β-Adrenoceptor Blocking Activity of Halogenated Thienylethanolamine Derivatives

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The synthesis of a number of ring-halogenated *N*-isopropyl- and *N*-*tert*-butyl-2-amino-1-(2-thienyl)ethanols has been carried out in order to ascertain the influence of chloro or bromo substitution at the thiophene moiety on their blocking β-adrenoceptor activity. It was found that chloro- and bromo-substituted compounds exhibited a similar activity. Monohalo substitution at positions C_4 or C_5 of the thiophene ring resulted in comparable blocking potency, whereas C_3 halo-substituted compounds were practically devoid of activity. The highest activity in these series was observed with compounds dihalogenated at C_4 and C_5, their effect on myocardial β-receptors being comparable to that of propranolol.

The pharmacological study of some N-substituted 2-amino-1-(2-thienyl)ethanols showed a strong β-adrenoceptor blocking activity[1,2] together with interesting antiarrhythmic actions[2,3] in chlorinated thiophene derivatives with *N*-isopropyl or *tert*-butyl substituents. Since in our previous work only a limited number of possibilities for chloro substitution on the thiophene ring were considered, no definite structure–activity relationships were reached. In consequence, the first aim of the present work was to define these relationships in the complete series of these chlorothienylethanolamines. It was also considered of interest to study whether the change of chlorine atoms on the thiophene moiety by bromine could affect the action of thienylethanolamine derivatives on adrenergic β-receptors.

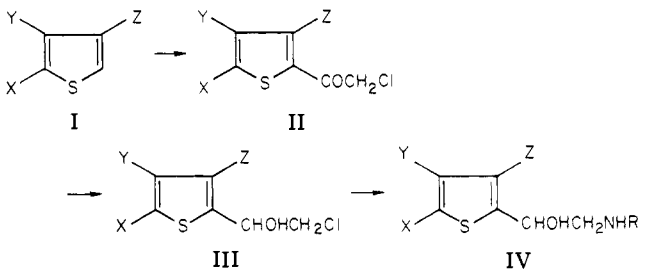
Chemistry. All the thienylethanolamines derivatives IV (Table III) reported in this work are racemic modifications and were prepared by the sequence of reactions shown in Scheme I. The appropriate halothiophene I was chloroacetylated by the Friedel–Crafts method. The chloroacetylthiophenes II (Table I) were reduced by the Meerwein–Pondorff method to the corresponding 2-chloro-1-(2-thienyl)ethanols III (Table II) which upon treatment with *tert*-butyl- or isopropylamine yielded the corresponding thienylethanolamine derivative IV (Table III).

Bagli and Ferdinandi[4] have isolated by chromatographic procedures two regioisomeric thienylethanolamines from the reaction of some 2-bromo-1-(2-thienyl)ethanols with isopropylamine. In our case, the reaction of compounds III with the amines led, after recrystallization, only to compounds IV, as shown by the chemical shifts of the >CH–O– and the $-CH_2-N<$ protons in their NMR spectra.

Chloroacetylation of 3-chloro- and 3-bromothiophene yielded, as expected, a mixture of the three possible isomers in each case which were isolated by fractional crystallization and column chromatography on silica gel and identified by their NMR spectra.

Pharmacology and Discussion. All the ring-halogenated thienylethanolamines were tested for β-adrenoceptor blocking activity by studying their inhibitory effect on the tachycardia response to isoproterenol in anesthetized rats. The results obtained are presented in Table IV. All the compounds tested antagonized to different degrees the isoproterenol effect and decreased moderately the resting heart rate, the only exception being thienylethanolamines monohalogenated in position 3 of the thiophene ring. 3-Chloro or 3-bromo derivatives such as compounds **1**, **2**, and **11** were inactive whereas compound **12** only showed a very weak β-blocking activity. It can also be observed in Table IV that there are not important differences in β-blocking potency between compounds monohalogenated in position 4 or in position 5 of the thiophene ring. 5-Chlorothienylethanolamine derivatives, described in our previous papers, [1,2] also behave pharmacologically like the above-mentioned compounds.

Scheme I



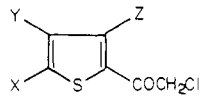
I II III IV

When both positions 4 and 5 of the thiophene ring are halogenated, the effect is optimum with regard to β-adrenoceptor blocking potency. The 4,5-dibrominated compounds **15** and **16** are the most potent β-blockers of this new series and, likewise, 4,5-dichloro derivatives previously described[1,2] showed the highest potency in the series of chlorinated compounds. It can be inferred from these data that the change of a chlorine by a bromine atom does not substantially modify the biological activity of these substances. It should be mentioned in this regard that compound **15** was found equivalent with its dichloro analogue in a study of antihypertensive activity in rats.[5] However, while monobromo compound **9** showed some antihypertensive activity, there was a complete loss of activity in its monochloro analogue.[5] It thus seems that the structural requirements are not the same for lowering blood pressure in spontaneously hypertensive rats or for antagonizing the tachycardia response to isoproterenol.

Trihalogenated thiophene derivatives appear to be less potent β-blockers than the corresponding 4, 5-dihalogen derivatives. Thus, compounds **7** and **8** are less active than the corresponding 4,5-dichloro derivatives,[2] and compounds **21** and **22** are also less potent antagonists of isoproterenol tachycardia than the dibrominated compounds **15** and **16**. It appears also, from the experiments in cats, that the trihalogenated compounds **8**, **21**, and **22** tend to block more readily the hypotension induced by isoproterenol than the tachycardia. Together with compound **20**, these are the only examples of the series in which vascular β-receptors of the cat are blocked to a greater extent than myocardial β-receptors.

With regard to the influence of the *N*-alkyl substituent on the β-adrenoceptor blocking potency of this series of compounds, no general conclusion can be drawn from the

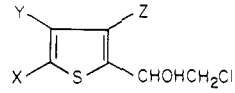
Table I. 2-(Chloroacetyl)thiophenes



X	Y	Z	% yield	Bp, °C (mm)	Mp, °C	Recrystn solvent[a]	Formula	Analyses
H	H	Cl	56		77-78	EtOH	$C_6H_4Cl_2OS$	C, H, S
H	Cl	H	37		98-99	Pe	$C_6H_4Cl_2OS$	C, H, S
Cl	H	Cl	82	125-128 (2.5)	76-77	EtOH	$C_6H_3Cl_3OS$	C, H, S
Cl	Cl	Cl	91	120-121 (1.2)	75-76	EtOH	$C_6H_2Cl_4OS$	C, H, S
Br	H	H	78	108-109 (0.6)	96-97	EtOH	$C_6H_4BrClOS$	C, H, S
H	H	Br	56		79-80	EtOH	$C_6H_4BrClOS$	C, H, S
H	Br	H	37		57-58	Pe	$C_6H_4BrClOS$	C, H, S
Br	Br	H	91	128-129 (0.8)	90-91	EtOH	$C_6H_3Br_2ClOS$	C, H, S
Br	H	Br	89	130-131 (0.6)	92-93	EtOH	$C_6H_3Br_2ClOS$	C, H, S
H	Br	Br	95	151-152 (0.8)	98-99	EtOH	$C_6H_3Br_2ClOS$	C, H, S
Br	Br	Br	65	159-160 (1.0)	114-115	Pe	$C_6H_2Br_3ClOS$	C, H, S

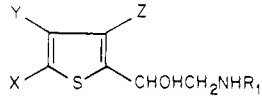
[a] Pe = petroleum ether, bp 50-70 °C.

Table II. 2-Chloro-1-(2-thienyl)ethanols



X	Y	Z	Yield, %	Bp, °C (mm)	Formula	Analyses
H	H	Cl	85	95-96 (0.8)	$C_6H_6Cl_2OS$	C, H, S
H	Cl	H	85	95-96 (0.5)	$C_6H_6Cl_2OS$	C, H, S
Cl	H	Cl	81	109-111 (1.0)	$C_6H_5Cl_3OS$	C, H, S
Cl	Cl	Cl	71	124-125 (1.0)	$C_6H_4Cl_4OS$	C, H, S
Br	H	H	66	111-112 (0.8)	$C_6H_6BrClOS$	C, H, S
H	H	Br	89	111-112 (0.8)	$C_6H_6BrClOS$	C, H, S
H	Br	H	85	138-140 (5.0)	$C_6H_6BrClOS$	C, H, S
Br	Br	H	77	110-111 (1.5)	$C_6H_5Br_2ClOS$	C, H, S
Br	H	Br	86	128-130 (0.6)	$C_6H_5Br_2ClOS$	C, H, S
H	Br	Br	77	142-143 (0.8)	$C_6H_5Br_2ClOS$	C, H, S
Br	Br	Br	88	159-162 (0.6)	$C_6H_4Br_3ClOS$	C, H, S

Table III. 2-Alkylamino-1-(2-thienyl)ethanols



Compd	X	Y	Z	R_1	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	Analyses
1	H	H	Cl	i-C_3H_7	65	105-106	He	$C_9H_{14}ClNOS$	C, H, N
2	H	H	Cl	t-C_4H_9	49	99-100	He	$C_{10}H_{16}ClNOS$	C, H, N
3	H	Cl	H	i-C_3H_7	84	84-85	He	$C_9H_{14}ClNOS$	C, H, N
4	H	Cl	H	t-C_4H_9	85	57-58	He	$C_{10}H_{16}ClNOS$	C, H, N
5	Cl	H	Cl	i-C_3H_7	48	109-111	Pe	$C_9H_{13}Cl_2NOS$	C, H, N
6	Cl	H	Cl	t-C_4H_9	54	73-75	He	$C_{10}H_{15}Cl_2NOS$	C, H, N
7	Cl	Cl	Cl	i-C_3H_7	60	135-136	Pe	$C_9H_{12}Cl_3NOS$	C, H, N
8	Cl	Cl	Cl	t-C_4H_9	56	106-107	Pe	$C_{10}H_{14}Cl_3NOS$	C, H, N
9[b]	Br	H	H	i-C_3H_7	40	79-80	He	$C_9H_{14}BrNOS$	C, H, N
10	Br	H	H	t-C_4H_9	45	95-96	He	$C_{10}H_{16}BrNOS$	C, H, N
11	H	H	Br	i-C_3H_7	58	113-114	Hp	$C_9H_{14}BrNOS$	C, H, N
12	H	H	Br	t-C_4H_9	53	95-96	He	$C_{10}H_{16}BrNOS$	C, H, N
13	H	Br	H	i-C_3H_7	40	87-88	Pe	$C_9H_{14}BrNOS$	C, H, N
14	H	Br	H	t-C_4H_9	40	70-71	Pe	$C_{10}H_{16}BrNOS$	C, H, N
15[b]	Br	Br	H	i-C_3H_7	40	115-116	Pe	$C_9H_{13}Br_2NOS$	C, H, N
16	Br	Br	H	t-C_4H_9	48	105-106	Pe	$C_{10}H_{15}Br_2NOS$	C, H, N
17	Br	H	Br	i-C_3H_7	40	114-115	Pe	$C_9H_{13}Br_2NOS$	C, H, N
18	Br	H	Br	t-C_4H_9	44	97-98	Pe	$C_{10}H_{15}Br_2NOS$	C, H, N
19[b]	H	Br	Br	i-C_3H_7	59	127-128	Hp	$C_9H_{13}Br_2NOS$	C, H, N
20	H	Br	Br	t-C_4H_9	57	109-111	Hp	$C_{10}H_{15}Br_2NOS$	C, H, N
21	Br	Br	Br	i-C_3H_7	70	135-136	Hp	$C_9H_{12}Br_3NOS$	C, H, N
22	Br	Br	Br	t-C_4H_9	60	143-144	Hp	$C_{10}H_{14}Br_3NOS$	C, H, N

[a] He = hexane; Hp = heptane; Pe = petroleum ether, bp 50-70 °C. [b] These compounds are described in the literature[5] as their hydrochlorides.

data included in Table IV. In consequence, the pharmacological activity of these thienylethanolamine derivatives seems to be determined by the number and position of halogen atoms on the thiophene ring rather than by the use of *N*-isopropyl or *tert*-butyl substituents.

Compound **15** was the most active of the β-blockers tested in the present work and was slightly more potent than propranolol on myocardial β-receptors, while its

Table IV

Compd	% inhibn of isoproterenol tachycardia in rats[a]	% decrease of heart rate in rats[a]	% inhibn of isoproterenol effects in cats				% antagonism of bronchodilator effect of isoproterenol in guinea pigs[c]	Local anesthesia in mice: % inhibn of response[d]	Approx iv LD_{50} in mice
			Tachycardia		Hypotension				
			0.1[b]	1	0.1	1			
1	0	0							38
2	0	0							25
3	86	8	62	90	57	75			35
4	53	6							38
5	70	28							35
6	75	32	65	74	55	65			30
7	90	20	58	100	52	85			35
8	89	26	69	98	87	100	100	52	40
9	87	11	67.5	82	50	72		52	45
10	55.5	8							27
11	0	0							35
12	12.5	10							25
13	89.5	11	70	90	53	82			42
14	50	17	33	67	0	50	25		35
15	100	25	92.5[e]	100	75	100	40[f]	72.5	45
16	92	18	87.5[e]	100	58	95	100	100	38
17	77.5	14							35
18	78	17	50	88	45	89		82	42
19	92	10							27
20	95	36	53	92	64	97	100	75	28
21	75	10	50	95	65	88		40	35
22	90	12	72.5	100	77.5	100			32
Propranolol	95	32	87	100	85	100	100	93	35

[a] Single iv doses of 4 mg/kg. All standard errors of the mean fell within the range of 10–18% of the mean. [b] Cumulative iv doses in mg/kg. All standard errors of the mean fell within the range of 8–15% of the mean. [c] Results obtained after an iv dose of 0.3 mg/kg. The mean values of compounds 14 and 15 were significantly different from 100 ($p < 0.01$, Student's t test). [d] 0.5% solution of test compounds. A virtually complete inhibition of response was observed in all cases with 1% solutions. [e] 0.05 mg/kg of compounds 15 and 16 blocked tachycardia by 78 and 61%, respectively. [f] 0.01 mg/kg of compound 15 did not modify the isoproterenol effect whereas the same dose of propranolol fully antagonized the bronchodilation.

potency on vascular receptors was lower. Since the absence of effects of β-blockers on receptors of bronchial smooth muscle is a desirable feature of this class of drugs,[6] this aspect was also investigated with compound **15** and other selected compounds of this series. The results obtained are also recorded in Table IV. In this test, propranolol, at the low iv dose of 0.01 mg/kg, fully antagonized the bronchodilating effect of isoproterenol while compound **15** only blocked the isoproterenol effect by 40% when given at a tenfold higher dose.

Compound **15** and other representative compounds were also tested for local anesthetic activity in mice. Of the seven new compounds tested, compound **16** was more active than propranolol, whereas the potent β-blocker **15** was considerably less active. An approximate acute iv toxicity study was finally carried out on mice, and no important differences between propranolol and the new compounds of this series were observed.

In conclusion, bromo derivatives of thienylethanolamine appear to be as active β-blockers as the corresponding chloro analogues, and disubstitution by halogen atoms in positions 4 and 5 of the thiophene ring leads to the highest β-adrenoceptor blocking activity found in this series.

Experimental Section

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. IR spectra were recorded for all compounds and are consistent with assigned structures.

Chemical Methods. Chlorothiophenes and Bromothiophenes. 3-Chloro-, 2,4-dichloro-, and 2,3,4-trichlorothiophenes were made from the corresponding bromothiophenes by a transhalogenation method.[7] 2-Bromo-,[8] 3-bromo-,[9] 2,3-dibromo-,[10] 2,4-dibromo-,[11] 3,4-dibromo-,[12] and 2,3,4-tribromothiophenes[10] were prepared according to literature procedures.

Chloroacetylthiophenes (Table I). To a stirred mixture of chloroacetyl chloride (26 g, 0.23 mol) and anhydrous aluminum chloride (30 g, 0.23 mol) in dry carbon disulfide (200 mL) was added dropwise the corresponding halothiophene (0.2 mol). The mixture was stirred at room temperature overnight and then refluxed for 1 h. To the ice-cooled mixture, enough 3 N hydrochloric acid was added cautiously to make the solid disappear. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled in vacuo to give the corresponding chloroacetylthiophene.

Chloroacetylation of 3-chlorothiophene yielded (97%) a mixture of isomers, bp 99–100 °C (0.6 mm), of which a great part of 2-chloroacetyl-3-chlorothiophene was separated by fractional crystallization from ethanol. The isomers in the mother liquors were isolated by column chromatography on silica gel (EtAc-hexane 1:7).

So were obtained 2-chloroacetyl-3-chlorothiophene [58% of the mixture; NMR ($CDCl_3$) δ 4.67 (s, 2 H, CH_2), 7.05 (d, 1 H, J = 4.3 Hz, HCCCl), 7.69 (d, 1 H, J = 4.3 Hz, HCS)], 2-chloroacetyl-4-chlorothiophene [38% of the mixture; NMR ($CDCl_3$) δ 4.46 (s, 2 H, CH_2), 7.49 (d, 1 H, J = 1.5 Hz, HC=CCO), 7.63 (d, 1 H, J = 1.5 Hz, HCS)], and 3-chloroacetyl-4-chlorothiophene [4% of the mixture; mp 102–103 °C (EtOH); NMR ($CDCl_3$) δ 4.53 (s, 2 H, CH_2), 7.20 (d, 1 H, J = 3.2 Hz, NHC=CCl), 8.13 (d, 1 H, J = 3.2 Hz, HC=CCO)].

Chloroacetylation of 3-bromothiophene yielded (95%) a mixture of isomers, bp 108–114 °C (0.8 mm), of which a great part of 2-chloroacetyl-3-bromothiophene was separated by fractional crystallization from ethanol. The isomers in the mother liquors were isolated as above.

So were obtained 2-chloroacetyl-3-bromothiophene [59% of the mixture; NMR ($CDCl_3$ δ 4.72 (s, 2 H, CH_2), 7.13 (d, 1 H, J = 4.5 Hz, HCCBr), 7.65 (d, 1 H, J = 4.5 Hz, HCS)], 2-chloroacetyl-4-chlorothiophene [39% of the mixture; NMR ($CDCl_3$) δ 4.50 (s, 2 H, CH_2), 7.60 (d, 1 H, J = 1.5 Hz, HC=CCO), 7.69 (d, 1 H, J = 1.5 Hz, HCS)], and 3-chloroacetyl-4-chlorothiophene [2% of the mixture; NMR ($CDCl_3$) δ 4.55 (s, 2 H, CH_2), 7.42 (d, 1 H, J = 2.8 Hz, HC=CBr), 8.23 (d, 1 H, J = 2.8 Hz, HC=CCO)].

2-Chloro-1-(2-thienyl)ethanols (Table II) were prepared as colorless liquids by Meerwein-Ponndorf reduction of the corresponding chloroacetylthiophene following a standard procedure.[13]

2-Isopropyl- and 2-*tert*-Butylamino-1-(2-thienyl)ethanols (Table III). The corresponding 2-chloro-1-(2-thienyl)ethanol (0.03 mol) and the appropriate amine (0.075 mol) were heated at 100 °C for 24 h in a sealed tube. The cooled mixture was treated with Et_2O and H_2O. Drying (Na_2SO_4) and evaporation of the ethereal extracts yielded the crude product which was purified by recrystallization (decoloring charcoal if necessary). In some cases the low yield was due to the high solubility of the compound in the recrystallization solvent.

Pharmacological Methods. Compounds for pharmacological testing were dissolved in 0.05 N HCl and neutralized with $NaHCO_3$ to pH 7. Compounds **7**, **16**, **21**, and **11** were not soluble in HCl and were dissolved in 0.1 N acetic acid and neutralized as above.

Antagonism of Isoproterenol Effects in Blood Pressure and Heart Rate in Rats and Cats. Male Wistar rats were anesthetized with urethane (1.5 g/kg ip). Heart rate was measured by integration of ECG (lead II). Injections were made into the jugular vein. Standard submaximal doses of isoproterenol were given at 10-min intervals until constant responses were obtained. Test compounds were then given at the same dose of 4 mg/kg and injections of isoproterenol were repeated another three times at the same intervals of time. Blockade of the tachycardia response to isoproterenol was expressed as the percent mean inhibition of the mean control response. The percent change in resting heart rate after the test compounds was also calculated. Each compound was studied at least on five animals.

Cats were anesthetized with a mixture of chloralose (80 mg/kg ip) and pentobarbital (5 mg/kg ip) and maintained on artificial respiration. Blood pressure was measured from a carotid artery with a Statham transducer. Heart rate was measured as above. Records were displayed on a Grass polygraph. The effects of cumulative doses of test compounds were studied as above on the tachycardia and hypotension response to isoproterenol. Each compound was studied at least in four animals.

Antagonism of the Bronchial Effects of Isoproterenol in Guinea Pigs. Guinea pigs were anesthetized with a mixture of urethane (500 mg/kg ip) and chloralose (40 mg/kg ip). Intratracheal pressure was measured in artificially ventilated animals[14] and recorded on the polygraph by means of a Grass volumetric transducer. Bronchospasm was induced by iv injections of histamine at intervals of 10 min until three identical responses were obtained. Histamine effect was antagonized by iv isoproterenol, 20 s prior to histamine, and another three constant responses were obtained. Test compounds were iv given 3 min before this combined treatment. Each compound was studied on five animals.

Local Anesthesia in Mice. Test compounds (0.1 mL of 0.1–1% solutions) were intradermically administered to ICR Swiss mice at about 1 cm from the root of the tail.[15] Twenty minutes later an artery clip was applied to the area of the injection and the response of mice was then evaluated by means of a graded subjective scale from 0 to 2. The percent reduction in the summed scores of control groups was calculated. Each solution was tested on five animals.

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Improved Synthesis and in Vitro Antiviral Activities of 5-Cyanouridine and 5-Cyano-2′-deoxyuridine

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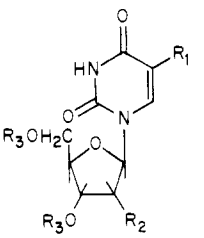
In order to evaluate the influence of the cyano group on the antiviral activity of pyrimidine deoxyribonucleosides, a moderate yield, unified approach to the synthesis of both 5-cyanouridine and 5-cyano-2′-deoxyuridine was developed. Thus, treatment of the appropriate acetylated 5-bromouracil nucleoside with NaCN or KCN in Me_2SO at 90–110 °C gave, after deblocking, 35–45% yields of the corresponding 5-cyanouracil nucleosides. 5-Cyanouridine was devoid of significant activity against vaccinia virus, herpes simplex-1, and vesicular stomatitis virus, but 5-cyano-2′-deoxyuridine, while lacking activity against herpes simplex, showed significant inhibition of vaccinia virus; for instance, 5-cyano-2′-deoxyuridine inhibited vaccinia virus replication at concentrations 10–20 times that required for inhibition by the known antivirals, 5-iodo-2′-deoxyuridine and 1-(β-D-arabinofuranosyl)adenine. Replacement of the 5-halogeno substituents of pyrimidine deoxyribonucleosides thus decreases, but does not abolish, antiviral activity.

A number of 5-substituted 2′-deoxyuridines possess significant in vivo and/or in vitro antiviral activity against a variety of DNA viruses. The most well known of these, 5-iodo-2′-deoxyuridine,[1,2] 5-bromo-2′-deoxyuridine,[1,2] and 5-trifluoromethyl-2′-deoxyuridine,[3] express their inhibitory action primarily after they have been incorporated into viral DNA. These nucleosides have pioneered our understanding of viral replication and have demonstrated the promise of nucleosides as antiviral agents; nonetheless, they possess several important limitations. All are incorporated into viral DNA and host cell DNA with resultant mutagenic events in phage, bacteria, and eukaryotic cells as well as oncornavirus activation in mammlian cell culture.[1,2] Additionally, 5-iodo- and 5-bromo-2′-deoxyuridine are embryotoxic and may also lead to immunosuppression, at least in vitro.[1,2]

For these reasons, we felt it would be interesting to expand the variety of substituents available at the pyrimidine C-5 position of the pyrimidine deoxyribonucleosides to take advantage of the multitude of steric and electronic alterations which could be thus obtained. Such alterations would surely influence the biochemistry of the pyrimidine deoxyribonucleoside analogues, thereby providing additional information for the design of useful nucleoside antivirals.

One such alteration of interest is the cyano group which is somewhat unique with respect to other substituents that endow 2′-deoxyuridine with antiviral activity. For steric purposes, the C–CN moiety can be considered as a cylinder with a diameter of 3.6 Å whereas the C–Cl, C–Br, and C–I groups may be considered roughly as spheres with diameters of 3.6, 3.9, and 4.2 Å, respectively.[4] The trifluoromethyl group can be regarded as a hemisphere with an overall diameter of 5.0 Å.[4] Thus sterically, the CN group most closely approximates either a chloro or bromo substituent. The cyano group, however, shows the greatest electrical effect of any common substituent; e.g., the dipole moments of CH_3X increase in the order Cl, CF_3, NO_2, and CN.[4] The inductive and resonance σ values for cyano are comparable to the values for NO_2 but exceed the values for F, Cl, CF_3, etc.[4] It can be reasonably expected that substitution of CN for H, I, Br, F, or CF_3 will bring about a marked difference in biological behavior compared to the parent compounds.

In fact, both 5-cyanouridine (I) and 5-cyano-2′-deoxyuridine (II) have been reported earlier in the literature.



I, R_1 = CN; R_2 = OH; R_3 = H
II, R_1 = CN; R_2 = H; R_3 = H
III, R_1 = Br; R_2 = OAc; R_3 = Ac
IV, R_1 = Br; R_2 = H; R_3 = Ac

Watanabe and Fox[5] used the $Hg(CN)_2$–nitromethane procedure to prepare the tribenzoate of I in 70% yield from the polyacetylated glycosyl halide and 5-cyanouracil. Inoue and Ueda[6] and Ueda et al.[7] reported a 70% yield of the 5′-acetyl-2′,3′-isopropylidene derivative of I when the corresponding 5-bromo derivative was treated with NaCN according to methods developed for the simpler uracil derivatives.[8–11] Prystas and Sorm[12] reported deblocking such an intermediate, obtained via a Hilbert–Johnson type synthesis, to give a 29% yield of I. It is noteworthy that the condensation type reactions required preparation of 5-cyanouracil in two steps from ureidomethylene malonitrile. Shaw et al.[13] condensed tri-O-benzoylated D-ribosylamine with α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide to give, after deblocking, a 20% yield of I which was also obtained by a similar condensation using the isopropylidene derivative of the furanosylamine to give an