1977).
182. R. A. Earl and L. B. Townsend, J. Heterocycl. Chem., **9**, 1141 (1972).
183. L. B. Townsend and R. A. Earl, US Patent Appl. 405532 (1973); Chem. Abs., **81**, 63664 (1974).
184. Ferrer International S. A., Spanish Patent No. 458886 (1978); Chem. Abs., **89**, 197596 (1978).
185. O. Miyashita, K. Matsumura, H. Shimadzu, and N. Hashimoto, Belgian Patent No. 853065 (1977); Japanese Patent No. 118480 (1977); Japanese Patent No. 71086 (1978); Chem. Abs., **89**, 215427 (1978); Japanese Patent No. 124276 (1978); Derwent CPI 70715Y/40.
186. O. Miyashita, K. Matsumura, H. Shimadzu, and N. Hashimoto, Chem. Pharm. Bull., **29**, 3181 (1981).
187. Takeda Chem. Ind. Co., Japanese Patent No. 102573 (1980); Derwent CPI 66722C/38.

188. Y. Kojima and M. Odate, Japanese Patent No. 137974 (1978); Chem. Abs., **90**, 121645 (1979); Japanese Patent No. 2716 (1982); Derwent CPI 3334B/02.
189. Y. Fujimori, Japanese Patent No. 59290 (1979); Chem. Abs., **91**, 175388 (1979).
190. Y. Fujimori, Japanese Patent No. 66688 (1979); Chem. Abs., **91**, 157762 (1979).
191. M. Yasumoto, J. Yamashita, S. Hashimoto, and T. Suzue, Japanese Patent No. 40781 (1978); Chem. Abs., **89**, 109568 (1978).
192. M. Yasumoto, J. Yamashita, and S. Hashimoto, Japanese Patent No. 39082 (1979); Chem. Abs., **91**, 91662 (1979).
193. ABIC, Japanese Patent No. 98980 (1978); Chem. Abs., **90**, 72225 (1979).
194. A. Osamu and K. Fumiyoshi, Japanese Patent No. 124275 (1978); Chem. Abs., **90**, 121644 (1979).
195. Taiho Pharm. Co., Japanese Patent No. 23986 (1978); Japanese Patent No. 33030 (1986); Derwent CPI 29321A/16.
196. I. Minami, Y. Yoshioka, and H. Nomura, Japanese Patent No. 53671 (1978); Chem. Abs., **89**, 197588 (1978).
197. Taiho Pharm. Co., Belgian Patent No. 847886 (1977); Derwent CPI 18206Y/11.
198. S. Hashimoto, M. Yasumoto, T. Marunaka, N. Unemi, K. Kitazato, and S. Fujii, British Patent No. 1518391 (1978).
199. Taiho Pharm. Co., Japanese Patent No. 23985 (1978); Derwent CPI 29320A/16.
200. Taiho Pharm. Co., Japanese Patent No. 23987 (1978); Derwent CPI 29322A/16.
201. Taiho Pharm Co., Japanese Patent No. 136687 (1976); Japanese Patent No. 49077 (1980); Derwent CPI 2864Y/02.
202. Y. Hoshide, Y. Hashimoto, H. Ogawa, and N. Tasaka, Japanese Patent No. 39083 (1979); Chem. Abs., **91**, 91661 (1979).
203. Y. Yoshioka and M. Nomura, Japanese Patent No. 108988 (1978), Chem. Abs., **90**, 137856 (1979); Japanese Patent No. 20509 (1979); Derwent CPI 77593A/43.
204. S. Ozaki, H. Mizuno, K.Ishikawa, and H. Mori, Japanese Patent No. 33683 (1977); Chem. Abs., **87**, 168350 (1977).