Effects of Alkyl and Aryl Substitution on the Myocardial Specificity of Radioiodinated Phosphonium, Arsonium, and Ammonium Cations†

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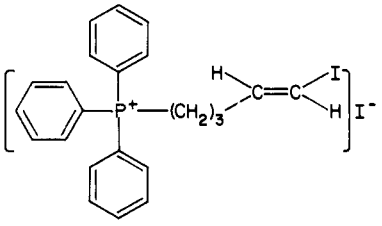
Several radioiodinated iodopentenyl-trisubstituted phosphonium, arsonium, and ammonium iodides have been prepared and evaluated in rats to determine the effects of structural variations of the cations on myocardial uptake and retention. The synthesis of (*E*)-(1-iodo-1-penten-5-yl)-trisubstituted phosphonium, arsonium, and ammonium iodides via the condensation of trisubstituted phosphine, arsine, and amine precursors, respectively, with (*E*)-1,5-diiodopentene is described. In some cases a second route involved condensation with (*E*)-1-borono-5-iodo-1-pentene followed by iodination. In the phosphonium series, the compounds triphenyl 1, dicyclohexylphenyl 5, tricyclohexyl 6, and dimethyl-*n*-octyl 8 were prepared. The triphenylarsonium 10 and triethylammonium 11 compounds were also prepared. The corresponding radioiodinated analogues were prepared and tissue distribution studies performed in rats. The results (percent dose/gram, 30 min) demonstrate that replacement of phosphorus with arsenic (1, 3.99%; 10, 3.17%) or the replacement of the phenyl ring with the cyclohexyl ring system (6, 2.67%) has no apparent effect on heart uptake. In the series of compounds studied, replacement of the cyclic ring system with alkyl groups, however, significantly decreased heart uptake with both the phosphorus (8, 1.95%) and nitrogen agents (11, 1.11%). γ camera imaging studies with [^{123}I]-5 and [^{123}I]-8 further substantiated the decreased heart uptake with alkyl substitution and the apparent hepatobiliary clearance of 8.

Thallium-201 is the most widely used cationic perfusion agent for the differentiation of ischemia from irreversible myocardial damage but has the disadvantages of inefficient detection of its low-energy X-rays and redistribution during the imaging period. A myocardial perfusion agent labeled with an isotope having more attractive radionuclidic properties would be an advantage. In addition, nuclear medicine techniques could be of even greater benefit to the cardiologist if agents were available for measuring early indices of myocardial disease as well as regional perfusion.

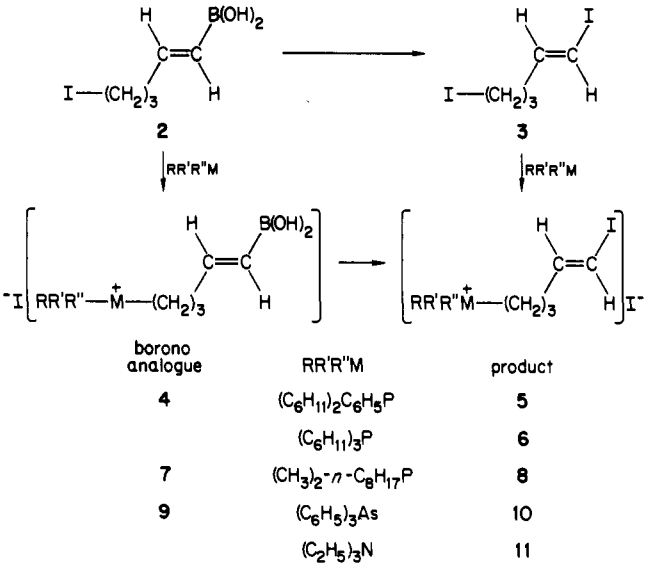
Recent studies have shown that the uptake of organic cations such as tetraphenylphosphonium bromide (TPP) in various cells grown in vitro is related to the cell membrane potential gradient.[1-4] In addition, pronounced myocardial uptake of the [^{3}H]tetraphenylphosphonium and ([^{123}I]iodobenzyl)dimethylphenylammonium cations[5] have suggested the potential use of such radiolabeled cations for evaluation of heart disease. A model radioiodinated phosphonium cation, [(*E*)-1-[^{123}I]iodo-1-penten-5-yl]triphenylphosphonium iodide (1), used in our



recent preliminary studies,[6,7] shows high heart/blood ratios in Fischer rats and both high myocardial and hepatobiliary uptake in dogs. Since a balance between charge, molecular size, and polar and nonpolar characteristics of the molecule are required for biliary secretion, modification of this type of phosphonium cation could potentially increase myocardial uptake and minimize hepatobiliary uptake. To study the relationship between tissue specificity and the structural features of this type of cation, several analogues of 1 and model arsonium and ammonium cations have now been prepared and evaluated in rats.

Chemistry. The preparation of a model compound, [(*E*)-1-iodo-1-penten-5-yl]triphenylphosphonium iodide (1)

Scheme I



borono analogue	RR'R"M	product
4	$(C_6H_{11})_2C_6H_5P$	5
	$(C_6H_{11})_3P$	6
7	$(CH_3)_2$-*n*-$C_8H_{17}P$	8
9	$(C_6H_5)_3As$	10
	$(C_2H_5)_3N$	11

by the two methods illustrated in Scheme I has been reported earlier.[7] The same strategy was followed for the synthesis of various derivatives and model arsonium and ammonium agents. In method A, the borono analogue 2 was first iodinated[7] to yield (*E*)-1,5-diiodo-1-pentene (3), which was condensed with the trisubstituted precursor (RR'R"M) to give the desired product. Alternatively, method B involves initial quaternization of 2 with RR'R"M to give borono analogues that are generally stable, crystalline substrates. the boronic acids are readily iodinated to the desired cation in a one-step procedure. Method B

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Table I. Summary of Experimental Details for the Synthesis of Iodopentenyl-Substituted Cations 1–6 (Scheme I)

cation	mp, °C	yield, %	RR′R″M substrate	general procedure (method)	anal.
4	161–163	52	dicyclohexylphenylphosphine	1	($C_{23}H_{37}BIO_2P$) C, H, B
5	169–170	75, method A 50, method B	dicyclohexylphenylphosphine	2 (A or B)	($C_{23}H_{35}I_2P$) C, H
6	159–160	55	tricyclohexylphosphine	2 (A, CP)	($C_{23}H_{41}I_2P$) C, H, I, P
7	(syrup)	86	dimethyl-*n*-octylphosphine	1 (CP)	analyzed after conversion to 8
8	(syrup)	45	dimethyl-*n*-octylphosphine	2 (B, CP)	($C_{15}H_{31}I_2P$) C, H, P
9	143–146	20	triphenylarsine	1	($C_{23}H_{25}AsBIO_2$) C, H, As, I
10	168	25, method A 62, method B	triphenylarsine	2 (A or B)	($C_{23}H_{23}AsI_2$) C, H, As, I
11	135–136	25	triethylamine	2 (A, CP)	($C_{11}H_{23}I_2N$) C, H, I, N

Table II. Summary of Radiochemical Yields and Specific Activity Values of Radiolabeled Cations

^{125}I-labeled cation	sp act., mCi/mmol	radiochemical yield,[a] %	synthesis, general procedure 3
[^{125}I]-5	300	20	method A
[^{123}I]-5	600	30	method B
[^{125}I]-6	310	80	method A
[^{125}I]-8	400	29	method A
[^{123}I]-8	389	25	method B
[^{125}I]-10	300	40	method A
	300	25	method B
[^{125}I]-11	310	20	method A

[a] The radiochemical yields by method A are based on the amount of (*E*)-1,5-1-[^{125}I] diiodopentene consumed (or recovered).

is thus the most attractive strategy for the preparation of radioiodinated cations. The borono analogues [(*E*)-1-borono-1-penten-5-yl]dicyclohexylphenylphosphonium iodide (**4**), [(*E*)-1-borono-1-penten-5-yl]dimethyl-*n*-octylphosphonium iodide (**7**), and [(*E*)-1-borono-1-penten-5-yl]triphenylarsonium iodide (**9**) were prepared and iodinated with use of sodium iodide and chloramine T to yield [(*E*)-1-iodo-1-penten-5-yl]tricyclohexylphosphonium iodide (**5**), [(*E*)-1-iodo-1-penten-5-yl]dimethyl-*n*-octylphosphonium iodide (**8**), and [(*E*)-1-iodo-1-penten-5-yl]-triphenylarsonium iodide (**10**), respectively. Compounds **5** and **10** were also synthesized by the alternate method A. The sensitivity of tricyclohexylphosphine toward oxidation and solubility of ammonium compounds in aqueous and organic phases indicated losses may be encountered by preparation of these products by method B. Therefore, the two compounds [(*E*)-1-iodo-1-penten-5-yl]tricyclohexylphenylphosphonium iodide (**6**) and [(*E*)-1-iodo-1-penten-5-yl]triethylammonium iodide (**11**) were synthesized by method A. The details of the preparation of these compounds are summarized in Table I.

The corresponding radiolabeled agents **5**, **8**, and **10** could be prepared either by method A or by method B. However, when the labeled agent had to be prepared in a relatively short period of time, such as in case of iodine-123 (half-life 13.6 h), method B using the borono analogue and chloramine T radioiodination was followed. The iodine-125-labeled analogues **6** and **11** were prepared by initial preparation of 5-[^{125}I]iodopentenyl iodide followed by coupling with the phosphine or amine substrates, respectively (method A). The results of specific activity, radiochemical yield, and the procedure used are given in Table II. The crude products were treated thoroughly with excess NaI to insure that iodide was the anion. The products were then purified by adsorption column chromatography. All agents showed one radioactive spot which cochromatographed with the unlabeled standard.

Biological Studies. The results of the tissue distribution studies in rats are summarized in Table III. The dicyclohexylphenyl- and tricyclohexylphosphonium cations **5** and **6** both show good heart uptake and retention similar to the parent agent **1**. Thus, replacement of the phenyl ring with the cyclohexyl ring system has little apparent

Table III. Distribution of Radioactivity[a] in Tissues of Female Fischer Rats after Intravenous Administration[c] of Iodine-125-Labeled Cations 1–6

min after injection and agent	mean % dose/g (range) heart	blood	liver	lungs	kidneys	thyroid	mean heart/blood
5 min							
1[b]	4.40 (3.80–5.74)	0.29 (0.27–0.33)	1.48 (1.04–2.56)	1.72 (1.41–2.17)	1.48 (1.04–2.56)	37 (26–49)	15
5	3.44 (2.82–3.86)	0.37 (0.32–0.46)	1.39 (1.06–1.70)	1.32 (1.18–1.44)	13.07 (11.7–14.6)	25 (16–32)	9
6	2.99 (2.72–3.52)	0.47 (0.44–0.52)	1.06 (0.93–1.20)	1.31 (1.20–1.52)	11.06 (9.87–11.9)	31 (29–36)	6
8	2.51 (2.20–2.97)	0.42 (0.40–0.45)	3.72 (3.12–4.56)	1.18 (0.96–1.35)	17.54 (14.4–20.1)	16 (13–18)	6
10	3.22 (2.78–3.62)	0.31 (0.25–0.34)	1.78 (1.26–2.45)	1.24 (0.95–1.49)	13.14 (10.7–16.9)	23 (22–25)	11
11	1.12 (0.90–1.46)	0.12 (0.10–0.14)	5.16 (4.12–6.30)	0.57 (0.51–0.66)	7.46 (4.78–9.72)	6 (5–8)	9
30 min							
1[b]	3.99 (3.17–4.70)	0.12 (0.10–0.13)	0.62 (0.55–0.71)	1.28 (0.91–1.74)	9.36 (8.28–10.72)	31 (26–40)	34
5	3.17 (2.67–3.69)	0.20 (0.18–0.24)	0.26 (0.22–0.30)	1.24 (1.12–1.39)	8.41 (6.47–10.2)	38 (29–44)	16
6	2.67 (2.47–2.96)	0.28 (0.25–0.32)	0.25 (0.23–0.29)	1.20 (1.07–1.30)	6.89 (6.28–7.41)	45 (33–60)	12
8	1.95 (1.39–2.43)	0.22 (0.19–0.24)	1.84 (1.51–2.23)	1.05 (0.83–1.21)	7.51 (7.21–7.95)	21 (19–24)	8
10	3.17 (2.67–4.31)	0.26 (0.22–0.32)	0.64 (0.57–0.72)	1.09 (0.99–1.23)	12.01 (10.5–14.4)	37 (32–42)	13
11	1.11 (0.95–1.44)	0.08 (0.07–0.09)	2.76 (2.30–3.12)	0.39 (0.34–0.47)	0.27 (0.24–0.31)	5 (4–7)	14
60 min							
1[b]	4.19 (3.51–5.44)	0.14 (0.12–0.14)	0.49 (0.44–0.54)	1.18 (1.07–1.26)	6.80 (5.67–8.41)	33 (26–42)	32
5	3.47 (3.21–3.92)	0.17 (0.15–0.20)	0.17 (0.15–0.19)	1.15 (0.94–1.36)	5.66 (5.02–6.57)	39 (32–43)	21
6	3.42 (2.88–4.32)	0.19 (0.16–0.21)	0.17 (0.14–0.19)	1.16 (0.97–1.54)	4.15 (3.33–4.68)	71 (55–102)	19
8	2.73 (1.93–3.58)	0.14 (0.13–0.15)	0.93 (0.73–1.19)	0.95 (0.81–1.13)	5.15 (4.62–5.60)	41 (35–53)	19
10	3.37 (3.00–3.70)	0.19 (0.15–0.23)	0.27 (0.24–0.30)	1.31 (0.83–2.11)	6.92 (4.59–8.81)	43 (30–53)	18
11	1.21 (1.05–1.57)	0.09 (0.08–0.09)	1.55 (1.08–2.31)	0.29 (0.28–0.33)	0.21 (0.17–0.25)	9 (5–12)	14

[a] The percent dose/gram data are the mean and range for five rats. [b] See ref 7. [c] Radioactivity dose in μCi (of compounds) administered in animals: 4.20 (1), 6.5 (5), 3.13 (6), 2.85 (8), 3.66 (10), 8.38 (11).

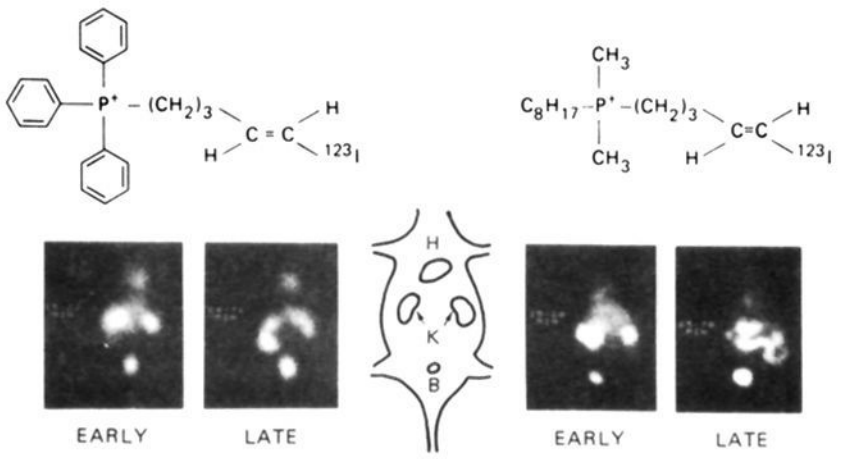

Figure 1. γ camera images (anterior view) illustrating the early and late distribution patterns of [(*E*)-1-[^{123}I]iodo-5-pentenyl]-dicyclohexylphenylphosphonium iodide (**5**) and [(*E*)-1-[^{123}I]-iodo-5-pentenyl]dimethyl-*n*-octylphosphonium iodide (**8**) in rats.

effect. Likewise, the triphenylarsonium analogue **10** shows properties very similar to those of **1**, demonstrating that both phosphorus and arsenic cations behave similarly. The aryl or cyclohexyl substitutions yield substances that are lypophilic in nature and are insoluble or have very low solubility in water. The related acyclic trialkyl compounds were synthesized to introduce more hydrophilic groups in the molecule and to examine their effect on heart uptake and clearance as compared to the other cations. Our systematic evaluation indicates that the relative heart uptake and hepatobiliary clearance properties of the acyclic dimethyl-*n*-octyl analogue **8** are quite different. This difference was further demonstrated and evaluated by comparing the sequential γ camera images of ^{123}I-labeled **5** and **8** in rats (Figure 1). [^{123}I]-**5** showed distinctive heart, kidney, and bladder uptake in the early (15–22 min) and later (64–71 min) images, with apparent hepatobiliary clearance beginning at 64–71 min. In contrast, [^{123}I]-**8** showed much lower heart uptake and high kidney, liver, and bladder uptake in the early image (15–20 min). The apparent hepatobiliary excretion of radioactivity is observed and the intestinal tract appears as a highly radioactive region in the late (65–70 min) image. These combined results demonstrate that structural changes may lead to altered biodistribution properties. Introduction of alkyl groups (e.g., **8**) appears to alter the lypophilicity and tissue specificity of phosphonium cations from high heart uptake to principally hepatobiliary excretion. Similarly, alkyl substitution in the ammonium cation (e.g., **11**) results in increased solubility in water and lower heart uptake as compared to aryl substitution (e.g., ([^{123}I]iodobenzyl)dimethylphenylammonium cation.[5] These data coupled with the properties of **8** may indicate that alkyl substitution of cations results in diminished myocardial specificity. The thyroid uptake of radioiodide after injection of these compounds is low (0.1–0.2% dose/organ) and would present no danger for potential clinical studies with the ^{123}I-labeled agents since thyroid uptake of radioiodide is routinely predisposed by blocking with Lugol's solution or perchlorate.

Discussion

These studies were directed toward determining the effects of various group 15[10] elements of the periodic table such as P, As, and N and their functional groups on the biodistribution properties of radioiodopentenyl-substituted cations. The iodopentenyl group was common to all the analogues evaluated since it represented a convenient method that had been developed for the introduction and stabilization of radioiodide.[7,9] From a comparison of the biodistribution properties of the triphenylphosphonium and triphenylarsonium analogues **1** and **10** (Table III), it appears that the nature of the group 15 element has little effect. The similarity in general tissue distribution properties of the dicyclohexylphenylphosphonium and tricyclohexylphosphonium analogues **5** and **6** suggests that charge delocalization is not an important factor in determining tissue distribution properties. In contrast, the dimethyl-*n*-octylphosphonium analogue **8** showed lower heart uptake and much more prevalent hepatobiliary clearance. Introduction of alkyl groups on nitrogen exemplified by **11** in this study behaves very similar to **8**. These combined studies demonstrate that ligand structure can drastically effect relative tissue specificity and elimination kinetics and that these interesting compounds should be further evaluated as myocardial imaging agents. Future studies will include further structural alterations to potentially increase myocardial specificity and biodistribution and imaging studies in dogs.

Experimental Section

General Procedures. All chemicals and solvents were analytical grade and were used without further purification. The petroleum ether (pet eth) had a boiling range of 30–60 °C. The iodine-125 was purchased from New England Nuclear, Inc. (North Billierica, MA). The iodine-123 was purchased either from the Brookhaven National Laboratory [p,5n] or from RadPharm, Inc. [p,2n]. The melting points (mp) were determined in capillary tubes with a Buchi SP apparatus and are uncorrected. The thin-layer chromatographic analyses (TLC) were performed with 250-μm-thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The infrared spectra (IR) were recorded on a Beckman 18-A spectrophotometer with NaCl plates or KBr pellets. The low-resolution mass spectra (MS) were determined with a Kratos MS-25 instrument at 70 eV. The proton nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with a Varian 360-L instrument or at 200 MHz with a Nicolet high-resolution instrument. Samples (30–40 mg) were dissolved in $CDCl_3$ or CCl_4 and the resonances (ppm) are reported downfield (δ) from the internal tetramethylsilane standard. The elemental analyses were determined at Galbraith Laboratories, Knoxville, TN.

Animal Tissue Distribution Studies. The distribution of radioactivity was determined in tissues of 10–12 week old female Fischer 344 rats (170–200 g) after intravenous administration of the radioiodinated cation. The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radioiodinated compounds were dissolved in dimethyl sulfoxide (Me_2SO) and diluted with saline to a final concentration of 1% Me_2SO. The solution was filtered through a 0.22-μm Millipore filter and injected via a lateral tail vein into the ether-anesthetized animals. After the times indicated, the animals were killed by cervical fracture, and blood samples were obtained by cardiac puncture. The organs were then removed, rinsed with saline solution, and blotted dry to remove residual blood. The organs were weighed and counted in a NaI autogamma counter (Packard Instruments). Samples of the injected radioactive solutions were also assayed as standards to calculate the percent injected dose per gram of tissue values. The thyroid glands were

(8) In the case of RR′R″M = dimethyl-*n*-octylamine, before $CHCl_3$–H_2O extraction, the volume of H_2O was reduced by evaporating under argon and kept to a minimum (ca. 5 mL/mmol scale) during the extraction process to avoid the loss of water-soluble product in the aqueous phase.

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(10) In this paper the periodic group notation is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the *p*-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

not weighed directly. The weight of the thyroid glands was calculated in the usual manner by multiplying the animal weight by (7.5 mg/100 g).

Imaging Studies. Imaging studies were obtained with sodium pentabarbital anesthetized rats following administration of the ^{123}I-labeled agents. Images were obtained with a 20% window with a Technicare 414 camera with a 5-mm pinhole collimator. Images were accumulated as 128 × 128 matrices.

General Procedure 1. Synthesis of (*E*)-1-Borono-1-penten-5-yl-Trisubstituted Onium Iodides. A solution of (*E*)-1-borono-5-iodo-1-pentene (**2**, 5 mmol) and trisubstituted substrate (5 mmol) in 2-butanone (5 mL) was refluxed for 16 h. The (*E*)-1-borono-1-penten-5-yl-trisubstituted onium iodide separated from the reaction solution as a crystalline precipitate and was collected by filtration and washed with cold acetone to yield 57 ± 5% of the pure product. An analytical sample was obtained by recrystallization from chloroform–acetone: NMR (Me_2SO-d_6) δ 5.3 and 6.3 (d and d, 1 H and 1 H, vinyl), 1.68, 2.3, and 3.5 [m, m and m, 2 H, 2 H, and 2H, $(CH_2)_3$].

General Procedure 2. Synthesis of (*E*)-1-Iodo-1-penten-5-yl-Trisubstituted Onium Iodides. Method A. A solution of diiodopentene **3** (322 mg, 1 mmol) and trisubstituted substrate (1 mmol) in 2-butanone (4 mL) was refluxed for 18 h. Separated (*E*)-1-iodo-1-penten-5-yl-trisubstituted onium iodide was collected by filtration and washed with acetone to yield the pure iodo compound. After crystallization (chloroform–acetone), the compound obtained by method A was identical (melting point, TLC, NMR) with an authentic sample prepared by method B.

Method B. A solution of chloramine-T (450 mg, 1.6 mmol) in 50% aqueous tetrahydrofuran (THF, 15 mL) was added to a stirred solution of borono analogue (general procedure, 1, 1 mmol) and NaI (150 mg, 1 mmol) in 50% aqueous THF (15 mL) protected from light. The solution was stirred at room temperature for 30 min in the dark. The reaction mixture was diluted with $CHCl_3$ and washed with water.[8] The $CHCl_3$ layer was separated and washed thoroughly with 10% aqueous $Na_2S_2O_5$ followed by water. The $CHCl_3$ portion was dried (Na_2SO_4) and the solvent was evaporated under vacuum. The syrupy residue was treated with acetone (10 mL) containing NaI (150 mg, 1 mmol) to give a crystalline product, which was collected by filtration, washed with acetone, and recrystallized from $CHCl_3$–petroleum ether: yield 288 mg (49, ±5% of the iodo compound); NMR ($CDCl_3$) δ 6.13–6.51 (m, 2 H, vinyl), 1.29–2.24 (m, 2 H $CH_2CH_2CH_2$).

General Chromatographic Purification (CP). The compounds obtained as a syrup (general procedures 1–3) were passed through a column packed with silica gel (Davison, Sigma Sil B was used for RR′R″M = NEt_3) slurry in $CHCl_3$. Elution with $CHCl_3$ (10 fractions, 25 mL each) removed unreacted substrates and/or less polar impurities. The more polar, desired quaternary product was isolated by elution with 10–15% (v/v) CH_3OH in $CHCl_3$ or 30% (v/v) acetone in $CHCl_3$ and identified by TLC, NMR, and elemental analyses.

General Procedure 3. Radiolabeling Synthesis of (*E*)-1-[^{125}I]Iodo-1-penten-5-yl-Trisubstituted Onium Iodides. Method A. The radioactive (*E*)-1,5-[1-^{129}I]diiodo-1-pentene was prepared as described previously[7,9] and condensed with RR′R″M in 2-butanone [toluene was used for RR′R″M = $(C_6H_{11})_3P$] according to the general procedure 2, method A. The solvent was evaporated and the desired radioiodinated quaternary product was isolated by general chromatographic purification method (Table II).

Method B. The direct radioiodination of borono analogues was accomplished as follows. A solution of (*E*)-1-borono-1-penten-5-yl-trisubstituted onium iodide (25 μmol, prepared by general procedure 1) and Na^{125}I (10–15 mCi, 3.8 mg, 25 μmol) in 50% aqueous THF (3 mL) was stirred with chloramine-T (7 mg, 25 μmol) for 30 min in the dark. Excess NaI (30 mg, 0.2 mmol) was added, and the reaction solution was stirred for an additional 10 min. The solution was partitioned between $CHCl_3$ (15 mL) and H_2O (15 mL).[9] The $CHCl_3$ layer was washed with 10% aqueous $Na_2S_2O_5$ followed by H_2O, dried (Na_2SO_4), and evaporated under argon to provide a residue. The quaternary radioiodinated product was isolated from the residue by using the general chromatographic purification procedure. The corresponding iodine-123-labeled compounds were prepared similarly (Table II). Each radiolabeled agent showed a single radioactive spot which cochromatographed with the unlabeled standard on thin-layer radiochromatographic analysis.

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Registry No. **2**, 84928-70-1; **3**, 84928-71-2; **4**, 96151-48-3; **5**, 96151-49-4; [^{125}I]-**5**, 96151-56-3; [^{123}I]-**5**, 96164-22-6; **6**, 96151-50-7; [^{125}I]-**6**, 96151-57-4; **7**, 96151-51-8; **8**, 96151-52-9; [^{125}I]-**8**, 96151-58-5; [^{123}I]-**8**, 96151-59-6; **9**, 96151-53-0; **10**, 96151-54-1; [^{125}I]-**10**, 96151-60-9; **11**, 96151-55-2; [^{125}I]-**11**, 96151-61-0.

Synthesis and Biological Activities of 2-Pyrimidinone Nucleosides. 2. 5-Halo-2-pyrimidinone 2′-Deoxyribonucleosides†

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1-(2-Deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (BrPdR) and 1-(2-deoxy-β-D-ribofuranosyl)-5-iodo-2-pyrimidinone (IPdR) have been synthesized by condensation of the appropriate silylated bases **2a** and **2b**, respectively, with 3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride (**8**) in 1,2-dichloroethane, in the presence of $SnCl_4$, followed by separation of the anomeric blocked nucleosides via column chromatography and subsequent deprotection with methanolic ammonia. Both BrPdR and IPdR exhibited significant antiherpes activities against various strains of HSV-1 and HSV-2, the latter compound (IPdR) showing the higher activity as well as the stronger binding to the virus-specific thymidine kinase.

A number of uracil and cytosine nucleosides have shown significant activity against herpes viruses.[1,2] Among the uracil nucleosides, 2′-deoxyuridine derivatives carrying the following substituents at C-5 of the pyrimidine moiety were found to have antiviral activity: iodo,[2] ethynyl,[3] propyl,[4] nitro,[5] trifluoromethyl,[6] and propynyl.[7] For many of the

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