Structure–Activity Relationship in a New Series of Atropine Analogues. 1. N,N′-Disubstituted 6,7-Diazabicyclo[3.2.2]nonane Derivatives

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The synthesis of a new series of N,N′-disubstituted 6,7-diazabicyclo[3.2.2]nonane derivatives is described. The antimuscarinic potency of these drugs was evaluated in the guinea pig ileum and compared to that of atropine sulfate. All the drugs tested competitively inhibited the acetylcholine-induced contractions. K_d values were calculated and, in several cases, compared to those obtained by direct binding to the muscarinic receptor from mouse brain. The order of potencies followed that which is known for various tropine and pseudotropine esters; that is, the 3α configuration is more potent than the 3β configuration, and the quaternary analogues are more potent than the tertiary ones. The antimuscarinic activity of the drugs is discussed in terms of their acetylcholine-like molecular arrangement that gives rise to a characteristic interaction pharmacophore.

The study of the reaction of cyclohepta-2,6-dienone with hydrazines[1] made possible the synthesis of the starting materials for a new series of atropine analogues, whose structure is given in Chart I.

The molecular determinants for the action of these drugs on the muscarinic receptor can be analyzed in terms of the acetylcholine (AcCh)-like molecular arrangement[2] that gives rise to a characteristic muscarinic interaction pharmacophore.[3,4] The ability of drug molecules to generate an acetylcholine-like interaction pharmacophore in the amino alcohol portion of amino ester derivatives of tropine has been characterized[2] and correlated directly to their action on muscarinic receptors. Moreover, structural changes that modify this parameter of receptor recognition have a direct and predictable effect on the affinities of the molecules for the receptor (see ref 4 and references cited therein).

The present work describes the synthesis of a new series of atropine analogues and their affinities to the muscarinic receptor from guinea pig ileum, in relation to various structural features of the drug-receptor recognition pattern including (1) the C_3-site configuration (α/β), (2) the ability to assume various conformations (chair-boat), and (3) N-substitution (tertiary/quaternary).

Results and Discussion

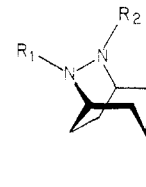
The drugs investigated here were found to possess remarkable antimuscarinic activity, both in vivo and in vitro.

Figure 1 illustrates typical results obtained with drugs 2 and 5 in the guinea pig ileum test. The dose–response curves for AcCh are shifted in a parallel fashion toward higher AcCh concentrations, indicating competitive antagonistic activity of the two drugs.

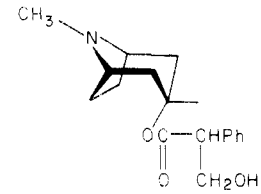
Binding to the muscarinic receptor from mouse brain was examined using a potent, highly specific antagonist, which possesses the AcCh-like molecular arrangement,[3] i.e., *N*-methyl-4-piperidyl benzilate (4-NMPB), which was tritium-labeled to a high specific activity (6 Ci/mmol). The ability of the nonradioactive drugs under study to compete with the labeled ligand for the muscarinic binding sites was tested and the dissociation constants were estimated, as explained in detail elsewhere.[6]

Table I summarizes the data obtained for the various drugs. As can be seen, replacement of the aza with a diaza moiety resulted in analogues that are very potent muscarinic antagonists in the guinea pig ileum ($K_d = 10^{-9}$–10^{-11} M). These K_d values were confirmed using the binding experiments to the muscarinic receptor from mouse brain; for example, the K_d of drug **5** in the brain was found to be 2.1×10^{-9} M, as compared to 1.6×10^{-9} M in the ileum. N substituents which alter the electron density of the nitrogen in atropine (and thereby influence the salt stability) are known to change the drug activity also. The reported diaza series is an interesting atropine analogue in which the single nitrogen is replaced by two conformationally flexible N atoms, an arrangement which enables, after monoprotonation or quaternization, the simultaneous existence of a cationic head (known to increase activity vide infra) together with a basic neighboring N atom, a combination which might improve the ligand–receptor interaction.

Chart I. N,N′-Disubstituted 6,7-Diazabicyclo[3.2.2]nonane Derivatives, in Comparison to Atropine



R_1, R_2 = Me or $PhCH_2$;
R_3 = α/β OCOCH(Ph)CH_2OH
(see Table I)



atropine

Quaternization of one of the N atoms (either by methyl iodide or by methyl methanesulfonate) resulted in a 20–100-fold increase in antimuscarinic activity, a phenomenon which is well documented for various atropine analogues.[8-12] The extent of increase in activity seems to be related to the potency of the drugs; that is, the less active the drug in its tertiary form, the more pronounced the increase (compare pair **1**–**2** (or **1**–**3**) to pair **4**–**5** in Table I).

Another parameter investigated was the $C_{3\alpha}$-ester vs. $C_{3\beta}$-ester configuration. (The α and β terminology are by analogy to the one used in case of tropine and ψ-tropine esters; i.e., α means that the C_3-OH is closer to the C_8–C_9 linkage.) In all cases, the ester with the 3α configuration was much more active than the one with the 3β configuration, both in the tertiary (drugs **1** and **4**) and quaternary (drugs **2** and **5**) pairs. Again, the extent of increase in

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Table I. K_d Values for Drugs 1-6 in the Guinea Pig Ileum Test

drug no.	R_1[a]	R_2[a]	config (C_3)	form[b]	K_d, M[c]
1	CH_3	CH_3	α	base	$(1.7 \pm 1.3) \times 10^{-9}$
2	CH_3	CH_3	α	CH_3I	$(6.6 \pm 3.1) \times 10^{-11}$
3	CH_3	CH_3	α	CH_3SO_3H	$(9.1 \pm 4.9) \times 10^{-11}$
4	CH_3	CH_3	β	base	$(1.7 \pm 0.3) \times 10^{-7}$
5	CH_3	CH_3	β	CH_3I	$(1.6 \pm 0.2) \times 10^{-9}$
6	$C_6H_5CH_2$	CH_3	α	base	d
atropine	CH_3		α	sulfate	$(4.9 \pm 2.1) \times 10^{-10}$

[a] See Chart I. [b] See the Experimental Section for detailed nomenclature and syntheses. [c] Mean, calculated from two to four separate experiments, ± SD. [d] Could not be determined (see Results and Discussion).

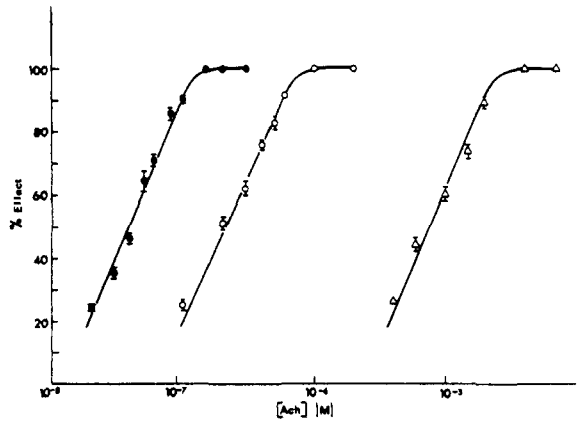


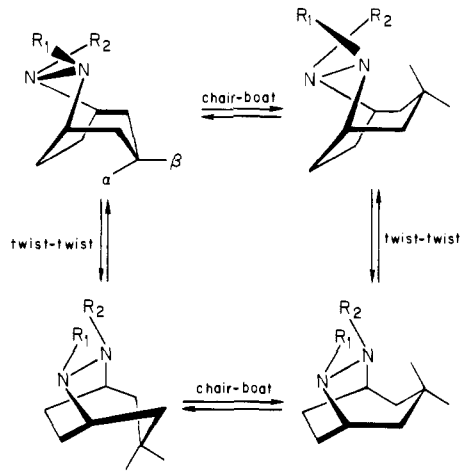
Figure 1. Dose–response curves for the AcCh-induced contraction of the guinea pig ileum. AcCh was tested alone (●–●) and in the presence of 1×10^{-8} M drug **2** (○–○) and 1.1×10^{-8} M drug **5** (△–△).

activity upon transition from the β to the α configuration was higher when the activity was weaker; that is, it was more pronounced in the tertiary drugs. Similar results were obtained for various tropine and pseudotropine esters.[9,13]

Drug **6** exhibited a peculiar behavior, revealed in a nonparallel shift of the AcCh dose–response curve in its presence. In addition, the "off" rate of this drug was found to be very slow, so that the muscle did not recover after its administration. Consequently, the K_d value could not be determined. Similar problems were encountered with another potent antimuscrinic drug—3-quinuclidinyl benzilate[14]—and the reasons are yet unclear.

The diazabicyclic system may exist in two twisted conformations, in addition to the twist-boat ⇌ twist-chair equilibrium, as shown in Scheme I. Surprisingly, the twist-boat form is the preferred conformer (Figure 2), as shown by X-ray analysis for 6-benzyl-7-methyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol. The crystals of this compound are monoclinic, the space group and unit cell dimensions being $P2_1/c$, $Z = 4$, $a = 11.185$ (2), $b = 10.255$ (2), and $c = 12.828$ (3) Å, and $\beta = 114.00$ (1)° (unpublished results). Our ^1H NMR and ^{13}C NMR studies show that the twist-boat conformer preference is true also for both α and β alcohol series. It was found that the conformational equilibrium depends on the size of the N substituent; thus, by the synthesis of suitable model compounds we were able to measure the $\Delta\omega$ values of the separate conformers with high accuracy (unpublished results). The populations of the two conformers in solution were estimated from the width of the C_3-H signal, the limiting values used being 21 Hz for the twist-chair and 36 Hz for the twist-boat conformers in the 3α series and vice versa in the 3β series. Accordingly the twist-boat conformation was found to be greatly preferred in both 3α and 3β alcohols. The esterification of the 3-ol function in both isomers increases the preference of the chair conformer, but about 20% boat conformer still remains in the α isomer, as shown by ^1H NMR.

Scheme I. Possible Conformations of the Diazabicyclo[3.2.2]nonane System



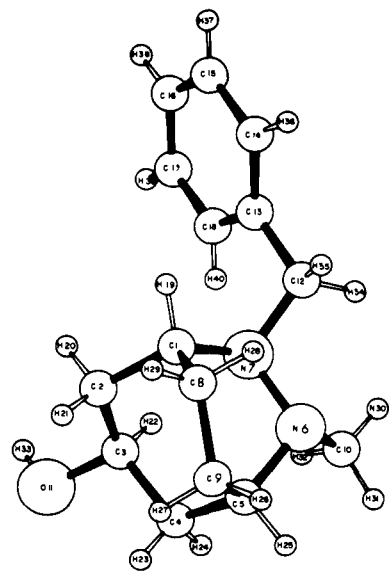


Figure 2. 6-Benzyl-7-methyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol (structure according to X-ray analysis).

Recently, Lambrecht[15,16] suggested that in the piperidine and analogous systems, the boat conformation may also be interacting with the cholinergic receptor. It should be noted that the preferred conformation (in terms of energy) is not necessarily the one which is pharmacologically active and that any conformation may be stabilized by its interaction with the receptor.[17] Furthermore, using X-ray analysis and space-filling models, we were able to show that, in the drugs of this system, both conformers may assume the appropriate N–O distance and fit the muscarinic pharmacophore,[3,4] owing to the presence of two nitrogen atoms.

In preliminary studies, LD_{50} values were calculated by injecting mice ip with the drugs. It seems that while the tertiary drugs are a little more toxic than atropine (e.g., LD_{50} of drug 1 is 150 mg/kg while that of atropine is 250 mg/kg), the quaternary analogues are three to four times more toxic. Nevertheless, the relatively high activity of the latter may result in a good therapeutic index. This, together with the existence of a nonnegligible boat population in the α isomer and of two nitrogen binding sites, raises intriguing pharmacological implications regarding the activity of this system.

Experimental Section

Synthesis. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 177 spectrophotometer. NMR spectra were taken on a Varian HA-100 spectrometer on 5–10% solutions in $CDCl_3$ (unless otherwise indicated) containing Me_4Si as an internal standard, and chemical shifts are quoted in δ units. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6 instrument.

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol. A solution of 10 g (60 mmol) of 6,7-dimethyl-6,7-diazabicyclo[3.2.2]nonan-3-one in 100 mL of water was hydrogenated under 1–2 atm of hydrogen in the presence of 1 g of Raney nickel (Degussa). After the hydrogen uptake ceased, the catalyst was filtered off and the water evaporated to yield 10 g of crude alcohol. A solution of the crude alcohol in 30 mL of 2-propanol was treated with 15 g of 20% 2-propanolic HCl. The suspension obtained was cooled, and the solid was filtered off, washed with 2-propanol, and dried, yielding 9.8 g (79%) of 6,7-dimethyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol hydrochloride: mp 212–213 °C. Anal. ($C_9H_{19}N_2OCl$) C, H, N, Cl.

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]non-3α-yl Tropate (1). A mixture of 9.8 g (58 mmol) of 6,7-dimethyl-6,7-diazabicyclo-[3.2.2]nonan-3α-ol hydrochloride and 14.5 g (64 mmol) of acetyltropoyl chloride[5] was heated for 4 h at 80 °C. To the reaction mixture were added 30 mL of dioxane and 50 mL of 1.5% aqueous HCl, and the solution was heated at 50 °C for 4 h, extracted with ether, made basic with $NaHCO_3$, and extracted with chloroform. The chloroform extracts afforded on evaporation 12 g (65%) of crude 1 which was purified by dry-column chromatography on alumina (a 2-in. flat diameter column; $CHCl_3$–MeOH, 90:10) affording 8 g (43%) of 1: NMR ($CDCl_3$) δ 1.30–1.80 (m, $C_{8,9}$-H, 4 H), 1.80–2.10 (m, $C_{2,4}$-H, 4 H), 2.44 (s, NCH_3, 6 H), 2.86 (m, $C_{1,5}$-H, 2 H), 3.46–4.30 (ABC, $CHCH_2OH$, 3 H), 5.34 (quin, J = 6.0 Hz, C_3-H, 1 H), 7.27 (m, Ph, 5 H); IR (neat) 3700–3000, 2950, 1730 (C=O), 1640, 1580, 1460, 1410, 1300, 1170, 1070, 1050, 1030, 750, 700 cm^{-1}; MS (m/e) 318 (M^+, 100), 303 ($M^+ - CH_3$, 55), 288.7 (m*, 318 → 303).

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]non-3α-yl Tropate Methiodide (2). A solution of 1 g (3.1 mmol) of 1 and 2 mL (31 mmol) of methyl iodide in 5 mL of acetone was refluxed for 24 h. The suspension obtained was filtered, and the solid was washed with acetone and dried, yielding 1.1 g (77%) of white 2: mp 123–125 °C dec. Anal. ($C_{19}H_{29}N_2O_3I$) C, H, N, I.

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]non-3α-yl Tropate Methyl Methanesulfonate (3). Twenty grams (208 mmol) of methanesulfonic acid was added dropwise to a solution of 10 g (59 mmol) of silver nitrate in a minimum amount of water. The white solid formed was collected on a filter, washed with methanol, and dried in the dark to yield 8.01 g (68%) of silver methanesulfonate. A second crop (1.87 g, 9%) precipitated from the mother liquors: mp 265 °C. Compound 2, 1.2 g (2.6 mmol), was dissolved in 50 mL of 95% ethanol, and the solution obtained was treated dropwise with a solution of 0.53 g (2.6 mmol) of silver methanesulfonate in 50% ethanol. The mixture was stirred for 10 min, and the solid was filtered off and washed with 95% ethanol. The filtrate and washings were evaporated to dryness, affording 1.12 g (98%) of 3 in the form of a yellowish oil. Anal. ($C_{20}H_{32}O_6N_2S$) C, H, N, S.

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]nonan-3β-ol. Ten grams (60 mmol) of 6,7-dimethyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol was dissolved in a solution of 10 g (435 mg-atom) of sodium in 300 mL of amyl alcohol, and the mixture was refluxed for 48 h, allowed to cool, and poured into 500 mL of water. The solution obtained was acidified with HCl and extracted with ether and then made basic with $NaHCO_3$ and extracted with chloroform. The chloroform extracts were dried on K_2CO_3 and evaporated to dryness, yielding 5 g (40%) of crude 6,7-dimethyl-6,7-diazabicyclo-[3.2.2]nonan-3β-ol hydrochloride.

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]non-3β-yl Tropate (4). One gram (4.8 mmol) of 6,7-dimethyl-6,7-diazabicyclo[3.2.2]-nonan-3β-ol hydrochloride was reacted with acetyltropoyl chloride as described for 1, yielding 0.6 g (40%) of 4: NMR ($CDCl_3$) δ 1.59–1.99 (m, $C_{8,9}$-H, 4 H), 1.99–2.30 (m, $C_{2,4}$-H, 4 H), 2.52 (s, NCH_3, 3H), 2.54 (s, NCH_3, 3H), 2.94 (m, $C_{1,5}$-H, 2H), 3.71–4.27 (ABC, $CHCH_2OH$, 3 H), 5.28 (quin, J = 8.8 Hz, C_3-H), 7.31 (m, Ph, 5 H); IR (neat) 3700–3000, 2950, 2880, 2800, 1730, (C=O), 1500, 1460, 1360, 1170, 1050, 975, 707 cm^{-1}; MS (m/e) 318 (M^+, 100), 303 ($M^+ - CH_3$, 100), 288.7 (m*, 318 → 303), 153 (21).

6,7-Dimethyl-6,7-diazabicyclo[3.2.2]non-3β-yl Tropate Methiodide (5). Two grams (6.3 mmol) of 4 was converted to its methiodide 5 (2.3 g, 80%), mp 167–168 °C dec, as described for 2. Anal. ($C_{19}H_{29}N_2O_3I$) C, H, N, I.

6-Benzyl-7-methyl-6,7-diazabicyclo[3.2.2]non-3α-yl Tropate (6). 6-Benzyl-7-methyl-6,7-diazabicyclo[3.2.2]nonan-3α-ol hydrochloride, 4.5 g (18 mmol), prepared in a manner similar to that described above for its 6,7-dimethyl analogue, was treated with 6.75 g (30 mmol) of acetyltropoyl chloride, as described for 1, yielding 2.77 g (39%) of 6. After purification by chromatography on alumina as described for 1, the TLC of 6 exhibited two spots (R_f 0.3 and 0.35) of equal intensity (SiO_2 chromatoplate developed in a 95% chloroform–5% methanol mixture), corresponding to the two diastereomers. The properties of the diastereomeric mixture are described as follows: NMR ($CDCl_3$) δ 1.2–1.75 (m, $C_{8,9}$-H, 4 H), 1.75–2.29 (m, $C_{2,4}$-H, 4 H), 2.52, 2.54 (s, CH_3, 3 H), 2.54–3.12 (m, $C_{1,5}$-H, 2 H), 3.71–4.31 (m, CH_2CH, 3 H), 5.46 (quin, J = 6 Hz, C_3-H, 1 H), 7.33 (m, Ph, 5 H); IR (neat) 3700–3100, 2950, 1725 (C=O), 1600, 1495, 1455, 1370, 1170, 1060, 750, 700 cm^{-1}; MS (m/e) 394 (M^+, 8), 303 ($M^+ - C_7H_7$, 100), 285 (303 − H_2O, 25), 233 (m*, 394 → 303), 91 ($C_7H_7^+$, 85).

Affinity Determination. Antagonism of AcCh-induced contraction of the isolated guinea pig ileum was determined. About 2 cm of ileum was taken from freshly killed guinea pigs. This was suspended in a 10-mL organ bath containing Tyrode solution at 37 °C. Air was bubbled through the solution. Contractions of the ileum were recorded on a Narco-bio physiograph using an isotonic lever. The affinity constants of the drugs toward the muscarinic receptor were calculated from the dose–response curves of acetylcholine in the absence and in the presence of antagonist, according to the dose ratio.

In several experiments, binding to muscarinic receptors from mouse brain preparations was determined according to Kloog and Sokolovsky.[6,7]

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Nucleosides. 110. Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuranosylpyrimidine Nucleosides[1]

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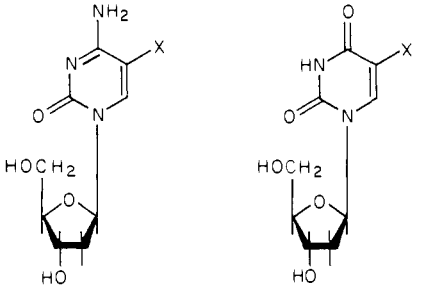
A series of 5-substituted 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosines **7a–d** and their corresponding uracils **9a–d,f** were prepared by condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide (**5**) with appropriately trimethylsilylated pyrimidines followed by saponification of the protected nucleosides **6** or **8**. 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (**7e**) was obtained by iodination of **7a**. Iodination of **8a** followed by removal of the protecting acyl-protecting groups afforded the 5-iodo nucleoside **9e**. Several of these 2'-fluoro-substituted nucleosides completely obviated replication of herpes simplex virus type 1 (HSV-1) in monolayers of Vero cells at concentrations of 10–100 μg/mL. The 5-iodocytosine analogue **7e** was the most effective, showing 99.5% suppression of viral replication even at concentrations of 0.1 μg/mL. The cytotoxicity of **7e** to L5178Y or P815 cells in culture was minimal. A comparison of the efficacy of **7e** against HSV-1 with other known nucleoside antiviral agents indicates that further in vitro and in vivo evaluation of **7e** is warranted.

Studies by Cooper[2] and Schildkraut et al.[3] showed that 5-bromo- and/or 5-iodo-2'-deoxycytidine (**1**, X = Br or I) inhibit the replication of herpes simplex virus (HSV) as effectively as their corresponding deoxyuridine analogues **2**. Their studies also showed that these deoxycytidine analogues are significantly less toxic to uninfected cells than are 5-iodo- (or 5-bromo-) 2'-deoxyuridine (**2**) apparently as a result of a virus-induced pyrimidine nucleoside kinase which converts the 5-halogenated deoxycytidines to their 5-halogenated deoxycytidylates and thence to the corresponding deoxyuridylates.



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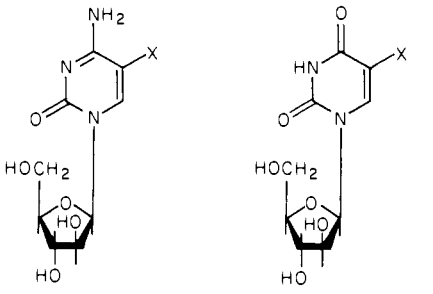

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series a, X = H; b, X = F; c, X = Cl; d, X = Br; e, X = I; f, X = CH_3

1-β-D-Arabinofuranosylcytosine (*ara*-C, **3a**), a potent anticancer drug,[4] also inhibits the multiplication of several DNA viruses in cell culture.[5] Therapeutic trials of *ara*-C in herpes infections in animal models were not encouraging because its therapeutic to toxic ratio approached unity.[6] Although 1-β-D-arabinofuranosyluracil (*ara*-U, **4a**) is devoid of antiviral or anticancer activity, the 5-halogeno analogues (**4**, X = Cl, Br, I) show antiviral activity in cell culture[7] and in vivo.[8] Gentry et al.[9] demonstrated that *ara*-T (**4f**) also is active against HSV types 1 and 2 as well as against equine herpes virus. More recently they[10] showed that 5-Me-*ara*-C (**3f**) is also active against herpes virus infected cells in which deoxycytidine deaminase is present, indicating that this nucleoside serves as an intracellular donor of *ara*-T that is phosphorylated to the nucleotide which then inhibits viral replication. (5-Me-*ara*-C is devoid of anticancer activity.[11]) The 5-halogeno-*ara*-C derivatives (**3**, X = F, Cl, Br, I) have also shown antiherpes virus activity in culture and were also active against experimental herpes keratitis in rabbits.[12]

It is apparent from the above-mentioned data that the nature of the substituent at C-5 of the pyrimidine nucleosides **1–4** is an important factor in the determination of biological activity. Moreover, since activity is noted for both 2'-deoxyribo- as well as 2'-deoxyarabinopyrimidine nucleosides, the C-2' substituent also plays a role in the determination of biological activity. This report describes the syntheses and preliminary evaluation of a series of 5-substituted 1-(2-deoxy-2-fluoroarabinofuranosyl)pyrimidines (**7** and **9**) as part of our program in the design and syntheses of nucleosides of potential value as anticancer and/or antiviral agents.

We had previously developed[13] a practical synthesis of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (**5**), a key intermediate in the syntheses of the desired nucleosides. Thus, condensation of halogenose **5** with trimethylsilylated cytosines afforded the blocked nucleosides **6** which were deprotected by saponification to the 2'-F-*ara*-C type nucleosides **7a–d**. The 5-iodo analogue **7e** was obtained by iodination of **7a**. The uracil nucleoside analogues **9a–d,f** were obtained by condensation of **5** with the corresponding trimethyl-

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